NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Pazopanib (Votrient®) for the first-line treatment of patients with advanced renal cell carcinoma (RCC)

16 April 2010

GlaxoSmithKline UK

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Acknowledgements

GlaxoSmithKline would like to acknowledge:

- Heron Evidence Development for their help with the Systematic Review.
- Analysis Group Inc. and Dr. James Robbins, Harvard School of Public Health for their help with conducting the analyses to adjust for cross-over in the pazopanib. pivotal trial (VEG105192) and Dr. Lee-Jen Wei, Harvard School of Public Health and Ian White, University of Cambridge for reviewing the analyses.
- Policy Analysis Inc. for their help with development of the economic model and the cost effectiveness section of this submission.
- Peter West, York Health Economics Consortium, University of York for his help with the development of the economic model.
- Professor Steve Morris, Health Care Evaluation Group, University College London for validation of the economic model.

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Background:

Renal cell carcinoma (RCC) is a relatively uncommon but aggressive tumour that originates in the renal parenchyma. RCC accounts for 3% of all adult malignancies in the UK and for 90% of kidney cancers. Approximately 7,000 new cases of RCC are diagnosed in the UK each year. It is a male predominant disease with age-standardised incidence rates of 13.9 and 7.0 per 100,000 in men and women, respectively (CRUK 2010). (see Section 2.1)

Around 80% of RCC tumours have clear cell histology and are associated with a high incidence of inactivation of the Von Hippel-Lindau (VHL) tumour suppressor gene, leading to over-expression of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). These growth factors promote angiogenesis which is essential for tumour growth and tumour cell proliferation (Athar 2008; Sonapavde 2007). (see Section 2.1)

In its early stages, RCC is usually asymptomatic or has only mild symptoms and individuals are often diagnosed incidentally as a result of imaging performed for unrelated reasons. However, approximately a third of patients present with advanced/metastatic disease and around 40% of patients treated for localised disease subsequently develop metastases (Lam 2005). (see Section 2.1)

Advanced/metastatic RCC is one of the most difficult-to-treat malignancies being largely unresponsive to chemotherapy, radiotherapy and hormonal therapy (NICE TA 169). Such patients have a dismal prognosis with a 5-year survival rate in absence of effective therapy of less than 10% (Oudard 2007). Quality of life for patients with advanced/metastatic RCC is impacted not only by disease-related symptoms but also by treatment-related adverse events (Cella 2009; Gupta 200). (see Section 2.1)

Until recently, the cytokines, interferon-α (IFN) and interleukin-2 (IL-2), were the only available treatments. However, their use has been limited by their modest response rates and significant toxicity (Athar 2008; Garcia 2007; Harrison 2007). The introduction of agents targeted at the VEGF and related pathways has greatly improved the management of this malignancy, with clinical activity demonstrated in both treatment-naïve and cytokine pre-treated patients. However, only sunitinib has been recommended by NICE for the first-line treatment of advanced/metastatic RCC.

Despite improvements in efficacy, the toxicities observed with sunitinib and other VEGF targeted therapies remain a challenge. Consequently there is an unmet need for alternative treatments that offer a favourable side effect profile without compromising efficacy for patients with advanced/metastatic RCC. The availability of such a treatment in the UK will provide clinicians and patients with another option that could allow tailoring of therapy for patients. (see Section 2.4)

The technology:

Pazopanib, the intervention under consideration, is an orally-administered, selective, multi-targeted tyrosine kinase inhibitor (TKI). It has a distinct pharmacodynamic profile in terms of its potency and selectivity of kinase inhibition. It is a potent inhibitor of VEGFR 2, the primary mediator of VEGF-induced angiogenesis, and also inhibits VEGFR 1 and 3, PDGFR α and β, and c-Kit. Pazopanib is a more selective TKI than sunitinib and has a higher affinity for VEGFR 2 (Kumar 2009). Unlike sunitinib, it has minimal activity against Flt-3 (Kumar 2009), a critical regulator in the proliferation and differentiation of haematopoietic progenitor cells (Lyman 1998), inhibition of which is potentially associated with the development of haematological toxicities (Kumar 2009; van Erp 2009). In addition, pazopanib does not appear to have off-target kinase activity whereas sunitinib inhibits a number of off-target kinases, including ribosomal S6 kinase (RSK) and AMP-activated protein kinase (AMPK), which is thought to be the basis for sunitinib-induced cardiotoxicity (Fabian 2005; Hasinoff 2008) (see Section 1.2)

Pazopanib received positive CHMP opinion on 19th February 2010 recommending a conditional marketing authorisation for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease. (see Section 1.5) It is anticipated that pazopanib will receive marketing authorisation in June 2010, and will be made commercially available in the UK during 2Q 2010. (see Sections 1.3 and 1.7) The conditional licence is linked to the provision of further data supporting the efficacy and safety of pazopanib compared with sunitinib, including the outcome of the ongoing head-to-head non-inferiority trial of pazopanib versus sunitinib in patients with advanced RCC (VEG108844; COMPARZ) and a pooled analysis of data from VEG108844 and VEG113078 (a sub-study of VEG108844 in Asian subjects). It should be noted that the favourable risk/benefit tolerability profile of pazopanib led to the CHMP adopting a positive opinion in the absence of head-to-head comparative data. (see Section 1.4)

Pazopanib is available as 200mg and 400mg film-coated tablets. The recommended dose is 800mg once daily taken continuously until disease progression or unacceptable toxicity occurs. The dose can be modified in 200mg decrements/ increments in a step-wise fashion in order to manage adverse reactions. The anticipated list price of pazopanib is £560.50 per 30 x 200mg pack and £1121.00 per 30 x 400mg pack. This would equate to a daily cost of £74.73 per 800mg dose, equivalent to the daily cost of sunitinib (Sutent®, Pfizer) at list price (i.e. without the sunitinib patient access programme). This is the price used in the economic evaluation presented in this submission. However, GlaxoSmithKline (GSK) UK will be submitting a proposal to the Patient Access Scheme Liaison Unit (PASLU) shortly for a patient access scheme that would make pazopanib a more affordable treatment option for the NHS.

Comparator(s):

The primary comparator in this appraisal is sunitinib, the current standard of care for the first-line treatment of advanced/metastatic RCC in the UK. Recent UK market research data indicate that more than 80% of patients with advanced/metastatic RCC eligible for first-line treatment are now receiving sunitinib (IMS Oncology Analyzer Q3 2009). It should be noted that since no head-to-head data for pazopanib versus sunitinib are currently available, an indirect comparison via interferon-α (IFN) and

placebo/best supportive care (BSC) has been performed for the comparative clinical and economic evaluations in this appraisal.

In line with the scope for this appraisal, the other comparators considered in this submission are IFN and BSC since these might be relevant treatment options in patients for whom sunitinib is unsuitable. Again, in the absence of head-to-head data, the clinical and economic comparison with IFN has been conducted indirectly via placebo/BSC.

We recognise that sunitinib was approved by NICE under the Supplementary Advice on appraising end-of-life (EoL) medicines. The Supplementary Advice states that treatments approved following application of the advice will not necessarily be regarded as standard comparators for future assessments, under this advice, of new treatments introduced for the same condition. As this appraisal of pazopanib follows closely behind that of sunitinib, we believe that pazopanib should be afforded the same considerations under this guidance as sunitinib (i.e. assessed in the context of EoL relative to IFN), and as such, fulfils the criteria set out in the guidance as follows:

(i) The treatment is indicated for patients with a short life expectancy, normally less than 24 months

The prognosis for patients with advanced/metastatic RCC is poor with a 5-year survival rate of <10% (Oudard 2007). In the absence of effective treatment, median survival after diagnosis of metastatic disease is generally less than 1 year (Gupta 2008). In the MRC RE-01 trial comparing IFN with medroxyprogesterone acetate (MPA) in 350 patients with metastatic RCC in the UK, median survival was 9 months and 6 months in the IFN and MPA arms, respectively (Hancock 2000). In the more recent pivotal study of sunitinib versus IFN, median survival in the group randomised to IFN was 21.8 months (95% CI: 17.9-26.9) in the final ITT analysis (Motzer 2009).

(ii) The treatment is licensed, or otherwise indicated, for small patient populations

Patients with advanced/metastatic RCC represent a small population. Approximately, 7,000 patients are diagnosed with RCC in the UK each year, of whom about half (3,500 to 4,000 patients) present with advanced/metastatic disease. Such patients are either first diagnosed with advanced/metastatic disease or develop recurrence following treatment for localised disease.

(iii) ***The treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment***

An indirect comparison conducted for the purposes of this submission estimated the hazard ratio (HR) for pazopanib versus IFN for overall survival (OS) to be 0.432 (95% CI: 0.106-1.750), indicating a significant reduction in risk of death for patients receiving pazopanib compared with IFN. Median OS estimated using the Weibull survival model employed in the economic evaluation for this submission was 15.8 months (95% CI: 15.8-15.8) for IFN and 43.5 months (95% CI: -81.9-169.0) for pazopanib. This equates to a survival gain of 27.7 months for patients receiving pazopanib, thereby exceeding the EOL criterion of an extension to life of at least 3 months. (see section 5.7.6)

Clinical evidence:

A systematic review was undertaken to identify clinical evidence for pazopanib and its comparators in the first-line treatment of patients with advanced/metastatic RCC.

One randomised controlled trial (RCT) evaluating pazopanib in this population was identified, VEG105192 (Sternberg 2010). Twelve further RCTs of other targeted agents or of cytokine-based regimens in the treatment of advanced/metastatic RCC were also identified as meeting the inclusion criteria for the systematic review; 6 of these studies could be utilised in an indirect comparison with pazopanib, comprising the sunitinib pivotal trial (Motzer 2009) and 5 studies comparing IFN with a non-IFN control therapy (considered equivalent to BSC) (MRC RE-01, Negrier 2007, Pyrhonen 1999, Steineck 1990, Kriegmair 1995). (see Section 5.2.2)

The placebo-controlled VEG105192 study provides the primary evidence for the efficacy and safety profile of pazopanib; results from the treatment-naive sub-population form the main focus of this submission in line with the scope of this appraisal (first-line treatment). The rationale for the choice of comparator in this study is discussed in detail in section 5.3.1. When the study was initiated in April 2006, access to the TKIs, sunitinib and sorafenib, was limited making it difficult to use either as a comparator. Since the initial protocol was to enrol only cytokine pre-treated patients, placebo plus BSC was considered an appropriate comparator. However, with the emerging data for the TKIs and the diminishing use of cytokine therapy in RCC due to its unfavourable risk:benefit profile, the protocol was amended to allow the inclusion of treatment-naive patients. Placebo plus BSC was retained as the control arm and patients on the placebo arm had the opportunity to cross over to pazopanib or to receive other active treatments on progression. Two non-RCTs provide supportive clinical data for pazopanib in this setting: a phase II study (VEG102616) and the open-label extension study (VEG107769) to VEG105192.

Efficacy:
The primary endpoint of VEG105192 was progression-free survival (PFS), a valid measure of clinical benefit and an acceptable surrogate for overall survival in RCC (George 2009; Bracarda 2009). (see Section 5.3.5) The study was powered to examine progression-free survival in the treatment-naive sub-group as well as the combined study population. PFS was significantly prolonged with pazopanib compared with placebo (11.1 vs. 2.8 months; HR 0.40 [95% CI: 0.27-0.60]; p<0.0001). This was confirmed by sensitivity analyses including assessments based on scan dates (HR 0.36 [95% CI: 0.24-0.55]) and investigators' determination of progression (HR 0.47 [95% CI: 0.33-0.68]). (see Section 5.5.1.1)

Pazopanib was associated with a 26% reduction in risk of death compared with placebo in the pre-specified ITT analysis (HR 0.74 [95% CI: 0.47-1.15]; p=0.0079, based on a Pike estimator); however, the data are currently immature and a large proportion of patients in the placebo arm (40% at the clinical cut-off) crossed over to receive pazopanib at disease progression which is likely to have improved survival times for the placebo group. (see Section 5.5.1.2.1)

Since there is no universally accepted way to adjust for cross-over from control to active treatment in survival analysis in RCTs and because conventional approaches can lead to bias, several approaches were utilised to comprehensively evaluate this effect: i) censoring on cross-over; ii) considering cross-over as a time-dependent covariate; iii) inverse probability of censoring weighted (IPCW) analysis; and iv) rank preserved structural failure time (RPSFT) analysis.

The results of all these analyses are presented in this submission and indicate that treatment with pazopanib was associated with a clinically relevant reduction in risk of death compared with placebo (HRs adjusted for cross-over ranging from 0.206 to

0.684, depending on methodology and whether adjusted for baseline patient characteristics, see Table 5.22). The univariate HR of 0.345 (95% CI: 0.086-1.276) for OS for pazopanib vs. placebo estimated using the RPSFT technique was chosen for use as the base case in the indirect comparison and in the economic evaluation, based on the benefits of this approach in preserving randomisation and not making the assumption of no unmeasured confounders, unlike the IPCW analysis (NICE TA 179; Everolimus ACD, Feb 2010). It does, however, have some limitations when applied to immature OS data due to the re-censoring required, which is likely to be less of an issue when applied to the updated OS data (Note: GSK is liaising with NICE to ensure these data are made available to the committee as soon as possible – expected to be in 3Q 2010). (see Section (see Section 5.5.1.2.2)

Tumour shrinkage as demonstrated by the objective response rate ORR: (complete [CR] and partial response [PR]) was significantly greater in patients receiving pazopanib compared with placebo (32% vs. 4%; p<0.001). Tumour response was durable with a median duration of response of 13.5 months. Since tumour stabilisation can result in clinical benefit for patients, the CR + PR + 6-month stable disease (SD) rate of 49% in the pazopanib arm vs. 12% in the placebo arm (p<0.001) is also clinically relevant. (see Section 5.5.1.2.4)

The quality of life (QoL) assessments (based on scores from the EORTC QLQ C30 and EQ-5D questionnaires) showed no statistical or clinically important differences between pazopanib and placebo at any of the assessment time points in subjects who continued on therapy, indicating maintenance of QoL over time and no detrimental effects on QoL in patients receiving pazopanib relative to placebo. (see Section 5.5.1.3)

Consistent with VEG105192, the overall response rate in VEG102616 was 34% in treatment-naive subjects and was 32% in VEG107769 (all subjects). Median PFS in these studies was similar to that reported in VEG105192. This underscores the consistent efficacy demonstrated by pazopanib in the setting of advanced RCC. (see Section 5.8)

Comparative clinical effectiveness:
Since there are no data directly comparing pazopanib with IFN or sunitinib, a clinical comparison was only possible using indirect comparison methodology (Bucher 1997). The 5 trials comparing IFN to control therapy (equivalent to placebo/BSC) identified in the systematic review were utilised to provide the indirect pathway from pazopanib to IFN and then to sunitinib. (see Section 5.7)

Results of the base case analysis (using RPSFT to adjust for cross-over and pooled IFN trials) showed that pazopanib is associated with a reduced risk of progression and death compared with IFN (HRs: 0.512 [95% CI: 0.326-0.802] for PFS and 0.432 [95% CI: 0.106-1.750] for OS and has broadly comparable efficacy to sunitinib in terms of PFS and OS (HRs: 0.949 [95% CI: 0.575-1.568] and 0.667 [95% CI: 0.160-2.788], respectively).

Sensitivity analyses conducted maintaining the RPSFT-derived HR but varying the IFN trials included (i. MRC RE-01 trial only; ii. excluding trials using vinblastine therapy) and then repeated using the IPCW-adjusted HR for OS from the VEG105192 trial confirm the results of the base case analysis. The 95% CIs around the HR estimates for OS for pazopanib vs. sunitinib and the OS medians for pazopanib and sunitinib are wide indicating uncertainty in these estimates. The

ongoing head-to-head COMPARZ study, which is designed to demonstrate non-inferiority of pazopanib versus sunitinib, will help to address this uncertainty.

Safety: (see Section 5.9)
Overall, pazopanib demonstrated acceptable safety and tolerability in patients receiving first-line treatment for advanced/metastatic RCC. Although the majority of AEs observed with pazopanib have also been reported with other VEGFR inhibitors, the incidence and severity of events varies from agent to agent (McCann 2010), reflecting differences in their spectrum of activity and potency of kinase inhibition (Karaman 2008; Kumar 2009).

The most common treatment-emergent adverse events (AEs) in patients treated with pazopanib in VEG105192 and the pooled analysis of RCC studies were diarrhoea, hypertension, hair colour changes, anorexia, nausea and vomiting. Most events were mild to moderate (grades 1 to 2) and were clinically manageable; few led to permanent discontinuation of study medication. The most common grade 3 and/or 4 AEs were hypertension (4%) and diarrhoea (3%), which can be managed through dose modifications and use of anti-hypertensive and anti-diarrhoeal agents, respectively.

The most common treatment-emergent laboratory abnormalities observed in the pazopanib RCC studies were increased AST and increased ALT. Most cases of drug-induced liver enzyme elevations were asymptomatic and reversible upon dose reduction or interruption. These events usually occurred early (within the first 4 months of treatment) and can be detected with regular liver function monitoring conducted as part of routine clinical practice and managed with dose adjustments as necessary.

Qualitative and formal indirect comparison of data from the pivotal clinical trials suggests that pazopanib has a favourable safety profile compared with sunitinib (see Section 5.9.2.5). It is particularly relevant that certain adverse events that can adversely impact patients' quality of life and daily functioning (Hutson 2008; Pyle 2008) such as hand-foot syndrome (palmar-plantar erythrodysaesthesia, PPE), stomatitis, mucositis and fatigue appear to occur at a lower rate with pazopanib than with sunitinib, the current standard of care in the UK. Pazopanib also appears to be associated with a reduced risk of haematological AEs (including grade 3/4 cytopenias) and cardiotoxicity in the form of decreased left ventricular ejection fraction and congestive heart failure compared with sunitinib, which may be explained by differences in potency of inhibition of the Flt-3 receptor (Kumar 2009) and in off-target kinase activity (Hasinoff 2008), respectively.

Economic evaluation:

The cost-effectiveness of pazopanib in the treatment-naïve advanced/metastatic RCC population has been examined, consistent with the scope for this appraisal.

In the evaluation, a "partitioned-survival" model was used to project expected clinical and economic outcomes for patients with advanced/metastatic RCC who were assumed to receive either pazopanib or one of the comparators for this appraisal, sunitinib, IFN or BSC. This type of model is similar in structure to state-transition (Markov) models that are commonly used to estimate incremental cost-effectiveness of cancer therapies. The time horizon evaluated was 10 years, with no additional benefits assumed beyond this time frame. The model structure is based on PFS and OS health states, consistent with clinical outcomes employed in oncology trials, and

specifically with those examined in the VEG105192 trial. The model employed in this analysis contains three mutually exclusive health states: *"Alive Pre-Progression", "Alive Post-Progression",* and *"Dead".* While residing in a particular health state, patients are assigned a cost of care and health-state preference weight (i.e. utility value), both of which are assumed to depend upon disease status. (see section 6.2)

In the model, pazopanib and comparators are assumed to be administered until disease progression or death (if occurring prior to progression). It should be noted that the present cost-effectiveness evaluation is based on the understanding that currently there are no further treatment options recommended by NICE for the second-line treatment of advanced/ metastatic RCC. Hence, BSC will be offered to those patients who progress while receiving first-line therapy. Outcomes were measured in terms of quality adjusted life years (QALYs) based on individual residual life expectancy data and health related quality of life (EQ-5D; see section 6.4). The incremental cost components were drug acquisition costs, drug administration costs, pre and post-progression monitoring/supportive care costs and the costs of treating adverse events. (see section 6.5)

As noted earlier, OS data from VEG105192 are currently immature and 40% of patients in the placebo arm crossed over to receive pazopanib at disease progression potentially diluting the treatment effect. Several approaches were utilised to adjust for this cross-over, including the IPCW and RPSFT methods, since there is currently no consensus on which is the most appropriate.

The decision to use RPSFT for the economic base case was based on expert opinion from leading academics in this field. In addition, the ERG involved in the recent everolimus RCC appraisal considered RPSFT to be a more methodologically robust method than IPCW because it does not break randomisation and does not assume that there are no unknown confounders (everolimus ACD, Feb 2010).

Although the RPSFT-derived HR was used for the economic base case, cost-effectiveness results using IPCW-derived estimates as well as results obtained using a more simplistic Cox regression model with censoring on cross-over have also been provided for balance. (see section 6.7)

Patient Access Scheme

GSK will be submitting a patient access scheme to support this submission to PASLU shortly. This would address the difference between the list price of pazopanib and the effective price of sunitinib to the NHS under the sunitinib patient access scheme, as well as the uncertainty in the comparative evidence of pazopanib versus sunitinib pending the results of the ongoing COMPARZ study. The impact of the proposed scheme with respect to clinical and cost effectiveness is not included in the current submission. This will be provided as an addendum to the current submission at an appropriate time point to be agreed with NICE.

Results of economic evaluation

Table 1: Base-case cost-effectiveness results for pazopanib vs. sunitinib, IFN and BSC

	Pazopanib	Sunitinib	IFN	BSC
Technology acquisition cost, disc.	33,127	28,856*	40	0

Other costs, disc.	9,954	7,371	5,649	4,094
Total costs, disc.	43,081	36,228	8,403	4,094
Difference in total costs		6,853	34,678	38,988
LYG, disc	4.058	3.018	2.020	1.598
LYG difference		1.040	2.038	2.459
QALYs, disc.	2.533	1.898	1.249	0.990
QALY difference		0.635	1.284	1.543
ICER		10,787	27,000	25,264

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio
*Includes patient access programme of one cycle free

Table 2: Incremental cost-effectiveness results

Technology (and comparators)	Total cost	Total QALY	Incremental cost	Incremental QALY	ICERs versus baseline	Incremental analysis
BSC (baseline)	4,094	0.990	0	0		
IFN	8,404	1.249	4,310	0.259	16,650	16,650
Sunitinib	36,228	1.898	32,135	0.908	35,395	Extended domination by pazopanib
Pazopanib	43,082	2.533	38,989	1.543	25,264	27,000

QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios

Relative to sunitinib, pazopanib appears to be a cost-effective first-line treatment for patients with advanced/metastatic RCC. The baseline estimate of the incremental cost per QALY gained versus sunitinib was £10,787 and versus IFN was £27,000. Probabilistic sensitivity analysis for the base case estimate of pazopanib versus sunitinib demonstrated that at cost-effectiveness thresholds of £30,000/QALY and £20,000/QALY pazopanib would be cost effective relative to sunitinib in approximately 65% and 61% of cases respectively.

A range of deterministic sensitivity analyses suggests that in the majority of cases pazopanib is cost effective vs. sunitinib in the base case at a threshold of £20,000-£30,000/QALY. The main driver of uncertainty was the estimate of the relative efficacy of pazopanib versus IFN, which in turn impacts on the relative efficacy of pazopanib and sunitinib, mainly due to the method used to account for cross-over in the VEG105192 trial. Results of sensitivity analyses in which the method for accounting for cross-over in VEG105192 was varied are displayed below.

Table 3: Cost effectiveness estimates for pazopanib using alternative methods to adjust for cross over.

Method for adjusting for cross over	Pazopanib costs (£)	Pazopanib QALYs	ICER vs. Sunitinib (£)	ICER vs. IFN (£)	ICER vs. BSC (£)
ITT	37,919	1.420	Dominated	172,598	78,869
Cox model censored on cross over	40,354	1.945	87,496	45,894	37,968
IPCW	41,203	2.128	21,622	37,311	32,611
RPSFT	43,082	2.533	10,787	27,000	25,264

These estimates will become more robust once final OS data for pazopanib and head to head data for pazopanib versus sunitinib from the COMPARZ study become available.

In the present evaluation, the ICER for pazopanib versus IFN is £27,000/QALY in the base case analysis but the method of accounting for cross-over again has a large impact on the estimate. It should be noted that sunitinib was approved by NICE under the Supplementary Advice on appraising end of life medicines based on an ICER of £54,366/QALY versus IFN (TA 169). The corresponding estimates for sunitinib and pazopanib versus IFN in the current evaluation of £42,872/QALY, and £27,000/QALY respectively suggest that given the same consideration, pazopanib should be considered as a cost effective option for this patient population. Similarly the ICER for pazopanib versus BSC is £25,264/QALY. Pazopanib is therefore likely to be a cost effective option for patients for whom sunitinib or IFN is not appropriate.

The impact of introducing pazopanib at list price as an alternative to sunitinib would result in a net budget impact of £2.5 million, rising to £3.7 million annually over a period of 5 years. However, as GSK plans to offer a patient access scheme to the NHS, the introduction of pazopanib as a treatment alternative to sunitinib for advanced/metastatic RCC may offer resource savings.Derivation of these figures is described in section 7.3 of this submission.

Conclusion:

In conclusion, studies involving over 350 treatment-naive patients with advanced/ metastatic RCC demonstrate that pazopanib significantly improves PFS and response rates in this population compared with BSC. Comprehensive analyses adjusting for the impact of cross-over in the VEG105192 trial demonstrate that pazopanib offers a significant survival benefit over BSC. Pazopanib is a more selective tyrosine kinase inhibitor than sunitinib and this may partially explain the favourable tolerability profile observed. Of particular importance was that pazopanib did not negatively impact on quality of life for these patients as measured by validated tools.

The indirect comparison undertaken as part of this submission confirms that pazopanib has comparable efficacy and a favourable safety profile to sunitinib, the current UK standard of care. The CHMP opinion was that the risk/benefit profile of pazopanib was favourable despite the lack of comparative data and recommended that the drug be made available as the tolerability profile was seen to offer an improvement over the currently available agents. In addition, we believe that pazopanib fulfils the EoL criteria set out by NICE in being a treatment for a small patient population with a life expectancy of less than 24 months, which improves survival by more than 3 months.

GSK is committed to pazopanib in advanced/metastatic RCC and is investing in an extensive clinical trial programme to evaluate the efficacy and tolerability profile of pazopanib compared with sunitinib in order to ensure that appropriate evidence is generated to guide future treatment decisions. Major ongoing GSK-sponsored studies of pazopanib versus sunitinib include the head-to-head COMPARZ trial with the primary endpoint of PFS, and the PISCES patient preference trial examining patient preference based on the tolerability of the two agents.

The base case ICER is estimated to be £10,787 per QALY versus sunitinib and £27,000 per QALY versus IFN; sensitivity analyses indicate that there is uncertainty in these estimates. Nevertheless, in the context of being an end-of-life medicine we strongly believe that pazopanib will represent a cost-effective use of NHS resources and a positive recommendation would allow clinicians a choice in selecting the most appropriate treatment for their patients with advanced/metastatic RCC.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Generic name: pazopanib hydrochloride

Brand name: Votrient®

Approved name: Votrient® 200mg and 400mg film-coated tablets

Therapeutic class: Antineoplastic agents – Protein kinase inhibitor. ATC Code: L01XE11.

1.2 What is the principal mechanism of action of the technology?

Angiogenesis plays a critical role in the growth and metastases of renal cell carcinoma (RCC). Vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) have potent pro-angiogenic activity, leading to increased tumour vasculature and metastatic growth (Garcia 2007; Sonpavde 2007). Clear cell RCC, which constitutes approximately 80% of RCC, is associated with a high incidence of inactivation of the von Hippel-Lindau (VHL) tumour suppressor gene. Loss of the VHL gene leads to over-expression of VEGF and PDGF. Consequently, inhibiting the VEGF and PDGF pathways are rational therapeutic targets in clear cell RCC (Oudard 2007).

Pazopanib is an orally-administered, potent, selective, multi-targeted tyrosine kinase inhibitor (TKI). Pazopanib inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3; platelet derived growth factor receptors (PDGFR) α and ß; and stem cell factor receptor (c-Kit), with IC_{50} values of 10, 30, 47, 71, 84 and 74nM, respectively. (Sonpavde 2007; Sonpavde 2008). Pazopanib has minimal activity against the Fms-like tyrosine kinase 3 (Flt-3) (Kumar 2009), a critical regulator in the proliferation and differentiation of haematopoietic progenitor cells (Lyman 1998).

The activity of pazopanib against various kinases has been compared *in vitro* to the agents, sunitinib and sorafenib. Pazopanib appears to be a more selective kinase

inhibitor than sunitinib; in a binding assay against a panel of 290 kinases, sunitinib bound five times more kinases than pazopanib, with a dissociation constant (K_d) <100nM (Karaman 2008). In another study, pazopanib had a higher affinity for VEGFR-2 than sunitinib while the two agents had similar inhibitory activity against c-Kit. However, sunitinib was a more potent inhibitor of Flt-3 than pazopanib (Kumar 2009).

The clinical significance of the differences in the receptor selectivity/potency profiles of these agents is currently unknown but may explain their differing tolerability profiles observed in clinical practice (Mickisch 2010, Kumar 2009). The favourable tolerability profile of pazopanib led to the Committee for Medicinal Products for Human use (CHMP) adopting a positive opinion in the absence of head-to-head comparative data.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

No. A Marketing Authorisation Application (MAA) was submitted to the European Medicines Agency (EMA) on 27th February 2009 and is currently under review via the Centralised procedure. Based on review of data on quality, safety and efficacy, the CHMP considered by a majority decision that the risk-benefit balance of pazopanib in the treatment of advanced RCC was favourable and therefore adopted a positive opinion on 19th February 2010, recommending a conditional marketing authorisation in the European Union. It is estimated that this will be received during Q2 2010.

Note:
A conditional marketing authorisation is granted to a medicinal product with a positive benefit/risk assessment that fulfils an unmet need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorisation is renewable annually.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The main issue discussed during the regulatory process has been the choice of placebo as comparator in the pivotal phase III trial of pazopanib (VEG105192) in advanced/metastatic RCC. GSK prepared and submitted detailed responses to address the questions of the regulatory agency regarding this matter. The rationale for selection of placebo as a comparator is detailed in section 5.3.1. The oncology Scientific Advisory Committee (o-SAG) to the CHMP unanimously agreed that from a clinical perspective the efficacy benefits of pazopanib, particularly in terms of progression-free survival (PFS), as observed in VEG105192 compared favourably

against the toxicity. The draft European Product Assessment Report (EPAR) for pazopanib states that "*the addition of a safe treatment option that is associated with clear clinical benefits and with a distinct pharmacodynamic profile is considered to offer a major advantage in the context of therapies for this disease*." Therefore, the CHMP considered that the current unmet medical needs would be fulfilled for the treatment of advanced RCC and adopted a positive opinion recommending that a conditional marketing authorisation for pazopanib be granted.

As part of the conditions of the conditional marketing authorisation for pazopanib, GSK is required to provide further data supporting the efficacy and safety of pazopanib compared with sunitinib in patients with advanced/metastatic RCC, including the outcome of the ongoing head-to-head study of pazopanib vs. sunitinib as first-line treatment (VEG108844; COMPARZ) and a pooled analysis of data from studies VEG108844 and VEG113078 (a sub-study of the VEG108844 study in Asian subjects).

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The following is the indication for which positive opinion has been adopted by the CHMP:

"Votrient is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease".

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

VEG105192

The main clinical trial providing evidence for in the treatment of advanced/metastatic RCC is the VEG105192 (NCT003384282) study (Sternberg 2010). This is a phase III, randomised, double-blind study evaluating the efficacy and safety of pazopanib (n=290) compared with placebo (n=145) in patients with locally advanced and/or metastatic RCC who were either treatment-naïve (n=233) or had received previous cytokine-based therapy (n=202). The primary endpoint was progression-free survival (PFS) (by independent review). The principal secondary endpoint was overall survival (OS); other secondary endpoints included overall response rate (ORR), duration of response, health-related quality of life and safety assessments. One analysis for PFS was performed with an interim analysis for OS conducted at this time (clinical cut-off 23 May 2008). A final analysis of OS is to be conducted when 287 events have accrued and a report containing these data will be available in 3Q 2010. Data are available separately for the treatment-naïve and cytokine pre-treated populations.

VEG107769

An open-label extension study (NCT00337764) is ongoing to provide access to pazopanib for patients who progressed on placebo in VEG105192. The primary objective is to evaluate the safety and tolerability of pazopanib in RCC; secondary

outcome measures include PFS, OS and ORR. Interim data are available (clinical cut-off 23 May 2008). The next data cut is planned for 2Q 2010.

VEG102616
Supportive data are available from a phase II study (NCT00244764) of pazopanib in patients with locally advanced and/or metastatic RCC (n=225) using a randomisation discontinuation design (Hutson 2010). The study included 155 patients who had received no prior systemic therapy. The original study design had been 12 weeks of pazopanib treatment; treatment would be continued in those who demonstrated a complete or partial response; those who demonstrated stable disease would be randomised to continue pazopanib or receive placebo; and those who developed progressive disease would discontinue treatment. Based on robust clinical activity observed at the interim analysis in the first 60 patients enrolled (Hutson 2007), randomisation was discontinued and all patients on placebo were crossed-over to pazopanib and the study continued as an open-label, single-arm study. The primary endpoint was ORR; secondary objectives included duration of response, PFS and safety assessments. A final study report is available conducted with a clinical cut-off of 24 March 2008.

COMPARZ (VEG108844): Comparing the efficacy, safety and tolerability of pazopanib vs sunitinib
A phase III, randomised, open-label, parallel group study is ongoing to evaluate the efficacy and safety of pazopanib compared to sunitinib in subjects with locally advanced and/or metastatic RCC who have received no prior systemic therapy (NCT00720941). A target of 876 patients will be randomised 1:1 to receive either pazopanib or sunitinib. The primary endpoint is PFS; secondary endpoints include OS, duration of response, QoL, medical resource utilisation, and safety assessments. A final study report will be available in 2Q 2012.

PISCES (VEG113046): Patient preference study of pazopanib versus sunitinib in advanced/metastatic RCC
A randomised, double-blind, cross-over study of pazopanib versus sunitinib in patients with locally advanced/metastatic RCC with no prior systemic therapy is planned to start shortly (NCT01064310). Approximately 160 patients will receive pazopanib and sunitinib treatment sequentially in a double-blinded fashion separated by a wash-out period. The primary objective of the study is to assess how the tolerability and safety differences between pazopanib and sunitinib translate into patient preference, defined by the patient's stated preference for which drug they may prefer to continue treatment with at end of study. Secondary objectives include: reason(s) for patient preference, QoL and safety.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is estimated that pazopanib will be made commercially available in the UK during Q2 2010, once marketing authorisation is received.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Pazopanib received FDA approval in the United States for the treatment of patients with advanced renal cell carcinoma under the brand name Votrient® on the 19th October 2009.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

GSK expects to submit data on pazopanib for advanced/metastatic RCC to the Scottish Medicines Consortium (SMC) during 3Q 2010, to allow guidance on the use of the product to be issued to NHSiS during 4Q 2010.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1: Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated tablet (200mg and 400mg)
Acquisition cost (excluding VAT)	**Commercial in Confidence** NHS list price: £74.73 per daily dose of 800mg (equivalent to NHS list price for sunitinib at 50mg daily dose). This is the price used in the economic evaluation presented in this submission. However, a patient access scheme to support this submission is proposed. The Deterministic Sensitivity Analyses presented in section 6.6 explore a range of discounts.
Method of administration	Oral
Doses	800mg.
Dosing frequency	Once daily
Average length of a course of treatment	Continuous until disease progression or unacceptable toxicity
Average cost of a course of treatment	**Commercial in Confidence** Median cost per patient: £23,221. Based on a treatment duration of 11.1 months and a daily cost of £74.73
Anticipated average interval between courses of treatment	N/A
Anticipated number of repeat courses of treatment	N/A
Dose adjustments	Dose modification in 200mg increments/ decrements in stepwise fashion based on individual tolerability to manage adverse reactions.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

There are no specific tests or investigations needed for selection of patients for treatment with pazopanib.

Pazopanib should be initiated only by a physician experienced in the administration of anti-cancer agents.

Pazopanib is an oral tablet treatment that should be taken without food (at least one hour before food or two hours after a meal).

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Liver function should be monitored before initiation of pazopanib treatment and at least once every 4 weeks for the first 4 months of treatment, and as clinically indicated. Periodic monitoring should continue after this period. Feedback from clinicians experienced in managing RCC indicates that liver function is monitored routinely in patients with advanced/metastatic RCC and therefore this requirement is unlikely to impact on existing services.

It is also recommended that patients receiving pazopanib are monitored for hypertension and treated as needed with standard anti-hypertensive therapy. Baseline and periodic monitoring of thyroid function and electrocardiograms (ECGs) for QT prolongation and maintenance electrolytes (e.g. calcium, magnesium and potassium) within normal range is advised during pazopanib treatment. Baseline and periodic urinalysis and monitoring for worsening proteinuria are also recommended. The Summary of Product Characteristics for sunitinib, the current standard for the first-line treatment of advanced/metastatic RCC, contains similar warnings in these respects.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

There are no specific therapies that need to be administered in conjunction with pazopanib. However, patients with advanced/metastatic RCC may also be receiving concomitant medications such as anti-emetics and analgesics to manage nasea and pain associated with their condition, respectively.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

Key points:

- Renal cell carcinoma (RCC) is a relatively uncommon solid tumour that originates in the renal parenchyma and is highly vascularised.
- RCC accounts for 3% of all adult malignancies in the UK and for 90% of kidney cancers (approx. 7,000 new cases are diagnosed each year). Median age of presentation is around 60-65 years with a 2:1 male: female predominance.
- Around 80% of RCC tumours have clear cell histology and are associated with a high incidence of inactivation of the VHL tumour suppressor gene, leading to over-expression of VEGF and PDGF. These growth factors promote angiogenesis which is essential for tumour growth and tumour cell proliferation.
- Approximately a third of RCC patients present with advanced/metastatic disease and around 40% of patients diagnosed with localised disease subsequently develop metastases.
- Advanced/metastatic RCC is one of the most difficult-to-treat malignancies being largely unresponsive to chemotherapy, radiotherapy and hormonal therapy.
- In the absence of effective therapy, such patients have a dismal prognosis with a 5-year survival rate of <10% and a median survival of less than 1 year.
- Quality of life for patients with advanced/metastatic RCC is impacted not only by disease-related symptoms but also by treatment-related adverse events.
- Until recently, the cytokines, interferon-α and interleukin-2, were the only treatments available. However, their use has been limited by their modest response rates and significant toxicity.
- The introduction of agents targeted at the VEGF and related pathways, has greatly impacted the management of this disease area. However, despite improvements in efficacy, the toxicities seen with currently available targeted therapies remain a challenge.
- Following the publication of positive NICE guidance in March 2009, sunitinib has become the standard of care for the first-line treatment of advanced/metastatic RCC in the UK.
- Pazopanib is an oral, selective, multi-kinase angiogenesis inhibitor. It has a distinct pharmacodynamic profile in targeting VEGFR, PDGFR and c-Kit but with minimal activity at Flt-3.
- The CHMP has recently adopted a positive opinion recommending the conditional marketing authorisation of pazopanib for the treatment of advanced RCC on the basis of its favourable risk-benefit profile. It offers a valuable new treatment option for the first-line treatment of advanced and/or metastatic RCC.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Epidemiology
Renal cell carcinoma (RCC) is a relatively uncommon solid tumour that originates in the lining of the tubules of the kidney (renal parenchyma) and has a high vasculature.

In 2006, there were 6906 (CRUK 2010) cases of newly diagnosed kidney cancer registered in England and Wales. It is the eight most common cancer in men and tenth most common in women in the UK. RCC accounts for 90% of kidney cancers and approximately 3% of all adult cancers in the UK (NICE TA169). It is a male predominant disease (2:1) with age-standardised incidence rates (2006 data) of 13.9 per 100,000 in men and 7.0 per 100,000 in women (CRUK 2010).

The incidence of RCC, both worldwide and in the UK, has been rising steadily since the 1970s largely due to the wider application of diagnostic imaging techniques resulting in more incidental discoveries (CRUK 2010).

Within the UK, incidence rates are higher in the North than the South, following the geographical pattern of two known risk factors for the disease – smoking and obesity. Heavy smokers are 2 to 3 times more likely to develop RCC than non-smokers (Hunt 2005). Other risk factors include hypertension, polycystic kidney disease, long-term dialysis and several genetic disorders including Von Hippel-Lindau (VHL) syndrome. Exposure to toxic compounds such as asbestos, trichloroethylene, petroleum products and cadmium has also been implicated (Athar 2008; Rini 2009a).

Histology
There are five histological sub-groups of RCC, the most common being conventional clear cell, also called non-papillary, accounting for 80% of tumours. Clear cell RCC is associated with a high incidence of inactivation of the Von Hippel-Lindau (VHL) tumour suppressor gene. Under normoxic conditions, the VHL protein labels hypoxia inducible factor (HIF) for proteasomal degradation. In the presence of inactivated VHL protein, HIF is not degraded and translocates to the nucleus to stimulate the production of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). These growth factors act on vascular endothelial cells and pericytes promoting angiogenesis and contributing to tumour growth, proliferation and survival (Athar 2008; Sonapavde 2007).

Presentation and diagnosis
RCC typically presents from the age of 40 years with the highest rates seen in those over 75 years (median age at diagnosis is 60 to 65 years) (CRUK 2010; Rini 2009a).

In its early stages, RCC is usually asymptomatic or has only mild symptoms and the majority of affected individuals are diagnosed incidentally as a result of imaging performed for unrelated reasons (Larkin 2009). The classic triad of local presenting symptoms (haematuria, flank pain and palpable abdominal mass) is becoming uncommon. Paraneoplastic events occur in about 30% of patients with symptomatic RCC, the most common being hypertension, cachexia, weight loss, pyrexia, neuropathy, hypercalcaemia, erythrocytosis, anaemia and polycythaemia. A minority

of patients are diagnosed due to symptoms from metastatic disease; these include bone pain, adenopathy or pulmonary symptoms attributable to lung metastases (EAU 2009).

Over a third of renal cancers are diagnosed while at a local stage (CRUK 2010), around a third of patients have advanced/metastatic disease at diagnosis (Athar 2008; Lam 2005; Oudard 2007) and the remaining cases have unknown stage (CRUK 2010). Recurrence develops in about 40% of patients treated for localised disease (Lam 2005). Metastatic spread may involve the lungs, bones, liver, adrenal glands, lymph nodes, brain and other organs (Decision Resources 2008).

Prognosis

More than 40% of patients with RCC will die from their disease (Lam 2004). The most important prognostic determinants of 5-year survival are the tumour grade, local extent of the tumour, regional lymph node involvement and presence of metastases at time of presentation (Rini 2009a). For patients with clinically localised disease, the 5-year relative survival rates range from 90% for patients who present with organ-confined disease to 62% for those with regional spread. The prognosis for patients with metastatic disease is poor with a 5-year survival rate of 9.5% (Oudard 2007). In the absence of effective treatment, median survival after presenting with metastatic disease is less than 1 year (Gupta 2008). Renal cancer accounted for 3,255 deaths in England and Wales in 2007.

Models that combine several prognostic factors have been developed to provide superior predictive information for patients with advanced/metastatic disease. In the Memorial Sloan Kettering Cancer Center (MSKCC) model, five pre-treatment features (low Karnofsky performance status [<80%], low serum haemoglobin, high corrected calcium level, high serum lactate dehydrogenase and absence of nephrectomy) are associated with an adverse prognosis. Prognostic groups were defined as favourable risk (no risk factor), intermediate risk (1-2 risk factors) and poor risk (≥3 risk factors), with median overall survival times of 20, 10 and 4 months, respectively (Motzer 1999).

Burden of illness and impact on quality of life

RCC places a significant burden on healthcare resources. Renal cell cancers accounted for 13,153 hospital episodes and 75,610 hospital bed days in England in the 2005/6 financial year (HES 2005/6).

The costs of managing adverse events associated with treatment for RCC can be considerable as a consequence of a requirement for additional treatment, out-patient visits and/or hospitalisations (Dial 2008). One study identified the most costly AEs as being haemorrhage, hand-foot syndrome, hypertension, diarrhoea and fatigue (Dial 2008). A recent UK study put the average cost per patient, per episode, of managing grade 3 and 4 adverse events at £1,475 for sunitinib and £804 for bevacizumab plus interferon. The majority of the increased cost associated with sunitinib was related to the management of haematological toxicities (Mickisch 2010).

Both disease-related symptoms and treatment-related adverse effects contribute to the burden of renal cancer (Cella 2009). In a study of symptom burden among RCC patients, the five most frequent symptoms among patients with localised disease (n=14) were irritability (79%), pain (71%), fatigue (71%), worry (71%) and sleep disturbance (64%). Among metastatic patients (n=17), the five most frequent

symptoms were fatigue (82%), weakness (82%), worry (65%), shortness of breath (53%) and irritability (53%) (Harding 2007).

Health-related quality of life (HRQoL) has therefore become an important outcome in RCC trials (Cella 2009) in identifying the functional impact of the disease as well as the positive and negative impact of therapies (Cella 2007; Gupta 2008). Litwin *et al* found that HRQoL for advanced RCC patients treated with immunotherapy was poorer than that of the general population, similar to or worse than in patients with hypertension or type II diabetes, and at least comparable to patients with other malignancies (breast or prostate cancer) (Litwin 1997). In several studies, patients receiving tyrosine kinase inhibitors (TKIs) have reported fewer RCC-related symptoms and better quality of life (as assessed by both general and disease-specific instruments) than those receiving cytokine-based therapy (Cella 2008; Escudier 2009a). Other studies have shown that irrespective of adverse events associated with treatment, relative to placebo, targeted therapies do not have a negative impact on quality of life in patients with advanced/metastatic disease (Motzer 2008; Sternberg 2010).

2.2 How many patients are assumed to be eligible? How is this figure derived?

The population eligible for treatment with pazopanib, the technology under consideration, are patients with advanced and/or metastatic RCC.

The number of patients eligible for first-line pazopanib treatment in the UK has been estimated as follows:

Incidence of new cases of kidney cancer in the UK*[1]	10.1/100,000
Approximately 90% of cases are renal cell carcinoma [1,2]	9.1/100,000
Approximately 80% of RCC cases have clear cell histology[3]	7.3/100,000
Approximately 68% of patients with clear cell RCC develop advanced/metastatic disease, based on the following: • Approximately 36% of patients are diagnosed at a local stage[1]; approximately 40% of those treated for localised disease relapse[4] • Approximately 32% of patients have advanced/metastatic disease at diagnosis†[4] • Remaining patients have unknown stage at diagnosis[1] but assume that the above percentages apply[5]	5.0/100,000
Approximately 68% of patients have ECOG PS 0-1 and are eligible to receive a first-line systemic treatment[6]	3.4/100,000

* Age-standardised incidence rate per 100,000 population across men and women

† This assumes that 17% of patients present with Stage IV disease [2,7] and 15% have Stage IIIB disease not amenable to curative surgery and/or radiation therapy

1. CRUK (accessed Jan 2010)
2. NICE TA 169 (March 2009)
3. Harrison (2007)
4. Lam (2005)
5. GSK assumption
6. NICE sunitinib costing template (March 2009)
7. Decision Resources (2008)

Thus, approximately 3.4 per 100,000 patients are estimated to be eligible to receive first-line treatment with pazopanib per year in the UK, equating to around 2120 patients in England & Wales annually (see section 7).

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

The NICE guidance, *Improving Outcomes in Urological Cancers*, recommend immunotherapeutic agents for patients with metastatic kidney cancer but this was published prior to the availability of targeted agents (NICE 2002).

NICE has recently published guidance on the first-line treatment of advanced RCC with targeted agents. A Single Technology Appraisal (TA 169) was published in March 2009 recommending the use of sunitinib for the first-line treatment of advanced and/or metastatic RCC in patients who are suitable for immunotherapy and have an Eastern Oncology Group (ECOG) performance status of 0 or 1. A Multiple Technology Appraisal (TA 178) recommends aganist bevacizumab, sorafenib and temsirolimus as first-line treatment options.

In 2007, the All Wales Medicines Strategy Group (AWMSG) recommended against the use of sunitinib or sorafenib for advanced/metastatic RCC. However, NICE's recommendation in relation to the first-line use of sunitinib now takes precedence.

UK guidelines for the systemic treatment of renal cell carcinoma were published in May 2009. These aim to provide a consensus view on the use of systemic agents for renal cell carcinoma on the basis of available evidence for clinical utility (Nathan 2009).

European and international guidelines for RCC also exist. The European Association of Urology (EAU) guideline recommends the use of sunitinib or bevacizumab plus IFN as first-line treatments for patients with metastatic RCC, while temsirolimus is proposed for patients with poor risk features according to the MSKCC classification (Ljundberg 2009). The European Society of Medical Oncology (ESMO) guidelines are identical in this respect but also include high-dose IL-2 as an option for selected good risk patients (Escudier 2009c). The National Comprehensive Cancer Network (NCCN) Practice Guideline for kidney cancer is very similar but has been updated to include pazopanib as a first-line therapy for relapsed/stage IV RCC since it was approved by the FDA in October 2009 (NCCN v.2.2010).

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Treatment pathway and treatment options
For patients with localised RCC, partial nephrectomy for small tumours and radical nephrectomy for large tumours are the gold standard approach and can be curative in some patients. In recent years, there has been increasing emphasis on techniques that reduce invasiveness and preserve renal function (Rini 2009). However, approximately 40% of patients who undergo nephrectomy subsequently develop metastases, with a median time to relapse of 15-18 months (Athar 2007; Lam 2005).

Adjuvant therapies, both local and systemic, have been studied; however, to date none has demonstrated a survival benefit and they are not recommended outside controlled clinical trials (EAU 2009; Harrison 2007).

There are currently no treatments that reliably cure advanced and/or metastatic RCC. The primary objectives of medical intervention are relief of symptoms and maintenance of daily function (NICE TA169 2009). Surgical intervention may lead to palliation of symptoms, regression of metastases (Athar 2008) and an improvement in clinical prognosis. Metastatic RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy (NICE TA169) making it one of the most difficult-to-treat malignancies.

Until recently, immunotherapy using interferon α-2a (IFN) or interleukin-2 (IL2), administered alone or in combination, had been the standard therapeutic approach (NICE TA 169; Garcia 2007). However, use of these cytokines has been limited by their toxicity and generally low overall response rates (around 25% or less) (McDermott 2005; Negrier 1998; Negrier 2007; Yang 2003). There are some studies that suggest a modest impact of IFN on survival. In the RE-01 study by the Medical Research Council (Ritchie 1999; Hancock 2000), there was an improvement in median survival of 2.5 months for the IFN group compared with the medroxyprogresterone acetate (MPA) control group (9 vs. 6 months; HR 0.75; p=0.013). In the French PERCY Quattro study (Negrier 2007), neither IFN nor IL-2 offered a survival benefit over MPA in patients with metastatic RCC and both therapies were associated with a high risk of toxicity. The investigators concluded that cytokine therapy should no longer be recommended for such patients.

Greater understanding of the molecular biology of RCC has led to the development of agents which target the VEGF and related pathways. This includes small molecules that inhibit the tyrosine kinase portion of the intracellular receptor for VEGF (e.g. sunitinib, pazopanib), monoclonal antibodies which bind VEGF (e.g. bevacizumb) and inhibitors of mammalian target of rapamycin (mTOR), a molecule implicated in several downstream signalling pathways including activation of HIF (e.g. temsirolimus, everolimus).

The introduction of these targeted therapies has greatly impacted the management of advanced/metastatic RCC and significant clinical activity has been observed in both treatment-naive (Motzer 2007; Escudier 2007a; Rini 2008) and cytokine pre-treated patients (Escudier 2007b). Table 2.1 summarises the results of the pivotal trials for those agents currently licensed in Europe for the first-line treatment of advanced/ metastatic RCC.

Table 2.1: Summary of phase III trials for first-line treatment of advanced/metastatic RCC

Agent	Licence	Reference	Patient N	Treatment Arms	ORR % (95% CI)	Median PFS months (95% CI)	Median† OS months (95% CI)
Sunitinib	Treatment of advanced /metastatic RCC	Motzer NEJM 2007; JCO 2009	750	Sunitinib N=375	31 (26, 36)*	11 (10, 12)*	26.4 (23.0, 32.9)
				IFN N=375	6 (4, 9)*	5 (4, 6)*	21.8 (17.9, 26.9)
Bevacizumab	In combination with IFN for first-line treatment of advanced/metastatic RCC	AVOREN Escudier Lancet 2007; ASCO 2009	649	Bevacizumab + IFN N=369	31	10.2	23.3
				IFN N=363	13	5.4	21.3
Bevacizumab	In combination with IFN for first-line treatment of advanced/metastatic RCC	CALGB 90206 Rini JCO 2008; ASCO 2009	732	Bevacizumab + IFN	25.5 (20.9, 30.6)	8.5 (7.5, 9.7)	18.3 (16.5, 22.5)
				IFN	13.1 (9.5, 17.3)	5.2 (3.1, 5.6)	17.4 (14.4, 20.0)
Temsirolimus	First-line treatment of patients with advanced RCC who have at least 3 of 6 prognostic risk factors	Hudes NEJM 2007	626	Temsirolimus N=209	8.6 (4.8, 12.4)	5.5 (3.9, 7.0)*	10.9 (8.6, 12.7)
				IFN N=207	4.8 (1.9, 7.8)	3.1* (2.2, 3.8)	7.3 (6.1, 8.8)
				Temsirolimus + IFN N=210	8.1 (4.4, 11.8)	4.7* (3.9, 5.8)	8.4 (6.6, 10.3)

* By Independent Review Committee (IRC) assessment; † Uncensored
IFN = Interferon-α; ORR = objective response rate; PFS = progression-free survival; OS = overall survival

Whilst these targeted agents have done much to improve the prognosis of the disease, they can lead to significant short and long-term toxicities (Shepard 2009). Although the majority of adverse events experienced are mild to moderate (grade 1 or 2), a significant proportion of patients (around 10 to 25%) can develop grade 3 and/or 4 toxicities that often require dose reductions, interruptions to or even discontinuation of treatment (Shepard 2009; Wang 2009). Common grade 3 and/or 4 adverse events observed in the phase III trials and post-marketing studies of the targeted agents currently available for advanced/metastatic RCC include: diarrhoea, hypertension, decreased left ventricular fraction (LVEF), thyroid dysfunction, myelosuppression, hand-foot syndrome, fatigue/asthenia and mucosal inflammation/stomatitis (Escudier 2007; Gore 2009; Hudes 2007; Motzer 2009; Rini 2008; Schwandt 2009; Shepard 2008; Wang 2009).

As discussed in section 2.3 above, the only targeted agent recommended by NICE for the first-line treatment of advanced and/or metastatic RCC is sunitinib which has consequently become the current standard of care for patients in the UK. However, sunitinib is associated with a number of adverse events that can affect patients' daily functioning and impact on quality of life (Bird 2009; Schwandt 2008). Hand-foot syndrome is a frequent and often debilitating condition (Pyle 2008) whilst severe oral mucositis/stomatitis can cause profound pain and oral function impairment (Cheng 2009). Fatigue and/or asthenia are also common problems and may be exacerbated by the presence of hypothyroidism and anaemia (Pyle 2008; Torino 2009). Emerging safety data indicate that the incidence of cardiotoxicity with sunitinib may be higher than that seen in clinical trials. At one institution, 12.5% of patients developed Grade 3/4 heart failure 22 to 435 days after initiation of treatment (Hutson 2008). In a recent

meta-analysis involving 175 patients treated with sunitinib for metastatic RCC, 33 patients (19%) developed grade 1-3 LVEF dysfunction, of whom, 12 (7%) developed a grade 3 decline in LVEF decline with congestive heart failure. Ten of these patients developed this toxicity after at least 3 cycles of therapy (Di Lorenzo 2009).

Dose reductions due to sunitinib-related toxicity are common place. In the phase 3 trial (Motzer 2009), 50% of patients receiving sunitinib had a dose reduction due to adverse events compared with 27% of those in the IFN group. In the expanded access programme which enrolled over 4300 patients across Europe (Gore 2009), 33% of patients were dose reduced from 50mg to 37.5mg and a further 13% to 25mg.

The 4 weeks on/2 weeks off dosing schedule with sunitinib has led to tumour "flare" in RCC patients receiving sunitinib. During the 2-week drug holiday in each cycle, symptoms related to tumour burden can recur. This can manifest as bone pain from bony metastases or neurological symptoms if disease is present in the spinal cord. This has led to physicians using unlicensed dosing schedules such as 37.5mg continuously for which evidence suggests compromised efficacy (8.3 months median PFS was observed in a phase II study with this schedule [Srinivas 2007]).

Dose intensity is also important with targeted agents specifically in relation to continued, potent suppression of the VEGF pathway. A recent study examining the relationship between exposure to sunitinib and outcomes found that 38% more patients with advanced/ metastatic RCC would be expected to achieve a 30% reduction in tumour size with a sunitinib 50mg dose than with a 25mg dose (Houk 2009).

Differences in tolerability profiles between the targeted agents observed in clinical practice may be a reflection of their different mechanisms of action (Kumar 2009; Mickisch 2010). For example, the tyrosine kinase inhibitors inhibit an array of related receptors and differ in their spectrum of inhibitory effects and potency against any single receptor (Karaman 2008; Kumar 2009). Off-target activity of kinase inhibitors has been considered to be a potential liability and can add to the toxicities of the drug (Campillos 2008; Force 2007; Hasinoff 2008; Leibler 2005).

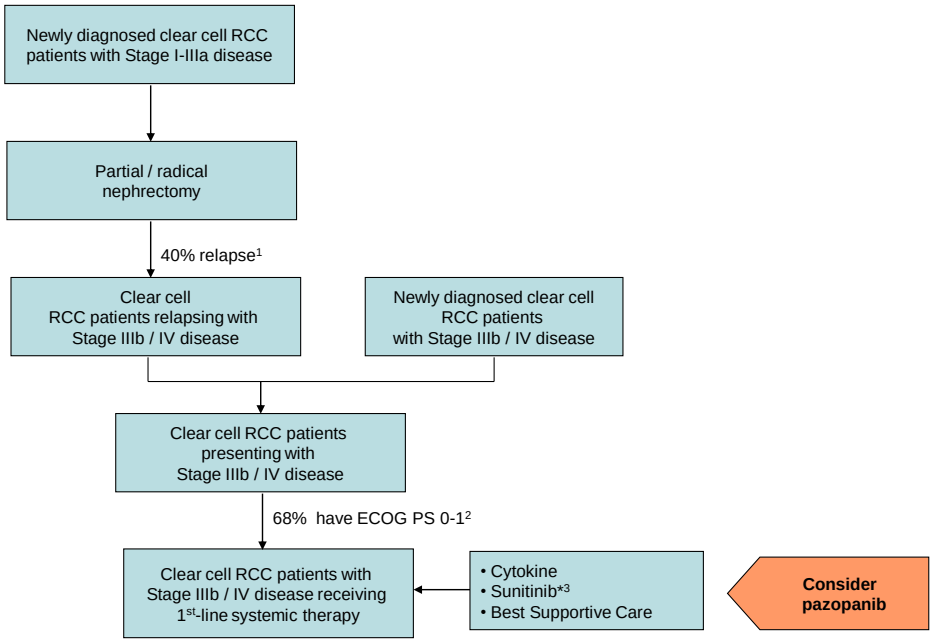
Pazopanib, the technology being appraised, is a potent inhibitor of VEGFR 2, the primary mediator of VEGF-induced angiogenesis. It also inhibits VEGFR 1 and 3, PDGFR α and β, and c-Kit but has minimal activity against Flt-3 (Kumar 2009), a critical regulator in the proliferation and differentiation of haematopoietic progenitor cells (Lyman 1998), inhibition of which is potentially associated with the development of haematological toxicities (Kumar 2009; van Erp 2009).

The activity of pazopanib against various kinases has been compared *in vitro* to the agents, sunitinib and sorafenib. Pazopanib appears to be a more selective kinase inhibitor than sunitinib. In a binding assay against a panel of 290 kinases, sunitinib bound five times more kinases than pazopanib (Karaman 2008). In another study, pazopanib had a higher affinity for VEGFR 2 than sunitinib while the two agents had similar inhibitory activity against c-Kit. However, sunitinib was a more potent inhibitor of Flt-3 than pazopanib (Kumar 2009). Sunitinib also inhibits a number of additional off-target kinases, including ribosomal S6 kinase (RSK) and AMP-activated protein kinase (AMPK), which is thought to be the basis for sunitinib-induced cardiotoxicity (Fabian 2005; Hasinoff 2008) (see Section 1.2) The draft European Product Assessment Report (EPAR) for pazopanib acknowledges that "*compared to other*

agents that have shown activity in advanced RCC, pazopanib has a distinct pharmacodynamic profile in terms of potency in inhibiting the main receptor tyrosine kinases involved in angiogenesis."

There is a need for alternative treatments that offer a favourable side effect profile without compromising efficacy for patients with advanced/metastatic RCC.
The favourable risk: benefit profile of pazopanib recently led to the Committee for Medicinal Products for Human use (CHMP) adopting a positive opinion in the absence of head-to-head comparative data. The oncology Scientific Advisory Committee (o-SAG) to the CHMP unanimously agreed that from a clinical perspective the efficacy benefits of pazopanib, particularly in terms of progression-free survival (PFS), as observed in the pivotal phase III VEG105192 trial compared favourably against the toxicity. The draft EPAR also states that "*the addition of a safe treatment option that is associated with clear clinical benefits and with a distinct pharmacodynamic profile is considered to offer a major advantage in the context of therapies for this disease*." Therefore, the CHMP considered that the current unmet medical needs could be fulfilled for the treatment of advanced RCC and adopted a positive opinion recommending that a conditional marketing authorisation for pazopanib be granted. Figure 2.1 shows the potential place of pazopanib in the treatment pathway for RCC.

Figure 2.1: Treatment pathway for RCC



1. Lam (2005)
2. NICE sunitinib costing template (March 2009)
3. NICE TA 169 (March 2009)

VEGFR = vascular endothelial growth factor receptor
PDGFR = platelet derived growth factor receptor
c-KIT = stem cell factor receptor
Flt-3 = fms-like tyrosine kinase 3

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

With the publication of positive NICE guidance for sunitinib (TA169) in March 2009 and a negative recommendation for sorafenib and bevacizumab in August 2009 (TA 178), there are few issues relating to current UK clinical practice in the first-line systemic treatment of advanced/metastatic RCC. Sunitinib appears to have been adopted as the standard of care for first-line therapy in the vast majority of patients while the use of interferon in this setting is declining. UK market research data from Q2 2009 indicate that, of patients with advanced/metastatic RCC eligible for first-line treatment, 63% were receiving sunitinib and 26% were receiving interferon. More recent data from Q3 2009 suggest that more than 80% of patients are now receiving sunitinib with less than 1% being treated with interferon (IMS Oncology Analyzer 2009).

Any variations in clinical practice are more likely to relate to the management of patients unsuitable for sunitinib therapy (e.g. those with ECOG performance status ≥2) and in the management of treatment-related toxicities. Although the majority of adverse events associated with sunitinib can be managed through dose reductions and/or interruptions, guidance in this area is limited (Pyle 2008) and most centres appear to follow their own local algorithms or protocols in this respect. For example, the permutations in sunitinib dose reductions used are variable between centres and for individual patients, including dosing 37.5mg daily continuously for which evidence of maintained efficacy is limited (Srinivas 2007). Anecdotal feedback suggests that approaches to monitoring for and managing specific drug-induced AEs in patients receiving treatment for advanced/metastatic RCC are also varied. For example, in some localities, hypertension in sunitinib-treated patients is managed in general practice while in other places it is managed within the secondary care setting. In a few areas, RCC patients with cardiac risk factors undergo regular electrocardiograms/ echocardiograms, while this is not part of standard of care in other areas.

2.6 Please identify the main comparator(s) and justify their selection.

The primary comparator in this appraisal is sunitinib (Sutent®, Pfizer), the current standard of care for the first-line treatment of advanced/metastatic RCC in the UK.

It should be noted that since no head-to-head data for pazopanib versus sunitinib are currently available, an indirect comparison via placebo/best supportive care [BSC] and interferon-α (IFN) has been performed for the comparative clinical and economic evaluations in this appraisal. A randomised head-to-head trial comparing pazopanib with sunitinib in the first-line treatment of advanced/metastatic RCC is currently ongoing (VEG108844; COMPARZ) and a final study report will be available in 2Q 2012.

In line with the scope for this appraisal, the other comparators considered in this submission are IFN and BSC since these might be relevant treatment options in patients for whom sunitinib is unsuitable. Again, in the absence of head-to-head data, the clinical and economic comparison with IFN has been conducted indirectly via placebo/BSC.

The comparator in the pivotal phase III study supporting the registration of pazopanib (VEG105192) was placebo plus BSC. BSC has been defined as “treatment administered with the intent to maximise quality of life without a specific antineoplastic regimen” but definitions vary and it is not standardised (Zafar 2008). In VEG105192, patients in both the pazopanib and placebo arms were allowed to receive full supportive care in addition to study medication, including treatment with

antibiotics, anti-emetics, anti-diarrhoeal agents, anti-hypertensive agents, erythropoietin, or bisphosphonates, transfusion of blood and blood products, when appropriate.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

In the pivotal trial supporting the registration of pazopanib (VEG105192; Sternberg 2010), pazopanib was generally well tolerated with an acceptable and manageable safety profile. The majority of adverse events observed in pazopanib-treated patients were mild to moderate (grades 1 and 2). Grade 3 and/or 4 adverse events experienced by patients receiving pazopanib included: hypertension (4%); diarrhoea (4%); nausea/vomiting (2%); asthenia (3%); fatigue (2%); anaemia (2%); neutropenia (1%).

Hypertension can be managed with standard anti-hypertensive therapy (e.g. ACE inhibitors). An anti-emetic (e.g. metoclopramide) may be prescribed for the symptomatic management of nausea/vomiting and standard anti-diarrhoeal therapy (e.g. loperamide) may be administered for the management of diarrhoea. The management of severe anaemia may require a whole blood/red blood cell transfusion and colony stimulating factors may be considered in the management of severe neutropenia.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Pazopanib treatment should only be initiated by an oncologist or urologist with experience in managing patients with renal cancer.

Pazopanib is a once-daily, continuous oral therapy, and therefore may be self-administered by the patient at home. The introduction of pazopanib should incur no additional hospital visits compared with the administration of sunitinib. Our economic model assumes a monthly consultant out-patient visit at a cost of £241 for the first attendance and £99 for subsequent attendances (Source: NHS PbR Tariff 2009/10).

As a drug in the same class as sunitinib, there should be little need for additional education of nursing staff and minimal impact on pharmacy workloads.

Liver function should be monitored prior to initiation of pazopanib treatment, at least every 4 weeks for the first 4 months of treatment, and periodically thereafter. It is our understanding that patients with advanced/metastatic RCC will receive regular blood tests (e.g. at clinic visits) which include liver function tests. This requirement is therefore unlikely to impact on existing services.

It is also recommended that patients receiving pazopanib are monitored regularly for hypertension and thyroid dysfunction. Baseline and periodic urinalysis and monitoring of electrocardiograms for QT prolongation are also advised. Again, these requirements are similar to those with the current standard of care, sunitinib. For the

purposes of our economic model, the costs of blood tests have been subsumed in the out-patient attendance costs.

It is estimated that a patient receiving pazopanib for advanced/metastatic RCC will have a CT scan every 3 months, at a cost of £140.40 per scan for 3 scanned areas (Source: National schedule of reference costs 2007/8 [£135] inflated for 2009/10).

With the exception of the pazopanib cost, medication costs used in our economic model have been taken from the September 2009 publication of the British National Formulary (BNF 58). The cost of sunitinib was calculated assuming one cycle is provided free, based on the manufacturer's patients access scheme (NICE TA 169). The pazopanib list price was set at parity with the sunitinib list price so that the cost of continuous daily treatment with pazopanib over 42 days would be equivalent to that of 42 days of intermittent dosing with sunitinib (i.e., 28 days on therapy followed by 14 days off therapy).

Post-progression supportive care costs were assumed to be managed by primary care.

2.9 Does the technology require additional infrastructure to be put in place?

It is not anticipated that the introduction of pazopanib will require any service re-organisation.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 **Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.**

None.

3.1.2 **Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?**

No.

3.1.3 **How have the clinical and cost-effectiveness analyses addressed these issues?**

Not applicable.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Patients with advanced and/or metastatic renal cell carcinoma who have received no prior systemic therapy	The CHMP has adopted a positive opinion (19th February 2010) recommending a conditional marketing authorisation for pazopanib for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease. The pivotal trial (VEG105192) supporting the registration of pazopanib was conducted in patients with advanced/ metastatic RCC who had either received no prior systemic therapy (treatment-naïve; n=233) or had received previous cytokine-based therapy (n=202). The focus of this submission is the sub-population of patients that had received no prior systemic therapy i.e. the treatment-naïve sub-population.	
Intervention	Pazopanib hydrochloride	Pazopanib hydrochloride	
Comparator(s)	• Sunitinib For people in whom sunitinib is unsuitable: • Immunotherapy (interferon-alfa, interleukin-2) • Best supportive care	The comparators that are considered in this submission are: a) Sunitinib However, it should be noted that since no head-to-head data for pazopanib versus sunitinib are currently available an indirect comparison via IFN-α has been necessary. b) Other comparators: • Immunotherapy with Interferon-alfa (INF-α) • Best supportive care (Note: This was the comparator in the pivotal pazopanib trial [VEG 105192]). Clinical and cost-effectiveness analyses comparing pazopanib versus both IFN-α and BSC has been undertaken and is discussed in this submission.	
Outcomes	• The outcome measures to be	The pivotal phase III trial supporting the registration of	

	considered include: • overall survival (OS) • progression free survival (PFS) • response rates • adverse effects of treatment • health-related quality of life.	pazopanib for advanced/metastatic RCC (VEG105192) provides efficacy (PFS, OS, and response rates), health-related quality of life and adverse event data for pazopanib. It should be noted that this study is ongoing and the data presented in this submission are from a planned interim analysis conducted for overall survival with a cut-off date of 23 May 2008. At the time of this analysis less than half of the patients in each of the treatment arms had died and therefore the OS data presented in this submission are immature. Final OS data should be available in Q2 2010. In addition, since 40% of patients randomised to placebo in the treatment-naive sub-population switched to pazopanib via an open-label extension study, analyses were conducted to adjust for this cross-over effect and are presented in the submission.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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.	A systematic literature review has been commissioned and provides the evidence base for the comparative efficacy, effectiveness and cost-effectiveness of available treatments for the first-line treatment of advanced/metastatic RCC (mRCC). A “partitioned survival model” will be employed to estimate expected PFS, OS, lifetime costs of treatment of mRCC, and quality adjusted life years (QALYs) in patients with mRCC who are assumed to receive pazopanib or other widely used treatments in the UK for treatment-naïve mRCC. Cost-effectiveness will be measured in terms of the cost per quality-adjusted life years (QALYs) gained. Cost-effectiveness will be evaluated from the perspective of the UK NHS. A 10-year timeframe will be employed. This time horizon for estimating clinical and cost effectiveness is considered to be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	

		Costs and QALYs will be discounted at 3.5% annually. Because pazopanib was compared to placebo in the VEG105192 trial, the HRs for PFS and OS for pazopanib vs. interferon-alpha (IFN-α) in treatment-naïve patients will be estimated by an indirect comparison using data from available randomized controlled trials of IFN-α versus placebo. The analysis of incremental cost-effectiveness ratios (ICERs) for pazopanib versus sunitinib will be supported by ICERs for pazopanib versus IFN and versus BSC. Costs and utility values will be based on data from the VEG105192 trial, secondary sources, and the literature. Probabilistic and deterministic sensitivity analyses will be conducted. NB: EQ-5D was included in the VEG105192 trial.	
Subgroups to be considered	• If evidence allows subgroups according to the following will be considered: • resected versus unresected primary tumour • clear cell component versus no clear cell component • performance status. Guidance will only be issued in accordance with the marketing authorisation	The evidence available from the VEG105192 trial does not allow these sub-groups to be considered: • Most patients (89%) in the trial had undergone a nephrectomy and therefore the unresected group is too small for interpretable results • All patients in the trial were required to have clear cell (90%) or predominantly clear cell histology. No patients were included without a clear cell component • Whilst PFS for the total population of patients included in the VEG105192 trial has been sub-analysed by ECOG performance status, this analysis has not been conducted for the sub-population of patients with no prior systemic treatment because the resulting sub-groups are too small for interpretable results.	
Special		None.	

considerations, including issues related to equity or equality			

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

Key points:

- One randomised controlled trial (RCT) of pazopanib (VEG105192) in treatment-naive and cytokine pre-treated patients with advanced/metastatic renal cell carcinoma (RCC) was identified via a systematic review. The treatment-naive sub-population forms the main focus of this submission in line with the scope of this appraisal (first-line treatment) and the key results are as follows:

Efficacy:

- Progression-free survival (PFS) was significantly prolonged with pazopanib compared with placebo (11.1 vs. 2.8 months; HR 0.40 [95% CI: 0.27-0.60]; p<0.0001). This was confirmed by sensitivity analyses including assessments based on scan dates (HR 0.36 [95% CI: 0.24-0.55]) and investigators' determination of progression (HR 0.47 [95% CI: 0.33-0.68]).

- Pazopanib was associated with a 26% reduction in risk of death compared with placebo in the pre-specified ITT analysis (HR 0.74 [95% CI: 0.47-1.15]; p=0.0079); however, the data are immature and a large proportion of patients in the placebo arm (40% at the clinical cut-off) crossed over to receive pazopanib after disease progression potentially diluting the treatment effect.

- Since there is no universally accepted way to adjust for cross-over from control to active treatment in survival analysis in RCTs, several approaches were utilised to comprehensively evaluate this effect; i) censoring on cross-over; ii) considering cross-over as time-dependent covariate; iii) inverse probability of censoring weighted (IPCW) analysis; and iv) rank preserved structural failure time (RPSFT) analysis.

- The results of these analyses indicate that treatment with pazopanib was associated with a clinically relevant reduction in risk of death compared with placebo (adjusted HRs for OS for pazopanib vs. placebo ranging from 0.206 to 0.684, depending on methodology and whether adjusted for baseline patient characteristics, Table 5.22).

- The univariate HR of 0.345 (95% CI: 0.086-1.276) estimated using the RPSFT method was chosen for use as the base case in the indirect comparison and in the economic evaluation based on the benefits of this technique in preserving randomisation and not making the assumption of no unknown confounders.

- Pazopanib therapy was associated with a significant improvement in objective response rate (ORR: complete response [CR] + partial response [PR]) compared with placebo (32% vs. 4%; p<0.001). Responses were durable with a median duration longer than 1 year (58.7 weeks). Since tumour stabilisation can result in clinical benefit for patients, the CR + PR + 6-month stable disease (SD) rate of 49% in the pazopanib arm vs. 12% in the placebo arm (p<0.001) is also clinically relevant.

- The quality of life (QoL) assessments (based on scores from the EORTC QLQ C30 and EQ-5D questionnaires) showed no statistical or clinically important differences between pazopanib and placebo at any of the assessment time points in subjects who continued on therapy, indicating no negative impact on QoL over time in patients receiving pazopanib relative to placebo.

- Two non-RCTs provide supportive data: a phase II study (VEG102616) and the open-label extension study (VEG107769) to VEG105192. Consistent with VEG105192, the response rate in VEG102616 was 34% in treatment-naive subjects and was 32% in VEG107769 (all subjects). Median PFS in these studies was similar to that reported in VEG105192.

Indirect comparison

- A further six studies were identified via the systematic review that would allow an indirect comparison of pazopanib to interferon-α (IFN) and to the main comparator of interest, sunitinib.

- Results of the base case indirect comparison showed that pazopanib is associated with a reduced risk of progression and death compared with IFN (HRs: 0.512 [95% CI: 0.326-0.802] for PFS and 0.432 [95% CI: 0.106-1.750] for OS) and has broadly comparable efficacy to sunitinib in terms of PFS and OS (HRs: 0.949 [95% CI: 0.575-1.568] and 0.667 [95% CI: 0.160-2.788], respectively). Sensitivity analyses conducted maintaining the RPSFT-derived HR but varying the IFN trials included (i. MRC RE-01 trial only; ii. excluding trials using vinblastine therapy) and then repeated using the IPCW-adjusted HR for OS from the VEG105192 trial confirm the results of the base case analysis.

- Median OS estimated using the Weibull survival model employed in the economic evaluation was 15.8 months (95% CI: 15.8-15.8) for IFN and 43.5 months (95% CI:-81.9-169.0) for pazopanib. This equates to a survival gain of 27.7 months for patients receiving pazopanib compared with IFN, thereby exceeding the End of Life (EOL) criterion of an extension to life of at least 3 months (see section 5.10.3).

- The 95% CIs around the HR estimates for OS for pazopanib vs. sunitinib and the OS medians for pazopanib and sunitinib are wide indicating uncertainty in these estimates. The ongoing head-to-head COMPARZ study, which is designed to demonstrate non-inferiority of pazopanib vs. sunitinib, will help to address this uncertainty.

Safety

- Overall, pazopanib was well tolerated with an acceptable and manageable safety profile in patients receiving first-line treatment for advanced/metastatic RCC.

- The most common adverse events (AEs) observed with pazopanib treatment were diarrhoea, hypertension, hair colour changes, anorexia, nausea and vomiting. Most events were mild to moderate (grades 1 and 2) and were reversible upon dose modification; few led to permanent discontinuation of study medication.

- The most common laboratory abnormalities observed in the pazopanib RCC studies were increased AST and increased ALT. Most cases of drug-induced liver enzyme elevations were asymptomatic and reversible upon dose reduction or interruption. This risk can be managed through regular liver function monitoring conducted as part of routine clinical practice and dose adjustments as necessary.

- Haematological AEs, including grade 3/4 cytopenias, occurred with a low rate in pazopanib-treated patients which may be explained by the fact that pazopanib is not a potent inhibitor of the Flt-3 receptor which is expressed on haematological progenitor cells.

- AEs previously observed with this class of drug such as proteinuria, hypothyroidism, hand-foot syndrome, stomatitis and mucositis were observed in less than 10% of patients treated with pazopanib.

- Arterial thrombotic and haemorrhagic events, also known class effects, occurred infrequently with pazopanib treatment. There was little evidence that pazopanib is associated with cardiotoxicity in the form of decreased left ventricular ejection fraction (LVEF) or congestive heart failure (CHF).

- Qualitative and formal indirect comparison of data from the pivotal clinical trials suggests that pazopanib has a favourable safety profile compared with sunitinib, particularly in relation to haematological AEs, cardiotoxicity and events that can affect patients' daily functioning and quality of life such as hand-foot syndrome, mucositis, stomatitis and fatigue.

5.1 Identification of studies

5.1.1 **Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.**

A systematic review was carried out to identify, report and if appropriate, meta-analyse or indirectly compare any clinical studies of relevance to this NICE appraisal. The review was conducted and reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.

The primary study question was: What is the relative clinical efficacy, safety and tolerability of pazopanib, the intervention under consideration, and other pharmacological interventions in the first-line treatment of advanced/metastatic renal cell carcinoma (RCC)? The population considered were therefore patients with advanced and/or metastatic RCC with no prior systemic treatment.

A comprehensive search strategy was designed to retrieve relevant clinical data from the published literature. The following electronic databases were searched:

Data source	Service provider
MEDLINE (23 November 2009; 1980 onwards)	Embase.com http://www.embase.com/
EMBASE (23 November 2009; 1980 onwards)	Embase.com http://www.embase.com/
Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Cochrane Methodology Register (23 November 2009; 1980 onwards)	Cochrane library http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html
MEDLINE In process (2 December 2009; 2009 only)	PubMed http://www.ncbi.nlm.nih.gov/sites/entrez

Only studies with the full-text in English were included in the review. Further details of the search strategies and search syntax for the individual databases can be found in section 9.2, appendix 2 to the main submission, and in Appendix 1 of the full Systematic Review report.

The following conference proceedings were hand-searched from 2007 to 2009:

- American Society of Clinical Oncology (ASCO)
- ASCO-Genitourinary (ASCO-GU)
- European Society of Medical Oncology (ESMO)
- European Conference for Clinical Oncology (ECCO).

Further searches were carried out in www.clinicaltrials.gov, UK Clinical Trials Gateway (UKCTG) and the International Standard Randomized Controlled Trial Number (ISRCTN) Register to identify any ongoing studies of relevance to this review. Further potential publications were identified by hand-searching of reference

lists in (i) clinical trial publications identified via the database search and (ii) in systematic reviews and qualitative reviews conducted in this disease area.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent.

Details of the inclusion and exclusion criteria employed for the systematic review are presented in Table 5.1. It should be noted that, whilst the comparators for this appraisal are sunitinib, interferon-alpha (IFN) and best supportive care, the Systematic Review included other targeted agents used in the treatment of RCC (sorafenib, bevacizumab and temsirolimus) as relevant interventions for completeness. The indirect comparison presented in section 5.8 of this submission involves a comparison of pazopanib with sunitinib via placebo/BSC and INF only.

Table 5.1: Eligibility criteria used in search strategy

	• **Criteria for clinical effectiveness search**	• **Rationale**
Inclusion criteria	• **Population** • Age: Adults (≥ 18 years) • Gender: Any • Race: Any • Stage of disease: Locally advanced / Advanced / Metastatic / Stage III / Stage IV • Line of therapy: No prior systemic therapy (treatment-naïve)	• The patient population has been restricted to match that stated in the decision problem for pazopanib in the first-line treatment of advanced and/or metastatic RCC. • Since the current treatments for RCC are only licensed for adult patients, studies including children or adolescents were excluded.
	• **Interventions** • Pazopanib monotherapy (or in combination with best supportive care [BSC]) • Interferon-alpha (IFN) monotherapy (or in combination with BSC) • Interleukin-2 (IL-2) monotherapy (or in combination with BSC) • Sunitinib monotherapy (or in combination with BSC) • Sorafenib monotherapy (or in combination with BSC) • Temsirolimus monotherapy (or in combination with BSC) • Bevacizumab in combination with IFN-α (and in combination with BSC)	• The included interventions are those which are either licensed for the first-line treatment of advanced/ metastatic RCC or for which RCT data in this setting exist. • The review was limited to studies of these agents administered as monotherapy (or with the exception of bevacizumab in combination with interferon) as per their licensed indications or as per the anticipated licence in the case of pazopanib.
	• **Comparator/controls** • Any of the included interventions • Placebo • Best supportive care (BSC)*	• These comparators were chosen to enable both direct and indirect comparisons between the interventions of interest.
	• **Outcomes of interest** • *Efficacy:* • Overall survival (OS) • Progression-free survival (PFS) • Time to progression (TTP) • Overall response rate (ORR: Complete response [CR] + Partial response [PR]) • Proportion of patients with stable disease (SD) • Time to and duration of response • Health-related quality of life • • *Safety:* • Incidence and severity of all adverse events (AEs) • Withdrawals due to AEs • Withdrawals due to death	• These outcomes were chosen since they are frequently measured and reported in trials of RCC, and will enable the study question of the review to be answered.

	• Serious adverse events (SAEs) • Incidence and severity of specific adverse events – see section 3.1.6 in the full Systematic Review report for listing	
	• **Study design** • Randomised controlled trials (RCTs) with any blinding status	• RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of the interventions. Therefore only these studies were included. To enhance the amount of evidence, studies with double blind, single blind and open label design were included.
	• **Language restrictions** • English only	• The restriction would not limit results substantially due to widespread data availability in English language.
	• **Publication timeframe** • 1980 onwards for literature searches • Last 3 years for conference searching	• This restriction would not limit results substantially due the vast majority of data for cytokines and targeted therapies being reported from 1980s onwards. • Studies which are presented at conferences are usually published in full within 3 years of presentation.
• **Exclusion criteria**	• **Outcome of interest** • Studies should report an outcome of interest.	• Studies not reporting at least one outcome of interest could not feature in any analyses and were therefore excluded.
	• **No subgroup analysis** • No subgroup analysis for disease of interest • No subgroup analysis for advanced/metastatic disease • No subgroup analysis for treatment naïve patients	• Studies not reporting outcome data specifically for the disease, disease stage and line of treatment of interest were excluded, since these studies would introduce heterogeneity into the review.

*BSC definition: no active treatment/observation/a method of care that is not a focused treatment/treatments which clinicians consider to be "placebo-equivalent" including medroxyprogresterone acetate and vinblastine. RCC= renal cell carcinoma , RCT = Randomised control led trial

5.2.2 **A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.**

Studies were included / excluded on the basis of the criteria detailed in Table 5.1 above and the results of each stage of the inclusion / exclusion process are summarised in Figure 5.1.

Citations were first screened based on the abstract supplied with each citation. Those that clearly did not match the eligibility criteria were excluded at this 'first pass'; where unclear, citations were included. Full-text copies of all references that could potentially meet the eligibility criteria were also ordered at this stage.
The eligibility criteria were then applied to the full-text citations. At each stage, two independent reviewers screened the abstract/full text, and any discrepancies were reconciled by a third independent reviewer.

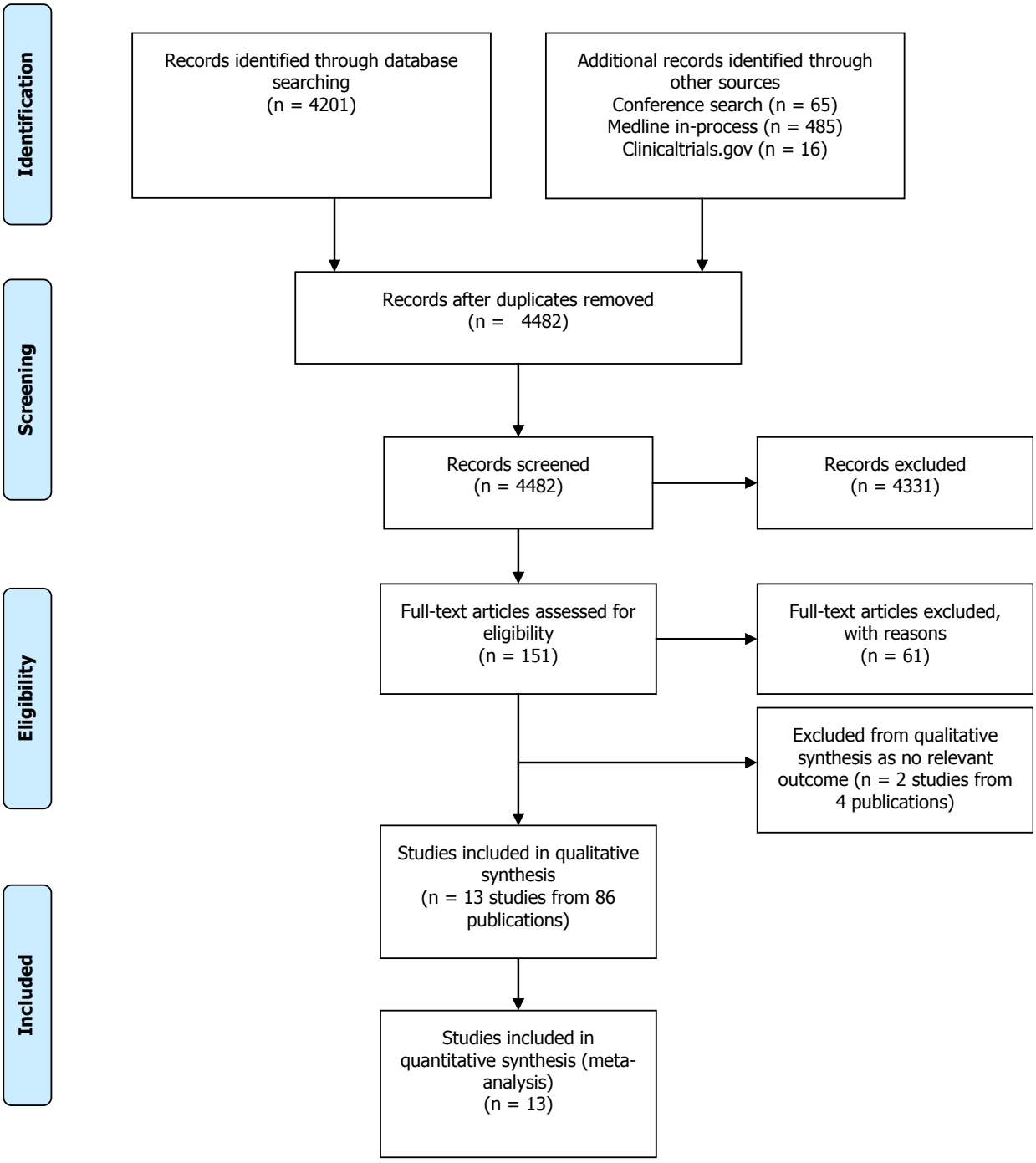
A total of 13 RCTs with relevant outcome data reported in 86 publications were identified as meeting the inclusion criteria for the systematic review and were extracted. Data from trials were extracted in parallel by two independent reviewers, with reconciliation of any differences by a third independent reviewer. Details of the excluded studies are available on request.

The 13 included studies comprise (see Table 5.3 for further details):

- One trial evaluating the efficacy and safety of pazopanib compared with placebo in treatment-naive and cytokine pre-treated patients with advanced/metastatic RCC (VEG105192)
- One trial evaluating the efficacy and safety of sunitinib compared with IFN in patients with previously untreated metastatic RCC (Motzer 2009)
- One trial evaluating the efficacy and safety of sorafenib compared with INF in patients with previously untreated metastatic RCC (Escudier 2009c). Another trial (TARGET) comparing sorafenib versus placebo in patients with advanced RCC with and without prior cytokine treatment
- Two trials (AVOREN and CALGB 90206) comparing the efficacy and safety of bevacizumb plus IFN versus IFN alone in patients with previously untreated metastatic RCC
- One trial (GARCC) comparing the efficacy and safety of temsirolimus, IFN or the combination in patients with previously untreated poor-prognosis metastatic RCC
- The remaining six trials compared a cytokine-based regimen (IFN or IL-2) with either best supportive care (BSC) or another immunotherapy (Kriegmair 1995; MRC RE01; Negrier 2007; Negrier 1998; Pyrhonen 1999; Steineck 1990).

Where trials included a mixed population of treatment/cytokine-naive and cytokine pre-treated patients, only those studies in which outcome data was specifically available via a sub-group analysis for the treatment/cytokine-naive sub-population were included in the review and only data for this sub-population were extracted.

Figure 5.1: Clinical studies trial flow



5.2.3 **When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.**

Data for the pazopanib pivotal phase III trial (VEG105192) has been drawn from a number of sources, as shown in Table 5.2, with the interim Clinical Study Report (CSR) and additional analyses for the treatment-naive sub-population forming the primary sources. It should be noted that the majority of analyses for the treatment-naive sub-population do not currently appear in any published form. It should also be noted that a full publication for the results for the total study population (Sternberg 2010) took place after the database search was conducted on 23 November 2009.

For the other trials identified as meeting the inclusion criteria for the review (see Table 5.3), the primary reference source is provided in the left hand column and other citations for the same trial are listed in the right-hand column.

Table 5.2: Data sources for pazopanib RCT

Author(s)	Source	Title
Sources for pazopanib trial VEG105192		
GlaxoSmithKline	Analyses of treatment-naive sub-population from VEG105192	-
GlaxoSmithKline	Clinical Study report (CSR) for VEG105192 (UM2008/00012/00)	A randomised, double-blind, placebo-controlled, multi-center phase III study to evaluate the efficacy and safety of pazopanib (GW786034) compared to placebo in patients with locally advanced and/or metastatic renal cell carcinoma.
Sternberg CN, Szczylik C, Lee ES, *et al*.	Abstract and oral presentation at American Society of Clinical Oncology Annual Meeting 2009. J Clin Oncol 2009; 27 (suppl 15s): Abstract no. 5021.	Phase III trial of pazopanib in locally advanced and/or metastatic renal cell carcinoma.
Sternberg CN, Davis ID, Wagstaff J, *et al.*	Abstract and oral presentation at the Joint ECCO and ESMO Multidisciplinary Congress 2009. Eur J cancer 2009; 7: 424 (Abstract no. 7106).	Predictive and prognostic factors in a Phase III study of pazopanib in patients with advanced renal cell carcinoma (RCC).
Hawkins R, Hodge R, Chen M, *et al.*	Abstract and poster presentation at the Joint ECCO and ESMO Multidisciplinary Congress 2009. Eur J Cancer 2009; 7: 424 (Abstract no. 7119 and poster 132).	Quality of life (QoL) in treatment-naïve and cytokine-pretreated patients with advanced renal cell carcinoma (RCC) treated with pazopanib: results from a Phase III double-blind, placebo-controlled trial.
Sternberg CN, Davis ID, Mardiak J, *et al*.	J Clin Oncol 2010; epub ahead of print publication (published online 26.01.10).	Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomised phase III trial.

Complete list of relevant RCTs

5.2.4 **Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form.**

No studies which directly compared pazopanib, the intervention under consideration, with one of the other interventions of interest for the systematic review (sunitinib, sorafenib, temsirolimus, bevacizumab plus interferon-alpha [IFN], interleukin-2 [IL-2]) were identified in the relevant patient population (treatment-naive advanced/metastatic RCC).

One trial (VEG105192) comparing pazopanib with placebo (equating to BSC) in treatment-naive and cytokine pre-treated patients with advanced/metastatic RCC was identified. In addition, 12 studies comparing the other interventions of interest to placebo/BSC or to IFN were identified, permitting indirect comparisons of the interventions. It should be noted that in section 5.7 of this submission (Indirect and mixed treatment comparisons), only those studies that permit an indirect comparison of pazopanib to IFN and to the main comparator of interest, sunitinib, are considered.

A second study of pazopanib in patients with advanced/metastatic RCC was identified in the review. This was a phase II study originally designed as a randomised discontinuation study but was revised to be treated like a single-arm open-label study on the recommendation of the study's data monitoring committee after a planned interim analysis gave an early indication of pazopanib's activity. Outcome data for the trial have been summarised across the open-label and randomised phases and no sub-group analysis for treatment-naive patients was conducted for the randomised phase. For these reasons, this study was excluded from the final list of included studies and further details are presented in section 5.8 of this submission as supportive non-RCT evidence.

Table 5.3: List of all RCTs identified as meeting inclusion criteria for the systematic review

Study	Year	Study type	N***	Intervention	Comparator	Patient population	Linked publications
Pazopanib							
#VEG105192 (GlaxoSmithKline 2008)	2009	R, DB, PC, MC-I, Phase III	233 (Total population = 435)	Pazopanib 800 mg od	Placebo	Locally advanced or metastatic clear cell/predominantly clear cell RCC, ECOG PS ≤ 1, Age ≥18 years	(Sternberg 2010; Sternberg 2009b; Sternberg 2009a; Hawkins 2009)
Sunitinib							
(Motzer 2009)	2009	R, AB, AC, MC-I, Phase III	750	Sunitinib 50 mg od (4 weeks on, 2 weeks off treatment)	IFN 9 MU TIW	Metastatic RCC with a clear-cell histological component, ECOG PS ≤ 1, Age ≥18 years	(Motzer 2008; Reddy 2006; Cella 2009; Patil 2009; Figlin 2008; Cella 2008a; Motzer 2007c; Eberhardt 2007; Cella 2008b; Motzer 2007b; Negrier 2008; Cella 2007a; Motzer 2007a; Motzer 2006a; Eberhardt 2006; Motzer 2006b; Castellano 2009)
Sorafenib							
(Escudier 2009c)	2009	R, OL, AC, MC, Phase II	189	Sorafenib 400 mg bid	IFN 9 MU TIW	Unresectable and/or metastatic, clear cell RCC, ECOG PS ≤ 1, Age ≥18 years	(Escudier 2006; Szczylik 2007)
#Target Study (Negrier 2009)	2009	R, TB, PC, MC-I, Phase III	161 (Total population = 903)	Sorafenib 400 mg bid	Placebo	Metastatic RCC, low or intermediate risk MSKCC score, ECOG PS 0 to 2, Age ≥18 years	(Autier 2008; Escudier 2009b; Eisen 2008; Bukowski 2009; Oudard 2009; Bukowski 2007b; Hutson 2009a; Eisen 2006; Escudier 2005; Escudier 2007a; Bellmunt 2007; Dhanda 2006; Jager 2005; Hutson 2009b; Bukowski 2007a)
Bevacizumab							
AVOREN trial (Escudier 2007c)	2007	R, DB, AC, MC-I, Phase III	649	Bevacizumab 10mg/kg q2wks plus IFN 9 MU TIW	Placebo plus IFN 9 MU TIW	Patients with clear-cell RCC and had undergone nephrectomy/partial nephrectomy, KPS of ≥70%, Age ≥18 years	(Melichar 2008; Melichar 2007; Escudier 2009a; Escudier 2008b; Melichar 2009; Bajetta 2008; Bellmunt 2009; Escudier 2007b; Bracarda 2007; Bracarda 2009; Ravaud 2008; Escudier 2008a)
CALGB 90206 (Rini 2008a)	2008	R, OL, AC, MC-I, Phase III	732	Bevacizumab 10mg/kg q2wks plus IFN 9 MU TIW	IFN 9 MU TIW	Metastatic RCC patients with clear cell histologic component, KPS of ≥70%, Age ≥18 years	(Rini 2004; Rini 2009; Rini 2008b)
Temsirolimus							
Global ARCC trial (Hudes 2007)[$]	2007	R, OL, AC, MC-I, Phase III	626	Temsirolimus 25 mg weekly	IFN 18 MU TIW	Advanced RCC (stage IV or recurrent disease) and a KPS of ≥60%	(Dutcher 2009; Bellmunt 2008; Figlin 2009; Moore 2006; Alemao 2009; Mallick 2008; Parasuraman 2007; de Souza P. 2007; Dutcher 2007; Dutcher 2008; Logan 2008; Pendergrass 2009;

Study	Year	Study type	N***	Intervention	Comparator	Patient population	Linked publications
							Rajagopalan 2009; Yang 2009; de Souza 2008)
IFN, Interleukin-2							
(Negrier 2007)	2007	R, BU, AC, BSC, MC	492	IFN 9 MU TIW	Interleukin-2 9 MIU bid Medroxyprogesterone	Clearly progressive metastatic RCC of all histologic subtypes, >1 metastatic organ site and good performance status (KPS ≥80%) or 1 metastatic organ site with KPS 80%, Age ≥18 years	Negrier 2006
MRC RE01 (Hancock 2000)	1999	R, BU, BSC, MC	350	IFN 10 MU TIW	Medroxyprogesterone	Histologically or cytologically confirmed metastatic RCC, WHO PS of 0 to 2	(Royston 2004; Royston 2008; Ritchie 1999; Ritchie 1998)
(Steineck 1990)	1990	R, AB, BSC	60	IFN 10-20 MU/m2 TIW	Medroxyprogesterone	Locally recurrent or metastatic adenocarcinoma of kidney, Patients with previous irradiation of the disease or excision of metastases, Age 18 to 70 years	No links
(Kriegmair 1995)	1995	R, BU, BSC, Phase III	89	IFN 8 MU TIW plus vinblastine	Medroxyprogesterone	History of tumour nephrectomy and a histologically confirmed diagnosis of progressive RCC with bimensionally measurable tumour lesion and a WHO PS of at least grade 2	No links
(Pyrhonen 1999)	1999	R, BU, BSC, MC, Phase III	160	IFN 18 MU TIW plus vinblastine	Vinblastine	histologically or cytologically confirmed measurable or nonmeasurable but assessable advanced RCC, KPS >50% (ECOG status of 0 to 2), Age ≤75 years	(Hernberg 1997)
CRECY Trial (Negrier 1998)**	1998	R, AB, AC, MC, Phase II/III	425	Interkeukin-2 18 MU per m2 body surface area per day	IFN 18 MU TIW	Progressive metastatic RCC, ECOG PS<2, Age 18 to 65 years	(Negrier 1996; Lasset 1992)

*R = randomised, AB = assessor blind, AC = active controlled, BSC = best supportive care controlled, BU = blinding unclear, DB = double blind, ECOG = Eastern Cooperative Oncology Group, KPS = Karnofsky Performance Status, MC = multicentre, MC-I = multicentre-international, MSKCC = Memorial Sloan-Kettering Cancer Centre, MU = million units, od = once daily, OL = open label, PC = placebo controlled, TB = Triple blind, TIW = three times per week.
#subgroup analysis for treatment naïve patients; ***This is the number of treatment naïve patients in the study.
**This study also included an IFN-IL-2 combination treatment arm which was not extracted since it did not meet the inclusion criteria for intervention/comparator.
$ This study also included an IFN plus temsirolimus combination treatment arm which was not extracted since it did not meet the inclusion criteria for intervention/comparator.

5.2.5 **Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.**

Only the VEG105192 trial directly compares the intervention, pazopanib, with a comparator stated in the decision problem, in this case versus BSC. No other studies directly comparing pazopanib with another active intervention were identified.

5.2.6 **When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.**

Not applicable.

List of relevant non-RCTs

5.2.7 **Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table.**

Non-RCTs were excluded from the systematic review. However, two non-RCTs are included in this submission as they provide relevant supportive data for pazopanib in the patient population under consideration (Table 5.4).

Table 5.4: Relevant non-RCTs

Trial no. / Primary reference source	Study design	Objective	Intervention(s)	N	Population	Justification for inclusion
VEG102616 (Hutson *et al*., 2010)	• Phase II • MC-I • Randomised Discontinuation design	To evaluate the efficacy and safety of pazopanib 800mg o.d. in patients with locally recurrent/metastatic RCC	Pazopanib 800mg o.d. Placebo	12-week OL phase N=225 Randomised N=55 • Pazopanib N=28 • Placebo N=27 Not randomised/OL N=170	• Locally recurrent or metastatic RCC • Treatment-naive (n=155) • Prior systemic treatment (n=70) • ECOG PS 0 or 1	Provides supportive data for pazopanib in relevant patient population
VEG107769 (Hawkins *et al*., 2009)	• OL extension study to Phase III study VEG105192 • MC-I	An open-label extension study to evaluate the pazopanib in patients with advanced/metastatic RCC The study was designed to provide access to pazopanib for subjects enrolled in VEG105192 who progressed after being randomised to the placebo arm.	Pazopanib 800mg o.d.	71	• Advanced / metastatic RCC • Patients with no other systemic therapy since PD on placebo in VEG105192 • Treatment-naive (n=34)* • Prior systemic treatment (n=37)* • ECOG PS ≤ 2	Provides supportive data for pazopanib in relevant patient population

* At baseline in VEG105192. ECOG = Eastern Cooperative Oncology Group; MC-I = multicentre-international; od = once daily; OL = open-label; PD = progressive disease; wk = week.

5.3 Summary of methodology of relevant RCTs

5.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

An overview of the study design and methodology of VEG105192 is provided in Table 5.5. Patient enrolment commenced on 18 April 2006. Outcome data presented in this submission are from a planned interim analysis conducted for overall survival with a cut-off date of 23 May 2008. Final overall survival data will be available during 3Q 2010.

The study initially enrolled only patients with advanced/metastatic RCC who had progressed on one prior cytokine-based systemic therapy. The protocol was subsequently amended to include treatment-naive patients (after enrolment of 7 patients) because of emerging evidence of the activity of angiogenesis inhibitors and decreased use of cytokines in the first-line setting. Patients without prior systemic therapy could be enrolled provided: they were living in countries where the new targeted therapies were not approved or readily accessible or where cytokines were not recognised as an effective treatment modality for advanced/metastatic RCC.

The initial study design selected placebo plus BSC as the choice of comparator because at that time (April 2006) there was no other choice of therapy after patients had failed cytokines. Sunitinib and sorafenib were not readily accessible making it difficult to use either as a comparator (they were either not approved or reimbursed in all but 3 of the 23 participating countries during the conduct of VEG105192). Placebo with BSC was therefore retained as the control arm following the protocol amendment to include treatment-naive patients for the following reasons:

(i) Cytokines as a standard of care were being challenged in many of the participating countries on the basis of their unfavourable risk: benefit profile and emerging efficacy data for targeted agents;
(ii) Final results from the phase III trials of sunitinib, sorafenib and other targeted agents in treatment-naive advanced/metastatic RCC patients were still pending.
(iii) GSK was unable to access wholesale supply of targeted agents to use as comparator drugs.

Using a placebo control in a randomised, double-blind study enabled better characterisation of the safety and efficacy profile of pazopanib. Exposure of patients to placebo in the study was minimised by 2:1 random assignment. In addition, pazopanib was offered as a treatment option for patients who were found to have progressed on placebo (following unblinding) via an open-label extension study, VEG107769, providing they met the pre-defined eligibility criteria. Further details of

this study are presented in section 5.8 of this submission as supportive non-RCT evidence.

An Independent Review Committee (IRC) was established prior to the start of VEG105192 to evaluate all imaging data from study subjects in a blinded fashion for assessment of subjects' disease status. A cross-study Independent Data Monitoring Committee (IDMC) was established for VEG105192 (and VEG102616) to monitor safety over the course of the studies, to review the interim data and make recommendations on the course of the pazopanib studies. Upon review of the safety and/or interim survival data from VEG105192, the IDMC could recommend stopping the study due to significant safety issues, or due to significantly superior efficacy or lack of efficacy of pazopanib compared to placebo. The IDMC could also recommend study modifications.

A CONSORT flow diagram for VEG105192 is provided in Figure 5.2 (p. 67).

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.

Table 5.5: Summary of methodology of the RCTs

Trial no. (acronym)	VEG105192
Location	Multi-centre study involving 80 centres in 23 countries across Europe, Asia, South America, Australia and New Zealand. 4 centres in the UK randomised a total of 28 subjects.
Design	Randomised, double-blind, placebo-controlled, parallel-group study.
Population	Patients with locally advanced/metastatic RCC (n=435): • Treatment-naive patients (n=233) • Cytokine pre-treated patients (n=202)
Duration of the study	Ongoing. Enrolment commenced 18 April 2006.
Method of randomisation	Upon completion of all the required baseline assessments, eligible patients were registered into the GSK interactive voice response system (RAMOS; Registration and Medication Ordering System), by the investigator or authorised study staff, for stratification and central randomisation. Registered patients were assigned a unique subject number for the duration of the study. Subject number and the following baseline subject information for stratification were entered into the system to obtain the blinded treatment assignment: • ECOG PS: 0 or 1 • Prior nephrectomy: yes or no • Prior systemic therapy for advanced/ metastatic RCC: Treatment naive or cytokine pre-treated Subjects in each stratum were then centrally randomised in a 2:1 ratio to receive pazopanib or placebo according to a randomisation schedule computer-generated by the GSK Biomedical Data Sciences Department.
Method of blinding	Blinding was achieved through the use of matching placebo tablets. Treatment assignment remained blinded to investigators and study staff throughout the study treatment period or until objective evidence of disease progression. Only in the case of an emergency when knowledge of the investigational product was essential for the clinical management or welfare of the subject could the investigator unblind a subject's treatment assignment. Subjects who progressed were unblinded by the investigators via an independent unblinding system run by a CRO, allowing GSK study personnel to remain blinded to subjects' treatment assignments until after the clinical database was locked. Subjects who entered the open-label extension study (VEG107769) were allocated a different subject number for that study. Central 2:1 randomisation meant that the investigator could not infer the treatment arm for subjects who remained blinded based on knowledge of the treatment arm of unblinded subjects.

	All imaging scans from the study were evaluated centrally by an Independent Review Committee (IRC) in a blinded fashion. The central review by the IRC was completed prior to database freeze and unblinding.
Interventions and comparators	Pazopanib 800mg once daily N=290 Matching placebo once daily N=145 Patients received continuous treatment until disease progression, death, unacceptable toxicity or withdrawal of consent for any reason. Subsequent anticancer therapy for patients with progressive disease was at the discretion of patients and their physicians. Patients who progressed were unblinded, and if found to be on placebo, had the option of receiving pazopanib via an open-label study (VEG107769), providing they met pre-defined eligibility criteria. Details of pre-specified guidance on dose modifications (dose reductions, treatment interruptions or discontinuations) in order to manage toxicities can be found in the CSR provided with this submission.
Concomitant therapy	Patients were permitted to receive full supportive care during the study, including transfusion of blood and blood products, antibiotics, anti-emetics, anti-diarrhoeal agents, analgesics, erythropoietin or bisphosphonates, when appropriate. Certain concomitant medications were to be used with caution, particularly inhibitors and inducers of CYP3A4. Certain medications were prohibited within 14 days prior to the first dose of study drug until discontinuation of study treatment. Further details can be found in the VEG105192 Study Protocol. Concomitant anti-cancer treatments for RCC were not permitted.
Primary outcomes (including scoring methods and timings of assessments)	Progression-free survival (PFS) in overall study population, as assessed by the IRC according to RECIST (Therasse 2000) criteria. PFS was also examined in pre-specified sub-groups including: • Treatment-naive • Cytokine pre-treated Imaging-based (CT or MRI) disease assessments were performed at baseline, every 6 weeks until week 24, and every 8 weeks thereafter until progression. Bone scans were performed every 24 weeks in all patients and to confirm a CR or PR.
Secondary outcomes (including scoring methods and timings of assessments)	*Efficacy:* The principle secondary outcome was overall survival (OS) in the overall study population. Other secondary endpoints: • Overall response rate (ORR: CR+PR) • Rate of CR + PR+ 6-months SD • Time to response • Duration of response Supportive analyses of PFS and response rates were conducted using the investigator-assessed data. *Health-related quality of life assessments:* • EQ-5D utility score and VAS • EORTC-QLQ-C30 administered at baseline and weeks 6, 12, 18, 24 and 48 (if the subject had not already discontinued study medication). *Safety:* • Incidence and severity of adverse events (AEs) • Serious adverse events (SAEs) • AEs leading to discontinuations, dose reduction or interruptions • Clinical laboratory evaluations • 12-lead ECG • Vital signs • Physical examinations Safety assessments were conducted at baseline, day 8, every 3 weeks until week 24, and every 4 weeks thereafter until study treatment discontinuation. Thyroid function tests were performed every 12 weeks and if TSH levels were abnormal, evaluations of free triiodothyronine/thyroxine were obtained.
Duration of follow-up	Subjects were followed every 3 months until death, withdrawal of consent, or until study completion, whichever came first. Median duration of follow-up at the clinical cut-off (23 May 2008) was 58.6 weeks and 62.6 weeks in the placebo and pazopanib arms, respectively.

CR = Complete response; CT = Computed tomography; ECG = Electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D = EuroQol questionnaire; PFS = Progression-free survival; PR = Partial response; OS = Overall survival; RECIST = Response Evaluation Criteria in Solid Tumours; SD = Stable disease; TSH = Thyroid stimulating hormone.

Dose rationale

The rationale for the 800mg once daily dose of pazopanib was based on the phase I dose-finding study (VEG10003; Hurwitz 2009). Among the 12 subjects with RCC enrolled in this study, 7 subjects received ≥800mg once daily or 300mg twice daily and 5 received ≤400mg once daily. A plateau in steady-state exposure to pazopanib was observed at doses of 800mg once daily. A mean target trough concentration ≥ 15µg/mL was achieved at this dose. Five of the 6 patients (83%) with RCC who had either a partial response or stable disease as their best response achieved a steady-state trough concentration of ≥15 µg/mL. All 4 patients with RCC who developed progressive disease, achieved a steady-state trough concentration of <15 µg/mL.

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. Highlight any differences between the trials.

Table 5.6: Eligibility criteria in the RCTs

Trial no. (acronym)	Main inclusion criteria	Main exclusion criteria
VEG105192 (Sternberg *et al*, 2010)	• Diagnosis of clear cell RCC or RCC with predominantly clear cell histology • Locally advanced RCC (defined as RCC not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to Stage IV according to AJCC staging) • Measurable disease i.e. presenting with at least one measurable lesion* according to RECIST • ECOG Performance Status 0 or 1 • Age ≥ 18 years • Additionally, at least 4 weeks had to have elapsed since the last surgery and 2 weeks had to have elapsed since radiotherapy or last systemic cytokine therapy • Adequate renal, hepatic and haematological function	• History of another malignancy • History or presence of CNS metastases or leptomeningeal tumours • Malabsorption syndrome or other condition that could affect absorption of pazopanib • Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation; abdominal fistula; gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to beginning study treatment • History of HIV infection • Presence of uncontrolled infection • QTc interval ≥470 milliseconds • History of the following cardiac and vascular conditions within 6 months of screening: o Class III/IV congestive heart failure per NYHA classification o Cardiac angioplasty or stenting o Myocardial infarction o Unstable angina o Cerebrovascular accident or deep venous thrombosis • Poorly controlled hypertension (SBP ≥140mmHg or DBP ≥90mmHg despite anti-hypertensive therapy) • Evidence of bleeding diathesis or coagulopathy • Prior use of an investigational anti-cancer drug within 4 weeks of study start • Prior use of an investigational or licensed drug that targeted VEGF or VEGF receptors

* Defined as lesions that can be accurately measured in at least one dimension with the longest diameter ≥20mm using conventional techniques or ≥10mm with spiral CT scan.
AJCC = American Joint Committee on Cancer; DBP = diastolic blood pressure; ECOG = Eastern Cooperative Oncology Group; NYHA = New York Heart Association; SBP = systolic blood pressure.

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Demographic and disease characteristics were generally well balanced across treatment arms, for both the treatment-naive and total population assigned to each treatment (Table 5.7), with the exception of a shorter time since initial diagnosis of

RCC and diagnosis of stage IV disease in treatment-naive subjects as expected. Around 90% of subjects had clear cell histology with the remainder having predominantly clear cell histology. All subjects had Stage IV (metastatic) disease at screening and more than 50% had lesions involving at least 3 organs, indicating a relatively large tumour burden in these subjects. The most common metastatic sites were lung (>70%), lymph nodes (>50%), followed by bone (>25%). Around 40% of subjects had a favourable MSKCC prognostic risk and more than 50% had an intermediate prognostic risk. Similarly, around 40% of subjects had ECOG Performance Status (PS) scores of 0 with 60% having scores of 1. Just under 90% of subjects had undergone a nephrectomy and 60% had a concurrent medical condition, with hypertension being the most common.

Table 5.7: Baseline characteristics of participants (VEG105192, ITT population, 23 May 2008 cut-off)

Parameter	Pazopanib		Placebo	
	Treatment naive N=155	Total N=290	Treatment naive N=78	Total N=145
Age (years)				
Mean	59.3 (10.10)	59.1 (10.06)	59.4 (12.40)	59.6 (11.04)
Median	59.0 (28-82)	59.0 (28-85)	62.0 (25-81)	60.0 (25-81)
Sex, n (%)				
Female	49 (32)	92 (32)	20 (26)	36 (25)
Male	106 (68)	198 (68)	58 (74)	109 (75)
Race, n (%)				
White	132 (85)	252 (87)	64 (82)	122 (84)
Asian	1 (<1)	36 (12)	0	23 (16)
Black	21 (14)	1 (<1)	14 (18)	0
Other	1 (<1)	1 (<1)	0	0
Histology*				
Clear cell	135 (87)	264 (91)	69 (88)	129 (89)
Predominantly clear cell	19 (12)	25 (9)	9 (12	16 (11)
Time since initial diagnosis				
Median (months)	7.9	15.7	8.5	13.8
Range	1-176	0-184	1-152	1-152
Time since diagnosis of stage IV disease				
Median (months)	3.0	6.1	3.5	5.8
Range	0-149	0-149	0-89	0-89
Stage of disease at initial diagnosis				
I	15 (10)	22 (8)	8 (10)	13 (9)
II	22 (14)	43 (15)	14 (18)	24 (17)
III	24 (31)	93 (32)	24 (31)	46 (32)
IV	32 (41)	127 (44)	32 (41)	61 (42)
Missing	0	5 (2)	0	1 (<1)
Stage of disease at screening				
Stage IV	155 (100)	290 (100)	78 (100)	145 (100)
Most common sites of metastases†				
Lung	114 (74)	214 (74)	55 (71)	106 (73)
Lymph nodes	89 (57)	157 (54)	48 (62)	86 (59)
Bone	49 (32)	81 (28)	22 (28)	38 (26)
Liver	41 (26)	75 (26)	17 (22)	32 (22)
Kidney	40 (26)	66 (23)	22 (28)	36 (25)
Number of organs involved†				
1	23 (15)	53 (18)	10 (13)	20 (14)
2	46 (30	78 (27)	25 (32)	50 (34)
≥3	86 (55)	159 (55)	43 (55)	75 (52)
ECOG Performance Status				
0	63 (41)	123 (42)	33 (42)	60 (41)
1	92 (59)	167 (58)	45 (58)	85 (59)
MSKCC Risk Category‡				
Favourable risk	56 (36)	113 (39)	31 (40)	57 (39)
Intermediate risk	87 (56)	159 (55)	40 (51)	77 (53)
Poor risk	6 (4)	9 (3)	5 (6)	5 (3)
Unknown$	6 (4)	9 (3)	2 (3)	6 (4)
Prior nephrectomy	65 (83)	258 (89)	130 (84)	127 (88)
Co-morbid medical conditions				
Any	96 (62)	174 (60)	45 (58)	87 (60)

Essential hypertension	63 (41)	110 (38)	33 (42)	64 (44)

ECOG = Eastern Co-operative Oncology Group; MSKCC = Memorial Sloan-Kettering Cancer Center.
*Histology at initial diagnosis was missing for one patient in the pazopanib arm
† As defined by the investigator
‡ 108 of the MSKCC risk group assignments required the use of total calcium measurements because of missing baseline albumin levels to calculate corrected calcium
$ Subjects with an unknown MSKCC risk category were missing results for 1 or more of the 5 risk criteria.

Outcomes

5.3.5 **Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).**

Table 5.8: Primary and secondary outcomes measures in VEG105192

Primary outcomes and measures	Reliability/validity/current use in clinical practice

• Progression-free survival (PFS) in overall study population, as assessed by the IRC according to RECIST (Therasse 2000) criteria.
 	
• PFS was defined as the interval between the date of randomisation and the earliest date of radiologically documented disease progression or death due to any cause
 	
RECIST Criteria for evaluation of target lesions*:
• *Complete response (CR)* – Disappearance of all target lesions
• *Partial response (PR)* – At least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD
• *Progressive disease (PD)* – At least a 20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
• *Stable disease (SD)* – Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since treatment started
• *Not evaluable (NE)* – Any subject who cannot be classified by one of the four preceding definitions.
 	
• PFS was also examined in pre-defined sub-groups:
  • Treatment-naive / Cytokine pre-treated
  • ECOG PS 0 / 1
  • Age (<65 years / ≥65 years)
  • Gender
  • MSKCC favourable / intermediate risk category
	To ensure quality assessment of PFS, determination of progression was made centrally for each patient by an Independent Review Committee (IRC), comprising 6 board-certified radiologists, who reviewed all radiological imaging for each subject blinded to their study treatment and the investigator's assessment of their disease status. Two radiologists independently read each subject's set of scans (double-read), with a third acting as an adjudicator if necessary.
	
	Disease progression was determined by the IRC using the internationally recognised and widely used Response Evaluation Criteria In Solid Tumours (RECIST) (Therasse 2000; see left-hand column) following radiological review of the imaging scans. Imaging assessments were performed every 6 weeks until week 24 and every 8 weeks thereafter. The frequency of imaging in the study is similar to that performed routinely in clinical practice (every 6-8 weeks).
	
	Progression dates for the primary analysis were assigned to the visit time point for scheduled visits and not the actual dates of the assessments to protect the result from bias associated with one arm being assessed systematically earlier than the other. If a subject came in early for an assessment and progression was found, the progression date was assigned to the date of the subject's next scheduled visit.
	
	PFS is recognised by oncologists and the regulatory authorities as an important endpoint, a valid measure of clinical benefit and acceptable surrogate for survival in late-stage oncology trials, including RCC (George 2009; Bracarda 2009; EMA 2005). A number of treatments for advanced/metastatic RCC have received regulatory approval on the basis of statistically significant and clinically meaningful improvements in PFS as a primary endpoint. NICE has previously recommended sunitinib (TA 169) for the first-line treatment of advanced/metastatic RCC on the basis of a study in which the primary outcome was PFS.
	
	PFS is not subject to influence of post-study therapy and is therefore particularly acceptable in situations where it is expected that further lines of treatment may hamper the detection of a treatment effect on OS. Nevertheless, treatment effects on disease progression endpoints, especially PFS, have been shown to be predictive of treatment effects on OS in patients with metastatic RCC (Delea 2009).
	
	Sensitivity analyses are now recommended for a rigorous assessment of PFS (EMA 2008; Bhattacharya 2009). A number of sensitivity analyses of PFS were therefore performed in VEG105192 to confirm the robustness of the primary results using various assumptions. This included analyses of PFS conducted using actual scan dates rather than scheduled visit dates and using the investigators' assessments of progression (based on imaging data using RECIST). The investigators were blinded to study treatment and the results (see Section 5.5.1.1) indicate no evidence of systematic bias in estimation of the treatment effect.
	
	The study was designed with sufficient power to detect a treatment effect in the treatment-naive

	and cytokine pre-treated sub-groups.
Secondary outcome measures	**Reliability/validity/current use in clinical practice**
Principal secondary endpoint: • Overall survival in the overall study population – defined as the interval between date of randomisation and date of death due to any cause.	OS is considered the gold standard for measurement of efficacy in phase III RCTs of cancer therapies being a direct measure of clinical benefit that is unambiguously measured (Farley 2010). However, further lines of treatment following discontinuation of study medication can hamper the detection of a relevant treatment effect on OS. In particular, in many trials including VEG105192, for ethical reasons patients randomised to the control arm can cross-over to active treatment following disease progression, potentially diluting the effect of study treatment on OS.
Other secondary endpoints included: • Objective overall response rate (ORR) – defined as the percentage of patients achieving either a confirmed CR or confirmed PR as per RECIST criteria as their best overall response • Rate of CR + PR + 6-months SD – defined as the percentage of patients achieving either a confirmed CR or confirmed PR as per RECIST criteria as their best overall response or those subjects who have SD after 6 months in the study • Time to response – defined as the time from randomisation until the first documented evidence of CR or PR (whichever status was recorded first) • • Duration of response – defined as time from first documented evidence of CR or PR until the first documentation of disease progression or death due to any cause, whichever was first.	ORR is considered to be an appropriate and valid secondary endpoint in the evaluation of some new anti-cancer treatments and/or in some cancers. However, use of ORR in the setting of novel targeted agents can be problematic. There are several reported examples of agents with unexceptional response rates in the phase II setting going on to demonstrate prolongation of PFS or OS in phase III studies suggesting that tumour stabilisation as well as tumour shrinkage can result in clinical benefit (Ratain 2004; Farley 2010). RR is therefore now recognised as not being a particularly good surrogate in RCC as it is not a reliable predictor of OS (Blute 2006). Since targeted agents for RCC have been associated with high rates of tumour stabilisation (Motzer 2007), the rate of CR+PR+6-month SD is a more clinically useful measure. Tumour response evaluations were made using the established Response Evaluation Criteria In Solid Tumours (RECIST) (Therasse 2000; see above). Separate response analyses were performed using the investigator-assessed and IRC data. All response analyses were based on responses confirmed using bone scans 8 weeks after the initial response was noted.
Health outcomes assessments: • EQ-5D (EuroQoL-5D questionnaire) • EORTC-QLQ-C30 (European Oragnaisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3)	At the time of protocol development, there were no validated disease-specific questionnaires or symptom scales for RCC available. Subsequently, the Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI) has become available. The EQ-5D was therefore included in this study as a standardised and validated instrument considered to be relevant in the assessment of HRQoL in subjects with RCC (Cella 2009). It comprises a visual analogue rating scale (VAS; rated 0 to 100) and a 5-item health status measure (Rabin 2001). The EORTC-QLQ-C30 is a self-reporting 30-item cancer specific instrument (Aaronson 1993). Scoring of the QLQ in this study was based on published methods that transformed all scales to scores between 0 and 100 (Fayers 2001). The EORTC QLQ-C30 has been validated in over 60 languages and been shown to have cross-cultural acceptability. The instrument has also been shown to be responsive to change.

Safety assessments:
 	
• Adverse events (AE) – collected and recorded from randomisation until 28 days following discontinuation of study treatment
 	
• Serious adverse events (SAE)
 	
• AEs leading to discontinuations, dose reduction or interruptions
 	
• Clinical laboratory tests including:
  ○ Biochemistry: sodium, potassium, calcium, glucose, blood urea nitrogen, creatinine, AST, ALT, ALP, total bilirubin, total protein
  ○ Haematology: haemoglobulin, hematocrit, RBC count, WBC count, neutrophil count, lymphocyte count, platelets count
 	
• Vital signs
 	
• Physical examination
 	
• 12-Lead ECG
 	
• ECOG PS
	AEs were coded using the MedDRA dictionary and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) (version 3.0), a descriptive terminology that is well accepted and widely used for recording the severity of adverse events. Investigators were responsible for the detection and documentation of events meeting the criteria/definition of an AE and SAE and for judging whether or not they were related to the investigational drug.
	
	Details of adverse events experienced by patients receiving treatment for advanced/metastatic RCC would be recorded routinely in clinical practice.
	
	Laboratory safety data (haematology, biochemistry and coagulation parameters) were graded programmatically according to the NCI CTCAE.
	
	Regular biochemistry and haematology assessments are performed routinely in patients being treated for advanced/metastatic RCC in clinical practice.
	
	Assessment of vital signs and physical examination are routine clinical procedures.
	
	ECOG PS is a reliable, widely accepted and widely used method (5-point scale) of assessing the functional status and ability to self-care of cancer patients (Buccheri 1996).

* At baseline, all lesions were categorised as “Target” or Non-target” lesions. *Target lesions*: All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically) were identified and recorded and measured at baseline. A sum of the longest diameter (LD) of all target lesions was calculated and reported as the baseline sum LD and used as reference by which to assess tumour response. *Non-target lesions*: All other lesions (or sites of disease).
AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; ALP = Alkaline phosphatise; INR = International normalised ratio; RBC = red blood cells; WBC = White blood cells.

Statistical analysis and definition of study groups

5.3.6 **State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).**

Table 5.9: Summary of the statistical analysis and definition of the study groups for VEG105192

Hypothesis objective	The primary objective of this study was to evaluate and compare PFS in patients treated with pazopanib compared with those treated with placebo. The study was designed to provide evidence to support the null hypothesis H_0:λ = 1 or to reject it in favour of the alternative hypothesis H_A: λ <1, where λ is the hazard ratio for the PFS between pazopanib and placebo. Assuming the PFS survival curves were consistent with proportional hazards, the null hypothesis represents equality of the median PFS in the two treatment arms, and the alternative hypothesis represents an increased median PFS in the pazopanib arm.
Sample size, power calculations	Target enrolment and event requirements were defined to provide at least 90% power to detect an 80% improvement (hazard ratio [HR], 0.56) in PFS (primary endpoint) and 90% power to detect a 50% improvement (HR, 0.67) in OS (secondary endpoint). After the amendment to include treatment-naive patients, PFS event requirements were amended to allow sufficient power in each of the treatment-naive and cytokine pre-treated sub-populations. The final requirements provide approximately 80% power to detect an 80% improvement (HR, 0.56) or 90% power to detect a 100% improvement (HR, 0.5) in PFS in each sub-population (i.e. treatment-naive and cytokine pre-treated). There were no planned (or unplanned) interim analyses for PFS. An interim analysis of OS was to be performed at the time of the final PFS analysis. Thus, the sample size calculation for OS included one planned interim analysis (after approximately 70% of the required deaths) using flexible O'Brien-Fleming type error spending functions for superiority and futility. All sample size calculations were performed assuming a one-sided 2.5% α and a 2:1 randomisation. The final requirements included an additional condition that at least 55% of the deaths (160 deaths) be accrued prior to the interim analysis of OS. Based on these requirements, final PFS analysis was planned to be performed after at least 90 PFS events (by IRC) in each sub-population and at least 160 deaths; final analysis of OS was planned to be performed after 287 deaths. The resulting planned enrolment of the study was a total of 400 patients with 150 to 250 patients in each sub-population.
Analysis populations	The intention-to-treat (ITT) population which comprised all randomised patients was used for the analysis of the efficacy data based on assigned randomised treatment. Safety analyses were performed on the basis of actual treatment received in patients who were randomised and received at least one dose of investigational product.
Statistical analysis	Kaplan-Meier methods were used to analyse PFS and OS. Comparisons between arms were made using a stratified log-rank test (one sided) tested at the 2.5% significance level . The three stratification factors (baseline ECOG PS, prior systemic treatment and prior nephrectomy status) were originally to be incorporated according to the analysis plan; however, nephrectomy was not incorporated as the number of subjects without prior nephrectomy was too small. Hazard ratios were calculated using a stratified Pike estimator (Berry 1991) together with 95% Confidence Intervals (CIs). The primary analysis of PFS was based on IRC assessments. Nine pre-defined sensitivity analyses of PFS in the total study population were performed to confirm the robustness of the primary result using various assumptions, including alternate definitions of progression and censoring dates, data sources (IRC vs. Investigator) and analysis methods. Sensitivty analyses based on determination of progression using scan dates and investigators' assessment of progression were conducted for the treatment-naive sub-population. Response rates were compared between treatment arms using a Fisher's exact test (two-sided) tested at the 5% significance level. Approximate 95% CIs for the difference in RRs were calculated. Duration of response and time to response were summarised descriptively using medians and quartiles.

	The health outcomes endpoint was change from baseline in HRQoL based on blinded patient self-reported scores collected using the EORTC QLQ-C30 and EQ-5D questionnaires. The analyses for EORTC-QLQ-C30 were focussed on the Global Health Status/QoL score and the analyses for the EQ-5D were focussed on the EQ-5D Index and EQ-5D Visual Analogue Scale (VAS). A mixed-model repeated-measures (MMRM) analysis was used. The minimal important differences (MID) for these questionnaires were previously established as 5 to 10 for EORTC QLQ-C30 (Osoba 1998), 0.08 for the EQ-5D Index and 7 for the EQ-5D VAS (Pickard 2007).
	An Independent Data Monitoring Committee (IDMC) was established to review accumulating safety and efficacy (survival) data and to provide an opportunity to terminate the study early if: • there were concerns regarding safety • there was strong evidence of superior survival for pazopanib • there was strong evidence that pazopanib will fail to show superiority in OS if the study was allowed to run to its planned completion. The initial IDMC review for efficacy occurred at the time of the time of the interim OS analysis and final PFS analysis. One-sided p-values were compared to the O'Brien-Fleming error spending boundaries in order to determine superiority or futility. Given 61% of the required OS events had accrued at the time of the interim analysis, the boundaries for the interim analysis of OS were as follows: stop for efficacy if one-sided p≤0.004 and stop for futility if one-sided p>0.201.
Data management, patient withdrawals	Patients were treated until disease progression or withdrawal from study due to unacceptable toxicity. Patients could also withdraw for other reasons prior to disease progression or unacceptable toxicity. All subjects who withdrew were included in analyses up to the time of withdrawal, regardless of the duration of treatment. As the period of treatment for any patient was dependent on its efficacy and toxicity, the duration of follow-up could vary between patients. Consequently, there was no imputation for missing data. Where appropriate, available data was summarised over specified intervals (e.g. from randomisation until withdrawal from the study) using suitable summary statistics. For the PFS endpoint, the date associated with the last visit with adequate assessment was used for those patients who are alive and have not progressed at the time of analysis; such patients were censored in the analysis. If a progression event occurred after an extensive lost-to-follow-up time (≥12 weeks) the primary analysis censored those patients at the date of their last visit with an adequate assessment.

5.3.6.1 Statistical methodology for dealing with effect of cross-over

The ability to detect an effect of study treatment on overall survival (OS) may be influenced by subsequent anti-cancer therapies received by subjects after discontinuation of study medication, particularly cross-over from control to active treatment. At the time of the clinical cut-off, 31 (40%) of 78[1] placebo-treated patients in the first-line sub-population had crossed over to receive pazopanib and thus the true effect of pazopanib treatment is likely to be underestimated in the ITT analysis. There is no universally accepted statistical methodology to adjust for the confounding effects of cross-over in survival analysis and this is an area of genuine academic debate. Several approaches were therefore considered to evaluate the impact of this effect on the interim OS data in VEG105192:

(i) Kaplan-Meier analysis censoring cross-over patients at time of cross-over

This is an analysis where any subject who crossed over is censored at the date of cross-over. For all other subjects, OS is measured from time of randomisation to death or last contact. This analysis is limited by the fact that subjects could have died soon after cross-over. Also, only those patients who progressed crossed over, so their health status is likely to be worse than subjects at a comparable level of follow-up who did not progress. Hence, the analysis is effectively estimating what would happen to these subjects if they continued on placebo together with patients who may be healthier than them. Additionally, it does not account for the time that those

[1] It should be noted that 33 patients randomised to placebo crossed-over to pazopanib treatment in total. However, 2 of these patients have a last contact date within 1 week of their crossover date. There is no impact of crossover expected for these subjects and they have therefore not been treated as cross-over subjects in the analyses conducted to adjust for crossover.

patients who crossed over spent on pazopanib. It has previously been acknowledged that censoring subjects at cross-over can be an unreliable method for controlling for cross-over (NICE TA 179).

(ii) Cox regression analysis considering cross-over as time-dependent covariate

In this analysis, patients are modelled in one of two states over time: the first state represents the placebo arm to which the patient was randomised; the second state represents cross-over to pazopanib. The model reflects the time at which the patient changed from placebo to pazopanib treatment. The hazard up to the time point of cross-over for patients in the placebo arm is due to placebo therapy; the hazard from the time the patient crossed over to the pazopanib arm is due to pazopanib therapy. This approach controls for the breaking of randomisation attributable to cross-over and accounts for both time on placebo as well as time on pazopanib but can often bias the result against active treatment.

Two further statistical approaches have been used recently to control for cross-over in analyses of OS in RCTs: inverse probability of censoring weighted (IPCW) analysis and Rank Preserving Structural Failure Time (RPSFT) analysis. Both methods are more sophisticated than simply censoring on cross-over and aim to produce the results that would havebeen obtained had placebo patients not crossed over. The RPSFT method was used to analyse OS in a sunitinib trial in gastrointestinal stromal tumours (GIST) in which a high proportion of patients crossed over from placebo to active treatment (NICE TA 179). Both methods have been used to estimate the effects of everolimus on OS among metastatic RCC patients who had failed VEGF/TKI therapy (NICE TA 198; Wiederkehr 2009; Korhonen 2009). Full technical details regarding the application of these methods to the interim OS data from the treatment-naive sub-population in the VEG105192 trial can be found in Appendix 9.14 and are summarised below.

The analyses were conducted in consultation with experts in the conduct of these methods including Dr. James Robins, Department of Epidemiology and Department of Biostatistics, Harvard School of Public Health. Dr. Robins is a leader in the development of analytic methods for drawing causal inferences from complex observational and randomised studies with time-varying exposures or treatments, including RPSFT and IPCW. The analyses were also reviewed by Ian White, an independent statistician from the MRC Biostatistics Unit, University of Cambridge, who has published on this method (White 2005). Both the IPCW and RPSFT analyses were double-coded by independent analysts at different institutions to ensure the validity of the results.

(iii) Inverse probability of censoring weighted (IPCW) analysis

This method aims to adjust for cross-over by recreating the population that would have been evaluated if cross-over had not occurred. Subjects who do not cross-over get a greater weighting in order to correct for the resulting bias. The IPCW analysis consisted of three steps as follows:

1. *Create Panel Data*: For placebo patients who progressed, follow-up time from disease progression until cross-over or end of follow-up (defined as death, withdrawal of consent, or end of study, whichever occurred first) was partitioned into intervals based on visits dates[2]. For each of these intervals,

[2] In VEG105192 trial, visits were scheduled at 3-week intervals from Day 1 to Week 24 and then 4-week intervals from Week 24 to treatment discontinuation.

time-dependent variables that might be predictive of cross-over and mortality (e.g. ECOG performance status, occurrence of grade 3/4 adverse events (AEs), and number of weeks since disease progression) were calculated.

2. *Calculated Stabilised Weights*: Using the panel data created in the Step 1, for each placebo patient (i) and interval (j), stabilised weights, $SW_i(j)$, were estimated. The denominator of the weights is the probability of remaining uncensored (i.e. not crossing over to pazopanib) to the end of interval (j) given baseline and time-dependent confounders. The numerator of the weights is the probability of remaining uncensored (i.e. not crossing over to placebo) to the end of interval (j) given only baseline confounders. Estimates were obtained by fitting pooled logistic models with censoring (cross-over) as the dependent variable.

3. *Run IPCW Cox Regression*: A hazard ratio (HR) for OS was estimated using a weighted Cox proportional hazard regression model, where patient intervals were weighted by the stabilised weights calculated in Step 2. For all patients who were randomised to pazopanib, the weight was equal to 1.0 (i.e. $SW_i(j) =1$). Placebo patients who crossed over were censored (i.e. for placebo patients who crossed over were censored (i.e. for placebo patients who crossed-over, intervals after cross-over had a weight of zero and were therefore dropped from the model).

Each of these steps is described in greater detail in Appendix 9.14. It has previously been acknowledged that IPCW can be a valid option to correct for cross-over bias (NICE Pre-briefing meeting for everolimus, Dec 2009); however, it is subject to the assumption of no unmeasured confounders. In addition, the results of our IPCW analysis (see Section 5.5.1.2.2) are limited by the lack of information on time-varying clinical and other factors that might be predictive of cross-over and OS.

(iv) Rank preserved structural failure time (RPSFT) analysis

The RPSFT method estimates the difference in OS between treatment groups as if placebo patients had not crossed-over to pazopanib treatment (i.e. had remained on placebo for the duration of the trial). It proportionally 'shrinks' the estimated amount of additional survival conferred to subjects who crossed over. The technique is based on an accelerated time failure (AFT) model which uses a structural assumption of time proportionality (instead of a proportional hazards assumption as in the Cox model). Since the RPSFT method is based on an intention-to-treat population, it avoids the potential pitfalls and biases that may be introduced by methods that adjust for post-randomisation time-dependent covariates. The method maintains the original randomised group definitions and thus preserves the validity of between-group comparisons and therefore is said to produce "randomisation-based effect estimators" (Branson 2002).

The RPSFT approached employed in our analysis consisted of the following steps:

1. An estimate of the effect of exposure to the active treatment on survival time, ψ^*, was obtained, where our estimate of ψ^* is the value of ψ that results in equivalence of OS for the two treatment arms (see Appendix 9.14 for further methodological details).

2. The HR for OS for randomisation to pazopanib vs. randomisation to placebo with no cross-over to pazopanib was estimated by fitting a Cox proportional hazards

regression model to the pazopanib failure times as observed in the VEG105192 trial and re-censored adjusted failure times for placebo patients based on the estimate of $\exp(\psi^*)$.

The Evidence Review Groups (ERGs) involved in the everolimus RCC and sunitinib GIST appraisals (NICE TA 179; Everolimus ACD, Feb 2010) concluded that RPSFT represents a methodically robust approach to adjust for cross-over because:

(i) it is based on a comparison between treatment groups as randomised (Branson 2002) and

(ii) it does not make the assumption of no unmeasured confounders in the placebo arm (i.e. assumes that all key characteristics have been included in the analysis).

The RPSFT method does, however, have some limitations when applied to immature data due to the level of re-censoring in the placebo group required to ensure an unbiased estimate of ψ^*.

Certain baseline patient characteristics and clinical features can influence survival outcomes in RCC. The MSKCC scoring system is a widely accepted and validated predictive tool for survival in RCC (Motzer 1999). This categorises patients into 3 risk groups (favourable, intermediate and poor) based on five factors, including performance status and presence/absence of prior nephrectomy. Disease stage at diagnosis and time from initial diagnosis are also strong independent predictors of outcome in RCC (Furniss 2008; Elson 1988). As well as the presence of advanced/metastatic disease, the number and site of metastases have also been shown to have some prognostic significance (Furniss 2008; Elson 1988).

In order to control for such factors and isolate the pure treatment effect on OS, the cross-over analyses described above were all conducted as multivariate analyses adjusting for the following factors, selected on the basis of clinical opinion and the availability of data in VEG105192:

- age (continuous variable)
- gender (female / male)
- MSKCC risk score (intermediate-poor / favourable)
- time since diagnosis (<1 year / ≥ 1 year)
- stage of disease at initial diagnosis (stage I or II / stage III or IV)
- number of metastatic sites (continuous variable)
- presence of liver metastases (yes / no).

In the case of the IPCW analysis, this adjustment is an integral part of step 3 of the analysis while in the RPSFT analysis it is not essential as randomisation is preserved. These characteristics were generally well balanced between the treatment groups at baseline, with only a few minor imbalances (see Table 5.7).

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

The following pre-specified sub-groups were explored in the analysis of some efficacy and safety data for the total study population:

- Prior systemic therapy for advanced/metastatic RCC: No prior systemic therapy / one prior cytokine-based systemic treatment

- Baseline ECOG PS: 0 / 1
- Age: <65 years / ≥65 years
- Gender: male / female
- MSKCC risk groups: favourable / intermediate

An analysis by race sub-groups was planned but there were insufficient subjects in these sub-groups for the analysis to be meaningful. Similarly, an analysis of the MSKCC poor risk sub-group was planned but there were insufficient subjects to make this statistically meaningful. Comparison of PFS and OS between treatment arms based on the above sub-groups was done using the stratified log-rank test and hazard ratios calculated using a stratified Pike estimator.

It should be noted that sub-group analyses (e.g. by ECOG PS) were not conducted for the treatment-naive or cytokine pre-treated subpopulations, other than adjustments being made for baseline covariates or by stratification, as the resulting sub-groups were too small to allow for interpretable results.

Participant flow

5.3.8 **Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

Of the 435 patients with advanced and/or metastatic RCC (233 treatment naive; 202 cytokine pre-treated); 290 patients were randomly assigned to pazopanib and 145 to placebo. At the cut-off date (23 May 2008), 78% of patients in the pazopanib arm and 90% of patients in the placebo arm had discontinued study treatment. Disease progression was the most common reason for death and discontinuation (Figure 5.2).

Figure 5.2: CONSORT diagram (VEG105192, Total study population)

AE, adverse event; PFS, progression-free survival. * This does not include three patients who in addition to AEs, had concurrent other reasons at the time they discontinued participation in the study.

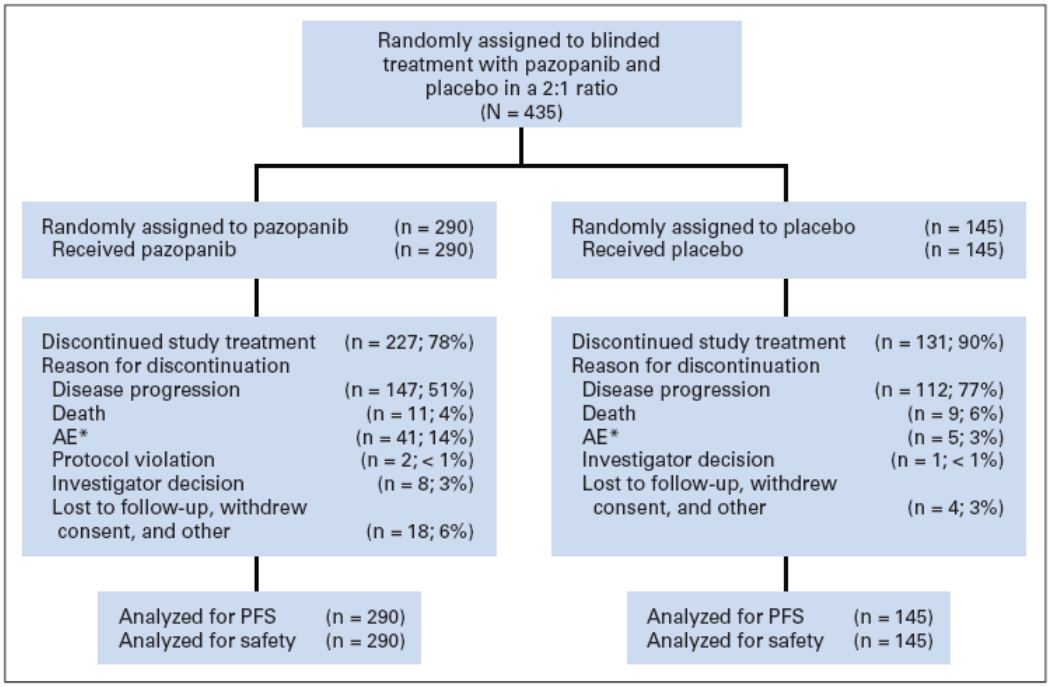


Table 5.10: Summary of subject disposition (VEG105192, ITT treatment-naive population, 23 May 2008 cut-off)

	Pazopanib N=155 n (%)	Placebo N=78 n (%)
Subjects		
Died	57 (37)	33 (42)
Ongoing	85 (55)	41 (53)
Still on study treatment	38 (25)	10 (13)
Off study treatment, in follow-up	47 (30)	31 (40)
Early termination from study	13 (8)	4 (5)
Primary reason for early termination from study		
Lost to follow-up	7 (5)	2 (3)
Subject withdrew consent	6 (4)	1 (1)
Other	0	1 (1)
Reasons for discontinuation	**N=117**	**N=68**
Disease progression	75 (48)	56 (72)
Adverse event	17 (11)	4 (5)
Subject decided to withdraw from study	7 (5)	1 (1)
Death	6 (4)	6 (8)
Investigator decision	5 (3)	0
Other	4 (3)	0
Lost to follow-up	2 (1)	1 (1)
Protocol violation	1 (<1)	0

5.4 Critical appraisal of relevant RCTs

5.4.1 **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be**

used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG.

The quality assessment of VEG105192 has been undertaken using the descriptive criteria recommended by NICE in their guidance to manufacturers on Single Technology Appraisals (STA).

Table 5.11: Critical appraisal of VEG105192

Critical appraisal criterion	Assessment
Was randomisation carried out appropriately	Yes. Eligible subjects were first registered into the GSK interactive voice response system (IVRS) called RAMOS (Registration And Medication Ordering System). Registered subjects were assigned a unique subject number. Subject number and the following baseline subject information for stratification: • ECOG PS (0 or 1) • Prior nephrectomy (yes or no) • Prior systemic therapy for advanced/ metastatic RCC (treatment naive or cytokine pre-treated) were entered into the system to obtain the blinded treatment assignment. Subjects in each stratum were then centrally randomised in a 2:1 ratio to receive pazopanib or placebo according to a randomisation schedule computer-generated by the GSK Biomedical data Sciences Department.
Was the concealment of treatment allocation adequate?	Yes. Adequate blinding was achieved by using matching placebo tablets. Additionally, disease assessments were conducted by independent reviewers who reviewed all radiological imaging data blinded to subjects' treatment assignment.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. Treatment groups were well balanced at baseline in terms of demographic and disease characteristics (age, gender, histology, organs involved, number of metastatic sites, ECOG performance status and MSKCC risk category).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. Treatment assignment remained blinded to investigators and study staff throughout the study treatment period or until objective evidence of disease progression. Subjects who progressed were unblinded by investigators via an independent unblinding system run by a CRO, allowing GSK study personnel to remain blinded to subjects' treatment assignments until after the clinical database had been locked.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Reasons for withdrawal of patients were reported adequately. Patients mainly withdrew due to the following reasons: disease progression; death; adverse events; lost to follow-up; protocol violation; patient or investigator's decision; or other reasons.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. The authors reported all the outcomes as specified in the protocol of the study.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. An ITT analysis was used for the analysis of efficacy endpoints and appropriate methods were used to account for missing data.

In addition to above qualitative assessment, study quality was also graded according to two scales. The first assesses the adequacy of concealment of allocation and is graded A (adequate) to D (not used). The second is the Jadad score, which assesses study quality and study reporting and scores one point for each positive answer to 5 questions (Jadad 1996). Further details of these scales can be found in the full Systematic Review report. VEG105192 was awarded an allocation grade of A and a Jadad score of 5.

5.4.2 **Please provide as an appendix a complete quality assessment for each RCT.**

Quality assessment for the 12 other (i.e. non-pazopanib) RCTs identified by the Systematic Review can be found in section 9.3 (Appendix 3 to the main submission) and in Appendix E of the Systematic Review report provided with this submission. These studies were assessed qualitatively using the assessment criteria recommended in NICE's guidance to manufacturers on Single Technology Appraisals and by means of a Jadad score and allocation grade.

5.4.3 **If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.**

See response to the above question.

5.5 Results of the relevant RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses. The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

5.5.1.1 Primary efficacy endpoint

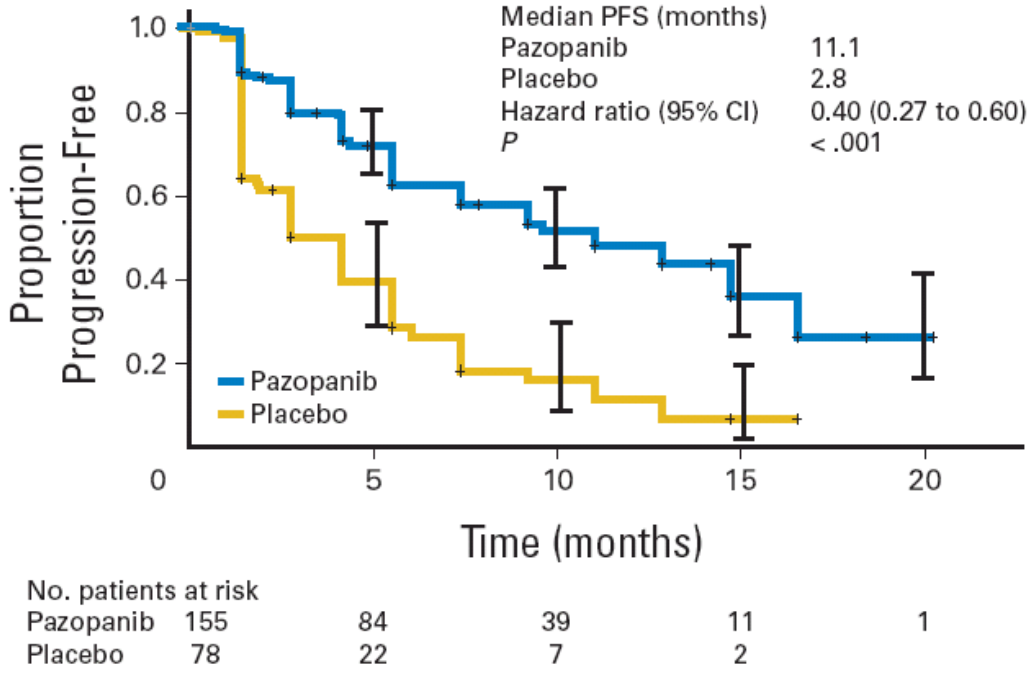
The primary endpoint of the study was PFS in the overall study population based on blinded imaging assessment by the IRC. The study was also adequately powered to detect a clinically meaningful improvement in PFS in the pazopanib arm compared to the placebo arm in each of the treatment-naive and cytokine pre-treated sub-groups. Pazopanib significantly prolonged PFS compared with placebo in the overall study population (median PFS 9.2 vs. 4.2 months; HR 0.46 [95% CI: 0.34-0.62]; p<0.0001) and in the treatment-naive sub-population (median PFS 11.1 vs. 2.8 months; HR 0.40 [95% CI: 0.27-0.60]; p<0.0001) by IRC assessment (Table 5.12, Figure 5.3).

Table 5.12: PFS in VEG105192 (IRC assessment, ITT population, 23 May 2008 cut-off)

	Overall study population		Treatment-naive population	
	Pazopanib N=290	**Placebo N=145**	**Pazopanib N=155**	**Placebo N=78**
Subjects progressed or died, n (%)	148 (51)	98 (68)	73 (47)	57 (73)
Kaplan-Meier estimates for PFS, median (months)	9.2	4.2	11.1	2.8
95% CI	7.4-12.9	2.8-4.2	7.4-14.8	1.9-5.6
Hazard ratio* (95% CI)	0.46 (0.34-0.62)		0.40 (0.27-0.60)	
Stratified log-rank p-value	p<0.0000001		p<0.0000001	

* Hazard ratios estimated with a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log-rank test were adjusted in the total population analysis for ECOG status and prior systemic treatment at baseline, and in the treatment-naive population analysis for ECOG status at baseline.

Figure 5.3: Kaplan Meier curve of PFS by IRC (Treatment-naive ITT population, 23 May 2008 cut-off)



Sensitivity analyses of PFS

Sensitivity analyses of PFS performed to confirm the robustness of the primary analysis indicate a statistically significant improvement in PFS with pazopanib compared with placebo. The results of sensitivity analysis 1 based on using actual scan dates to determine dates of censoring and progression are shown in Table 5.13.

Table 5.13: PFS in VEG105192 – Sensitivity Analysis 1 (IRC assessment, ITT population, 23 May 2008 cut-off)

	Overall study population		Treatment-naive population	
	Pazopanib N=290	**Placebo N=145**	**Pazopanib N=155**	**Placebo N=78**
Subjects progressed or died, n (%)	148 (51)	98 (68)	73 (47)	57 (73)
Kaplan-Meier estimates for PFS, median (months)	9.3	3.0	10.8	2.9
95% CI	7.3-13.0	2.7-4.2	7.4-14.8	1.9-5.4
Hazard ratio* (95% CI)	0.42 (0.31-0.57)		0.36 (0.24-0.55)	
Stratified log-rank p-value	p<0.0000001		p<0.0000001	

* Hazard ratios estimated with a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log-rank test were adjusted in the total population analysis for ECOG status and prior systemic treatment at baseline, and in the treatment-naive population analysis for ECOG status at baseline.

Results of the PFS analysis based on investigators' assessments (Sensitivity analysis 3; Table 5.14) were also supportive of the improvement in PFS observed in the primary analysis. The investigators were blinded to study treatment. Despite some differences in evaluation of individual subjects, the comparability of the HRs for the IRC and investigator assessments demonstrates no evidence of systematic bias in the assessment of PFS.

Whilst the medians in the analysis based on investigator assessment are discordant with those by IRC assessment, this may be explained by the smaller size of the treatment-naive sub-population since the HRs and medians in the overall study

population for IRC and investigator-assessed PFS correlate closely. The median point estimate of 7.5 months in the pazopanib arm of the treatment-naive sub-population is very close to the lower limit of the 95% CI (7.2 months to 10.3 months). This is because investigators reported a large number of progression events around 32 weeks (7.4 months) whereas the IRC did not agree with several of the events called by the investigators at this time point and reported more events at later time points.

Table 5.14: PFS in VEG105192 – Sensitivity Analysis 3 (Investigator assessment, ITT population, 23 May 2008 cut-off)

	Overall study population		Treatment-naive population	
	Pazopanib N=290	Placebo N=145	Pazopanib N=155	Placebo N=78
Subjects progressed or died, n (%)	178 (61)	126 (87)	93 (60)	64 (82)
Kaplan-Meier estimates for PFS, median (months)	9.0	3.0	7.5	4.1
95% CI	7.4-10.9	2.8-4.2	7.2-10.3	1.9-5.6
Hazard ratio* (95% CI)	0.44 (0.34-0.57)		0.47 (0.33-0.68)	
Stratified log-rank p-value	p<0.0000001		p=0.0000009	

* Hazard ratios estimated with a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log-rank test were adjusted in the total population analysis for ECOG status and prior systemic treatment at baseline, and in the treatment-naive population analysis for ECOG status at baseline.

Sub-group analyses of PFS

The pre-specified sub-group analyses showed that PFS in the overall study population was improved for patients treated with pazopanib compared with placebo regardless of MSKCC risk category, sex, age, or ECOG PS (HR range: 0.40-0.52; p<0.001 by log-rank test for all). Sub-group analyses of PFS by these characteristics could not be conducted for the treatment-naive sub-population as the resulting sub-groups were too small for interpretable results.

5.5.1.2 Secondary efficacy endpoints

5.5.1.2.1 Interim overall survival – unadjusted analysis

The interim analysis of OS in the overall study population was based on 176 deaths (at 23 May 2008 cut-off), which was 61% of the required 287 death events for the final OS analysis. OS appeared to be prolonged in the pazopanib arm relative to placebo; however, the data are immature and the results did not cross the pre-specified O'Brien-Fleming boundaries for either superiority or futility.

Pazopanib was associated with a 26% reduction in risk of death compared with placebo in the treatment-naive sub-population (HR 0.74 using a stratified Pike estimator; p=0.079). However, there were fewer events and the study was not powered to show an OS advantage in the treatment-naive sub-population, especially at an interim analysis.

Table 5.15: OS in VEG105192 – unadjusted for cross-over (ITT population, 23 May 2008 cut-off)

	Overall study population		Treatment-naive population	
	Pazopanib N=290	Placebo N=145	Pazopanib N=155	Placebo N=78
Subjects died, n (%)	109 (38)	67 (46)	56 (36)	34 (44)
Kaplan-Meier estimates for OS, median (months)	21.1	18.7	19.8	20.0
95% CI	(19.3-NC)	14.6-20.1	15.8-NC	10.5-NC
Hazard ratio* (95% CI)	0.73 (0.53-1.00)		0.74 (0.47-1.15)	
Stratified log-rank p-value†	p=0.020		p=0.079	

NC = Not calculable; * Hazard ratios estimated with a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log-rank test were adjusted in the total population analysis for ECOG status and prior systemic treatment at baseline, and in the treatment-naive population analysis for ECOG status at baseline.

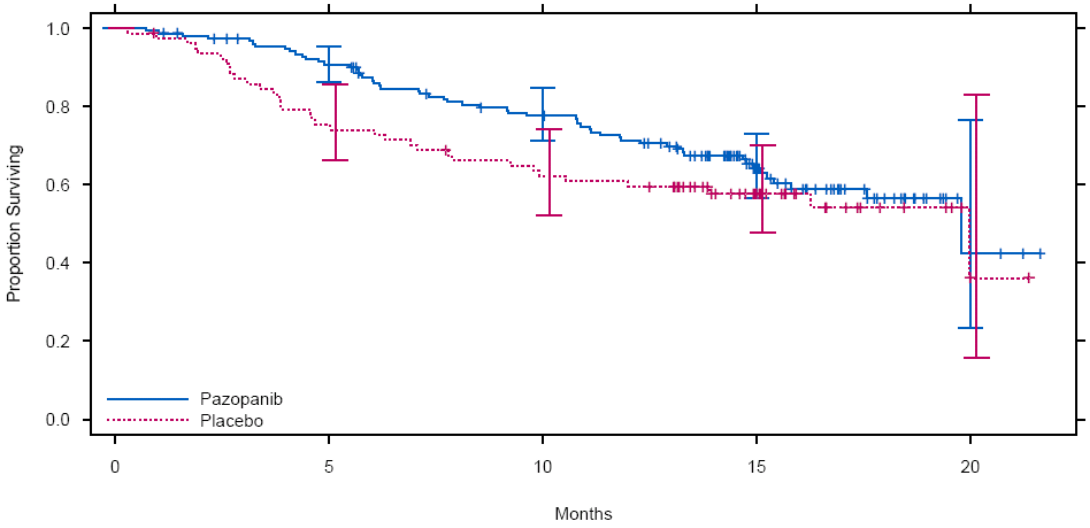
† O'Brien-Fleming boundary for futility / superiority: p>0.201 / p≤0.004.

In a univariate analysis of OS in the treatment-naive subpopulation using a Cox proportional hazards model, the HR for pazopanib vs. placebo was very similar: HR 0.752 (95% CI: 0.491-1.153; p=0.1909).

The Kaplan Meier curve for OS in the treatment-naive population is shown in Figure 5.4. The curves separate early indicating the effect of pazopanib treatment but come back together, most likely due to the accumulating impact of placebo cross-over. Additionally there is a high level of uncertainty in the curves past 1 year of follow-up as denoted by the high level of censoring (each censored subject is denoted by a vertical line through the curve) and large error bars.

The estimate of OS at 1 year for the treatment-naive sub-population was 71.3% (95% CI: 63.2-77.9%) in the pazopanib arm and 59.6% (95% CI: 47.7-69.6%) in the placebo arm.

Figure 5.4: Kaplan Meier curve of overall survival in VEG105192 (Treatment-naive population, 23 May 2008 cut-off)



Covariate analysis of OS

Using a Cox proportional hazards model and controlling for the baseline patient characteristics discussed earlier (age, gender, MSKCC risk score, years since diagnosis of RCC, stage of disease at diagnosis, presence of liver metastases, number of metastatic sites), resulted in an HR for the treatment effect adjusted for these factors of 0.524 indicating a 48% reduction in risk of death for patients treated with pazopanib compared with placebo (Table 5.16).

Table 5.16: OS in VEG105192 – Unadjusted for cross-over but adjusted for baseline characteristics (Treatment-naive ITT population, 23 May 2008 cut-off)

Variable	Treatment-naive population N=233	
	HR (95% CI)	p-value
Pazopanib	0.524 (0.336-0.817)	p=0.0043
Age (Continuous variable)	0.992 (0.972-1.013)	p=0.4571
Gender (Female / Male)	1.601 (1.015- 2.525)	p=0.0431
MSKCC risk score (Intermediate-poor / Favourable)	1.716 (1.043-2.825)	p=0.0337
Years since diagnosis (<1 year / ≥1 year)	2.531 (1.480-4.328)	p=0.0007
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.371 (0.741-2.651)	p=0.3153
Presence of liver metastases (Yes / No)	1.194 (0.705-2.022)	p=0.5090
No. of metastatic sites (Continuous)	1.446 (1.204-1.736)	P<0.0001

For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested.
Patients with missing values for the covariates were assigned the mean value for the trial population. [3]

5.5.1.2.2 Analyses of OS conducted to adjust for impact of cross-over

For treatment-naive subjects in the placebo arm who crossed over, median time from date of randomisation to first dose of pazopanib (in VEG107769) was 7.6 months (range: 2 to 17 months).
Results of the different methodologies employed to adjust for the potential effects of the cross-over are presented overleaf.

(i) Censoring cross-over patients at time of cross-over

Censoring patients at time of cross-over resulted in a significant improvement in OS for patients randomised to pazopanib compared with placebo alone.

a) Kaplan-Meier analysis / Pike estimator

The HR improved from 0.74 unadjusted for cross-over (Table 5.15) to 0.66 (p=0.037) with censoring on cross-over when estimated using a stratified Pike estimator (unadjusted for baseline characteristics with the exception of ECOG PS) (Table 5.17).

Table 5.17: OS in VEG105192 – Subjects censored at cross-over (Treatment-naive population, 23 May 2008 cut-off)

	Overall study population		Treatment-naive population	
	Pazopanib N=290	Placebo N=145	Pazopanib N=155	Placebo N=78
Subjects died, n (%)	109 (38)	46 (32)	56 (36)	26 (33)
Subjects censored, cross-over to pazopanib	1 (<1)	70 (48)	1 (1)	33 (42)
Kaplan-Meier estimates for OS, median (months)	21.1	18.7	19.8	NC
95% CI	19.3-NC	13.9-20.1	15.8-NC	9.8-NC
Hazard ratio* (95% CI)	0.70 (0.48-1.02)		0.66 (0.40-1.10)	
Stratified log-rank p-value	p=0.018		p=0.037†	

NC = Not calculable; * Hazard ratios estimated with a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log-rank test were adjusted in the total population analysis for ECOG status and prior systemic treatment at baseline, and in the treatment-naive population analysis for ECOG status at baseline.
† CI and p-value not adjusted for interim analysis.

b) Cox proportional hazards model

Repeating this censoring approach using a Cox model and adjusting for the same baseline characteristics, resulted in an HR of 0.508 indicating a 49% reduction in risk

[3] Two subjects had unknown stage of disease at initial diagnosis, 8 subjects had unknown Motzer risk category, and 19 subjects had missing dates of initial diagnosis. For these patients, we imputed the sample mean of each categorical variable in order to keep these patients for the survival analysis of pazopanib relative to placebo. The imputation affected a total of 27 subjects (2 subjects had more than one variable with missing information), representing 11.6% of the first-line treatment population.

of death for patients treated with pazopanib compared with placebo (p=0.0062†) (Table 5.18).

Table 5.18: OS in VEG105192 – Subjects censored at cross-over (Treatment-naive population, 23 May 2008 cut-off)

Variable	Treatment-naive population N=233	
	HR (95% CI)	p-value†
Univariate analysis		
Pazopanib	0.683 (0.426-1.093)	p=0.1123
Mutivariate analysis		
Pazopanib	0.508 (0.312-0.825)	p=0.0062
Age (Continuous variable)	0.993 (0.971-1.015)	p=0.5251
Gender (Female / Male)	1.756 (1.088-2.834)	p=0.0212
MSKCC risk score (Intermediate-poor / Favourable)	1.864 (1.084-3.204)	p=0.0244
Years since diagnosis (<1 year / ≥1 year)	2.276 (1.269-4.080)	p=0.0058
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.389 (0.699-2.761)	p=0.3478
Presence of liver metastases (Yes / No)	1.156 (0.669-1.998)	p=0.6027
No. of metastatic sites (Continuous)	1.4401 (1.190-1.742)	p=0.0002

For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested.
Patients with missing values for the covariates were assigned the mean value for the trial population.
† Not adjusted for interim analysis.

(ii) Cox regression analysis with cross-over as time-dependent covariate

Another Cox model with cross-over to pazopanib entered as a time-dependent covariate and including the same baseline covariates showed very similar results (Table 5.19). Again, the adjusted HR (0.517) for the treatment effect demonstrates a survival benefit in favour of pazopanib (p=0.0073†).

Table 5.19: OS in VEG105192 – Including time-dependent cross-over status as covariate (Treatment-naive population, 23 May 2008 cut-off)

Variable	Treatment-naive population N=233	
	HR (95% CI)	p-value†
Univariate analysis		
Pazopanib	0.684 (0.428-1.095)	p=0.1137
Time-dependent crossover (Yes / No)	0.698 (0.302-1.613)	p=0.4008
Mutivariate analysis		
Pazopanib	0.517 (0.319-0.837)	p=0.0073
Age (Continuous variable)	0.992 (0.972-1.013)	p=0.4529
Gender (Female / Male)	1.607 (1.016-2.542)	p=0.0428
MSKCC risk score (Intermediate-poor / Favourable)	1.714 (1.041-2.823)	p=0.0343
Years since diagnosis (<1 year / ≥1 year)	2.523 (1.471-4.325)	p=0.0008
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.366 (0.736-2.533)	p=0.3228
Presence of liver metastases (Yes / No)	1.195 (0.706-2.023)	p=0.5080
No. of metastatic sites (Continuous)	1.443 (1.200-1.735)	p<0.0001
Time-dependent crossover (Yes / No)	0.940 (0.396-2.235)	p=0.8890

For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested.
Patients with missing values for the covariates were assigned the mean value for the trial population.
† Not adjusted for interim analysis.

(iii) Inverse probability of censoring weighted (IPCW) analysis

Results of the IPCW Cox model to adjust for the effect of cross-over with the inclusion of baseline factors are shown in Table 5.20. The results are consistent with the previous approaches. The adjusted HR of 0.450 indicates a 55% reduction in risk of mortality associated with pazopanib compared to placebo (p=0.0009†). A similar result was achieved without imputation of missing data (HR 0.424 [%% CI: 0.257-0.699).

Table 5.20: Summary of IPCW adjusted Cox proportional hazards model for OS in VEG105192 (Treatment-naive population, 23 May 2008 cut-off)

Variable	Treatment-naive population N=233	
	HR (95% CI)	p-value†
Pazopanib	0.450 (0.280-0.721)	p=0.0009
Age (Continuous variable)	0.995 (0.974-1.018)	p=0.6831
Gender (Female / Male)	1.774 (1.106-2.846)	p=0.0175
MSKCC risk score (Intermediate-poor / Favourable)	1.770 (1.047-2.992)	p=0.0331
Years since diagnosis (<1 year / ≥1 year)	2.223 (1.263-3.915)	p=0.0056
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.333 (0.686-2.590)	p=0.3957
Presence of liver metastases (Yes / No)	1.094 (0.640-1.871)	p=0.7420
No. of metastatic sites (Continuous)	1.456 (1.208-1.755)	p<0.0001

For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested.
Patients with missing values for the covariates were assigned the mean value for the trial population.
† Not adjusted for interim analysis.

As mentioned earlier, these results are limited by the lack of information on time-varying clinical and other factors that might be predictive of cross-over and OS. In particular, ECOG performance status, history of grade 3/4/5 AEs and ongoing grade 3/4/5 AEs up to time of progression, and time since progression and time since progression squared were the only characteristics available as time-dependent covariates. Data on presence of liver metastases, and number of metastatic disease sites were not available after disease progression and therefore could not be used in estimation of the denominator for the stabilised weights. The extent to which this may have biased our findings in unknown.

(iv) Rank preserved structural failure time (RPSFT) analysis

Two separate RPSFT analyses were performed (Table 5.21). In the first there were no adjustments for baseline patient characteristics. In the second, adjustments were made for the same characteristics as in the other analyses as well as the patient theoretical maximum follow-up time (C_i), as defined by time from patient's randomisation date to the cut-off date (23 May 2008).

Table 5.21: Summary of RPSFT analysis for OS in VEG105192 (ITT treatment-naive population, 23 May 2008 cut-off)

Variable	Treatment-naive population N=233
	HR (95% CI)†
Not adjusted for patient characteristics	
Pazopanib	0.345 (0.086-1.276)
Adjusted for patient characteristics*	
Pazopanib	0.206 (0.054-0.593)
Ci	1.000 (0.995-1.004)
Age (Continuous variable)	0.991 (0.963-1.017
Gender (Female / Male)	1.512 (0.845-2.842
MSKCC risk score (Intermediate-poor / Favourable)	1.332 (0.755-2.507
Years since diagnosis (<1 year / ≥1 year)	2.757 (1.452-6.148)
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.309 (0.577-3.552)
Presence of liver metastases (Yes / No)	1.081 (0.563-2.173)
No. of metastatic sites (Continuous)	1.600 (1.272-2.046)

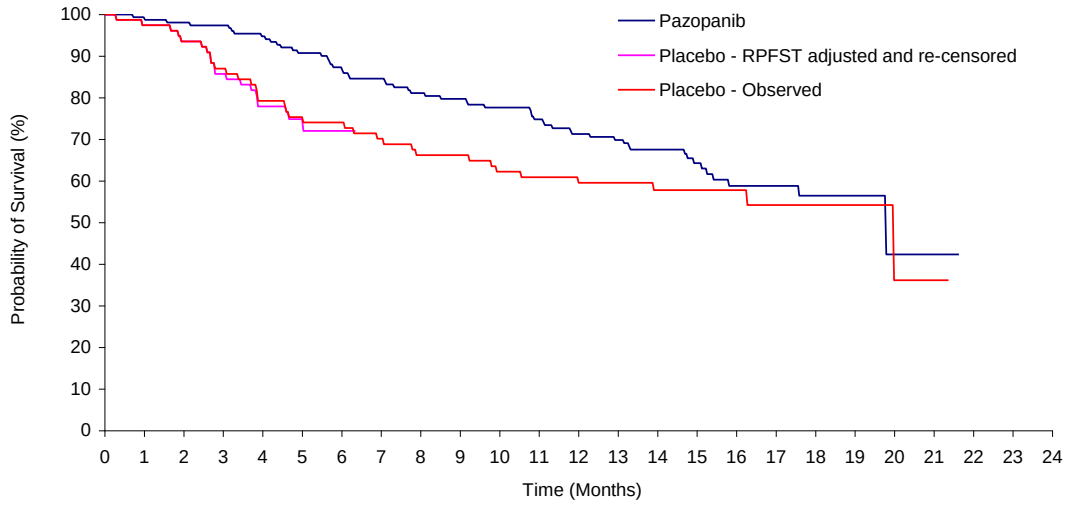
For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested.
* Patients with missing values for the covariates were assigned the mean value for the trial population.
† P-values are inappropriate in this analysis.

Again, the HRs adjusted for cross-over (0.345 and 0.206) indicate that pazopanib reduced the risk of mortality compared with placebo. The 95% CIs for the RPSFT-derived HRs are wide since the method is based on randomisation and does not change the level of evidence around the null hypothesis.

Additionally, the results are limited by the re-censoring of placebo patients required by this method. The analysis is therefore is therefore heavily weighted toward the early follow-up period (approximately 200 days in the multivariate analysis) which may not be representative of treatment effects over the entire un-recensored follow-up period. This method may have greater utility when updated survival data become available as an additional 2 years of follow-up will be available and the results may be less affected by re-censoring.

The Kaplan-Meier plot of the observed failure times for active treatment in patients and adjusted re-censored failure times for placebo patients is shown in Figure 5.5 (unadjusted for baseline characteristics). The early separation of the curves reflects the earlier event times in the placebo arm when adjusted for the cross-over. The truncated placebo survival curve reflects the re-censoring that occurred in this analysis.

Figure 5.5: Kaplan-Meier plot of the observed failure times (months) for pazopanib patients and observed and RPSFT adjusted and re-censored survival times for the placebo patients based on univariate RPSFT model (Treatment-naive population)



No. at risk									
Pazopanib	155	146	127	114	101	51	19	2	0
Placebo									
Observed	78	67	57	50	45	25	7	1	0
Adjusted	78	66	2	0	0	0	0	0	0

5.5.1.2.3 Summary of OS analyses

The results of the OS analyses for treatment-naive patients in VEG105192 are summarised in Table 5.22.

Pazopanib was associated with a 26% reduction in risk of death relative to placebo in the pre-specified ITT analysis (HR 0.74 [95% CI: 0.47-1.15]; p=0.0079, estimated by a stratified Pike estimator). Since 40% of patients in the placebo arm crossed over to receive pazopanib after disease progression, the ITT analysis does not represent a meaningful comparison of treatment effect on OS.

The baseline patient characteristics (age, gender, MSKCC risk score, years since diagnosis of RCC, stage of disease at diagnosis, presence of liver metastases, number of metastatic sites) were identified as having a significant impact on OS (HR

of 0.524 when adjusted for these characteristics vs. 0.752 with no adjustment, estimated using a Cox proportional hazards model).

The optimal method to adjust for the confounding effect of cross-over in survival analysis in RCTs remains an area of academic debate and all approaches have their strengths and limitations. Several methods were therefore utilised for the purposes of this submission in order to provide a comprehensive and balanced approach.

The results of these analyses consistently demonstrate that the cross-over does attenuate the OS benefit attributable to pazopanib in the ITT analysis as evidenced by the downward shift in HRs (i.e. they are numerically lower than the unadjusted HR). In all the analyses, pazopanib was associated with a clinically relevant reduction in risk of death compared with placebo (adjusted HRs for OS for pazopanib vs. placebo ranging from 0.206 to 0.684, depending on methodology and whether adjusted for baseline patient characteristics, Table 5.22).

The univariate HR of 0.345 (95% CI: 0.086-1.276) for OS for pazopanib vs. placebo using the RPSFT method has been chosen for use as the base case in the indirect comparison and in the economic evaluation. This was based on expert advice and is in line with a recent NICE appraisal in which RPSFT was acknowledged as being a more methodologically robust than IPCW since randomisation is preserved and it does not make the assumption of no unmeasured confounders (Everolimus ACD, Feb 2010). RPSFT does, however, have some limitations when applied to immature data due to the degree of re-censoring required. It is likely that re-censoring will be less of an issue when this technique is applied to the updated VEG105192 OS data.

Table 5.22: Summary of interim OS results for treatment-naive population in VEG105192 (23 May 2008 cut-off)

Method for adjusting for cross-over	Adjusted for baseline patient characteristics	Log rank/ Pike estimator HR (95% CI) p-value	Cox proportional hazards model HR (95% CI) p-value†
None	None	0.74 (0.47- 1.15)* p=0.079	0.752 (0.491-1.153) p=0.1909
	Age, gender, MSKCC risk score, years since diagnosis of RCC, stage of disease at diagnosis, presence of liver metastases, number of metastatic sites		0.524 (0.336-0.817) p=0.0043
Censoring on cross-over	None	0.66 (0.40-1.10)* p=0.037†	0.683 (0.426-1.093) p=0.1123
	Age, gender, MSKCC risk score, years since diagnosis of RCC, stage of disease at diagnosis, presence of liver metastases, number of metastatic sites		0.508 (0.312-0.825) p=0.0062
Cross-over as a time dependent covariate	None		0.684 (0.428-1.095) p=0.1137
	Age, gender, MSKCC risk score, years since diagnosis of RCC, stage of disease at diagnosis, presence of liver metastases, number of metastatic sites, crossover		0.517 (0.319-0.837) p=0.0073
IPCW	Age, gender, MSKCC risk score, years since diagnosis of RCC, stage of disease at diagnosis, presence of liver metastases, number of metastatic sites		0.450 (0.280-0.721) p=0.0009
RPSFT‡	None		0.345 (0.086-1.276)

	Age, gender, MSKCC risk score, years since diagnosis of RCC, stage of disease at diagnosis, presence of liver metastases, number of metastatic sites, maximum potential censoring time		0.206 (0.054-0.593

Patients with missing values for the covariates were assigned the mean for the trial population.
*Not adjusted for baseline characteristics except stratification on baseline ECOG PS
† Not adjusted for interim analysis; ‡ p-values not appropriate in this analysis.

5.5.1.2.4 Response analyses

The overall response rate by independent review in the treatment-naive sub-population was significantly higher for patients who received placebo compared with those who received placebo (32% vs. 4%). The results based on investigator-assessed best confirmed response were similar (Table 5.23). The rate of CR, PR or 6-months SD was also significantly higher in the pazopanib compared with the placebo arm (Table 5.24).

Table 5.23: Best confirmed response per RECIST in VEG105192 treatment-naive population using Method A (ITT population, 23 May 2008 cut-off)

	Independent review		Investigator-assessed	
	Pazopanib N=155	**Placebo N=78**	**Pazopanib N=155**	**Placebo N=78**
Best response, n (%)				
Complete response	0	0	0	2 (1)
Partial response	49 (32)	3 (4)	5 (6)	58 (37)
Stable disease*	56 (36)	31 (40)	34 (44)	55 (35)
Progressive disease	28 (18)	31 (40)	33 (42)	29 (19)
Unknown†	22 (14)	13 (17)	6 (8)	11 (7)
Overall response rate (CR+PR), n (%)	49 (32)	3 (4)	60 (39)	5 (6)
95% CI (%)	24.3-38.9		31.0-46.4	1.0-11.8
p-value	p<0.001		p<0.001	

* In order to qualify as best response of SD, a response of SD had to be observed for a minimum of 12 weeks.
† A subjects was classified as unknown if they never had progressive disease, or did not have SD for long enough to be classified as SD. This includes subjects with no follow-up and some subjects censored by independent review, where the investigator called disease progression.

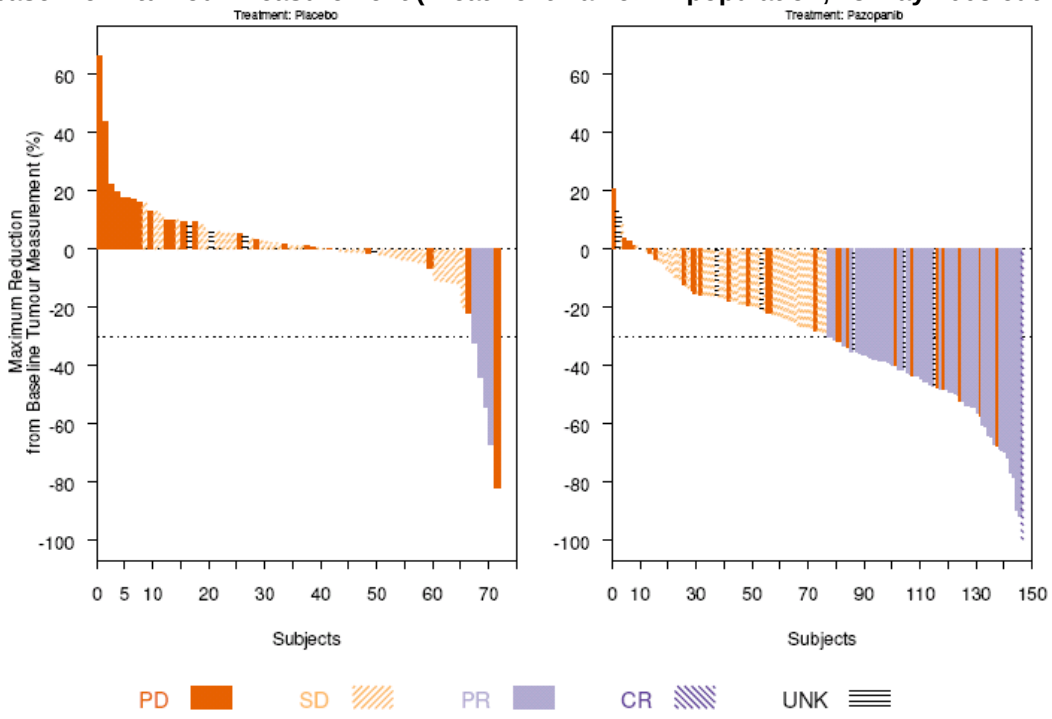
Table 5.24: Rate of CR+PR+6-months SD per RECIST in VEG105192 treatment-naive population (ITT population, 23 May 2008 cut-off)

	Independently-evaluated		Investigator-assessed	
	Pazopanib N=155	**Placebo N=78**	**Pazopanib N=155**	**Placebo N=78**
Best response, n (%)				
Complete response	0	0	2 (1)	0
Partial response	49 (32)	3 (4)	58 (37)	5 (6)
6-months stable disease*	27 (17)	6 (8)	23 (15)	14 (18)
Progressive disease	45 (29)	49 (63)	55 (35)	51 (65)
Unknown	34 (22)	20 (26)	17 (11)	8 (10)
Rate of CR+PR+6-months SD, n (%)	76 (49)	9 (12)	83 (54)	19 (24)
95% CI (%)	4.4-18.6	41.2-56.9	45.7-61.4	14.8-33.9
p-value	p<0.001		p<0.001	

* This table summarises patients by their best response, so subjects with a best response of CR or PR would not be counted as subjects with 6-months SD

The waterfall plot (Figure 5.6) displaying the maximum percentage reduction in tumour measurement indicates the improved target lesion shrinkage with pazopanib compared with placebo.

Figure 5.6: Independently-assessed per cent change at maximum reduction from baseline in tumour measurement (Treatment-naive ITT population, 23 May 2008 cut-off)



In treatment-naive patients, the median time to a CR or PR with pazopanib treatment was 11.6 weeks by IRC and investigator-assessment. For treatment-naive patients who responded to treatment, the median duration of response was 58.7 weeks by IRC and 67.7 weeks by investigator assessment.

Table 5.25: Summary of time to and duration of response* per RECIST in VEG105192 treatment-naive population (ITT population, 23 May 2008 cut-off)

	Independently-evaluated		Investigator-assessed	
	Pazopanib N=155	**Placebo N=78**	**Pazopanib N=155**	**Placebo N=78**
Number subjects*, n (%)	49 (32)	3 (4)	60	5
Time to response (weeks)† Median (95% CI)	11.6 (6.4-12.3)	23.6 (18.1-24.1)	11.6 (6.7-12.3)	26.1 (12.3-32.1)
Duration of response (weeks)‡ Median (95% CI)	58.7 (44.9-66.1)	NC (37.7-NC)	67.7 (31.1-NC)	27.9 (14.1-32.7)

NC = Not calculable
* These analyses are restricted to the sub-group of patients who experienced a response during the study
† Time to response defined as the time from start of treatment until the first documented evidence of a confirmed PR or CR whichever comes first.
‡ Duration of response defined as the time from documented evidence of a CR or PR until the first documented sign of disease progression or death due to RCC.

5.5.1.3 Health-related quality of life assessments (HRQoL)

The mixed-model repeated measures (MMRM) analyses for change from baseline consistently showed no statistical differences between the pazopanib and placebo arms in the treatment-naive sub-population at each assessment timepoint for the three QoL key endpoints: EORTC QLQ-C30 Global Health Status score, EQ-5D utility score and EQ-5D VAS (Table 5.26). Additionally, the between-group differences were smaller than the established minimally important differences (MID) for the questionnaires[†]. The within-group differences were also smaller than the MIDs, suggesting that any declines or improvements from baseline were not clinically meaningful in either arm. There was a difference in the rate of withdrawal of patients from the placebo arm because of disease progression, which became apparent after

week 6 and was especially evident at later time points. In spite of this limitation, the results indicate a trend for maintenance of QoL over time in patients receiving pazopanib relative to placebo.

Table 5.26: Mixed-model repeated measures analyses for QoL change from baseline in VEG105192 treatment-naive population (ITT population, 23 May 2008 cut-off)

Instrument	Number of patients		Difference in adjusted means†	95% CI	p-value
	Pazopanib	Placebo*			
EORTC QLQ-C30 Global Health Status by week					
6	133	78	-2.28	-7.859 to 3.299	0.421
12	118	44	-0.33	-6.231 to 5.573	0.913
18	100	34	-2.95	-9.401 to 3.510	0.369
24	87	27	-1.12	-7.870 to 5.622	0.742
48	45	15	0.80	-7.404 to 9.014	0.845
EQ-5D utility score by week					
6	137	65	-0.010	-0.081 to 0.061	0.784
12	120	45	-0.010	-0.080 to 0.061	0.789
18	102	34	0.003	-0.067 to 0.073	0.930
24	88	28	-0.008	-0.094 to 0.079	0.861
48	46	14	0.026	-0.059 to 0.111	0.548
EQ-5D VAS by week					
6	132	59	0.23	-5.160-5.626	0.932
12	117	43	3.17	-3.394-9.741	0.342
18	100	33	1.12	-5.159-7.398	0.725
24	86	27	0.06	-6.036-6.153	0.985
48	45	14	1.96	-7.656-11.572	0.685

* More patients in the placebo arm discontinued study treatment because of disease progression compared with patients in the placebo arm.

† The minimally important differences (MID) for the questionnaires have previously been established as 5 to 10 for the EORTC QLQ-C30; 0.08 for the EQ-5D Index; and 7 for the EQ-5D VAS. Values greater than 0 indicate a trend in favour of pazopanib, and values less than 0 indicate a trend in favour of placebo.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 **The following steps should be used as a minimum when presenting a meta-analysis.**

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**

- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

Since only one RCT (VEG105192) directly comparing pazopanib, the technology being appraised, with another intervention in the relevant patient population was identified in the systematic review, a meta-analysis could not be carried out.

5.6.2 **If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.**

Only one RCT of pazopanib (VEG105192) was identified in the systematic review and therefore, a meta-analysis, which evaluates the relative efficacy of treatments with reference to single comparator(s), could not be conducted.

VEG105192 was a well-conducted global trial. Patients were centrally randomised in a 2:1 manner to receive pazopanib or placebo. Blinding was achieved through the use of matching placebo tablets. Disease assessments were conducted by an IRC who was blinded to subjects' treatment assignment. Treatment groups were well balanced at baseline with regard to demographic and disease characteristics. Reasons for withdrawal of patients from the study have been reported adequately. Efficacy endpoints were analysed on the basis of ITT analysis and appropriate methods have been used to account for missing data. An overview of the efficacy results of the VEG105192 trial in the treatment-naive sub-population (n=233) is provided in section 5.10.1.

5.6.3 **If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.**

The remaining studies included in the systematic review compared other interventions (sunitinib, sorafenib, bevacizumab plus INF, temsirolimus, INF or IL-2) to either placebo/BSC or to INF, some of the data of which have been used in the indirect comparison (see section 5.7).

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 **Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published**

literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

Details of the search strategies and methodology employed to identify relevant clinical data on comparators can be found in section 5.1 and section 9.2 (Appendix 2).

5.7.2 **Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.**

Study identification and selection

Details of the eligibility criteria used in the selection and identification of studies can be found in Table 5.1, section 5.2. A flow diagram of the studies included and excluded at each stage of the systematic review is presented in Figure 5.1.

A total of 13 RCTs were identified as meeting the inclusion criteria for the systematic review. Of these, 7 studies were identified that would allow an indirect comparison of pazopanib to interferon and to the main comparator of interest, sunitinib. These studies comprised:

- The pivotal phase III trial of pazopanib versus placebo/BSC (VEG105192)
- The pivotal phase III trial of sunitinib versus IFN (Motzer 2009)
- Five studies which directly compared IFN with a non-IFN control therapy (vinblastine or medroxyprogesterone acetate). Consistent with data from controlled trials[4] and based on discussions with practising oncologists specialising in RCC, it was assumed that medroxyprogesterone acetate (MPA) and vinblastine (VBL) would have no impact on PFS and OS in this population and should therefore be considered as palliative treatment equivalent to placebo with best supportive care. Of importance is that another IFN trial, the Crecy trial (Negrier 1998), identified in our systematic review (see Table 5.3), could not contribute to the indirect analysis as a non-immunotherapy control arm was not used in this study.

An overview of these studies is presented in Table 5.27.The primary reference source for each study is provided in the right hand column and other citations for the same study are listed in the right hand column.

[4] None of the chemotherapeutic or hormonal agents evaluated in RCC has shown any clinically relevant therapeutic efficacy (Miller 1998).

Table 5.27: List of studies identified for use in an indirect comparison of pazopanib with sunitinib and interferon

Study	Year	Study type	N***	Intervention	Comparator	Patient population	Linked publications
Pazopanib							
#VEG105192 (GlaxoSmithKline 2008)	2009	R, DB, PC, MC-I, Phase III	233 treatment-naive (Total population = 435)	Pazopanib 800 mg od	Placebo	Locally advanced or metastatic clear cell/predominantly clear cell RCC, ECOG PS ≤ 1, Age ≥18 years	(Sternberg 2009b; Sternberg 2009a; Hawkins 2009b; Hawkins 2009a)
Sunitinib							
(Motzer 2009)	2009	R, AB, AC, MC-I, Phase III	750	Sunitinib 50 mg od	IFN 9 MU TIW	Metastatic RCC with a clear-cell histologic component, ECOG PS ≤ 1, Age ≥18 years	(Motzer 2008; Reddy 2006; Cella 2009; Patil 2009; Figlin 2008; Cella 2008a; Motzer 2007c; Eberhardt 2007; Cella 2008b; Motzer 2007b; Negrier 2008; Cella 2007a; Motzer 2007a; Motzer 2006a; Eberhardt 2006; Motzer 2006b; Castellano 2009)
IFN, Interleukin-2							
(Negrier 2007)	2007	R, BU, AC, BSC, MC	492	IFN 9 MU TIW	Interleukin-2 9 MIU bid Medroxyprogesterone	Clearly progressive metastatic RCC of all histologic subtypes, >1 metastatic organ site and good performance status (KPS ≥80%) or 1 metastatic organ site with KPS 80%, Age ≥18 years	(Negrier 2006)
MRC RE01 (Hancock 2000)	1999	R, BU, BSC, MC	350	IFN 10 MU TIW	Medroxyprogesterone	Histologically or cytologically confirmed metastatic RCC, WHO PS of 0 to 2	(Ritchie 1999; Royston 2004; Royston 2008; Ritchie 1998)
(Steineck 1990)	1990	R, AB, BSC	60	IFN 10-20 MU/m2 TIW	Medroxyprogesterone	Locally recurrent or metastatic adenocarcinoma of kidney, Patients with previous irradiation of the disease or excision of metastases, Age 18 to 70 years	No links
(Kriegmair 1995)	1995	R, BU, BSC, Phase III	89	IFN 8 MU TIW plus vinblastine	Medroxyprogesterone	History of tumour nephrectomy and a histologically confirmed diagnosis of progressive RCC with bimensionally measurable tumour lesion and a WHO PS of at least grade 2	No links
(Pyrhonen 1999)	1999	R, BU, BSC, MC, Phase III	160	IFN 18 MU TIW plus vinblastine	Vinblastine	histologically or cytologically confirmed measurable or nonmeasurable but assessable advanced RCC, KPS >50% (ECOG status of 0 to 2), Age ≤75 years	(Hernberg 1997)

*R = randomised, AB = assessor blind, AC = active controlled, BSC = best supportive care controlled, BU = blinding unclear, DB = double blind, ECOG = Eastern Cooperative Oncology Group, KPS = Karnofsky Performance Status, MC = multicentre, MC-I = multicentre-international, MSKCC = Memorial Sloan-Kettering Cancer Centre, MU = million units, od = once daily, OL = open label, PC =

placebo controlled, TB = Triple blind, TIW = three times per week. **This study also included an IFN-IL-2 combination treatment arm which was not extracted since it did not meet the inclusion criteria for intervention/comparator. #subgroup analysis for treatment naïve patients; ***This is the number of treatment naïve patients in the study.

Study methodology
A summary of the methodology of the 7 studies included in the indirect comparison is provided in Table 5.28. Further details of the methodology of the pazopanib VEG105192 study can also be found in section 5.3.2, Table 5.5.

As discussed earlier, the pazopanib VEG105192 study was a double-blind, parallel-group, placebo-controlled trial involving 233 treatment-naive patients with advanced/metastatic RCC. Pazopanib was administered orally once daily on a continuous basis. The sunitinib study (Motzer 2009) compared sunitinib with IFN control therapy in parallel-group fashion where treatment assignment was blinded to assessors; it was larger than VEG105192 with the enrolment of 750 treatment-naive patients. Sunitinib was administered orally once daily on a 4-weeks on, 2 week-off schedule. IFN was given by subcutaneous injection there times a week (q3w) at 3MU per dose the first week, 6 MU per dose the second week and 9MU per week thereafter. Both VEG105192 and Motzer 2009 were international multi-centre studies conducted in Europe, South America and Australia; VEG105192 also involved centres in Asia while the Motzer study included sites in North America. Cross-over from control to active treatment took place in both studies; in VEG105192, patients were allowed to cross-over after disease progression whereas cross-over was permitted in the sunitinib study after the interim analysis. In VEG105192, 31 (40%)[5] patients randomised to placebo in the treatment-naive sub-population who progressed had crossed over to receive pazopanib at the clinical-cut off. In the Motzer study, 33% of patients from the IFN group received subsequent therapy with sunitinib after discontinuation of study medication (Motzer 2009).

The largest of the five IFN trials was the MRC RE-01 trial with 350 randomised patients, followed by the Programme Etude Rein Cytokines (PERCY) Quattro trial (Negrier 2007) with 245 patients randomised to IFN or control. All 5 studies took place in Europe: the MRC RE-01 trial was conducted in the UK, the PERCY Quattro study in France and the smaller Steineck 1990, Kriegmair 1995 and Pyrhonen 1999 studies in Sweden, Germany and Finland, respectively. Control therapy was in the form of either medroxyprogesterone acetate (four studies) or vinblastine (Pyrhonen 1999). The studies took one of several slightly different approaches: the same non-immunotherapy control with or without IFN (Pyrhonen 1999); IFN versus a non-immunotherapy control (MRC RE01; Steineck 1990); IFN plus vinblastine versus control (Kriegmair 1995) or as in the case of Negrier 2007, a four arm study comparing IFN and IL-2 or a combination of the two (IFN and IL-2) versus a non-immunotherapy control. Duration of follow-up ranged from a median 39 weeks in Kriegmair 1995 to a median of 243 weeks in the MRC RE-01 trial. These studies used recombinant IFN in a dose range of 8 to 18 MU/dose administered q3w by subcutaneous injection, with the exception of the oldest study which used 10-20 MU/m^2 q3w intramuscularly, following a protocol amendment whereby 50 MU/m^2 resulted in unacceptable toxicity (Steineck 1990).

Details of the outcomes examined and the statistical analyses employed in these studies can be found in Tables 16 and 17 in the Systematic Review report. PFS was the primary outcome measure in the VEG105192 and Motzer studies, with OS as a secondary endpoint. OS was the primary outcome measure in the two largest IFN

5 It should be noted that 33 patients randomised to placebo crossed-over to pazopanib treatment in total. However, 2 of these patients have a last contact date within 1 week of their crossover date. There is no impact of crossover expected for these subjects and they have therefore not been treated as cross-over subjects in the analyses conducted to adjust for crossover.

studies (MRC RE-01; Negrier 2007). OS at 1 year and 5 years was the primary outcome in the Pyrhonen study (Pyrhonen 1999) and it was unclear as to the primary endpoint in the remaining two IFN studies (Kriegmair 1995; Steineck 1990).

Table 5.28: Comparative summary of methodology of RCTs included in the indirect comparison

Study	VEG105192	Motzer 2009	Negrier 2007	MRC RE01	Steineck 1990	Pyrhonen 1999	Kriegmair 1995
Publication type	CSR	Journal Articles					
Intervention	Pazopanib (N = 155)	Sunitinib (N = 375)	IFN (N = 122) IL-2 (N = 125)	IFN (N = 174)	IFN (N = 30)	IFN + BSC (N= 79)	IFN + BSC (N = 44)
Comparator	Placebo (N = 78)	IFN (N = 375)	MPA (N = 123)	MPA (N = 176)	MPA(N = 30)	BSC (N = 81)	BSC (N = 45)
Location	Argentina , Australia, Austria, Brazil, Chile, China, Czech Republic, Estonia, Hong Kong, India, Ireland, Italy, Korea, Latvia, Lithuania, New Zealand, Pakistan, Poland, Russia, Slovakia, Tunisia, Ukraine , UK	Australia, Brazil, Canada, France, Germany, Italy, Poland, Spain, UK, Russia, US	France	UK	Sweden	Finland	Germany
Design	R, DB, PC, MC-I, Phase III	R, AB, AC, MC-I, Phase III	R, BU, AC, BSC, MC	R, BU, BSC, MC	R, AB, BSC	R, BU, BSC, MC, Phase III	R, BU, BSC, Phase III
Randomisation	Adequate	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Blinding	Double blind, using matched placebo	Assessor-blind	Unclear	Unclear	Assessor-blind	Unclear	Unclear
Primary outcomes*	PFS	PFS	OS	OS	Not identified	OS at 1 year and 5 years	Not identified
Secondary outcomes*	OS, DOR, Response rate, TTR, QoL, Safety, Withdrawals,	Response rate, OS, QoL, Safety, Withdrawals	PFS, Response rate, QoL, Safety	PFS, Response rate, Safety, QoL	Response rate, Safety	Response rate, DOR, TTP, Safety, Withdrawals	DOR, OS, Response rate, Safety, Withdrawals
Timing of assessments	Every 6 weeks to week 24; every 8 weeks thereafter	Day 28 of cycle 1–4; every 2 cycles thereafter i.e. weeks 4, 10, 16, 22; every 12 weeks thereafter	12 weeks after start of treatment and between 24 and 26 in patients receiving further therapy	Clinical assess-ment every 4 weeks until week 12; imaging assessment at week 12; minimum follow-up of imaging at 6 months and every 6 months thereafter	Every 4 weeks	Every 2 months	Not clear
Duration of follow-up	Median follow-up at clinical	Unclear	Median 126.53	Median 242.67	Unclear	Unclear	Mean 39 weeks (IFN

Study	VEG105192	Motzer 2009	Negrier 2007	MRC RE01	Steineck 1990	Pyrhonen 1999	Kriegmair 1995
	cut-off for interim analysis was 58.5 weeks (range, 3.9-97.93 weeks) for placebo group and 62.4 weeks (range, 1.73-106.17 weeks) for pazopanib group		weeks (range, 0 to 236.6 weeks)	weeks			group; range, 4.33 to 104 weeks) and mean 27.3 weeks (BSC group; range, 4.33 to 95.33 weeks)

N = Number of patients randomised (cf included in analyses), R = Randomised, AB = Assessor blind, OL = Open-label, DB = Double-blind, TB = Triple blind, BU = Blinding unclear, MC = Multi-centre, MC-I = Multi-centre international, AC = Active controlled, PC = Placebo controlled, OS = Overall survival, PFS = Progression free survival, TTP = Time to progression, TTF = Time to failure, DFS = Disease free survival, DOR = Duration of response, QoL = Quality of life outcomes, TTR = Time to response

Study participants
Details of the eligibility criteria and characteristics of participants in the RCTs included in the indirect comparison can be found in Tables 5.29 and 5.30.

The populations in the pazopanib VEG105192 and sunitinib (Motzer 2009) trials were generally comparable; the only exception being that the sunitinib trial recruited a higher proportion of patients with a baseline ECOG PS of 0 than VEG1015192 (approximately 60% vs. 40%). Both trials restricted entry to RCC patients with either clear cell or predominantly clear cell histology. Age was around 60 years in both studies and the percentage of patients with prior nephrectomy was between 83 and 91%. The distribution of patients according to the MSKCC prognostic risk score was similar (with around a third having favourable scores and approximately half having intermediate scores) in both trials. In addition, there was little difference in the distribution of patients by site of metastases and in each number of metastatic site. Over a third of patients in each study had at least three metastatic sites and about a third had two sites of disease. In both studies, the lung was the organ most commonly involved (around 70-80% patients) followed by the lymph nodes (around 50-60% of patients) (Table 5.30a).

The patient populations in the five IFN studies were generally similar. All patients had advanced/metastatic RCC. Age ranged from 60 to 66 years and prior nephrectomy from 57% to 100% of participants. The Negrier 2007 study restricted entry to patients with a Karnofsky Performance Status (KPS) score ≥80% (equivalent to ECOG PS score ≤1) while the MRC RE-01, Kriegmair 1995 and Pyrhonen 1999 studies allowed participants with an ECOG status of ≤2. The proportion of fully active patients enrolled in the studies ranged from 15% to 35% while 48% to 67% were restricted in strenuous activities (Table 5.30b).

The PERCY Quattro trial (Negrier 2007) and the MRC RE-01 study (Ritchie 1999; Royston 2000) retrospectively categorised patients into good, intermediate and poor prognosis. The MRC RCC group (Royston 2000) used a prognostic index to retrospectively categorise the trial population into three approximately equal groups of good, intermediate and poor prognosis by way of WHO performance status, time since diagnosis, haemoglobin level and white cell count. The Percy Quattro study (Negrier 2007) included 20%, 55% and 25% of patients retrospectively defined, using criteria from a 1998 study by the Group Francais d'Immunotherapie (Negrier 1998), to have a good, intermediate and poor prognosis, respectively.

Table 5.29: Eligibility criteria in the RCTs included in the indirect comparison

Study	Inclusion criteria	Exclusion criteria	Prior nephrectomy
Pazopanib			
VEG105192	• Adult patients with a diagnosis of clear cell or predominantly clear cell locally advanced (defined as disease not amenable to curative surgery or radiation therapy) or metastatic (Stage IV) RCC • Measurable disease presenting with at least one measurable lesion per RECIST • Cytokine pre-treated or treatment naïve disease • Adequate haematological, hepatic and renal function and • ECOG performance status 0 or 1 • At least 4 weeks had elapsed since the last surgery and 2 weeks had elapsed since radiotherapy or last systemic cytokine therapy at time of enrolment	• History of other malignancy • CNS metastasis • Malabsorption syndrome • Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation; abdominal fistula; gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to beginning study treatment • History of HIV infection; uncontrolled infection • Cardiac angioplasty or stenting, or myocardial infarction, or unstable angina within the past 6 months • History of cerebrovascular accident or deep venous thrombosis (DVT) within the past 6 months • Poorly controlled hypertension; prolonged QTc interval	Approximately 84% of the patients had prior nephrectomy in the treatment-naïve subgroup.
Sunitinib			
Motzer 2009	• Patients aged ≥18 years with metastatic RCC with a clear-cell histologic component • Had not received previous treatment with systemic therapy. Presence of measurable disease • An ECOG performance status of 0 or 1 • Adequate hematologic, coagulation, hepatic, renal, and cardiac function	• Brain metastases • Uncontrolled hypertension • Clinically significant cardiovascular events or disease during the preceding 12 months	Prior nephrectomy was performed in 90% of the total randomised population.
IFN, IL-2			
Negrier 2007	• Patients (≥18 years of age) with histologically confirmed, clearly progressive, metastatic RCC of all histologic subtypes • >1 metastatic organ and good performance status (KPS ≥80%) or 1 metastatic organ with KPS 80% • Normal blood and liver functions with creatinine level ≤160 micromol/L	• Previous systemic treatment/ radiotherapy within 6 weeks of randomisation • Evidence of brain metastases • Uncontrolled cardiac dysfunction active infections • Current corticosteroid treatment • History of organ transplantation • Other cancer or seizure	Approximately 96% patients had undergone prior nephrectomy.
MRC RE01	• Patients with histologically or cytologically confirmed metastatic RCC • WHO performance status of 0 to 2	• Exclusion criteria were not reported in the study.	Patients with or without prior nephrectomy were included in the study; number of patients who underwent prior nephrectomy not stated.
Steineck 1990	• Patients with locally recurrent or metastatic adenocarcinoma of kidney • Aged between 18 years and 'a physiological age of 70'	• Patients with severe intercurrent disease • Any impaired function as judged by blood examinations	The initial protocol required a nephrectomy of the primary tumour but after the amendment of protocol this was

Study	Inclusion criteria	Exclusion criteria	Prior nephrectomy
	• With a life expectancy of > 12 weeks • Patients with previous irradiation of the disease or excision of metastases were included		not necessary; 3 patients in each group had not had the primary tumour excised prior to the outset of the trial.
Pyrhonen 1999	• Patients aged <75 years with histologically or cytologically confirmed measurable or non measurable but assessable advanced RCC • KPS >50% (ECOG status of 0 to 2) • Life expectancy >3 months • No abnormalities worse than mild (grade 1) in leucocyte, granulocyte, and platelet count, serum creatinine, and serum urea	• Brain metastases • Other malignancies • Serious concomitant illnesses • Radiotherapy involving more than 25% of the bone marrow reserve	71% patients in each group had undergone prior nephrectomy.
Kriegmair 1995	• Adult patients with a history of tumour nephrectomy • Histologically confirmed diagnosis of progressive RCC with dimensionally measurable tumour lesion • WHO performance status of at least grade 2	• Patients with fully resectable tumour lesions who underwent surgery and those with synchronous, bilateral tumour • Previous systemic treatment/radiotherapy • Other malignancies • Cardiovascular insufficiency (NYHA grade > 2) • Adequate hepatic, renal and blood function	All patients had undergone nephrectomy or partial nephrectomy.

ECOG = Eastern Cooperative Oncology Group, KPS = Karnofsky performance status, RCC = renal cell carcinoma, RECIST = Response Evaluation Criteria In Solid Tumours criteria, WHO = World Health Organisation

Table 5.30a: Characteristics of participants in the RCTs included in the pazopanib and sunitinib studies across randomised groups

Study	VEG105192		Motzer 2009	
Intervention	**Pazopanib**	**Placebo**	**Sunitinib**	**IFN**
N	155	78	375	375
Age (yrs)	59 (28-82)	62 (25-81)	62 (27-87)	59 (34-85)
Male (%)	68	74	71	72
Disease duration (yrs)	0.66	0.71		
ECOG performance status				
0	63 (40.6)	33 (42)	231 (61.6)	229 (61)
1	92 (59.4)	45 (58)	144 (38.4)	146 (39)
2				
MSKCC risk score				
0 (favourable)	56 (36)	31 (40)	143 (38)	121 (32)
1-2 (intermediate)	87 (56)	40 (51)	209 (56)	212 (56.5)
≥ 3 (poor)	6 (4)	5 (6)	23 (6)	25 (6.7)
Histology				
Clear cell / predominantly clear cell	155 (100)	78 (100)	375 (100)	375 (100)
Previous nephrectomy	130 (84)	65 (83)	340 (90.6)	335 (89)
Previous radiation therapy			53 (14)	54 (14.4)
No. metastases sites				
1	23 (15)	10 (13)	55 (14.7)	72 (19)
2	46 (30)	25 (32)	106 (28)	112 (30)
≥ 3	86 (55.5)	43 (55)	214 (57)	191 (51)
Most common sites of metastases				
Lung	114 (74)	55 (71)	292 (78)	298 (79)
Liver	41 (26)	17 (22)	99 (26)	90 (24)
Bone	49 (32)	22 (28)	112 (30)	112 (30)
Lymph	89 (57)	48 (62)	218 (58)	198 (53)

*Dichotomous outcomes are reported as n (%) and continuous as median (range) unless otherwise specified.
ECOG = Eastern Cooperative Oncology Group, KPS = Karnofsky Performance Status, MSKCC = Memorial Sloan-Kettering Cancer Centre.

Table 5.30b: Characteristics of participants in the RCTs included in the IFN studies across randomised groups

Study	Negrier 2007			MRC RE01		Steineck 1990		Pyrhonen 1999		Kriegmair 1995	
Intervention	**IL-2**	**IFN**	**BSC**	**IFN**	**BSC**	**IFN**	**BSC**	**IFN + BSC**	**BSC**	**IFN**	**BSC**
N	125	122	123	167	168	30	30	79	81	44	45
Age (yrs)	61 (33-80)					63 (39-73)	62 (40-77)	60 (30-74)	62 (39-77)	62.4 (44-78)**	65.9 (47-79)**
Male (%)	75			72	65	70	80	65	63	63.64	68.89
Disease duration (yrs)						0.73	0.57	0.20	0.18		
Performance status											
0	35			44 (26)	43 (25.6)			12 (15)	15 (18.5)		
1	65			83 (50)	80 (47.6)			53 (67)	49 (60.5)		
2	0			39 (24)	45 (27)			14 (18)	17 (21)	14 (32)	16 (35.6)
Previous nephrectomy	96			96 (57.5)	96 (57)			71 (90)	71 (88)	44 (100)	45 (100)
Previous radiation therapy	25							6 (7.6)	12 (15)	0	0
No. metastases sites											
1				28 (16.8)	26 (15.5)						
2											
≥ 3											

*Dichotomous outcomes are reported as n (%) and continuous as median (range) unless otherwise specified, **mean
IFN = Interferon alpha, IL-2 = Interleukin 2, MSKCC = Memorial Sloan-Kettering Cancer Centre. KPS = Karnofsky Performance Status. ECOG = Eastern Cooperative Oncology Group.

Quality assessment
Quality assessment for the pazopanib VEG105192 study can be found in section 5.4.1. Quality assessment for the other trials utilised in the indirect comparison can be found in section 9.3 (Appendix 3 to the main submission) and in Appendix D of the Systematic Review report provided with this submission. These studies were assessed qualitatively using the assessment criteria recommended in NICE's guidance to manufacturers on Single Technology Appraisals and by means of a Jadad score and allocation grade.

The method used to generate random allocation sequence was reported for only the VEG105192 trial and was judged as adequate. Only three studies reported the method used for concealment of allocation sequence (VEG105192, MRC RE-01, Negrier 2007). With each study, the treatment groups were generally comparable in terms of demographic and disease characteristics at baseline. Blinding status was clear for four of the studies (VEG105192 [double-blind]; Motzer 2009 [assessor-blind], Steineck 19990 [assessor-blind]; Negrier 2007 [open-label]) and was unclear for the remaining studies. The VEG105192 and Negrier 2007 studies showed no evidence of selective reporting. However, evidence of selective reporting could not be determined for the other studies because of a lack of published protocol. All of the studies except Kriegmair 1995 reported an ITT analysis; however, reporting of the methods used to account for missing data was variable. Overall, none of the studies used in the indirect comparison were identified as being at a high risk of bias, so the validity of the results is not affected by any individual study.

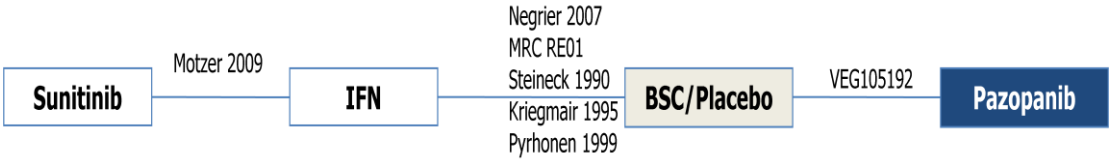
5.7.3 **Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.**

Table 5.31 and Figure 5.7 illustrate how the 7 identified studies have been used to conduct the indirect comparison, where the intervention is pazopanib, comparator B is placebo/BSC, comparator C is interferon and comparator D is sunitinib.
The 5 trials comparing IFN to control therapy (equivalent to placebo/BSC) were utilised to provide the indirect pathway from pazopanib to IFN and then to sunitinib.

Table 5.31: Summary of trials used to conduct indirect comparison

No. of trials	Trial name/reference source	Intervention (Pazopanib)	Comparator B (Placebo/BSC)	Comparator C (Interferon)	Comparator D (Sunitinib)
1	VEG105192	√	√		
5	Negrier 2007 MRC RE01 Steineck 1990 Kriegmair 1995 Pyrrhonen 1999		√	√	
1	Motzer 2009			√	√

Figure 5.7: Network diagram of indirect comparison



Note: It should be noted that in the Systematic Review report provided in conjunction with this submission, an indirect comparison using only one of the 5 IFN trials (the MRC RE-01 trial) is presented since this is the only study to report HRs for both PFS and OS in the trial publication. However, for the purposes of the base-case indirect comparison presented here, all 5 trials have been utilised with HRs where missing derived using validated methods (see section 5.7.4 below). Several sensitivity analyses have been conducted including one utilising the MRC RE-01 trial only (Sensitivity analysis 2). For completeness, the Systematic Review report also presents indirect comparisons of pazopanib with other targeted agents used in the treatment of RCC (sorafenib, bevacizumab and temsirolimus) as studies of these agents were identified in the systematic review process.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

Pazopanib vs. placebo/BSC

For pazopanib versus placebo/BSC, the HRs for PFS and OS were obtained from the VEG105192 study. The HR used for PFS was based on assessments by the IRC and on the scan date rather than on the visit date assessment used in the primary analysis to be consistent with the PFS assessment in the sunitinib trial. The OS data was from the pre-panned interim analysis. Because a high proportion of patients randomised to placebo crossed-over to pazopanib after progression (40% in the treatment-naive sub-population at the clinical cut-off), the HR for OS was estimated using several different approaches to adjust for the effect of the cross-over (see section 5.5.1.2.3). The univariate HR of 0.345 adjusted for cross-over using the RPSFT technique was chosen for use in the indirect comparison. The univariate HR was selected over the multivariate HR as the RPSFT method is based on a comparison of the groups as randomised.

Table 5.32: Data from the pazopanib VEG105192 trial used in indirect comparison

Endpoint	Intervention	HR (95% CI)	Data assessment
PFS	Pazopanib N=155 Placebo N=78	0.36 (0.24- 0.55) p<0.0000001	Independent review committee (IRC) Scan date assessment
OS	Pazopanib N=155 Placebo N=78	0.345 (0.09-1.31)	Adjusted for cross-over using the RPSFT method

* Patients with missing values for the covariates were assigned the mean for the trial population.

IFN vs. Placebo/BSC

HRs for IFN versus placebo/BSC were obtained by pooling results from the five identified studies of IFN versus control therapy (equivalent to placebo/BSC) representing 889 patients.[6] These data are summarised in Table 5.33 and their source or derivation is outlined below.

[6] The PERCY Quattro trial included 488 patients in four arms: IFN, MPA, IL2, and IFN+IL2. Only the IFN and MPA arms are considered here.

Table 5.33: Summary of data for trials of IFN vs. control used in the indirect comparison

	Treatments		N		HR PFS IFN vs. Control			HR OS IFN vs. Control		
	Tx	Ct	Tx	Ct	HR	95%CI		HR	95%CI	
MRC RE-01 (1999)	IFN	MPA	167	168	0.66	0.53	0.82	0.75	0.66	0.94
Negrier PERCY Quattro (2007)	IFN	MPA	122	123	0.88	0.63	1.24	0.98	0.72	1.31
Pyrhonen (1999)	IFN + VBL	VBL	79	81	0.61	0.41	0.93	0.65	0.47	0.91
Kriegmair (1995)	IFN + VBL	MPA	44	45	-	-	-	0.67	0.37	1.22
Steineck (1990)	IFN	MPA	30	30	-	-	-	1.05	0.64	1.72
Pooled (random effects)			442	447	0.704	0.580	0.854	0.799	0.674	0.948

Results of fixed effects meta-analysis were virtually identical to random effects estimates.
N = Number of patients included in analyses; MPA = Medroxyprogesterone; VBL = Vinblastine.

The HR for PFS for the MRC RE-01 study was taken from an update to this study presented at ASCO in 2000 (Hancock 2000). The HR for PFS for the Pyrhonen study were estimated from the survival curve presented in the publication (Pyrhonen 1999) using the method of Parmar (Parmar 1998). Only median PFS was reported for the PERCY Quattro trial (neither the HR nor the survival curves for PFS were reported). The HR for PFS for this trial was therefore estimated based on the ratio of median PFS for control versus median PFS for IFN (3.0 vs. 3.4 months respectively); this method was unbiased if the hazard rate for the event was relatively constant (Michiels 2005). The variance of ln(HR) for PFS for the PERCY Quattro trial was assumed to be equal to the average of the variances of ln(HR) for the MRC RE-01 and Pyrhonen studies. No information on PFS was available in the trial reports for the Kriegmair and Steineck studies, so these trials were not included in the pooled estimate for this outcome.

The HR for OS for the MRC RE-01 study was taken from an update to this study presented at ASCO 2000 (Hancock 2000) with recalculation of the 95% CIs[7]. Because the HRs for OS were not reported in the original publications, the HRs used in our analysis for the Kriegmair 1995, Pyrhonen 1999 and Steineck 1990 studies were based on estimates reported in a recent Cochrane review (Coppin 2008). HRs were estimated by the Cochrane group from the published survival curves for these studies using the Pamar method (Pamar 1998). The estimated HRs for each of the studies are presented in Table 5.33. The HR for OS for the PERCY Quattro trial (Negrier 2007) was not reported in the original publication or in the analysis by the Cochrane group (Coppin 2008) and was therefore calculated from published survival curves reported in a presentation of the final analysis (Negrier 2006) using the same method as employed by the Cochrane group for the other studies (Pamar 1998).

[7] The CI for the HR for OS for IFN vs. MPA reported in the Hancock abstract (0.53-0.82) was the same as that reported for the HR for PFS. It also was asymmetrical around the HR for OS (0.75) and skewed to the left. Because the HR is lognormal, the CI would normally be skewed to the right. This suggests that the reported HR was in error. The CI for the HR for OS was therefore re-calculated using the total number of events and log rank p-value and the method of Parmar (Parmar 1998) to obtain an HR=0.75 with a 95% CI of 0.60-0.94.

The HRs for OS and PFS for IFN versus control from the five trials were then pooled using random effects meta-analysis to give the following summary statistics:
PFS: HR 0.70 (95% CI: 0.58-0.85); OS: HR 0.80 (95% CI: 0.67-0.95). The pooled HR of 0.80 for OS with IFN versus control suggests that there is a modest survival benefit with the use of IFN in advanced renal cell cancer.

Interestingly, a recent commentary on the MRC RE-01 study by the MRC statistics department (Royston 2008) estimated the treatment effect of IFN at the level of the individual patient to be relatively small because the natural variation among survival times of patients was much larger than the treatment effect: the 10th, 50th (i.e. median), and 90th centiles of survival time for all patients were 1.2, 8.0, and 38.0 months, respectively. The explained variation (*R* 2) in the logarithm of the survival time that was attributable to treatment was only 2.2% (95% CI: 0.3%-6.4%). This result means that only approximately 2% of the variation in the length of survival observed among the patients could be attributed to the treatment received, further casting doubt on the efficacy of IFN in advanced RCC.

Sunitinib vs. interferon
The HRs for PFS and OS for sunitinib versus IFN were obtained from the pivotal sunitinib trial. The HR used for PFS was based on the final analysis (Motzer 2009), as assessed by an IRC (Motzer 2007) with progression dates determined by patients' scan dates. A high proportion of patients in the IFN arm received subsequent therapy with sunitinib on discontinuation of study medication (33%; Motzer 2009) thereby confounding the final survival data. The HR for sunitinib versus IFN for OS was taken from an analysis conducted in patients who did not receive any post-study cancer therapy, as reported in the Motzer 2009 publication (HR 0.647 [95% CI: 0.483-0.870]). This estimate is limited by the fact that only about half the trial participants were represented in this analysis and the group of patients included may not be representative of the original trial population. We also recognise that this HR has not been adjusted to account for post-study treatment in the same way as the HR for OS from the VEG105192 study (analysed using the RPSFT technique). A similar OS HR for sunitinib versus IFN was reported for an interim analysis prior to the cross-over in which only 13% of patients in the sunitinib group and 17% of those in the IFN group had died (HR 0.65 [95% CI: 0.45-0.94]). Other HRs for OS reported for the sunitinib study relate to the final ITT analysis (HR 0.821 [95% CI: 0.673-1.001]) and an analysis in which 25 patients (7%) who crossed over during the course of the study were censored (HR 0.808 [95% CI: 0.661-0.987]), which are less favourable towards sunitinib than the analysis in patients with no post-study therapy.

Table 5.34: Data from sunitinib trial used in indirect comparison

Endpoint	Intervention	HR (95% CI)	Data assessment
PFS (Motzer 2009)	Sunitinib N=375 IFN N=375	0.539 (0.451-0.643) p<0.001	Independent review committee (IRC) Scan date assessment
OS (Motzer 2009)	Sunitinib N=193 IFN N=162	0.647 (0.483-0.870) p=0.003	Patients with no post-study cancer therapy

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

A network diagram for the indirect comparison is shown in Figure 5.7 (section 5.6.3). The 5 trials comparing IFN to control therapy (equivalent to placebo/BSC) were utilised to provide the indirect pathway from pazopanib to IFN and then to sunitinib.

It was first necessary to estimate HRs for PFS and OS for IFN vs. placebo/BSC by pooling data from the 5 studies, using standard meta-analytical methods. The random- effects model was used to account for differences (heterogeneity) between the studies. Results were expressed as HRs with 95% CIs. Heterogeneity was assessed by measuring the degree of inconsistency in the studies' results (I^2) (see section 5.6.7). This measure (I^2) describes the percentage of total variation across studies that is due to heterogeneity rather than the play of chance and its value lies between 0% and 100%; a simplified categorisation of heterogeneity could be low, moderate and high for I^2 values of 25%, 50% and 75%, respectively (Higgins 2003).

Estimated HRs for pazopanib vs. IFN were then obtained by combining the HRs for pazopanib vs. placebo sourced from the VEG105192 study with the pooled estimated HRs for IFN vs. placebo/BSC, using the 'adjusted' indirect comparison methodology described by Bucher (Bucher 1997; Sutton 2008). This method adjusts the results using a common intervention arm to correct for differences in patient characteristics and prognostic factors across the trials. It preserves the benefits of a randomisation and assumes consistency of treatment effect within the different subgroups; the subgroups being defined by the different comparisons being made. In this case, one subgroup was 'pazopanib vs. placebo/BSC' and the other subgroup was 'IFN vs. placebo/BSC'. The difference between the summary effects in the two subgroups provides an estimation of the comparison of 'pazopanib vs. IFN'. Results were expressed as HRs with 95% CIs. A subsequent step was performed in the same way to combine the estimated HRs for 'pazopanib vs. IFN' with the HRs for 'sunitinib vs. IFN' sourced from the Motzer study, to estimate the HRs for 'pazopanib vs. sunitinib'.

Technical equation for adjusted indirect comparison:

HR of A vs. C: $HR_{AC}=HR_{AB}/HR_{CB}$
95% CI estimated under the assumption:
Var ($InHR_{AC}$) = Var ($InHR_{AB}$) + Var (In HR_{CB})

HR of A vs. D: $HR_{AD}=HR_{AC}/HR_{CD}$
95% CI estimated under the assumption:
Var ($InHR_{AD}$) = Var ($InHR_{AC}$) + Var (In HR_{CD})

where A = pazopanib, B = placebo/BSC, C = interferon, D = sunitinib.

The Weibull survival model employed in the economic evaluation was then used to estimate the median OS values for pazopanib vs. IFN and pazopanib vs. sunitinib (see Table 5.36).

5.7.6 **Please present the results of the analysis.**

Results for the base case analysis, where the HRs for IFN vs. placebo/BSC were estimated by pooling data from the five IFN trials (MRC RE-01 [Hancock 2000]; Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999) and the HR for OS for pazopanib vs. placebo/BSC in VEG105192 was estimated using the RPSFT method to adjust for cross-over with imputation for missing data (i.e. patients with missing values for the covariates were assigned the mean for the trial population), are as follows:

Table 5.35: Indirect comparison (base case results)

	PFS		OS	
	HR	**95% CI**	**HR**	**95% CI**
Pazopanib vs. IFN	0.512	0.326-0.802	0.432	0.106-1.750
Pazopanib vs. sunitinib	0.949	0.575-1.568	0.667	0.160-2.788

The results indicate that pazopanib is associated with a decreased risk of progression (49% reduction) and death (44% reduction) compared with IFN. Pazopanib appears to have broadly comparable efficacy in terms of PFS and OS to sunitinib. It should be noted that the 95% CI around the HR for OS for pazopanib vs. sunitinib is wide indicating a level of uncertainty with this estimate. This is largely driven by the uncertainty in RPSFT-derived OS HR for VEG105912.

Median PFS and OS for the interventions included in the indirect comparison were estimated using the Weibull survival model used in the economic evaluation. The confidence intervals were calculated by simulation based on percentiles and normal approximation (Table 5.36).

Table 5.36: Model projections of median PFS and OS for comparators

Outcome	Comparator	HR vs IFN	Median (months)	95% CI	
				Percentiles	Normal approximation
PFS	Pazopanib	0.5115	11.3	6.9-19.3	5.1-17.5
	Sunitinib	0.5390	10.7	8.2-13.5	7.9-13.4
	IFN	1.0000	5.4	5.4-5.4	5.4-5.4
	Placebo/BSC	1.4210	5.6	4.2-7.6	4.0-7.3
OS	Pazopanib	0.4317	43.5	8.3-248.1	-81.9-169.0
	Sunitinib	0.6470	26.8	18.8-38.0	17.0-36.5
	IFN	1.0000	15.8	15.8-15.8	15.8-15.8
	Placebo/BSC	1.2510	12.1	9.9-14.7	9.6-14.6

Medians calculated using formula t=[-ln(.5)/(HR x Lambda)]^(1/gamma). Confidence intervals calculated by simulation alternatively based on percentiles and normal approximation

The median PFS estimate for pazopanib and sunitinib is similar (the 95% CIs overlap). Whilst the median OS point estimate for pazopanib appears to be longer than that for sunitinib, the 95% CI around the estimates are wide highlighting the uncertainty.

Median PFS and OS for pazopanib appear to be considerably longer than those for IFN. Median OS was estimated to be 15.8 months (95% CI: 15.8-15.8) for IFN and 43.5 months (95% CI: -81.9-169.0) for pazopanib. As discussed in section 5.10.3, we believe that pazopanib should be afforded the same consideration under NICE's Supplementary Advice on appraising End of Life (EoL) medicines as sunitinib in relation to IFN. Based on the OS medians above, pazopanib offers a survival gain of 27.7 months compared with IFN, meeting the ≥3-month extension to life criterion set out in NICE's guidance, as well as being a treatment for a small patient population with a limited life expectancy of less than 24 months (see section 5.10.3).

5.7.7 **Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.**

One of the inputs in the indirect analyses was the results from the pooled analyses of IFN vs. placebo/BSC conducted using the random effects model due to likely heterogeneity between the trials. The I^2 statistic was calculated to be 19% for the pooled analysis of PFS and 20% for the pooled analysis of OS, indicating a low degree of heterogeneity in both cases. Sources of heterogeneity generally include diversity in study design, doses, participants, study quality, length of follow-up etc between studies. Details of the methodology of, and participants in, the studies used in the indirect comparison are provided in section 5.7.2.

The IFN studies were all of parallel design with control therapy in the form of either medroxyprogesterone acetate or vinblastine. In the Negrier 2007 study, treatments were administered unblinded; in Steineck 1990, the radiologist who reviewed the imaging data was unaware of treatment assignment while the blinding status of the other 3 studies was unclear. The largest study (MRC RE-01), involving 350 randomised patients, was conducted in the UK. The Negrier study with 245 patients randomised to IFN or control took place in France. The smaller Steineck 1990, Kriegmair 1999 and Pyrhonen studies were conducted in Sweden, Germany and Finland, respectively. Duration of follow-up ranged from a median 39 weeks in Kriegmair 1995 to a median of 243 weeks in the MRC RE-01 trial. IFN was administered in a dose range of 8-18 MU/dose q3w subcutaneously, with the exception of the oldest study which used 10-20 MU/m^2 q3w intramuscularly (Steineck 1990). The patient populations in the five studies were generally similar. Age ranged from 60 to 66 years and prior nephrectomy from 57% to 100%. The Negrier 2007 study restricted entry to patients with a KPS score ≥80% (equivalent to ECOG PS score ≤1) while the MRC RE-01, Kriegmair 1995 and Pyrhonen 1999 studies allowed participants with an ECOG status of ≤2. The proportion of fully active patients enrolled in the studies ranged from 15% to 35% while 48% to 67% were restricted in strenuous activities.

The VEG105192 and Motzer studies were both international, parallel group studies. VEG105192 was double-blind while Motzer was blinded to assessors. The study populations were very similar for age (around 60 years), prior nephrectomy (between 83-91%), MSKCC risk score (approximately a third of participants had favourable scores and half had intermediate scores) and number and sites of metastases (see section 5.7.2). The only difference in the characteristics of participants was in baseline ECOG PS score in that the sunitinib study recruited more patients with a score of 0 than VEG105192 (approximately 60% vs. 40%). The IFN dosage used in the sunitinib study fell within the range used in four of the IFN studies (9MU q3w by subcutaneous injection).

5.7.8 **If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.**

In the base case for the indirect comparison, the HRs for IFN vs. placebo/BSC were estimated by pooling data from the five IFN trials (MRC RE-01 [Hancock 2000]; Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999). The HR for OS for pazopanib vs. placebo/BSC in VEG105192 was estimated using the RPSFT method to adjust for cross-over. Several sensitivity analyses of the indirect comparison were performed as follows:

1. *Using the MRC RE-01 IFN trial only*: It was considered appropriate to conduct a sensitivity analysis using just the MRC RE-01 trial since this is the only IFN trial to report HRs for both PFS and OS in the trial publications. It is also the largest trial and was conducted in the UK. In addition, the HR used for OS for PERCY Quattro study (Negrier 2007) in the pooled analysis was based on an ITT analysis and therefore not adjusted for the small amount of cross-over (11.8% of patients) that occurred between treatment groups. As for the base case, this sensitivity analysis was conducted using an HR for OS from the VEG105192 study adjusted for cross-over using the RPSFT method (with imputation for missing data).

It should be noted that the indirect comparison utilising the MRC RE-01 trial presented in the Systematic Review report uses an HR for OS from VEG105192 that is not adjusted for cross-over.

Table 5.37: Indirect comparison: Sensitivity analysis 1

Sensitivity analysis 1 - MRC Trial only	PFS		OS	
	HR	95% CI	HR	95% CI
Data inputs				
Pazopanib vs. placebo/BSC	0.36*	0.24-0.55	0.345†	0.086-1.276
IFN vs. placebo/BSC‡	0.66	0.53-0.82	0.75	0.66-0.94
Sunitinib vs. IFN	0.539	0.451-0.643	0.647$	0.483-0.870
Results of indirect comparison				
Pazopanib vs. IFN	0.545	0.344-0.865	0.460	0.113-1.879
Pazopanib vs. sunitinib	1.012	0.606-1.689	0.711	0.169-2.992

* IRC assessment based on scan dates
† HR adjusted for cross-over using RPSFT method with imputation for missing data
‡ Includes MRC RE-01 trial as the only IFN vs. placebo/BSC trial (Hancock 2000 data)
$ Patients with no post-study cancer therapy (Motzer 2009)

2. *Excluding IFN studies using vinblastine:* Since vinblastine (VBL) is a chemotherapeutic agent that may have some activity (although unlikely) in RCC, the indirect comparison was repeated excluding the Kriegmair 1996 and Pyrhonen 1999 studies i.e. only the three IFN vs. medroxyprogesterone acetate (MPA) studies were included (MRC RE-01 [Hancock 2000]; Negrier 2007; Steineck 1990). Again, this analysis was conducted using an HR for OS from the VEG105192 study adjusted for cross-over using the RPSFT method.

Table 5.38: Indirect comparison: Sensitivity analysis 2

Sensitivity analysis 2 - IFN vs. MPA trials only	PFS		OS	
	HR	95% CI	HR	95% CI
Data inputs				
Pazopanib vs. placebo/BSC	0.36*	0.24-0.55	0.345†	0.086-1.276
IFN vs. placebo/BSC‡	0.728	0.586-0.903	0.863	0.706-1.056
Sunitinib vs. IFN	0.539	0.451-0.643	0.647$	0.483-0.870
Results of indirect comparison				
Pazopanib vs. IFN	0.495	0.313-0.783	0.400	0.098-1.627
Pazopanib vs. sunitinib	0.918	0.551-1.530	0.618	0.147-2.591

* IRC assessment based on scan dates
† HR adjusted for cross-over using RPSFT method with imputation for missing data
‡ Includes IFN vs. MPA trials only: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990
$ Patients with no post-study cancer therapy (Motzer 2009)

3. *Using HR for OS for VEG105192 adjusted for cross-over using IPCW method:* Since there is no universal agreement on the most appropriate method to adjust for cross-over in survival analyses, the indirect comparison was repeated using an HR for OS from the VEG105192 study adjusted for cross-over using the IPCWT method. This sensitivity analysis was repeated using the pooled IFN trials (3A), using the MRC RE-01 trial only (3B), and excluding the VBL studies (3C).

Table 5.39a: Indirect comparison: Sensitivity analysis 3A

Sensitivity analysis 3A - IPCW adjusted HR for OS for VEG105192 / Pooled IFN trials	PFS		OS	
	HR	95% CI	HR	95% CI
Data inputs				
Pazopanib vs. placebo/BSC	0.36*	0.24-0.55	0.450†	0.280-0.721
IFN vs. placebo/BSC‡	0.704	0.580-0.854	0.799	0.674-0.948
Sunitinib vs. IFN	0.539	0.451-0.643	0.647$	0.483-0.870
Results of indirect comparison				
Pazopanib vs. IFN	0.495	0.313-0.783	0.563	0.340-0.932
Pazopanib vs. sunitinib	0.918	0.551-1.530	0.870	0.486-1.559

* IRC assessment based on scan dates
† HR adjusted for cross-over using IPCW method with imputation for missing data

‡ Includes all 5 IFN 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 5.39b: Indirect comparison: Sensitivity analysis 3B

Sensitivity analysis 3B - IPCW adjusted HR for OS for VEG105192 / MRC RE -01 trial only	PFS		OS	
	HR	95% CI	HR	95% CI
Data inputs				
Pazopanib vs. placebo/BSC	0.36*	0.24-0.55	0.450†	0.280-0.721
IFN vs. placebo/BSC‡	0.66	0.53-0.82	0.75	0.66-0.94
Sunitinib vs. IFN	0.539	0.451-0.643	0.647$	0.483-0.870
Results of indirect comparison				
Pazopanib vs. IFN	0.495	0.313-0.783	0.600	0.355-1.014
Pazopanib vs. sunitinib	0.918	0.551-1.530	0.927	0.509-1.690

* IRC assessment based on scan dates
† HR adjusted for cross-over using IPCW method with imputation for missing data
‡ Includes MRC RE-01 trial as the only IFN vs. placebo/BSC trial (Hancock 2000 data)
$ Patients with no post-study cancer therapy (Motzer 2009)

Table 5.39c: Indirect comparison: Sensitivity analysis 3C

Sensitivity analysis 3C - IPCW adjusted HR for OS for VEG105192 /IFN vs. MPA trials only	PFS		OS	
	HR	95% CI	HR	95% CI
Data inputs				
Pazopanib vs. placebo/BSC	0.36*	0.24-0.55	0.450†	0.280-0.721
IFN vs. placebo/BSC‡	0.66	0.53-0.82	0.75	0.66-0.94
Sunitinib vs. IFN	0.539	0.451-0.643	0.647$	0.483-0.870
Results of indirect comparison				
Pazopanib vs. IFN	0.495	0.313-0.783	0.521	0.311-0.873
Pazopanib vs. sunitinib	0.918	0.551-1.530	0.806	0.445-1.457

* IRC assessment based on scan dates
† HR adjusted for cross-over using IPCW method with imputation for missing data
‡ Includes IFN vs. MPA trials only: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990
$ Patients with no post-study cancer therapy (Motzer 2009)

The results of the sensitivity analyses of the indirect comparison were similar to those of the base case analysis. In all the analyses, pazopanib was associated with a reduced risk of progression and death compared with IFN and appeared to have comparable efficacy in terms of PFS and OS to sunitinib (all 95% CIs crossed 1).

When using the RPSFT-derived HR of 0.345 for OS for pazopanib vs. placebo/BSC, the resulting HRs for pazopanib vs. IFN and for pazopanib vs. sunitinib improved slightly on excluding the VBL studies (i.e. were numerically lower) and were marginally less favourable (i.e. were slightly numerically higher) when using only the MRC RE-01 trial, compared with the base case results. This pattern was repeated when the analyses were conducted using the IPCW-derived HR (0.45), but as expected the resulting HRs for pazopanib vs. IFN and for pazopanib vs. sunitinib were a little numerically higher than in the base case results.

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable since there is no direct comparative evidence for pazopanib vs. IFN or sunitinib, and therefore a clinical comparison was only possible via indirect comparison methodology.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

Two non-RCTs of pazopanib are considered in this section as supportive evidence. As discussed earlier, the phase II VEG102616 study (Hutson 2010) was identified during the systematic review process but was excluded on the basis that its original randomised discontinuation design was amended to a single-arm open-label design following an interim analysis. The other supportive study is VEG107769, the unblinded extension study to VEG105192 enrolling subjects on open-label pazopanib who progressed on placebo in the pivotal study.

5.8.1 **If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.**

5.6.1.2 Data sources for non-RCTs

Data sources for the two pazopanib non-RCTs (VEG102616 and VEG107769) are shown in Table 5.40; in both cases, the Clinical Study Reports (CSR) formed the primary source.

Table 5.40: Data sources for pazopanib non-RCTs

Author(s)	Source	Title
Sources for pazopanib trial VEG102616		
GlaxoSmithKline	Clinical Study Report RM2007/00899/00	A Phase II Study of GW786034 Using a Randomized Discontinuation Design in Subjects with Locally Recurrent or Metastatic Clear-Cell Renal Cell Carcinoma.
Hutson TE, Davis ID, Machiels J-PH, *et al.*	J Clin Oncol 2010; 28: 475-480.	Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma.
Hutson TE, Davis ID, Machiels JH, *et al.*	Abstract and poster presentation at American Society of Clinical Oncology Annual Meeting 2008. J Clin Oncol 2008; 26 (suppl): abstract no. 5046.	Biomarker analysis and final efficacy and safety results of a phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor.
Hutson TE, Davis ID, Machiels JH, *et al.*	Abstract and poster presentation at American Society of Clinical Oncology Annual Meeting 2007. J Clin Oncol 2007; 25 (suppl 18S): abstract no. 5031.	Pazopanib (GW786034) is active in metastatic renal cell carcinoma (RCC): Interim results of a phase II randomized discontinuation trial (RDT).
Sources for pazopanib trial VEG107769		

GlaxoSmithKline	Clinical Study Report UM2008/00010/00	An open-label extension study to assess the safety and efficacy of pazopanib in subjects with renal cell carcinoma previously enrolled on protocol VEG105192.
Hawkins R, Hong SJ, Ullys A, *et al*.	Abstract and poster presentation at American Society of Clinical Oncology Annual Meeting 2009. J Clin Oncol 2009; 27 9suppl 15s): Abstract no. 5110.	An open-label extension study to evaluate safety and efficacy of pazopanib in patients with advanced renal cell carcinoma.

5.8.1.2 Methods

Table 5.41: Summary of methodology of the non-RCTs

Study	VEG102616	VEG107769
Location	43 sites in 9 countries across US, Australia, Asia, Middles East and Europe.	36 sites in 19 countries across S. America, Australia, New Zealand, Asia and Europe, including 2 centres in UK with 5 patients enrolled.
Design	Originally designed as a multicentre study utilising a randomisation discontinuation design. All subjects began on open-label pazopanib. After 12 weeks, 3 outcomes were possible: (i) Subjects with CR or PR continued to receive pazopanib and were followed until PD or death, whichever came first (ii) Subjects with PD were taken off pazopanib, had a follow-up visit and were then discharged from study (iii) Subjects with SD were entered into a randomised, double-blind, placebo-controlled phase. A planned interim analysis conducted after the first 60 patients had completed the 12-week lead-in phase demonstrated a 38% response rate. Based on this activity and on the recommendation of the Independent Data Monitoring Committee (IDMC), randomisation was halted and all continuing patients were treated with pazopanib on an open-label basis.	Open label, multicentre, single-arm extension study to VEG105192. Subjects randomised to placebo arm of VEG105192 who progressed had the option of being enrolled into study VEG107769 if they met the inclusion and exclusion criteria.
Intervention	Open-label phase: Pazopanib 800mg o.d. Randomised phase: Pazopanib 800mg o.d. or matching placebo After halt to randomised phase, all patients received open-label pazopanib until disease progression, unacceptable toxicity, withdrawal of consent or investigator discretion.	Pazopanib 800 mg o.d. until disease progression, unacceptable toxicity or withdrawal of consent
Population	Patients with locally recurrent /metastatic RCC (n=225) • Treatment-naive (n=155) • Prior systemic treatment (n=70)	Patients with locally advanced/metastatic RCC (n=71†) • Treatment-naive patients (n=34)* • Cytokine pre-treated patients (n=37)*
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was changed from PD rate at 16 weeks post-randomisation to • Response rate (CR + PR) as defined by RECIST criteria (for all enrolled subjects) • SD rate at week 12 (original co-primary endpoint to be performed for 12-week lead-in phase for interim analysis only, but performed *ad hoc* for all 225 enrolled patients in final analysis) Response was assessed at week 12 and every 8 weeks thereafter.	• Safety and tolerability (including incidence, severity and causality of all AEs, SAEs, and other safety parameters) Safety assessments were performed every 3 weeks until week 24, and then every 4 weeks until discontinuation of treatment.

Study	VEG102616	VEG107769
	RR was calculated separately using the investigator-assessed and IRC data. Responses at week 12 were categorised by the investigators for the purposes of conducting the study.	
Secondary outcomes (including scoring methods and timings of assessments)	*Efficacy*: • Duration of response • Time to response • Progression-free survival (i. all-enrolled patients with and without adjustment for randomisation to placebo; ii. comparison of randomised groups) *Safety*: • AEs • SAEs • Clinical laboratory evaluations • Vital signs and ECOG • 12-lead ECG Safety assessments were performed at baseline, day 8, day 28 and every 4 weeks thereafter.	• Response rate (CR + PR) as defined by RECIST criteria • CR + PR + 6- month SD as defined by RECIST criteria • PFS • OS Imaging-based disease assessments (CT or MRI) were performed every 6 weeks until week 24, and every 12 weeks thereafter until progression. Bone scans were performed only if clinically indicated.
Duration of study	First patient enrolled October 2005. Last subject screened Sept 2006. Clinical cut-off 24 March 2008 for safety data and 03 April 2008 for efficacy data.	Ongoing. First patient enrolled 30 September 2008. Interim analysis with clinical cut-off 23 May 2008.
Duration of follow-up	Subjects were followed up until 28 days after the last dose of pazopanib or withdrawing from study.	Subjects are followed every 3 months until death, withdrawal of consent, or until study completion, whichever comes first.

† Of the 71 subjects who entered VEG107769, 1 subject was randomised to the pazopanib arm in VEG105192. The subject was enrolled into Study VEG107769 as an exemption at the investigator's request due to improvement in clinical signs and symptoms despite progression. * Based on assessment at baseline in VEG105192
AE = Adverse Event; CR = Complete Response; ECG = Electrocardiogram; PD = Progressive disease; PFS = progression-free survival; OS = Overall survival; PR = Partial response; RECIST = Response Evaluation Criteria In Solid Tumours; SAE = Serious Adverse Events; SD = Stable disease.

5.8.1.3 Participants

Table 5.42: Eligibility criteria in the non-RCTs

Study no.	Main inclusion criteria	Main exclusion criteria
VEG102616	• Metastatic or locally recurrent RCC • Predominantly clear cell histology • Either no prior systemic therapy or failed 1 prior cytokine-based or bevacizumab-based therapy • Measurable disease as per RECIST • ECOG Performance Status of 0 or 1 • Adequate baseline bone marrow, hepatic and renal function	• Received non-cytokine or non-bevacizumab therapies • Received chemotherapy for RCC • Had major surgery, radiotherapy, hormonal therapy or immunotherapy within last 28 days and/or not recovered from prior therapy • History of hypercalcaemia within last two months • Poorly controlled hypertension (SBP ≥140mmHg or DBP ≥90mmHg despite anti-hypertensive therapy) • QTC prolongation ≥480 milliseconds • Class II / III /IV congestive heart failure per NYHA classification • History of cerebrovascular accident • History of myocardial infarction, unstable angina, cardiac angioplasty or stenting within last 12 weeks, • Current use of warfarin or use of antiplatelet drugs other than aspirin • Leptomeningeal or brain metastases • Prior history of malignancies other than RCC • Malabsorption syndrome or other condition that could affect absorption of pazopanib.
VEG107769	• Have been enrolled into study VEG105192 and have documented disease progression after being randomised into the placebo arm	• Have received any anti-cancer therapy since discontinuation of VEG105192 • Malabsorption syndrome or other condition that

	• ECOG Performance Status of 0, 1 or 2 • Adequate baseline haematologic, hepatic and renal function • At least 4 weeks must have elapsed since last surgery and 2 weeks must have elapsed since last radiotherapy • Complete recovery from prior surgery and/or reduction of all AEs to Grade 1 from prior systemic therapy or radiotherapy	could affect absorption of pazopanib • Symptomatic CNS metastases or leptomeningeal tumours • Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation; abdominal fistula; gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to beginning study treatment • History of HIV infection • Presence of uncontrolled infection • QTc interval ≥470 milliseconds • Class III / IV congestive heart failure per NYHA classification • History of one of the following cardiac conditions within past 6 months: o Cardiac angioplasty or stenting o Myocardial infarction o Unstable angina o Cerebrovascular accident, pulmonary embolus or deep venous thrombosis • Poorly controlled hypertension (SBP ≥140mmHg or DBP ≥90mmHg despite anti-hypertensive therapy) • Evidence of bleeding diathesis or coagluopathy.

* Lesions that could be accurately measured in at least one dimension with longest diameter ≥20mm using conventional techniques or ≥10cm with spiral CT. ECOG = Eastern Cooperative Oncology Group.

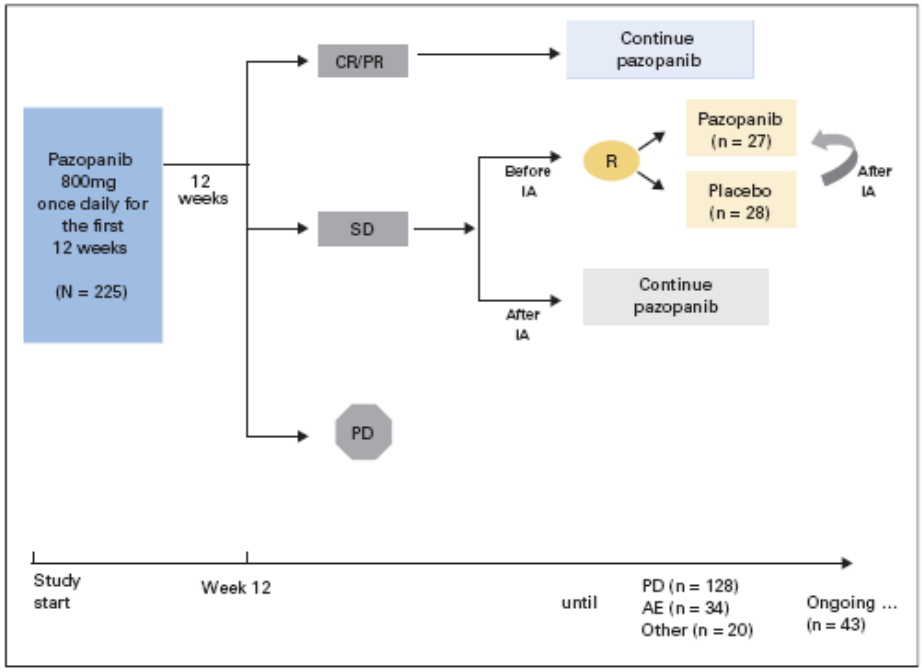
Participant flow

VEG102616

A total of 225 subjects were enrolled in the study. Fifty-five subjects with stable disease (SD) by investigator assessment at week 12 participated in the randomised part of the study (27 were randomised to pazopanib and 28 were randomised to placebo). The remaining 170 patients either did not qualify for random assignment (non-SD patients) or reached week 12 after the study was changed to an open-label design; these patients received open-label pazopanib throughout the duration of their participation in the study (Figure 5.8).

As of the clinical cut-off date of 24 March 2008, 43 subjects were ongoing. Disease progression (128 subjects [57%]) and AEs (34 subjects [15%]) were the most common reasons for discontinuation of pazopanib. (Note: One subject was recorded as discontinuing pazopanib due to disease progression and AEs and is counted here in the AE group).

Figure 5.8: Study flowchart and patient disposition VEG102616



IA = Interim analysis

VEG107769

A total of 71 subjects were enrolled in the study at the clinical cut-off of 23 May 2008; the study is ongoing. One subject was enrolled from the pazopanib arm of VEG105192 as an exemption at the investigator's request due to improvement in clinical signs and symptoms despite progression. At the time clinical cut-off, 31 subjects (44%) were still receiving pazopanib. The most common reasons for discontinuation of pazopanib were disease progression (34%), AEs (10%), withdrawal from the study (6%) and death (4%).

Table 5.43: Characteristics of participants in the non-RCTs

Characteristic	VEG102616 N=225	VEG107769 N=71
Age, years		
Median (range)	59.8 (32-81)	59.0 (25-80)
Sex, n (%)		
Male	156 (69)	53 (75)
Prior systemic therapy, n (%)		
Treatment-naive	155 (69)	34 (48)*
Cytokine pre-treated	70 (31)	37 (52)*
Prior nephrectomy, n (%)	205 (91)	71 (100)
Time since initial diagnosis		
Median (range)	26.4 months (4.7-161.6)	568 days (1-6871)
Most common sites of metastatic disease, n (%)		
Lung	176 (78)	57 (80)
Lymph nodes	96 (43)	40 (56)
Bone	62 (28)	18 (25)
Abdomen	NR	16 (23)
Kidney	49 (22)	NR
Liver	39 (17)	12 (17)
Adrenals	37 (16)	NR
ECOG Performance Status, n (%)		
0	147 (65)	23 (32)
1	78 (35)	37 (52)
2/unknown	NA	10 (14) / 1 (1)
MSKCC risk category†		
Favourable risk	97 (43)	29 (41)
Intermediate risk	92 (41)	33 (46)

Poor risk	5 (2)	1 (1)
Missing / Unknown	31‡ (14)	8 (11)

MSKCC = Memorial Sloan Kettering Cancer Center; NA = Not applicable; NR = Not reported.
* Assessed at baseline to previous phase III trial VEG105192; † For 162 patients in VEG102616, calcium instead of corrected-calcium was used to derive their MSKCC risk factor. All 71 of the MSKCC risk group assignments in VEG107769 required total calcium measurements because baseline albumin levels were not collected to calculate corrected calcium; ‡ 31 patients in VEG102616 were missing data on one or more of the 5 risk factors and thus did not have sufficient data to be assigned a risk category.

5.8.1.4 Outcomes

Table 5.44: Primary and secondary outcomes in the non-RCTs

	Primary outcome measure	Reliability/validity/current use in clinical practice
VEG102616	• Response rate (RR) – defined as percentage of subjects who achieved a confirmed CR or PR as per RECIST criteria. • SD rate at week 12 – defined as percentage of subjects with SD at 12 weeks after first dose of pazopanib. This analysis was originally to be performed for the interim analysis only but was performed for all 225 subjects in the final analysis. Overall RR (defined as percentage of subjects with either a confirmed or unconfirmed CR or PR) and PD rate (defined as percentage of subjects with progressive disease or unknown disease status) were also calculated for the week 12 time-point in the final analysis.	RR rate is an important endpoint for determining the efficacy of anti-cancer treatments and has traditionally been used in phase II trials. Tumour response was evaluated by investigators using the internationally recognised and widely used Response Evaluation Criteria In Solid Tumours (RECIST) (Therasse 2000; see Table 5.8). Bone scans were conducted to confirm a CR or PR no less than 4 weeks after first documented evidence of response. All imaging data were independently and centrally reviewed by an Independent Review Committee (IRC) blinded to the investigator's assessments and who also determined response using RECIST. The frequency of imaging assessments in the study (at week 12 then every 8 weeks) was similar to that performed routinely in clinical practice. Details of adjustments made in the RR analysis to estimate results as if subjects were continuously exposed to pazopanib can be found in Table 5.45.
	Secondary outcome measure	**Reliability/validity/current use in clinical practice**
	Efficacy: • PFS – defined as the time from first dose until the earliest date of disease progression or death due to any cause. • Duration of response (DOR) – defined as the time from documented evidence of response (CR/PR) until the first documented sign of disease progression or death, if sooner. • Time to response – defined as time from first dose until first documented evidence of CR or PR. *Safety*: • AEs • SAEs • Clinical laboratory evaluations • Vital signs	PFS is accepted as a valid measure of clinical benefit and adequate surrogate for survival in RCC trials (George 2009; Bracarda 2009). With PFS, the treatment effect is not diluted by post-study therapy following discontinuation of study treatment and it reflects the clinical benefits of disease stabilisation as well as a CR or PR (Farley 2010). Treatment effects on PFS have been shown to be predictive of treatment effects on OS in patients with metastatic RCC (Delea 2009). All assessments of response and progression were based on radiographic assessments conducted separately by investigators and the IRC using the well-established RECIST criteria. Bone scans were conducted to confirm a CR or PR. Any subject with an unconfirmed CR or PR at week 12 was considered a non-progressor. Progression and censoring dates were based on scan dates not assessment dates. Details of adjustments made in the efficacy analyses to account for patients who received placebo and thereby estimate results as if subjects were continuously exposed to pazopanib can be found in Table 5.45. AEs and laboratory safety data were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE)

	• ECOG PS • 12-lead ECG	(version 3.0), a descriptive terminology that is well accepted and widely used for recording the severity of adverse events. Investigators were responsible for the detection and documentation of events meeting the criteria/definition of an AE and SAE and for judging whether an event was related to study drug. Details of adverse events experienced by patients receiving treatment for advanced/metastatic RCC would be recorded routinely in clinical practice. Regular biochemistry and haematology assessments are performed routinely in patients being treated for advanced/metastatic RCC in clinical practice. Assessment of vital signs is a routine clinical procedure. ECOG PS is a reliable, widely accepted and widely used method (5-point scale) of assessing the functional status and ability to self-care of cancer patients (Buccheri 1996).
	Primary outcome measure	**Reliability/validity/current use in clinical practice**
VEG107769	*Safety*: • AEs • SAEs • Clinical laboratory evaluations • Vital signs • Physical examination • ECOG PS • 12-lead ECG	See above for details of reliability/validity/current use in practice of safety assessments.
	Secondary outcome measure	**Reliability/validity/current use in clinical practice**
	• Response rate (RR) – defined as percentage of subjects who achieved a confirmed CR or PR • Rate of CR + PR + 6-month SD – defined as percentage of subjects who achieved either a confirmed CR, PR or SD for at least 6 months • PFS – defined as time from first dose to date of progression or death due to any cause whichever came first. • OS – defined as time from first dose to date of death due to any cause.	See above for details of reliability/validity/current use in practice of tumour response and PFS assessments. RECIST criteria were used for imaging-based tumour response and PFS evaluations. Each subject's disease status is based on the investigator's assessments. There was no independent imaging review in this study.

5.8.1.5 Statistical analysis

Table 5.45: Summary of statistical analyses in non-RCTs

	VEG107769
Hypothesis objective	The primary objective of this ongoing study is to evaluate the safety of pazopanib given open-label to subjects randomised to placebo in VEG105192. No formal statistical hypotheses are being tested.
Sample size, power calculation	No formal sample size calculations were applied to this study. A maximum of 145 subjects randomised to placebo in VEG105192 were eligible for VEG107769 if they met the enrolment criteria.
Analysis populations	The All Treated Subjects (ATS) population (comprising all enrolled subjects who receive at least one dose of pazopanib) is being used for the analysis of all safety and efficacy data. An interim analysis was conducted with a cut-off date 23 May 2008.
Statistical analysis	PFS and OS were analysed using Kaplan-Meier methods. Categorical variables were summarised using descriptive methods. 95% CIs for response rates were calculated. Safety data were summarised descriptively.
Data management, patient withdrawals	Patients are being treated until disease progression or withdrawal from study due to unacceptable toxicity. Patients may also withdraw for other reasons prior to disease progression or unacceptable toxicity. Any subjects who withdraw are included in analyses up to the time of withdrawal, regardless of duration of treatment. There is no imputation for missing data. Where appropriate, available data is summarised over specified intervals (e.g. from start of open-label treatment until withdrawal from the study) using suitable summary statistics. For the PFS endpoint, the date associated with the last visit with adequate assessment is used for those patients who are alive and have not progressed at the time of analysis; such patients are censored in the analysis. If a progression event occurred after an extensive lost-to-follow-up time (≥12 weeks) the primary analysis censors those patients at the date of their last visit with an adequate assessment.
Sub-group analyses	Not conducted.

	VEG102616
Hypothesis objective	The objective of the study was to evaluate the efficacy and safety of pazopanib 800mg o.d. in patients with advanced/metastatic RCC. The original objective was to show that the PD rate at 16 weeks post-randomisation was lower in the pazopanib arm than the placebo. No other hypotheses were to be formally tested.
Sample size, power calculation	The sample size was based on the original primary endpoint, PD rate at 16 weeks post-randomisation. The study had aimed to detect 4 times greater risk of having PD in patients randomly assigned to placebo, with 5% significance level (two-sided) and 90% power using the Pearson $\chi 2$ test, which required 80 patients to be randomly assigned. Sample size was not re-calculated after the study became an open-label study.
Analysis populations	The All Enrolled population (N=225) accounts for complete pazopanib experience and included all subjects treated with pazopanib (regardless of whether they received placebo during the randomised phase). This was used for the interim efficacy analysis, the analysis of response rate and evaluation of safety. The Randomised Efficacy population consisted of all subjects randomised (N=55). Subjects were analysed based on the group to which they were randomised, regardless of subsequent cross-over. This was used for the comparison of PFS between pazopanib and placebo in the randomised phase.
Statistical analysis	The study was designed with a planned interim analysis conducted after 60 patients had completed the 12 week lead-in phase. The analysis had a futility boundary in place based on the SD rate at week 12 (if less than 40%) but no formal stopping rule for efficacy. Based on a RR of 38% at week 12 determined by independent review and confirmed on subsequent scans, the IDMC recommended halting randomisation, unblinding the study and offering pazopanib treatment to all subjects in the randomised phase of the study. In general, data for all 225 subjects were summarised together rather than maintaining a distinction between subjects in the Randomised phase and the Open-label treatment phase. Data from subjects receiving placebo were pooled and summarised together with data from subjects who received placebo. For the purposes of calculating RR, subjects who received pazopanib continuously or did not receive placebo for >28 days were assessed for response relative to baseline at the beginning of the trial (prior to first dose). Patients assigned to placebo for >28days who crossed back to pazopanib after PD had their baseline reset to the assessment just prior to cross-over if this new baseline reflected a worsening from the original baseline. The estimated response and SD rates were calculated along with corresponding exact 95% CIs. Duration of and time to response were summarised descriptively. An analysis of PFS was performed using data from all enrolled subjects, including those randomly assigned to placebo. Median PFS was estimated using Kaplan-Meier techniques and approximate 95% CIs were calculated. An adjusted analysis of PFS was also performed using Kalbfleisch-Prentice estimation (a modified version of Kaplan-Meier estimation where subjects are not restricted to have a weight of 1) to correct for potential bias caused by the inclusion of subjects randomised to placebo who did not have progression times that were indicative of continuous pazopanib therapy. Approximate 95% CIs for the quartiles were calculated using bootstrapping methods. PFS was compared between pazopanib and placebo for the randomised phase using a log-rank test. Safety data were summarised descriptively.
Data management, patient withdrawals	All subjects were included in analyses up to time of withdrawal from study regardless of duration of treatment. For the PFS endpoint, the date associated with the first scan of last adequate assessment was used for subjects who were alive and had not progressed at the time of the analysis; such subjects were considered censored in the analysis. If a progression event occurred after an extensive lost-to-follow-up time (≥16 weeks) the analysis censored those subjects at the date of their first scan of last adequate assessment prior to lost to follow-up. For endpoints which determined the percentage of responders, subjects with unknown or missing response were assumed to be non-responders. For subjects who did not progress or die, duration of response endpoint was censored on the date of last adequate disease assessment without progression.
Sub-group analyses	Overall RR was calculated for two sub-populations: (i) subjects who received prior systemic therapy and (ii) subjects who received no prior systemic therapy. A number of exploratory sub-group analyses were conducted to identify factors that affect overall RR and correlate with improved PFS including: ECOG PS, time since prior diagnosis, prior systemic therapy, prior nephrectomy and sites of metastases.

CI = Confidence Interval; IDMC = Independent Data Monitoring Committee; RR = Response rate.

5.8.1.6 Critical appraisal

Several tools exist for the quality assessment of non-randomised studies but none has been fully validated. The quality assessment of VEG102616 and VEG10769 was undertaken using a Centre for Reviews and Dissemination (CRD) quality assessment tool (Chambers 2009) for case series supplemented with some additional relevant descriptive criteria on trial quality assessment from NICE's guidance to manufacturers on STAs and from the CONSORT checklist. For the CRD tool, if the answer is "yes" to all 8 questions, then the quality rating is good; satisfactory if the answer is "yes" to criteria 2, 4-7; and poor if the answer is not "yes" to one or more of the criteria listed for satisfactory.

Table 5.46: Critical appraisal of non-RCTs

Critical Appraisal Criterion	VEG102616	VEG107769
CRD quality assessment tool for case series (Chambers 2009)		
1. Were selection/eligibility criteria adequately reported?	Yes. See Table 5.32 for inclusion/exclusion criteria.	Yes. See Table 5.32 for inclusion/exclusion criteria.
2. Was the selected population representative of that seen in normal practice?	Yes. Baseline characteristics of study population reflect those of patients with advanced/metastatic RCC receiving systemic treatment in clinical practice.	Yes. Baseline characteristics of study population reflect those of patients with advanced/metastatic RCC receiving systemic treatment in clinical practice.
3. Were appropriate measures of variability reported?	Yes	Yes
4. Was loss to follow-up reported or explained?	Yes	Yes
5. Were 90% of those included at baseline followed-up	Yes	Yes
6. Were patients recruited prospectively?	Yes	Yes
7. Were patients recruited consecutively?	Yes	Yes
8. Did the study report data for relevant prognostic factors?	Yes. See Table 5.33 for baseline disease characteristics.	Yes. See Table 5.33 for baseline disease characteristics.
Overall quality rating	Good	Good
Additional questions		
Was a justification of sample size provided?	Yes. See Table 5.35	No applicable given nature of study.
Was follow-up adequate?	Subjects were followed up until 28 days after the last dose of pazopanib.	Subjects followed until death, withdrawal of consent, or study completion, whichever comes first.
Were the individuals undertaking the outcomes assessment aware of allocation?	No. All imaging data were independently reviewed by an Independent Review Committee (IRC) blinded to the investigator's assessments.	Yes. Open-label study in which subjects' disease status was assessed by the investigators.
Was the study conducted in the UK (or were one or more centres of the multinational study located in the UK)?	Yes. Multicentre trial conducted in US, Asia and Europe.	Yes. Multicentre trial conducted in S. America, Australia, New Zealand, Asia and Europe, including 2 centres in UK with 5 patients enrolled.
How does dosage regimen used in the study compared with that detailed in the Summary of Product Characteristics?	Dosage regimen used in the study is same as dosage regimen proposed on SPC.	Dosage regimen used in the study is same as dosage regimen proposed on SPC.
Were the statistical analyses used appropriate?	Yes. See Table 5.35.	Yes. See Table 5.35.
Was an intention-to-treat analysis undertaken?	Yes for Randomised phase of study in which subjects were analysed based on the group to which they were randomised, regardless of subsequent cross-over. Not applicable to single arm 12-week lead-in phase and to open-label	Not applicable as non-randomised single-arm study. The All Treated Subjects (ATS) population (comprising all enrolled subjects receiving at least one dose of pazopanib) is used for the analysis of all safety and efficacy data.

	pazopanib treatment.	
Were there any confounding factors that may attenuate the interpretation of the results of the study?	Yes. The study was changed from a randomised discontinuation design to an open-label design following the IDMC's recommendation to halt randomisation. Since the All Enrolled population includes all subjects treated with pazopanib (regardless of whether they received placebo during the randomised phase), an adjustment has been made in the RR and PFS analyses to account for the fact that 28 patients were randomly assigned to placebo and thus did not have RRs and progression times indicative of continuous pazopanib treatment.	No.

5.8.1.7 Efficacy results

5.8.1.7.1 VEG102616

Primary efficacy results

The overall RR at the time of the efficacy data lock (03 April 2008) was 35% by Independent Review Committee (IRC) and 34% based on investigators' assessment. RR was similar in treatment-naive patients (34%) (Table 5.47), similar to that reported in the VEG105192 trial. The majority of patients (n=195) experienced a reduction in target tumour size (Figure 5.9).

Table 5.47: Overall best response and response rate (VEG102616, All enrolled population, 03 April 2008 cut-off)

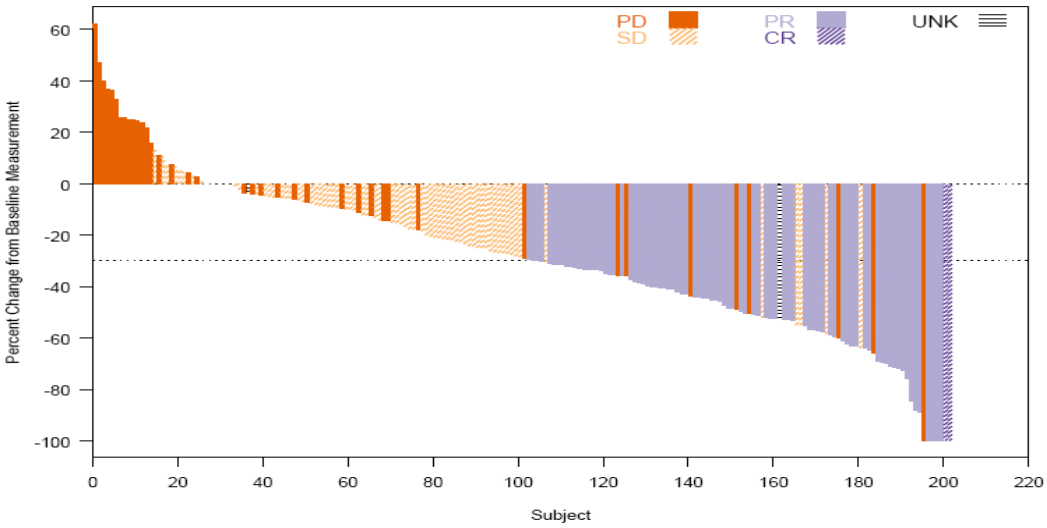
Efficacy measure	Independent Review, n (%)	Investigator Assessment, n (%)
Response category		
CR	3 (1.3)	2 (0.9)
PR	75 (33.3)	74 (32.9)
SD*	101 (44.9)	95 (42.2)
PD	24 (10.7)	37 (16.4)
NE†	22 (9.8)	17 (7.6)
Response rate (CR + PR), n (%) [95% CI]		
All enrolled subjects (N=225)	78 (34.7) [28.4-40.9]	76 (33.8) [27.6-40.0]
Treatment-naive subjects (N=155)	52 (33.5) [26.1-41.0]	NA

* Stable disease had to be assessed for a minimum of 8 weeks

† Not evaluable subjects were as follows: 19 subjects did not have post-baseline scans; however, 2 subjects did have symptomatic progression recorded. Two subjects had bone scans only at follow-up; no new lesions were identified by the independent reviewer. One subject had post-baseline scans recorded by the investigator at week 5; these were not reviewed by the independent reviewer.

NA = Not available.

Figure 5.9: Maximum percentage reduction from baseline in target tumour measurement by independent radiologist assessment (VEG102616, 03 April 2008 cut-off)



An original protocol defined primary endpoint was to assess SD in the first 60 subjects at week 12. This identified an SD of 47% by investigator assessment The RR at this time point was 38% as determined by IRC. These data were reviewed by the IDMC and led to the halt to randomisation. An *ad hoc* analysis of week 12 response for all 225 subjects determined the overall RR to be 28% and SD to be 47% by IRC. Again, RR was similar (26.5%) in patients with no prior systemic therapy at this time-point. The week 12 PD rate was 12% by IRC (Table 5.48).

Table 5.48: Response at week 12 (VEG102616, All enrolled population, 03 April 2008 cut-off)

Efficacy measure	Independent Review, n (%)	Investigator Assessment, n (%)
Response category		
CR	1 (0.4)	0
PR	61 (27.1)	65 (28.9)
SD	106 (47.1)	102 (45.3)
PD	24 (10.7)	36 (16.0)
Unknown*	3 (1.3)	4 (1.8)
Missing†	30 (13.3)	18 (8.0)
Response rate (CR + PR), n (%) [95% CI]		
All enrolled subjects (N=225)	62 (27.6) [21.7-33.4]	65 (28.9) [23.0-34.8]
Treatment-naive subjects (N=155)	41 (26.5) [19.5-33.4]	NA
PD rate (PD + unknown), n (%) [95% CI]		
All enrolled subjects (N=225)	27 (12.0 [7.8-16.2]	40 (17.8) [12.8-22.8]

* These subjects had a response rate of unknown recorded at week 12.
† These subjects did not have sufficient data entered to determine a week 12 response. Reasons for missing week 12 response are either no record of post-baseline response or available post-baseline data neither indicates a PD prior to week 12 nor had occurred past week 8.
NA = Not available.

Secondary efficacy results

Median time to and duration of response to pazopanib was 12 weeks and 68 weeks, respectively, by IRC. Median PFS attributable to pazopanib was estimated to be 52 weeks [11.9 months] per IRC (weighted to correct for potential bias caused by the inclusion of subjects who received placebo during the randomised phase). Again, the results are in line with the VEG105192 trial.

Median PFS for the all-enrolled population (unadjusted for those subjects who experienced disease progression while on placebo) was 45.3 weeks [10.4 months] per IRC. Median PFS in treatment-naive patients was shorter at 36.3 weeks but this estimation has not been adjusted for subjects randomised to placebo.

Table 5.49: Secondary efficacy endpoints (VEG102616, All enrolled population, 03 April 2008 cut-off)

Efficacy measure	Independent Review n (%)	Investigator Assessment n (%)
Duration of response		
Patients with CR + PR, n (%)	78 (35)	76 (34)
Median (weeks) [95% CI]	68.0 (53.7-NR)	71.1 (48.3-87.7)
Time to response		
Patients with CR + PR, n (%)	78 (35)	76 (34)
Median (weeks) [95% CI]	12.0 (11.7-12.1)	11.9 (11.6-12.0)
PFS (All enrolled subjects), Median (weeks) [95% CI]		
Patients who experienced PD or died, n (%)	109 (48)	142 (63)
Unadjusted (including subjects randomised to placebo)	45.3 (36.0-59.1)	37.0 (28.1-52.0)
Adjusted (adjusted for randomisation to placebo)	51.7 (43.9-60.3)	43.1 (29.6-59.3)
PFS (Treatment-naive subjects), Median (weeks) [95% CI]		
Patients who experienced PD or died, n (%)	99 (64)	NA
Unadjusted (including subjects randomised to placebo)	36.3 (27.6-52.0)	NA

NR = Not reached

For the 55 subjects who were randomised, PFS was performed as an ITT analysis regardless of cross-over to pazopanib at progressive disease. Patients in the pazopanib arm had a median PFS almost twice that of those in the placebo arm (52 vs. 27 weeks) by IRC. These data indicate that continuous pazopanib treatment is needed to maintain efficacy as patients switched to placebo had a marked drop in their median PFS.

Table 5.50: PFS, randomised comparison (VEG102616, Randomised population, 03 April 2008 cut-off)

Efficacy measure	Independent Review n (%)		Investigator Assessment n (%)	
	Pazopanib N=27	Placebo N=28	Pazopanib N=27	Placebo N=28
Patients who experienced PD or died, n (%)	10 (37)	22 (79)	18 (67)	19 (68)
Median (weeks)	51.6	27.1	59.4	37.0
95% CI	43.6-NR	19.9-47.3	35.3-87.7	19.7-61.0
p-value (Log rank test)	p=0.013		p=0.217	

Sub-group analyses

Results of exploratory sub-group analyses (including patients randomly assigned to placebo) identified the following factors to affect overall RR: ECOG PS status 1 better than 0 (p=0.003), haemoglobin ≥ lower limit of normal (p<0.001), metastasis to lymph nodes (p=0.032). The following factors were found to be correlated with improved PFS: ECOG PS score of 0 better than 1 (median PFS: 59 vs. 28 weeks; p=0.002) and more than one year from diagnosis to treatment (median PFS: 56 vs. 28 weeks; p=0.001).

5.8.1.7.2 VEG107769

As shown in Table 5.51, the RR was 32% and 49% of subjects achieved a CR+PR+6-month SD. As shown in the waterfall plot, the majority of patients had various degrees of tumour reduction (Figure 5.10) consistent with what has been observed in pazopanib-treated patients in the VEG105192 and VEG102616 studies. Median PFS for patients in this second-line setting 8.3 months and median OS was 16.3 months. The OS data are immature as the majority of patients were still being followed for survival and were censored for this analysis. The survival rates at 6, 12

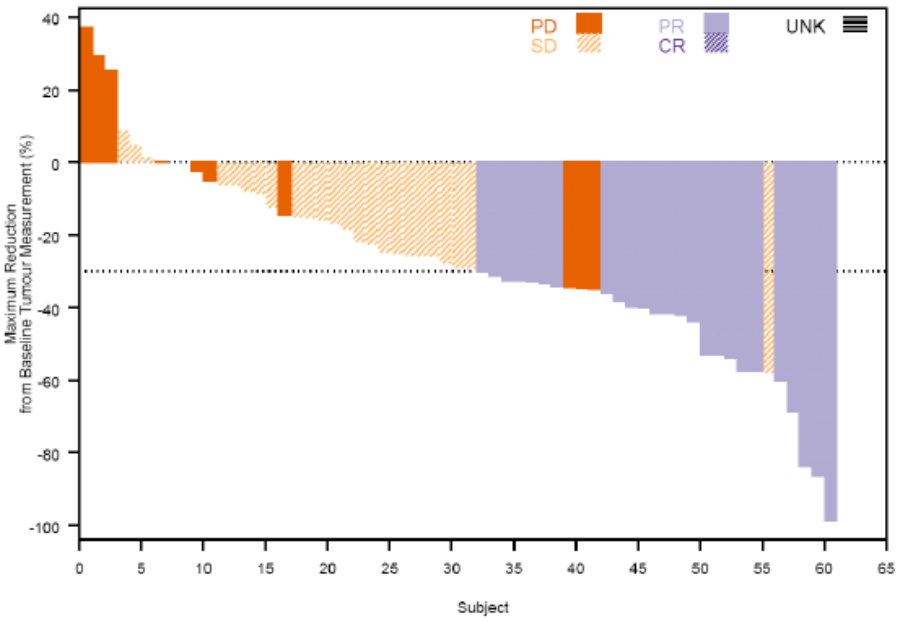
and 18 months were 82% (95% CI: 73-91%), 70% (95% CI: 58-83%) and 22% (95% CI: 0-55%), respectively.

Table 5.51: Summary of efficacy endpoints (VEG107769, investigator-assessed, 23 May 2008 cut-off)

	Pazopanib 800mg N=71
Best response, n (%)	
CR	0
PR	23 (32.4)
SD*	25 (35.2)
PD	10 (14.1)
Unknown	13 (18.3)
RR (CR + PR), n (%)	23 (32.4)
95% CI	21.5-43.3
CR + PR + 6-month SD, n (%)†	35 (49.3)
95% CI	37.7-60.9
PFS, median (months)‡	8.3
95% CI	6.1-11.4
OS, median (months)$	16.3
95% CI	13.6-NC

NC=Not calculable
* A confirmed response of SD required that the SD assessment occur no later than 12 weeks after the screening scans
† A best response of 6-month SD was achieved by 12 (16.9%) subjects
‡ 33 subjects (46%) had a progression event at the time of the analysis
$ 21 subjects (30%) had died at the time of the analysis.

Figure 5.10: Maximum decrease of tumour diameter from baseline (VEG107769, investigator-assessed, 23 May 2008 cut-off)



5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.9.1 **If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.**

The primary objective of the supportive study, VEG107769, was to assess the safety of pazopanib. The methodology, patient disposition, characteristics of participants, endpoints, statistical analysis, critical appraisal and efficacy outcomes are all presented in section 5.8. The safety results are presented in section 5.9.2 below.

5.9.2 **Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.**

5.9.2.1 VEG105192

5.9.2.1.1 Extent of exposure

The median duration of exposure to study medication was longer in the pazopanib arm compared with the placebo arm (7.4 vs. 4.2 months in the treatment-naive sub-population). At the time of the data cut-off, 27% of treatment-naive subjects on pazopanib and 19% on placebo had received treatment for more than 12 months.

Table 5.52: Summary of exposure to investigational product (VEG105192 Safety population, 23 May 2008 cut-off)

	Treatment-naive population		Overall study population	
	Pazopanib N=155	**Placebo N=78**	**Pazopanib N=290**	**Placebo N=145**
Duration of treatment (dose interruptions included)				
Median (range), months	7.4 (0-21)	4.2 (0-18)	7.4 (0-23)	3.8 (0-22)
< 3months	38 (25)	35 (45)	67 (23)	67 (46)
3-6	34 (22)	15 (19)	63 (22)	30 (21)
6-12 months	41 (26)	13 (17)	67 (23)	25 (17)
>12+ months	42 (27)	15 (19)	93 (32)	23 (16)
Duration of treatment (dose interruptions excluded)				
Median (range), months	7.1 (0-21)	4.2 (0-18)	7.3 (0-23)	3.8 (0-22)
Daily dose (dose interruptions included)				
Mean (SD), mg	696.0 (152.32)	784.2 (64.07)	687.5 (206.2)	779.3 (101.1)
Daily dose treatment (dose interruptions excluded)				
Mean (SD), mg	726.5 (128.57)	789.2 (55.07)	708.8 (169.6)	785.5 (73.87)

5.9.2.1.2 Adverse events

In the treatment-naive sub-population, 141 (91%) of subjects in the pazopanib arm and 58 (74%) in the placebo arm reported at least one AE during the study.

Table 5.53: Summary of adverse events by category (VEG105192 Safety population, 23 May 2008 cut-off)

	Treatment-naive population, n (%)		Overall study population, n (%)	
	Pazopanib N=155	**Placebo N=78**	**Pazopanib N=290**	**Placebo N=145**
Any AE	141 (91)	58 (74)	268 (92)	107 (74)
AE related to study medication	135 (87)	29 (37)	257 (89)	56 (39)
AE leading to permanent discontinuation of study medication	19 (12)	5 (6)	44 (15)	8 (6)
AE leading to dose reduction	36 (23)	3 (4)	69 (24)	5 (3)
AE leading to dose interruption	57 (37)	4 (5)	96 (33)	13 (9)
Serious AE (SAE)	33 (21)	13 (17)	69 (24)	27 (19)

Most common AEs

In the treatment-naive sub-population, the on-therapy AEs reported by >20% of patients in the pazopanib arm were diarrhoea (47%), hypertension (39%), hair colour changes (39%), nausea (26%), anorexia (25%), ALT increased (25%), vomiting (22%) and AST increased (20%) (Table 5.54). The proportions of patients experiencing an AE with maximum grade 3 or 4 were 37% and 6%, respectively, in the pazopanib arm compared with 13% and 6%, respectively, in the placebo arm. The most common grade 3/4 AEs in the pazopanib arm were ALT increased (11%) and AST increased (6%). The type and frequency of AEs experienced by treatment-naive subjects receiving pazopanib was similar to the overall safety profile for the pazopanib group.

Most AEs were considered by the investigator to be treatment-related in the pazopanib arm compared with the placebo arm (87% vs. 37% of treatment-naive

subjects, respectively). Treatment-related AEs reported for >10% patients in the pazopanib arm included diarrhoea, hypertension, hair colour changes, nausea, ALT increased, AST increased, anorexia, vomiting and fatigue (Table 5.55).

Deaths
Deaths resulting from AEs was reported in 12 (4%) subjects in the pazopanib arm and 4 (3%) of subjects in the placebo arm for the total study population. Four patients (1%) in the pazopanib arm had fatal AEs that were assessed by the investigator as attributable to study treatment: ischaemic stroke; abnormal hepatic function and rectal haemorrhage; peritonitis/bowel perforation; and abnormal hepatic function. The patients who died of peritonitis/bowel perforation had RCC metastasis present at the site of perforation. The patient who died of abnormal hepatic function was found on autopsy to have extensive infiltration of the liver with metastatic disease.

Serious adverse events (SAEs)
In the treatment-naive sub-population, SAEs were reported for 33 (21%) of patients in the pazopanib arm and 13 (17%) of those in the placebo arm. Diarrhoea was the most frequent SAE in patients receiving pazopanib (n=4 [3%]). All other individual SAEs were reported for ≤1% of patients in the pazopanib arm. Serious arterial/thrombotic events (including myocardial infarction/ischaemia) and serious hepatic abnormalities were each reported in 3 (2%) of pazopanib-treated patients in the treatment-naive stratum.

Table 5.54: On-therapy AEs reported for ≥5% subjects in pazopanib arm* by grade (VEG105192 Safety population, 23 May 2008 cut-off)

Preferred term	Treatment-naive population, n (%)						Overall study population, n (%)					
	Pazopanib N=155			Placebo N=78			Pazopanib N=290			Placebo N=145		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any adverse event*	141 (91)	57 (37)	9 (6)	58 (74)	10 (13)	5 (6)	268 (92)	96 (33)	20 (7)	107 (74)	21 (14)	8 (6)
Diarrhoea	73 (47)	4 (3)	1 (<1)	8 (10)	0	0	150 (52)	9 (3)	2 (<1)	13 (9)	1 (<1)	0
Hypertension	61 (39)	6 (4)	0	7 (9)	0	0	115 (40)	13 (4)	0	15 (10)	1 (<1)	0
Hair colour changes	60 (39)	1 (<1)	0	1 (1)	0	0	109 (38)	1 (<1)	0	4 (3)	0	0
Nausea	40 (26)	2 (1)	0	8 (10)	0	0	74 (26)	2 (<1)	0	13 (9)	0	0
Anorexia	39 (25)	3 (2)	0	8 (10)	0	0	65 (22)	6 (2)	0	14 (10)	1 (<1)	0
ALT increased	39 (25)	15 (10)	2 (1)	2 (3)	0	0	53 (18)	18 (6)	3 (1)	5 (3)	1 (<1)	0
Vomiting	34 (22)	4 (3)	1 (<1)	4 (5)	0	0	61 (21)	6 (2)	1 (<1)	11 (8)	3 (2)	0
AST increased	31 (20)	9 (6)	1 (<1)	2 (3)	0	0	43 (15)	13 (4)	1 (<1)	5 (3)	0	0
Fatigue	29 (19)	3 (2)	0	10 (13)	2 (3)	2 (3)	55 (19)	7 (2)	0	11 (8)	2 (1)	2 (1)
Asthenia	26 (17)	6 (4)	0	6 (8)	0	0	41 (14)	8 (3)	0	12 (8)†	0	0
Headache	21 (14)	0	0	4 (5)	0	0	30 (10)	0	0	7 (5)	0	0
Abdominal pain	19 (12)	4 (3)	0	1 (1)	0	0	32 (11)	6 (2)	0	2 (1)	0	0
Weight decreased	18 (12)	1 (<1)	0	2 (3)	1 (1)	0	26 (9)	1 (<1)	0	5 (3)	1 (<1)	0
Alopecia	14 (9)	0	0	0	0	0	23 (8)	0	0	1 (<1)	0	0
Back pain	14 (9)	1 (<1)	0	4 (5)	1 (1)	0	22 (8)	2 (<1)	0	13 (9)	3 (2)	0
Constipation	13 (8)	0	1 (<1)	3 (4)	0	0	17 (6)	0	1 (<1)	8 (6)	0	0
Dysgeusia	13 (8)	0	0	1 (1)	0	0	24 (8)	0	0	1 (<1)	0	0
Proteinuria	13 (8)	0	0	0	0	0	27 (9)	3 (1)	1 (<1)	0	0	0
Abdominal pain upper	12 (8)	0	0	1 (1)	0	0	25 (9)	2 (<1)	0	5 (3)	0	0
Rash	12 (8)	0	0	3 (4)	0	0	23 (8)	1 (<1)	0	4 (3)	0	0
Cough	12 (8)	0	0	12 (15)	0	0	22 (8)	0	0	14 (10)	0	0
Thrombocytopenia	12 (8)	2 (1)	1 (<1)	1 (1)	0	0	22 (8)	3 (1)	1 (<1)	2 (1)	0	1 (<1)
Pyrexia	11 (7)	0	0	4 (5)	0	0	15 (5)	0	0	8 (6)	0	0
Pain in extremity	10 (6)	0	0	6 (8)	1 (1)	0	18 (6)	1 (<1)	0	8 (6)	1 (<1)	0
Arthralgia	10 (6)	0	0	2 (3)	0	0	20 (7)	2 (<1)	0	11 (8)	0	0
Dyspnoea	10 (6)	1 (<1)	1 (<1)	7 (9)	1 (1)	0	21 (7)	2 (<1)	1 (<1)	11 (8)	2 (1)	0
Skin depigmentation	9 (6)	0	0	0	0	0	10 (3)			0	0	0
Blood creatinine increased	9 (6)	3 (2)	0	0	0	0	10 (3)	3 (1)	0	1 (<)	0	0
Hypothyroidism	8 (5)	0	0	0	0	0	19 (7)	0	0	0	0	0
Abdominal distension	8 (5)	0	0	1 (1)	0	0	10 (3)	1 (<1)	0	2 (1)	1 (<1)	0
Neutropenia	8 (5)	2 (1)	0	0	0	0	14 (5)	3 (1)	1 (<1)	0	0	0

* AEs are ranked by incidence in treatment-naive subjects in the pazopanib arm. Any AE, any grade includes grade 5 (fatal) events.

† One placebo subject had grade 5 asthenia.

AST = Aspartate aminotransferase; ALT = Alanine aminotransferase.

Table 5.55: On-therapy AEs reported for ≥5% subjects in pazopanib arm* by grade related to investigational product (VEG105192 Safety population, 23 May 2008 cut-off)

Preferred term	Treatment-naive population, n (%)						Overall study population, n (%)					
	Pazopanib N=155			Placebo N=78			Pazopanib N=290			Placebo N=145		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade*	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any adverse event*	135 (87)	44 (28)	3 (2)	29 (37)	3 (4)	0	257 (89)	74 (26)	11 (4)	56 (39)	5 (3)	1 (<1)
Diarrhoea	60 (39)	4 (3)	1 (<1)	4 (5)	0	0	128 (44)	9 (3)	2 (<1)	9 (6)	1 (<1)	0
Hypertension	59 (38)	5 (3)	0	7 (9)	0	0	106 (37)	12 (4)	0	13 (9)	1 (<1)	0
Hair colour changes	59 (38)	1 (<1)	0	1 (1)	0	0	107 (37)	1 (<1)	0	5 (3)	0	0
Nausea	34 (22)	2 (1)	0	4 (5)	0	0	63 (22)	2 (<1)	0	8 (6)	0	0
ALT increased	33 (21)	14 (9)	1 (<1)	0	0	0	43 (15)	15 (5)	0	3 (2)	0	0
AST increased	29 (19)	7 (5)	1 (<1)	0	0	0	38 (13)	9 (3)	1 (<1)	4 (3)	0	0
Anorexia	26 (17)	2 (1)	0	0	0	0	49 (17)	4 (1)	0	6 (4)	0	0
Vomiting	26 (17)	4 (3)	1 (<1)	3 (4)	0	0	48 (17)	4 (1)	0	5 (3)	1 (<1)	0
Fatigue	22 (14)	1 (<1)	0	0	0	0	46 (16)	5 (2)	0	2 (1)	0	0
Asthenia	18 (12)	4 (3)	0	0	0	0	26 (9)	5 (2)	0	3 (2)	0	0
Alopecia	13 (8)	0	0	0	0	0	20 (7)	0	0	1 (<1)	0	0
Abdominal pain	13 (8)	3 (2)	0	0	0	0	19 (7)	3 (1)	0	0	0	0
Weight decreased	12 (8)	0	0	0	0	0	17 (6)	0	0	1 (<1)	0	0
Dysgeusia	11 (7)	0	0	1 (1)	0	0	22 (8)	0	0	1 (<1)	0	0
Proteinuria	10 (6)	0	0	0	0	0	23 (8)	3 (1)	0	0	0	0
Rash	10 (6)	0	0	0	0	0	19 (7)	1 (<1)	0	2 (1)	0	0
Headache	9 (6)	0	0	0	0	0	15 (5)	0	0	1 (<1)	0	0
Skin de-pigmentation	9 (6)	0	0	0	0	0	10 (3)	0	0	0	0	0
Hypothroidism	8 (5)	0	0	0	0	0	20 (7)	0	0	0	0	0
Thrombocyopenia	8 (5)	2 (1)	0	0	0	0	18 (6)	2 (<1)	0	1 (<1)	0	1 (<1)
Abdominal pain upper	7 (5)	0	0	1 (1)			16 (6)	1 (<1)	0	1 (<1)	0	0
Abdominal distension	7 (5)	0	0	0	0	0	8 (3)	0	0	1 (<1)	0	0
Neutropenia	7 (5)	2 (1)	0	0	0	0	11 (4)	3 (1)	1 (<1)	0	0	0

***** AEs are ranked by incidence in treatment-naive subjects in the pazopanib arm. Any AE, any grade includes grade 5 (fatal) events; PPE = Palmar-plantar erythrodysesthesia syndrome.

AEs leading to permanent discontinuation of study medication

AEs leading to permanent discontinuation of study medication in the treatment-naive sub-population were reported for 19 (12%) subjects in the pazopanib arm and 5 (6%) in the placebo arm. The most common reasons for discontinuation of pazopanib were diarrhoea (3%) and AEs associated with liver function/enzyme abnormalities (including increased ALT/hepatic enzymes and hepatotoxicity) (2.6%).

Table 5.56: AEs leading to permanent discontinuation of study medication or early withdrawal from study in >1 subject in pazopanib arm* (VEG105192 Safety population, 23 May 2008 cut-off)

	Treatment-naive population n (%)		Overall study population n (%)	
	Pazopanib N=155	Placebo N=78	Pazopanib N=290	Placebo N=145
Any event	19 (12)	5 (6)	44 (15)	8 (6)
Diarrhoea	4 (3)	0	6 (2)	0
Liver function./ enzyme abnormalities	4 (3)	0	15 (5)	0
Hepatotoxicity	2 (1)	0	3 (1)	0
ALT increased	1 (<1)	0	4 (1)	0
Hepatic enzymes increased	1 (<1)	0	2 (<1)	0
AST increased	0	0	2 (<1)	0
Blood bilirubin increased	0	0	1 (<1)	0
Hyperbilirubinaemia	0	0	2 (<1)	0
Hepatic function abnormal	0	0	1 (<1)	1 (<1)
Vomiting	2 (1)	0	2 (<1)	0
Asthenia	2 (1)	0	3 (1)	1 (<1)

* Based on treatment-naive sub-population

AEs leading to dose reductions or interruptions

In the treatment-naive sub-population, more subjects in the pazopanib arm had AEs which led to dose reductions[8] than in the placebo arm (23% vs. 4%) (Table 5.57). The most common AEs leading to dose reductions were hypertension (12 subjects [8%]) and ALT increased (7 subjects [5%]).

Similarly, more patients receiving pazopanib had AEs leading to dose interruptions than those on placebo (37% vs. 5%). AEs leading to dose interruptions in >5% of pazopanib-treated patients included ALT increased (14 [9%] subjects), AST increased (12 [8%] subjects) and diarrhoea (9 [6%] subjects) (Table 5.58).

Table 5.57: AEs leading to dose reductions in >1 subject in pazopanib arm* (VEG105192 Safety population, 23 May 2008 cut-off)

	Treatment-naive population, n (%)		Overall study population, n (%)	
	Pazopanib N=155	Placebo N=78	Pazopanib N=290	Placebo N=145
Any event	36 (23)	3 (4)	69 (24)	5 (3)
Hypertension	12 (8)	2 (3)	21 (7)	2 (1)
ALT increased	7 (5)	0	9 (3)	0
Diarrhoea	5 (3)	0	16 (6)	0
AST increased	4 (3)	0	4 (1)	1 (<1)
Hepatic function abnormal	3 (2)	0	3 (1)	0
Fatigue	3 (2)	0	7 (2)	0
Asthenia	3 (2)	0	3 (1)	1 (<1)
Vomiting	2 (1)	0	5 (2)	0
Nausea	2 (1)	0	4 (1)	0
Anorexia	2 (1)	0	2 (<1)	1 (<1)

* Based on treatment-naive sub-population

[8] Note: These figures may be under-estimated because of the way in which the data were captured. Only one action was recorded. Thus, if the patient had a reduction followed by an interruption, only the interruption might have been recorded.

Table 5.58: AEs leading to dose interruptions in >1 subject in pazopanib arm* (VEG105192 Safety population, 23 May 2008 cut-off)

	Treatment-naive population, n (%)		Overall study population, n (%)	
	Pazopanib N=155	Placebo N=78	Pazopanib N=290	Placebo N=145
Any event	57 (37)	4 (5)	96 (33)	13 (9)
ALT increased	14 (9)	0	17 (6)	2 (1)
AST increased	12 (8)	0	15 (5)	2 (1)
Diarrhoea	9 (6)	0	16 (6)	0
Hypertension	8 (5)	0	14 (5)	2 (1)
Vomiting	7 (5)	0	13 (4)	1 (<1)
Fatigue	5 (3)	1 (1)	7 (2)	1 (<1)
Asthenia	4 (3)	0	4 (1)	0
Abdominal pain	4 (3)	0	5 (2)	0
Anorexia	4 (3)		5 (2)	0
Nausea	4 (3)	0	5 (2)	0
Proteinuria	2 (1)	0	5 (2)	0
Neutropenia	2 (1)	0	3 (1)	0
Anaemia	2 (1)	0	2 (<1)	0
Myocardial ischaemia	2 (1)	0	2 (<1)	0
Transaminases increased	2 (1)	0	2 (<1)	0
Intestinal obstruction	2 (1)	0	2 (<1)	0

* Based on treatment-naive sub-population

5.9.2.1.3 Clinical laboratory evaluations

Haematology assessments

Most treatment-emergent haematological toxicity grade increases from baseline were grade 1 or 2 in both groups in the treatment-naive sub-population. In the pazopanib arm, the incidences of post-baseline increases to grade 3 were low, occurring in between 0% and 5% of patients; increases to grade 4 haematological toxicity were infrequent (<1%).

Table 5.59: Summary of worst-case toxicity grade increase from baseline for haematological toxicities (VEG105192 Safety population, treatment-naive sub-population, 23 May 2008 cut-off)

Haematologic toxicity	Number (%) of subjects							
	Pazopanib N=155				Placebo N=78			
	N	Any grade*	Grade 3	Grade 4	N	Any grade*	Grade 3	Grade 4
Leukopenia	150	57 (38)	0	0	77	3 (4)	0	0
Neutropenia	150	56 (37)	3 (2)	0	77	3 (4)	0	0
Thrombocytopenia	150	52 (35)	1 (<1)	0	77	4 (5)	0	0
Lymphocytopenia	150	50 (33)	7 (5)	0	77	19 (25)	1 (1)	0
Anaemia	150	37 (25)	1 (<1)	1 (<1)	77	25 (32)	1 (1)	1 (1)

* Any grade increase from baseline; subjects with missing baseline grades were assumed to have a baseline grade of 0.

Clinical chemistry assessments

The most common treatment-emergent clinical chemistry abnormalities (any toxicity grade increase) in the pazopanib arm for the treatment-naive sub-population were ALT elevation (59%) and AST elevation (58%) (Table 5.60). Overall, the majority of toxicity grade increases in clinical chemistry parameters were grade 1 or 2 in both treatment arms. The most common grade 3 increases in the pazopanib arm were ALT elevation and AST elevation (14% and 10%, respectively, compared with 1% for both in the placebo arm). A toxicity grade increase to grade 4 occurred in ≤3% of patients in either treatment arm for any individual laboratory test.

Elevations in ALT ≥3 x upper limit of normal (ULN) occurred in 52 pazopanib-treated patients in the total study population (18%): ALT elevation recovered to ≤grade 1

after dose modification, interruption or discontinuation in 45 patients (87%); 7 patients (13%) did not have adequate follow-up data to assess recovery. These data have not been analysed for the treatment-naive sub-population due to the small size of the sub-group of patients with elevated liver enzymes.

Table 5.60: Summary of worst-case toxicity grade increase from baseline for clinical chemistry parameters (VEG105192 Safety population, treatment-naive sub-population, 23 May 2008 cut-off)

Haematologic toxicity	Number (%) of subjects							
	Pazopanib N=155				Placebo N=78			
	N	Any grade*	Grade 3	Grade 4	N	Any grade*	Grade 3	Grade 4
ALT increase	155	92 (59)	22 (14)	3 (2)	77	18 (23)	1 (1)	0
AST increase	154	90 (58)	16 (10)	2 (1)	77	16 (21)	1 (1)	0
Hyperglycaemia	150	64 (43)	2 (1)	0	77	26 (34)	0	0
Hypocalcemia	150	54 (36)	3 (2)	2 (1)	77	23 (30)	2 (3)	1 (1)
Total bilirubin increase	150	53 (35)	4 (3)	2 (1)	77	8 (10)	1 (1)	0
Hyponatremia	150	51 (34)	6 (4)	4 (3)	77	20 (26)	4 (5)	0
Hypophosphatemia	148	46 (31)	3 (2)	0	75	12 (16)	0	0
Alkaline phosphatase	150	46 (31)	3 (2)	1 (<1)	77	27 (35)	1 (1)	0
Creatinine	150	37 (25)	0	2 (1)	77	21 (27)	1 (1)	0
Hypomagnesemia	148	36 (24)	1 (<1)	1 (<1)	75	6 (8)	0	0
Hyperkalemia	150	34 (23)	4 (3)	1 (<1)	77	18 (23)	4 (5)	0
Hypercalcemia	150	23 (15)	0	4 (3)	77	15 (19)	2 (3)	0
Hypoglycemia	150	20 (13)	0	0	77	0	0	0
Hypernatremia	150	18 (12)	2 (1)	0	77	6 (8)	0	0
Hypermagnesemia	148	17 (11)	5 (3)	0	75	2 (3)	0	0
Hypokalemia	150	15 (10)	1 (<1)	2 (1)	77	2 (3)	0	0

* Any grade increase from baseline; subjects with missing baseline grades were assumed to have a baseline grade of 0.

5.9.2.1.4 AEs of special interest

Cardiac and vascular events

Thrombotic events due to inhibition of VEGF and subsequent rises in erythropoietin (Tam 2006) are clinically important as they can be fatal or lead to significant morbidity. In the treatment-naive sub-population, arterial thrombotic events occurred in 4% of pazopanib-treated patients (myocardial ischaemia 1%, transient ischaemic attack 1%, ischaemic stroke 1%, pulmonary embolism <1%) compared with none in the placebo arm.

Increasingly, cardiotoxicity is being recognised as a common side effect of tyrosine kinase inhibitors. Cardiotoxicity with pazopanib was low with congestive heart failure (CHF) being observed in 2 patients (1%) in the pazopanib arm, versus none in the placebo arm. There were no cases of arrhythmia, myocardial dysfunction or decreased left ventricular ejection fraction (LVEF) reported in the treatment-naive sub-population (however, it should be noted that ECHO/MUGA scans were not performed per-protocol in VEG105192 to collect LVEF data and only when clinically indicated).

Haematological events

Haematological toxicity occurred at a relatively low frequency with pazopanib in treatment-naïve patients and is clinically important as blood transfusions due to anaemia can impact local resource capability as well as the potentially life-threatening complication of febrile neutropenia. Any grade cytopenias ranged from 25 to 38% with a low incidence of grade 3/4 haematological toxicity (see Table 5.59). The relatively low incidence of haematological toxicity is partially explained by the lack of Flt-3 receptor activity of pazopanib which is expressed on haematological progenitor cells (Kumar 2009).

5.9.2.2 VEG102616

5.9.2.2.1 Adverse events

The most common treatment-emergent AEs reported were diarrhoea (63%), fatigue (46%), hair depigmentation (43%), nausea (42%) and hypertension (41%) (Table 5.61). The most common grade 3 or 4 treatment-related AEs were hypertension (8%), increased ALT (6%), increased AST (4%), diarrhoea (4%) and fatigue (4%).

Table 5.61: Treatment-emergent AEs occurring in ≥10% subjects (VEG102616, All enrolled population, 03 April 2008 cut-off)

Event	N=225		
	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Any event	221 (98)	97 (43)	22 (10)
Diarrhoea	142 (63)	9 (4)	0
Fatigue	103 (46)	11 (5)	0
Hair depigmentation	97 (43)	0	0
Nausea	94 (42)	2 (<1)	0
Hypertension	93 (41)	20 (9)	0
Anorexia	54 (24)	2 (<1)	0
Dysgeusia	54 (24)	0	0
Vomiting	45 (20)	2 (<1)	0
Headache	44 (20)	0	0
Cough	38 (17)	0	0
Abdominal pain	36 (16)	7 (3)	0
Rash	36 (16)	2 (<1)	0
Constipation	33 (15)	1 (<1)	0
ALT increased	32 (14)	12	2 (<1)
Arthralgia	29 (13)	1 (<1)	0
AST increased	28 (12)	7 (3)	2 (<1)
Back pain	27 (12)	2 (<1)	0
Dizziness	27 (12)	0	1 (<1)
PPE	24 (11)	4 (2)	0
Alopecia	23 (10)	0	0
Dyspepsia	23 (10)	3 (1)	0
Peripheral oedema	22 (10)	0	0

Deaths

A total of 22 deaths were reported in the study; 15 of which could be attributed to underlying disease. Two deaths were considered by the investigator to be treatment-related; these were due to large intestine perforation in the setting of diverticulitis and dyspnoea in the presence of malignant pleural effusions.

SAEs

SAEs (fatal and non-fatal) were reported by 74 subjects (33%). The most frequently observed SAEs were pleural effusion (5 subjects; 2%) and pulmonary embolism (4 subjects; 2%).

AEs leading to permanent discontinuation of study medication

Thirty-four patients (15%) discontinued pazopanib as a result of an AE. Elevations in liver enzymes led to discontinuations in 9 patients (4%). Hypertension, diarrhoea and fatigue/asthenia rarely led to discontinuation of study drug (<1% each).

AEs leading to dose reductions or interruptions

Dose reductions were implemented for 31% of patients, with subsequent re-escalations in approximately 50% of these patients. Adverse events that led to dose interruptions or dose reductions most frequently were diarrhoea, hypertension, or increased AST/ALT. After dose interruption or reduction, the majority of patients were able to continue treatment in the study.

5.9.2.2.2 Clinical laboratory evaluations

Elevations in AST (54%) and ALT (53%) were the most common treatment-emergent laboratory abnormalities. Isolated asymptomatic liver enzyme elevations occurred within the first few months of drug exposure. Elevations in ALT ≥3xULN range occurred in 45 patients (20%). Recovery to grade 1 or better was documented in 40 patients. Of the remaining five patients, four experienced ALT elevations after treatment was discontinued. Concomitant elevations in AST/ALT ≥3xULN, bilirubin ≥2xULN and ALP ≤ULN were observed in two patients. In one patient, liver enzyme elevations were attributed to rapidly progressive metastatic disease. The other patient was taking multiple traditional Chinese medications, including those (such as white peony root) thought to be hepatotoxic. Enzyme values recovered on discontinuation of medicines.

The majority of treatment-emergent haematological toxicity increases were grades 1 or 2. For decreased lymphocyte count, a shift to grade 3 was observed for 15 subjects and to grade 4 for 6 subjects. For the other parameters, shifts to grade 3 were observed in only 2 to 3 subjects and shifts to grade 4 were seen in 4 to 6 subjects with the exception of no grade 4 shifts in white blood cell count.

Table 5.62: On-therapy laboratory abnormalities reported in ≥10% subjects (VEG102616, All enrolled population, 03 April 2008 cut-off)

Laboratory abnormality	N=225		
	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Clinical chemistry			
AST elevation	121 (54)	13 (6)	2 (<1)
ALT elevation	118 (53)	19 (9)	2 (<1)
Hyperbilirubinaemia	63 (28)	2 (<1)	0
ALP elevation	60 (27)	4 (2)	0
Hyponatraemia	83 (37)	18 (8)	0
Creatinine elevation	71 (32)	0	1 (<1)
Hyperkalemia	59 (26)	9 (4)	2 (<1)
Lipase increased	52 (29)	14 (8)	3 (2)
Amylase increased	45 (24)	5 (3)	1 (<1)
Haematology			
Lymphopenia	102 (46)	15 (7)	6 (3)
Leukopenia	77 (35)	3 (1)	0
Neutropenia	61 (27)	2 (<1)	6 (3)
Thrombocytopenia	57 (26)	2 (<1)	4 (2)
Anaemia	57 (26)	2 (<1)	4 (2)

ALP = Alkaline phosphatase

5.9.2.3 VEG107769

5.9.2.3.1 Adverse events

The most common treatment-emergent AEs (reported by >20% subjects) were hypertension (46%), hair colour changes (39%), diarrhoea (38%), anorexia (24%) and nausea (24%). Most AEs were grade 1 or 2. Grade 3 AEs were reported for 15 (21%) subjects and grade 4 AEs for 5 (7%) subjects. The most common grade 3 AEs were hypertension (3 [4%] subjects), fatigue (2 [3%] subjects) and weight decreased (2 [3%] subjects). The most common grade 4 AE was pain (2 [3%] subjects). All other grade 3 or 4 events were reported in no more than 1 subject.

Table 5.63: AEs reported for ≥5% subjects (VEG107769, All treated subjects, 23 May 2008 cut-off)

Event	N=71		
	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Any AE	66 (93)	15 (21)	5 (7)
Hypertension	33 (46)	3 (4)	0
Hair colour changes	28 (39)	0	0
Diarrhoea	27 (38)	1 (1)	0
Anorexia	17 (24)	1 (1)	0
Nausea	17 (24)	0	0
Vomiting	13 (18)	0	0
Fatigue	11 (15)	0	0
ALT increased	10 (14)	1 (1)	0
Abdominal pain	9 (13)	1 (1)	0
AST increased	9 (13)	1 (1)	0
Headache	9 (13)	0	0
Proteinuria	9 (13)	0	0
Alopecia	8 (11)	0	0
Asthenia	8 (11)	0	0
Cough	8 (11)	0	0
Dysgeusia	8 (11)	0	0
Weight decreased	7 (10)	2 (3)	0

Deaths

In total, 21 of the 71 (30%) subjects enrolled in VEG107769 died. The primary cause of death for 14 of these patients was the disease under study. One subject died from an upper gastrointestinal (GI) haemorrhage which was considered by the investigator to be treatment-related. One subject died suddenly after 485 days of pazopanib treatment; the cause of death was reported as sudden death and was not considered treatment-related. The causes of the remaining deaths are reported as 'other' or 'unknown', with the exception of an additional three deaths where the cause of death was only recorded in the parent study.

SAEs

The overall incidence of SAEs was 24% (17 subjects). The only SAE to be reported by more than one subject was pain (2 [3%] subjects). Two subjects had fatal SAEs: the subject with the fatal upper GI haemorrhage and the subject with sudden death (see above).

AEs leading to permanent discontinuation of study medication

Eight (11%) subjects had an AE leading to permanent discontinuation of pazopanib; no AE was reported in more than one subject. Three subjects had more than one AE leading to discontinuation: one subject had ALT increased and AST increased; one subject had bilirubin increased and hepatic enzymes increased; and one subject had hypertension, leucopenia, respiratory tract infection and thrombocytopenia.

AEs leading to dose reductions or interruptions

Ten (14%) subjects had an AE that led to a dose reduction. The AEs that led to a dose reduction in more than one subject were: diarrhoea (3 [4%] subjects) and abdominal pain, fatigue, hypertension and nausea which were each reported in 2 [3%] subjects.

Twenty-one (30%) subjects had an AE that led to a dose interruption. The AEs that led to a dose interruption in more than one subject were: hypertension (6 [8%] subjects); diarrhoea (3 [4%] subjects); and abdominal pain, ALT increased, asthenia, PPE and vomiting which were each reported in 2 [3%] subjects.

5.9.2.3.2 Clinical laboratory evaluations

The majority of treatment-emergent haematological toxicity increases were grade 1 or 2. The only increases to grade 3 haematological toxicity reported in more than one subject were lymphocytopenia (3 [4%] subjects) and leucopenia (2 [3%] subjects). There were only two grade 4 haematological toxicities: lymphocytopenia and neutropenia.

The most common treatment-emergent clinical chemistry abnormalities were AST elevation (57%), increase in total bilirubin (51%), ALT elevation (49%) and hyperglycaemia (49%). The majority of toxicity grade increases in clinical chemistry parameters were grades 1 or 2. The most commonly observed grade 3 clinical chemistry toxicities were ALT elevation (5 [7%) subjects), hyponatraemia (5 [7%] subjects) and AST (4 [6%] subjects). No grade 4 clinical chemistry toxicities were observed.

Table 5.64: Summary of worst-case toxicity grade increase from baseline for haematology and clinical chemistry parameters (VEG107769, All treated subjects, 23 May 2008 cut-off)

Laboratory abnormality		N=71		
		Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Clinical chemistry				
AST increase	n=69	39 (57)	4 (6)	0
Total bilirubin increase	n=68	35 (51)	2 (3)	0
ALT increase	n=69	34 (49)	5 (7)	0
Hyperglycaemia	n=68	23 (34)	1 (1)	0
Hypophosphatamia	n=67	23 (34)	1 (1)	0
Hyponatremia	n=68	21 (31)	5 (7)	0
ALP increase	n=68	20 (29)	0	0
Creatinine increase	n=68	18 (26)	0	0
Hypomagnesia	n=68	10 (15)	0	0
Hypocalcemia	n=63	8 (13)	0	0
Hypokalemia	n=68	8 (12)	0	0
Hypoglycemia	n=68	3 (4)	0	0
Hypernatremia	n=68	1 (1)	0	0
Haematology				
Lymphocytopenia	n= 69	26 (38)	3 (4)	1 (1)
Leukopenia	n= 69	24 (35)	2 (3)	0
Neutropenia	n= 69	23 (33)	1 (1)	1 (1)
Thrombocytopenia	n= 69	23 (33)	1 (1)	0
Anaemia	n= 69	19 (28)	0	0

5.9.2.4 AEs pooled across pazopanib RCC studies

The integrated safety population for pazopanib in RCC includes 351 treatment-naive patients who received pazopanib from the phase III VEG105192 study, phase II VEG102616 study and the VEG107769 extension study. The overall safety profile of pazopanib across the 3 RCC studies was similar to that observed in the pazopanib arm of the VEG1015192 study.

Table 5.65: On-therapy AEs reported for ≥5% pazopanib-treated subjects* (Pooled data from VEG105192, VEG102616 and VEG107769))

Preferred term	Pazopanib treatment-naive subjects N=315 n (%)		
	Any grade	Grade 3	Grade 4
Any adverse event	333 (95)	138 (39)	26 (7)
Diarrhoea	188 (54)	10 (3)	1 (<1)
Hair colour changes	146 (42)	1 (<1)	0
Hypertension	141 (40)	22 (6)	0
Nausea	119 (34)	3 (<1)	0
Fatigue	111 (32)	12 (3)	0

Anorexia	90 (26)	5 (1)	0
Vomiting	68 (19)	5 (1)	1 (<1)
ALT increased	68 (19)	25 (7)	4 (1)
AST increased	57 (16)	15 (4)	3 (<1)
Abdominal pain	54 (15)	9 (3)	0
Cough	47 (13)	0	0
Rash	41 (12)	2 (<1)	0
Alopecia	37 (11)	0	0
Constipation	39 (11)	1 (<1)	1 (<1)
Back pain	39 (11)	3 (<1)	0
Asthenia	36 (10)	8 (2)	0
Weight decreased	36 (10)	2 (<1)	0
Arthralgia	33 (9)	0	0
Proteinuria	24 (7)	2 (<1)	0
Dyspepsia	25 (7)	2 (<1)	0
Peripheral oedema	25 (7)	0	0
Dyspnoea	25 (7)	3 (<1)	2 (<1)
Abdominal pain upper	22 (6)	6 (2)	1 (<1)
URTI	22 (6)	0	0
Nasopharyngitis	21 (6)	0	0

*reported at any grade

5.9.2.5 Comparison of AEs between treatments

5.9.2.5.1 Qualitative comparison

For studies included in the indirect comparison (see section 5.7), a summary of specific AEs (grouped by class) experienced at any grade by patients randomised to each intervention is provided in Table 5.66 (where such data were reported in the publications). On qualitative analysis, AEs in the blood and lymphatic system class of disorders appear to be more common for patients receiving sunitinib than those treated with pazopanib. The incidence of the following events also appears to be higher with sunitinib than with pazopanib treatment: nausea, mucositis/stomatitis, fatigue, hand-foot syndrome/PPE, skin discolouration and dysgeusia. A higher proportion of patients experienced hair colour changes and had increased AST and ALT levels after treatment with pazopanib as compared with sunitinib. A qualitative comparison between pazopanib and IFN could not be made since only the Steineck 1990 reported specific AEs at all grades.

A comparison of grade 3 and 4 AEs is presented in Table 5.67 (where such data were reported in the relevant publications).

Table 5.66: Specific AEs experienced by randomised patients (across all grades)

AEs by class		VEG105192*		Motzer 2009		Steineck 1990	
		PAZO	PLAC	SUN	IFN	IFN	BSC
	N	155	78	375	360	30	30
GI disorders	Abdominal pain	12.3	1.3	11	3		
	Diarrhoea	47.1	6.4	61	15	3.3	0
	Dyspepsia	3.9	1.3	31	5		
	Vomiting	21.9	5.1	31	12		10
	Nausea	25.8	10.3	52	35	3.3	0
	Mucositis/stomatitis	3.2	0	30	4		
General disorders	Asthenia	16.8	7.7	20	19		
	Fatigue	18.7	12.8	54	52	66.7	10
	Fever	7.1	5.1	8	35		
Skin and subcutaneous tissues disorders	Alopecia	9	0	12	9	3.3	0
	Hair colour change	38.7	1.3	20	1		
	Hand-foot syndrome	1.9	0	29	3		
	Rash	7.7	3.8	24	8	10	3.3
	Skin discolouration	5.8	0	27	1		

AEs by class		VEG105192*		Motzer 2009		Steineck 1990	
		PAZO	PLAC	SUN	IFN	IFN	BSC
Investigations	ALT increased	25.2	2.6	51	40		
	AST increased	20	2.6	56	38		
	Total bilirubin increased	1.9	1.3	20	2	3.3	0 (0)
Vascular disorder	Hypertension	39.4	9	30	4	0	6.7
Metabolism and nutrition disorders	Anorexia	25.2	10.3	34	28	20	3.3
	Hyperglycaemia	2.6	0				
	Hypophosphataemia	0.7	0	31	24		
Musculoskeletal and connective tissue disorders	Arthralgia	6.5	2.6	11	14		
	Flank pain	0	1.3				
Nervous system disorders	Altered taste	8.4	1.3	46	15		
	Headache	13.5	5.1	14	16		
Respiratory, thoracic and medistinal disorders	Epistaxis	1.3	0	18	2	3.3	0
Infections and infestations	Infection	22.6	17.9				
	Flu-like symptoms	2.6	2.6			100	3.3
Blood and lymphatic system disorders	Anaemia	3.2	7.7	79	70	40	30
	Leucopenia	3.2	0	78	57	46.7	0
	Lymphocytopenia	1.3	0	68	69		
	Neutropenia	5.2	0	77	50		
	Thrombocytopaenia	7.7	1.3	68	26	6.7	0
Psychiatric disorders	Depression	2.6	1.3				
Cardiac disorders	Congestive heart failure	0.6	0				
Endocrine disorders	Hypothyroidism	5.2	0	14	2		

Evaluable N was used to calculate %. * On-therapy AEs regardless of relationship to investigational product
No AE data for specific AEs (any grade) reported for Negrier 2007, MRC RE01, Kriegmair 1995 and Pyrhonen 1999.
Dark green represents 0% patients reported AE, **Light green** represents 1-25% patients with AE, **Yellow** represents 26-50% patients with AE, **Orange** represents 51-75% patients with AE, **Red** represents 76-100% patients with AE.

PAZO = pazopanib. SUN = Sunitinib. IFN = Interferon. BSC = Best supportive care.

Table 5.67: Specific Grade 3/4 AEs experienced by randomised patients

Study	VEG105192*		Motzer 2009[9]		Negrier 2007			MRC RE01[10]		Kriegmair 1995		Pyrhonen 1999[11]	
	PAZO	PLAC	SUN	IFN	IFN	IL-2	BSC	IFN	BSC	IFN + BSC	BSC	IFN + BSC	BSC
N	155	78	375	360	122	124	121	51	49	41	35	79	81
Abdominal pain	2.6	0	2/0										
Diarrhoea	3.2	0	9/0	1/0	0	4	0						
Dyspepsia	0	1.3	2/0	<1/0				7.8	32.7				
Vomiting	3.2	0	4/0	1/0	0.8	7.3	0.8						
Nausea	1.3	0	5/0	1/0	0.8	5.6	0	11.8	12.2				
Mucositis/stomatitis	0	0	1/0	<1/0	1.6	0	0						
Asthenia	0	0	7/<1	4/0									
Fatigue	1.9	5.1	11/0					58.8	53.1				
Fever	0	0	1/0	<1/0	3.3	11.3	0			14.63	0		
Alopecia	0	0								0	0		
Hair colour change	0.7	0											
Hand-foot syndrome	0	0	9/0	1/0									
Rash	0	0	1/<1	<1/0									
Skin discolouration	0	0	<1/0										
ALT increased	11	0 *	2/<1	2/0								2.5	1.2

[9] Reported as % (Grade 3/Grade 4)
[10] AE of moderate to severe intensity reported at week 12
[11] Grade 4 AEs reported

Study	VEG105192*		Motzer 2009[9]		Negrier 2007			MRC RE01[10]		Kriegmair 1995		Pyrhonen 1999[11]	
	PAZO	PLAC	SUN	IFN	IFN	IL-2	BSC	IFN	BSC	IFN + BSC	BSC	IFN + BSC	BSC
AST increased	6.5	0	2/0	2/0									
Total bilirubin increased	0.7	0	1/0										
Hypophosphataemia	0	0											
Hypertension	3.9	0	12/0	1/0	0.8	0	0						
Anorexia	1.9	0	2/0	2/0				39.2	8.2				
Hyperglycaemia	0	0											
Hypophosphataemia			6/<1	6/0									
Arthralgia	0	0	<1/0	<1/0									
Flank pain	0	0											
Altered taste	0	0	<1/0										
Headache	0	0	1/0										
Epistaxis	0	0	1/0	13/<1									
Infection	1.9	0											
Flu-like symptoms	0	0											
Anaemia	1.9	1.3	6/2	5/1	6.6	4.8	0			0	0		
Leucopenia	0	0	8/0	2/0						0	0		
Lymphocytopaenia	0	0	16/2	24/2	4.1	2.4	2.5						
Neutropenia	1.3	0	16/2	8/1	4.1	0	0					15.2	
Thrombocytopaenia	1.9	0	8/1	1/0	0	0.8	0			0	0		
Depression	0	0											
Congestive heart failure	0.7	0			0	0	0						
Hypothyroidism	0	0	2/0	<1/0									

Evaluable N was used to calculate %. * On-therapy AEs regardless of relationship to investigational product
No AE data for specific grade 3 / 4 AEs reported for Steineck 1990

Dark green represents 0% patients reported AE, **Light green** represents 1-25% patients with AE, **Yellow** represents 26-50% patients with AE, **Orange** represents 51-75% patients with AE, **Red** represents 76-100% patients with AE.

PAZO = pazopanib. SUN = Sunitinib. IFN = Interferon. BSC = Best supportive care.

5.9.2.5.2 Indirect comparison

The results from indirect analyses of pazopanib relative to sunitinib (via Steineck 1990) for specific AEs (all grades) are shown in Table 5.68. Details of the methodology employed can be found in section 8 of the Systematic Review report provided with this submission.

Pazopanib was associated with a reduced risk of almost all specific AEs compared to sunitinib where comparison was possible, these included the following: diarrhoea, vomiting, nausea; fatigue; hand-foot syndrome/PPE, rash; total bilirubin increased; anorexia; epistaxis; anaemia, leucopenia, thrombocytopenia. The difference observed, however, rarely reached statistical significance; the reduced risk was only observed to be statistically significant for fatigue. Alopecia and hypertension were the only AEs where pazopanib showed an increased but statistically insignificant risk compared to sunitinib. Steineck 1990 did not report data for increased AST and ALT, thus an indirect comparison of pazopanib vs. sunitinib was not possible for these outcomes.

Table 5.68: Result of indirect comparison of AEs (pazopanib vs. sunitinib, via Steineck 1990)

Class	Outcome	Sunitinib
Gastrointestinal disorders	Diarrhoea	0.60 (0.02, 16.11), p = 0.7619
	Vomiting	-
	Nausea	0.56 (0.02, 14.32), p = 0.7289
	Mucositis/stomatitis	-
General disorders and administration site conditions	Fatigue	0.21 (0.06, 0.77), p = 0.0181

Class	Outcome	Sunitinib
Skin and subcutaneous tissue disorders	Alopecia	3.63 (0.05, 253.99), p = 0.5524
	Hand-foot syndrome/PPE	-
	Rash	0.23 (0.02, 2.91), p = 0.2535
Investigations	Total bilirubin increased	0.05 (0, 2.55), p = 0.1346
Vascular disorders	Hypertension	2.69 (0.11, 63.56), p = 0.5387
Metabolism and nutrition disorders	Anorexia	0.4 (0.13, 1.29), p = 0.1258
Respiratory, thoracic and mediastinal disorders	Epistaxis	0.09 (0, 7.68), p = 0.2891
Infections and infestations	Flu-like symptoms	-
Blood and lymphatic system disorders	Anaemia	0.28 (0.07, 1.08), p = 0.0652
	Leucopenia	0.14 (0, 7.66), p = 0.3356
	Thrombocytopenia	0.46 (0.01, 17.29), p = 0.6773

Reported as risk ratio (95% CI). Black = point estimate favour pazopanib group; Red = point estimate favour sunitinib group. CI = confidence interval, IFN = interferon alpha.

5.9.3 **Give a brief overview of the safety of the technology in relation to the decision problem.**

The placebo-controlled pivotal study (VEG105192) allows for optimum assessment of the safety profile of pazopanib. The profile observed in this study is supported by consistent data from the supporting RCC studies (VEG102616 and VEG107769). Overall, pazopanib demonstrated acceptable safety and tolerability. This is important since patients with RCC are often asymptomatic when therapy is initiated and may remain on therapy for prolonged periods of time.

Although the majority of AEs reported with pazopanib have also been observed with other VEGFR inhibitors, the incidence and severity of events appears to vary from agent to agent. This may be explained by differences in the overall spectrum, selectivity and potency of kinases inhibited (Karaman 2008; Kumar 2009).

The most common treatment-emergent AEs in the first-line pazopanib-treated population in VEG105192 and the pooled analysis of pazopanib RCC studies were diarrhoea, hypertension, hair colour changes, anorexia, nausea and vomiting (occurring in ≥20% of patients). Most events were mild to moderate (grades 1 to 2) and were clinically manageable; few led to permanent discontinuation of study medication. The most common grade 3 and/or 4 AEs were hypertension (4%) and diarrhoea (3%), which can be managed with dose modifications and use of anti-hypertensive and anti-diarrhoeal agents, respectively.

The most common grade 3 and/or 4 chemistry abnormalities observed in the pazopanib RCC studies were increased ALT and increased AST. Most cases of drug-induced liver enzyme elevations were asymptomatic and reversible upon dose reduction, interruption or product discontinuation. These events usually occurred early in the course of treatment (within first 4 months) and can be detected with regular monitoring conducted as part of routine clinical practice; guidance is provided in the Summary of Product Characteristics (SPC) and in the EPAR.

Although leucopenia, neutropenia and thrombocytopenia were more common on pazopanib than placebo in the VEG105192 study, grade 3 and/or 4 cytopenias were uncommon (≤5%). Qualitative and formal indirect comparison indicates that pazopanib is associated with a reduced risk of haematological AEs compared with sunitinib (see section 5.9.2.5 of the main submission and sections 5.3.2 and 8.3.1.2 of the Systematic Review report, respectively). The low incidence of grade 3/4 myelosuppression observed with pazopanib may be explained by the fact that it is not a potent inhibitor of the Flt-3 receptor (Kumar 2009).

Certain other AEs known to occur with this class of agent such as proteinuria, hypothyroidism, hand-foot syndrome/PPE, mucositis and stomatitis each occurred with an incidence of less than 10% in patients receiving pazopanib in the VEG1015192 first-line sub-population, with grade 3/4 events reported at a very low rate (≤1% of patients). This compares with incidence rates of 14% [G3/4 2%] for hypothyroidism, 30% [G3/4 1%] for stomatits and 29% [G3/4 9%] for PPE observed in the sunitinib arm in the phase III pivotal study (Motzer 2009). The differences in incidence are clinically relevant since, if severe, these can be debilitating conditions with a profound impact on patients' quality of life (Pyle 2008; Cheng 2009).

Fatigue is another AE that can affect patients' daily functioning; this has been reported at a higher rate with sunitinib (Motzer 2009) than with pazopanib in patients receiving first-line

treatment for advanced/metastatic RCC (54% [G3/4 11%] vs. 19% [G3/4 2%], in the sunitinib and pazopanib pivotal studies, respectively).

Severe AEs previously described for other VEGFR inhibitors including cardiac/cerebral ischaemia, cardiac arrest, haemorrhage and bowel perforation were observed infrequently with pazopanib in treatment-naive patients.

There were no reports of decreased LVEF in the pazopanib arm of the treatment-naive sub-population in VEG105192 (however, it should be noted that ECHO/MUGA scans were not performed per-protocol to collect LVEF data and only when clinically indicated) and congestive heart failure (CHF) was reported in <1% of patients. A decline in LVEF was noted in 13% of patients (G3/4 3%) receiving sunitinib in the pivotal trial (Motzer 2009) and in a recent meta-analysis involving 175 patients treated with sunitinib for metastatic RCC, 19% developed grade 1-3 LVEF dysfunction (of whom 7% developed a grade 3 decline with CHF) (Di Lorenzo 2009). It has been suggested that off-target kinase activity may be the basis for sunitinib-induced cardiotoxicity (Fabian 2005; Hasinoff 2008).

Dose reductions[12] due to AEs were reported for 23% subjects in the pazopanib arm compared with 4% in the placebo arm in VEG105192; 12% of subjects on pazopanib had AEs which led to withdrawal of study medication versus 6% of those on placebo (treatment-naive safety population). Dose reductions were observed in 50% in patients receiving sunitinib versus 27% of patients in the IFN group in the sunitinib pivotal study (Motzer 2009).

In summary, pazopanib is generally well tolerated with an acceptable and manageable safety profile in patients receiving first-line treatment for advanced/metastatic with RCC. The incidence of many AEs reported is similar to or lower than reported for other VEGFR inhibitors. In particular, pazopanib appears to have a favourable safety profile compared with sunitinib, in relation to haematological AEs, cardiotoxicity and events that can affect patients' daily functioning and quality of life such as hand-foot syndrome, mucositis, stomatitis and fatigue. Most AEs reported with pazopanib were mild to moderate and were reversible upon dose reduction, interruption or discontinuation of treatment. The ongoing trial of pazopanib vs. sunitinib (VEG108844; COMPARZ) will provide direct evidence on the comparative safety of pazopanib and sunitinib.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The evidence base for pazopanib in patients with advanced/metastatic RCC with no prior systemic treatment consists of one RCT (VEG105192), supported by two non-RCTs (VEG102616 and VEG107769). The primary evidence for pazopanib's clinical efficacy is demonstrated in the pivotal VEG105192 study by the following findings:

- PFS was significantly prolonged with pazopanib compared with placebo (11.1 vs. 2.8 months; HR 0.40 [95% CI: 0.27-0.60]; p<0.0001). This was confirmed by sensitivity analyses including assessments based on scan dates (HR 0.36 [95% CI: 0.24-0.55]) and investigators' determination of progression (HR 0.47 [95% CI: 0.33-0.68]).

[12] Note: These figures may be under-estimated because of the way in which the data were captured. Only one action was recorded. Thus, if the patient had a reduction followed by an interruption, only the interruption might have been recorded.

- Pazopanib was associated with a 26% reduction in risk of death relative to placebo in the pre-specified ITT analysis (HR 0.74 [95% CI: 0.47-1.15]; p=0.079, estimated by a stratified Pike estimator); however, the data are immature and a large proportion of patients in the placebo arm (40% at clinical cut-off) crossed over to receive pazopanib at disease progression which is likely to have improved survival times in the placebo group.
- Since the ITT analysis is likely to have underestimated the benefits of pazopanib and as there is no universally accepted way to adjust for cross-over in survival analysis, several approaches were utilised to evaluate this effect. The results indicate that treatment with pazopanib was associated with a clinically relevant reduction in risk of death compared with placebo (adjusted HRs for OS for pazopanib vs. placebo ranging from 0.206 to 0.684, depending on methodology and whether adjusted for baseline patient characteristics, Table 5.22). These analyses will be repeated once the final survival data from VEG105192 are available (3Q 2010).
- The ORR (CR+PR) was 32% with pazopanib compared with 4% with placebo (p<0.001). Responses were durable with a median duration longer than 1 year (58.7 weeks). Since tumour stabilisation can result in clinical benefit for patients, the CR+PR+6-month SD rate of 49% in the pazopanib arm vs. 12% in the placebo arm (p<0.001) is also clinically relevant.
- The quality of life assessments (based on scores from the EORTC QLQ C30 and EQ-5D questionnaires) showed no statistical or clinically important differences between pazopanib and placebo at any of the assessment time points in subjects who continued on therapy, indicating maintenance of QoL over time in patients receiving pazopanib relative to placebo.

Efficacy data from the phase II study, VEG102616, and the extension study, VEG107769, support the results of the pivotal study. Consistent with VEG105192, the overall response rate in VEG102616 was 34% in treatment-naive subjects and was 32% in VEG107769 (all subjects). Median PFS in these studies was similar to that reported in the pivotal trial. This underscores the consistent efficacy demonstrated by pazopanib in the setting of advanced/metastatic RCC.

As discussed in section 5.9.3, pazopanib was generally well tolerated in treatment-naive subjects with advanced/metastatic RCC. The most common treatment-emergent AEs associated with pazopanib treatment were diarrhoea, hypertension, hair colour changes, anorexia, nausea and vomiting. Most events were mild to moderate in severity and were reversible upon dose modification. The most notable toxicity associated with pazopanib appears to be raised liver enzymes (ALT and AST); however, most cases were asymptomatic and reversible upon dose reduction or interruption. Although the majority of AEs observed with pazopanib have also been reported with other VEGFR inhibitors, the incidence and severity of events varies from agent to agent (McCann 2010), possibly reflecting differences in their spectrum and potency of kinase inhibition (Karaman 2008; Kumar 2009). Pazopanib is not a potent inhibitor of Flt-3 which may explain the low rate of grade 3/4 cytopenias observed with pazopanib (≤5%). There is little evidence that pazopanib is associated with cardiotoxicity in the form of decreased LVEF or CHF. Other class effects such as proteinuria, hypothyroidism, hand-foot syndrome, stomatitis and mucositis occurred with an incidence of less than 10%.

The draft European Product Assessment Report (EPAR) for pazopanib states that "*the addition of a safe treatment option that is associated with clear clinical benefits and with a distinct pharmacodynamic profile is considered to offer a major advantage in the context of therapies for this disease*." Therefore, the CHMP considered that the current unmet medical needs could be fulfilled for the treatment of advanced RCC and adopted a positive opinion recommending that a conditional marketing authorisation for pazopanib be granted.

5.10.2 **Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.**

VEG105192
The evidence base is limited by the lack of head-to-head trials for pazopanib, the intervention being appraised, versus an active comparator. Only one RCT of pazopanib was identified (VEG105192) and this was a placebo controlled study. The rationale for this study design is discussed in section 5.3.1. When the study was initiated in April 2006, access to the multi-targeted tyrosine kinase inhibitors (TKIs), sunitinib and sorafenib, was limited making it difficult to use either as a comparator. Since the initial protocol was to enrol only cytokine pre-treated patients, placebo with BSC was considered an appropriate comparator. It was also recognised that using a placebo control in a double-blind study would enable better characterisation of the efficacy and safety of pazopanib. However, with the emerging data for the TKIs and the diminishing use of cytokine therapy in RCC due to its unfavourable risk: benefit profile, the protocol was amended to allow the inclusion of treatment-naive patients. Placebo plus BSC was retained as the control arm. Exposure of patients to placebo was minimised by a 2:1 random assignment, and pazopanib was provided as a treatment option for patients who progressed on placebo.

In all other respects, VEG105192 was a well-conducted trial and the results indicate little or no evidence of systematic bias in estimation of the treatment effect. Blinding was achieved through the use of matching placebo tablets. Even though subjects were unblinded at the time of progression, steps were taken to preserve the blind as a whole. Subjects who progressed were unblinded by investigators at the site via an independent unblinding system allowing GSK study personnel to remain blinded to the subject's treatment assignment. Subjects who entered the open-label extension study (VEG107769) were allocated a different subject number for that study. Central randomisation meant that the investigator could not infer the treatment arm for subjects who remained blinded based on knowledge of the treatment arm of unblinded subjects.

An Independent Review Committee (IRC) was established prior to study start to determine patients' response and progression in an objective and consistent manner. The IRC reviewed imaging data from all study subjects blinded to their treatment assignment. Two IRC members independently read each subject's scans, with a third acting as an adjudicator if necessary. The central review of the IRC was completed prior to database freeze and unblinding.

The primary analysis of PFS was based on the disease assessments by the IRC. The study was designed with sufficient power to detect a treatment effect on PFS in the treatment-naive and cytokine pre-treated pre-specified sub-populations as well as in the total study population. The robustness of the primary analysis of PFS was confirmed by sensitivity analyses including assessments based on scan dates and investigators' determination of progression. There was no evidence of systematic bias between arms in timing of disease assessments and adherence to scheduled visits was similarly high in both treatment arms. Efforts were made to follow subjects who prematurely withdrew study treatments due to reasons other than progressive disease or death.

The study was set up with a planned interim analysis for OS to be conducted at the time of the final PFS analysis. However, it was not powered to evaluate OS in the treatment-naive/cytokine pre-treated sub-populations, especially at the interim analysis. In addition, the effect on OS attributable to pazopanib is likely to have been impacted by the cross-over that was allowed after disease progression for patients in the placebo arm. The utility of the ITT analysis is therefore limited and it is important to estimate the effect of pazopanib treatment

in a “counterfactual” setting where survival outcomes for patients in the placebo arm are considered equivalent to a hypothetical cohort of patients who received placebo but did not cross-over. Several different statistical techniques were employed (discussed in section 5.3.6.1) to address this since the optimal approach to control for cross-over remains an area of academic debate and there are strengths and limitations associated with all the available methods. The RPSFT-derived univariate HR (0.345 [95% CI: 0.086-1.276]) was used for the base case in our indirect comparison and economic analyses in line with a previous NICE appraisal (Everolimus ACD, Feb 2010) in which the RPSFT method was acknowledged as being more methodologically robust than IPCW because randomisation is preserved and it does not make the assumption of no unmeasured confounders. It does, however, have some limitations when applied to immature OS data due to the degree of re-censoring required, which is likely to be less of an issue when applied to the updated OS data.

Whilst the QoL assessments were based on blinded self-reported scores from the two questionnaires (EORTC QLQ C30 and EQ-5D), a limitation of these analyses is the extent of missing data particularly in the placebo arm and at later assessment time points, due to the fact that subjects only completed quality of life assessments while they were receiving investigational product.

Indirect comparison
Since there are no data directly comparing pazopanib with IFN or sunitinib, a clinical comparison was only possible using indirect comparison methodology (Bucher 1997).

This required the use of several trials comparing IFN with a control therapy (either medroxyprogesterone acetate or vinblastine). Consistent with data from controlled trials and based on discussions with RCC experts, it was assumed that medroxyprogesterone acetate and vinblastine would have no relevant therapeutic effect and should therefore be considered equivalent to placebo with best supportive care. Since the MRC RE-01 trial (Ritchie 1999; Hancock 2000) was the only one to report HRs for both PFS and OS, HRs for these endpoints in the other trials had to be derived using validated methods. These trials varied somewhat in numbers of participants, in their location and duration of follow-up, but were of similar design and largely involved patients with similar baseline characteristics (see section 5.7.2). The heterogeneity statistic (I^2) calculated for the pooling of their PFS and OS data was 19% and 20%, respectively, indicating a low degree of heterogeneity.

The pazopanib (VEG105192) and sunitinib studies (Motzer 2009) met the standard assumptions for indirect comparisons: they were of similar design/methodology and their participants were comparable (see section 5.6.2). It should be noted that the VEG105192 study is still ongoing and the OS data utilised in the base case comparison is from a pre-planned interim analysis adjusted for cross-over using the RPSFT technique while the OS data for the sunitinib study is from the final analysis in patients who received no post-study therapy (Motzer 2009). We recognise that the HR from the sunitinib study has not been adjusted in the same way as the HR for OS from the VEG105192 study; however, of four HRs reported for OS for sunitinib vs. IFN for this study (Motzer 2007, Motzer 2009), this is the most favourable towards sunitinib (see section 5.7.4). Results of sensitivity analyses conducted using the IPCW-derived HR for OS in VEG105192 confirm the results of the primary indirect analysis.

As discussed in section 5.7.2, none of the studies used in the indirect comparison were identified as being at a high risk of bias, so the validity of the results is not affected by any individual study.

5.10.3 **Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.**

Whilst treatment of advanced/metastatic RCC has been greatly impacted by the introduction of agents that target the VEGF and related pathways, the toxicities seen with the currently available therapies remain a challenge. Thus, there is a need for alternative treatments that offer a favourable side effect profile without compromising efficacy for patients with advanced/metastatic RCC. The CHMP has recently adopted a positive opinion recommending a conditional marketing authorisation for pazopanib on the basis of its favourable risk: benefit profile. The conditional licence is linked to the provision of further data supporting the efficacy and safety of pazopanib compared with sunitinib, including the outcome of the ongoing head-to-head non-inferiority trial of pazopanib versus sunitinib in patients with advanced RCC (VEG108844; COMPARZ).

The primary endpoint in the pivotal study (VEG105192) supporting the marketing authorisation was progression-free survival (PFS) in the total study population; the study was also powered to examine PFS in each of the treatment-naive and cytokine pre-treated sub-groups. PFS is accepted as a valid measure of clinical benefit and an adequate surrogate for survival in RCC trials (EMA 2005; George 2009; Bracarda 2009). With PFS, the treatment effect is not diluted by post-study therapy and it reflects the clinical benefit of disease stabilisation as well as a complete or partial response (Farley 2010). In addition, treatment effects on PFS have been shown to be predictive of treatment effects on overall survival in patients with metastatic RCC (Delea 2009). It is therefore highly relevant that pazopanib was associated with a large and statistically significant improvement in PFS compared with placebo in the treatment-naive sub-population. It is important that the robustness of the primary results was confirmed by sensitivity analyses based on the investigators' assessment and using scan dates.

Although overall survival is the gold standard for the efficacy assessment of cancer therapies, in many trials, including VEG105192, patients randomised to the control arm can cross-over to active treatment, hampering the detection of a significant treatment effect. It is therefore relevant to evaluate differences in OS between placebo and pazopanib treatment by adjusting for the potential impact of the cross-over. Several approaches were used to address this and the results consistently indicate that pazopanib is associated with a clinically meaningful survival benefit compared with placebo (adjusted HRs for OS for pazopanib vs. placebo ranging from 0.206 to 0.684, depending on methodology and whether adjusted for baseline patient characteristics, Table 5.22).

Tumour shrinkage is demonstrated by the objective overall response rate (ORR: CR+PR) and was significantly greater in patients receiving pazopanib compared with placebo. Tumour response was durable with a median duration of response greater than one year (13.5 months). Since ORR does not capture the benefits to patients of tumour stabilisation, the rate of CR+PR+6-month SD is also clinically relevant and was significantly improved for pazopanib- compared with placebo-treated patients.

Health-related quality of life (HRQoL) was assessed in VEG105192 using the validated EQ-5D and EORTC QLQ C30 instruments which are considered relevant to the assessment of HRQoL in subjects with RCC (Cella 2009). There was no evidence of any clinically important differences (relative to the MID) in quality of life for patients receiving pazopanib compared to placebo as measured using these instruments.

Results of the base case indirect comparison (using RPSFT to adjust for cross-over and pooled IFN trials) showed that pazopanib is associated with a reduced risk of progression and death compared with IFN (HRs: 0.512 [95% CI: 0.326-0.802] for PFS and 0.432 [95% CI: 0.106-1.750] for OS) and has broadly comparable efficacy to sunitinib in terms of PFS and OS (HRs: 0.949 [95% CI: 0.575-1.568] and 0.667 [95% CI: 0.160-2.788], respectively). Sensitivity analyses conducted maintaining the RPSFT-derived HR but varying the IFN trials included (i. MRC RE-01 trial only; ii. excluding trials using vinblastine therapy) and then repeated using the IPCW-adjusted HR for OS from the VEG105192 trial confirm the results of the base case analysis. The 95% CIs around the HR estimates for OS for pazopanib vs. sunitinib and the OS medians for pazopanib and sunitinib are wide indicating uncertainty in these estimates. The ongoing head-to-head COMPARZ study, which is designed to demonstrate non-inferiority of pazopanib vs. sunitinib, will help to address this uncertainty.

Discussion of the relevance of the safety evidence for pazopanib can be found in section 5.9.3. Overall, pazopanib was well tolerated with an acceptable and manageable safety profile in patients receiving first-line treatment for advanced/metastatic RCC. This is important since patients with RCC are often asymptomatic when therapy is initiated and may remain on therapy for prolonged periods of time. It is particularly relevant that certain adverse events that can adversely impact patients' quality of life and daily functioning (Hutson 2008; Pyle 2008) such as hand-foot syndrome (PPE), stomatitis, mucositis and fatigue appear to occur at a lower rate with pazopanib than with sunitinib, the current standard of care in the UK. Pazopanib also appears to be associated with a reduced risk of haematological AEs (including grade 3/4 cytopenias) and cardiotoxicity in the form of decreased LVEF and CHF compared with sunitinib, which may be explained by differences in potency of inhibition at the Flt-3 receptor (Kumar 2009) and in off-target kinase activity (Hasinoff 2008), respectively.

Diarrhoea and hypertension were observed commonly in association with pazopanib in the RCC clinical trials but were mainly grades 1 or 2 and can be managed through dose modifications and the use anti-hypertensive and anti-diarrhoeal medication, respectively. Elevations in liver enzymes also occurred commonly in pazopanib-treated patients (approx. 50%) but were largely asymptomatic and reversible upon dose reduction or interruption. These events usually occurred early (within the first 4 months of treatment) and can be detected with regular liver function monitoring conducted as part of routine clinical practice.

It is of particular relevance that pazopanib appears to fulfil the requirements set out in section 2.1 of NICE's Supplementary Advice on appraising end of life (EOL) medicines. We recognise that sunitinib was approved by NICE for the first-line treatment of advanced/metastatic RCC under this guidance. The Supplementary Advice states that treatments approved following application of the advice will not necessarily be regarded as standard comparators for future assessments under this advice of new treatments introduced for the same condition. As this appraisal of pazopanib follows closely behind that of sunitinib, we believe that pazopanib should be afforded the same considerations under this guidance as sunitinib (i.e. assessed in the context of EoL relative to IFN), and as such, meets the criteria as follows:

(i) The treatment is indicated for patients with a short life expectancy, normally less than 24 months

The prognosis for patients with advanced / metastatic RCC is poor with a 5-year survival rate of <10% (Oudard 2007). In the absence of effective treatment, median survival after diagnosis of metastatic disease is generally less than 1 year (Gupta 2008). In the MRC RE-01 trial comparing IFN with medroxyprogesterone acetate (MPA) in 350 patients with

metastatic RCC in the UK, median survival was 9 months and 6 months in the IFN and MPA arms, respectively (Hancock 2000). In the more recent sunitinib pivotal study, median survival in the group randomised to IFN was 21.8 months (95% CI: 17.9-26.9) in the final ITT analysis (Motzer 2009).

(ii) The treatment is licensed, or otherwise indicated, for small patient populations

Patients with advanced/metastatic RCC represent a small population. Approximately, 7,000 patients are diagnosed with RCC in the UK each year, of whom about half (3,500 to 4,000 patients) present with advanced/metastatic disease. Such patients are either first diagnosed with advanced/metastatic disease or develop recurrence following treatment for localised disease.

(iii) The treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

The indirect comparison estimated the HR for pazopanib vs. IFN for OS to be 0.432 (95% CI: 0.106-1.750) (see section 5.7.6), indicating a significant reduction in risk of death for patients receiving pazopanib compared with IFN. Median OS estimated using the Weibull survival model employed in the economic evaluation was 15.8 months (95% CI: 15.8-15.8) for IFN and 43.5 months (95% CI: -81.9-169.0) for pazopanib. This equates to a survival gain of 27.7 months for patients receiving pazopanib, thereby exceeding the EOL criterion of an extension to life of at least 3 months.

In conclusion, studies involving over 350 treatment-naive patients with advanced/metastatic RCC demonstrate that pazopanib significantly improves PFS and response rates in this population. Comprehensive analyses adjusting for the impact of the cross-over in the VEG105192 trial demonstrate that pazopanib offers a significant survival benefit over BSC. Pazopanib appears to be a more selective TKI than sunitinib and these differences may in part explain the favourable tolerability profile observed. Of particular importance was that pazopanib did not negatively impact patient's quality of life with no evidence of clinically important differences in QoL scores compared to placebo.

5.10.4 **Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?**

Pazopanib has received a positive opinion from the CHMP for a conditional marketing authorisation as a first-line treatment in patients with advanced RCC and for patients who have received prior cytokine therapy for advanced disease. This is entirely reflective of the patient populations who participated in the pazopanib clinical studies.

VEG105192 was a multi-national study involving 5 sites in the UK, which recruited 28 of the total 435 patients. There are no obvious reasons why any unidentified geographical differences would make the results of this study inapplicable in England and Wales.

The median age of patients in VEG105192 was around 60 years and over two-thirds were male. The most common metastatic sites were the lung and lymph nodes and more than

50% of subjects had metastatic lesions involving at least 3 organs. These demographic and disease characteristics are similar to those described in other phase III studies of advanced/metastatic RCC (Motzer 2009) and are likely to be representative of patients with advanced/metastatic RCC in the UK.

The VEG105192 study recruited participants with good performance status (ECOG PS of 0 or 1), although the VEG107769 extension study allowed patients with an ECOG PS of up to 2. Most (approx. 90%) of subjects had undergone prior nephrectomy and all had clear cell or predominantly cell clear RCC. The indication statement within the pazopanib SPC is less restrictive in not specifying these features.

The dosing schedule used in the pazopanib clinical studies is consistent with the dosing schedule detailed on the pazopanib SPC (800mg orally once daily continuously with dose modifications permitted to manage toxicities). This differs from the 4-weeks on/2-weeks off standard administration schedule for sunitinib, but nevertheless, since it is an oral targeted agent in the same class as sunitinib there should be little need for education of healthcare professionals working in this area.

Patients in VEG105192 were permitted supportive care, including antibiotics, anti-hypertensives, anti-emetics, anti-diarrhoeal agents, analgesics, erythropoietin or bisphosphonates, and transfusion of blood and blood products, when appropriate. It is highly likely that patients eligible for pazopanib in clinical practice will require similar concomitant medications for the management of co-morbid conditions, infections and other therapy or disease-related complications.

In VEG105192, disease assessments were performed every 6 weeks until week 24, and every 8 weeks thereafter. This is unlikely to differ significantly from routine clinical practice where patients are reviewed every 1-2 cycles of therapy.

The pazopanib SPC is consistent with the choice of patients in, and conduct of, the pazopanib clinical studies, and thus is reflective of the patients likely to receive pazopanib in clinical practice:

Pazopanib treatment has been associated with hepatobiliary laboratory abnormalities and cases of hepatotoxicity have been reported during pazopanib use. Patients had to have adequate hepatic function to be eligible for inclusion in the pazopanib clinical studies. The SPC contraindicates the use of pazopanib in patients with severe hepatic impairment and administration to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring. In addition, liver function tests are stipulated before initiation of treatment, at least once every 4 weeks for the first 4 months of treatment (the period during which elevated liver enzymes are most likely to be observed) and periodically thereafter. Since liver function is monitored routinely in patients with advanced/metastatic RCC, this requirement is unlikely to impact on existing services.

Patients with poorly controlled hypertension were excluded from the pazopanib clinical studies. Similarly, the SPC advises that blood pressure should be well controlled prior to initiating pazopanib and patients should be monitored for hypertension during pazopanib treatment.

Patients with clinically significant cardiac or vascular disease within the past 6 months (e.g. class III/IV NYHA congestive heart failure; myocardial infarction; unstable angina; cerebrovascular accident) were not eligible for inclusion in the pazopanib clinical studies. Arterial thrombotic events including transient ischaemic attack, ischaemic stroke and

myocardial ischaemia have been reported infrequently in association with pazopanib (<1% of patients in combined safety poopulation). The SPC cautions the use of pazopanib in patients at increased risk for any of these events.

Thyroid function was monitored every 12 weeks in the VEG105192 study and the SPC is consistent in recommending proactive monitoring of thyroid function during pazopanib treatment. Patients with a corrected QTc interval ≥470 milliseconds were excluded from the pazopanib clinical studies. The SPC cautions the use of pazopanib in patients with a history of QT interval prolongation, in patients taking anti-arrythmics or other medicinal products that may prolong QT interval and those with relevant pre-existing cardiac disease. Base line and periodic monitoring of ECGs and maintenance of electrolytes within the normal range is recommended. These requirements are similar to those recommended on the sunitinib SPC.

Patients with gastrointestinal (GI) conditions at increased risk of perforation and those with a history of abdominal fistula and GI perforation were not eligible for inclusion in the VEG105192 study. The use of pazopanib is cautioned on the SPC in patients at risk for GI perforation or fistula.

In summary, there are no reasons to believe that the clinical benefits of pazopanib seen in the VEG105192 and other RCC clinical studies would not be applicable to the patients eligible to receive pazopanib in UK clinical practice.

6 Cost effectiveness

Key points

- The present economic evaluation assessed the lifetime cost-effectiveness of pazopanib versus sunitinib, interferon-α (IFN) and best supportive care (BSC) in patients with advanced/metastatic RCC in the UK.
- A cost-effectiveness model was developed based on available RCT data. It was necessary to perform an indirect comparison of the evidence in order to compare pazopanib to IFN and subsequently sunitinib.
- Outcomes were measured in terms of quality adjusted life years (QALYs) based on individual residual life expectancy data and health related quality of life (EQ-5D). The incremental cost components were drug acquisition costs, drug administration costs, pre and post-progression monitoring/supportive care costs and the costs of treating adverse events.
- The base case estimates for ICERs versus sunitinib, IFN and BSC were £10,787/QALY, £27,000/QALY and £25,264/QALY respectively.
- Probabalistic sensitivity analysis demonstrated that the probability of pazopanib being cost-effective versus sunitinib at willingness to pay thresholds of £30,000 and £20,000 were 65% and 61% respectively in the base case.
- In the majority of cases deterministic sensitivity analyses on the base case indicated that pazopanib was cost effective versus sunitinib at a threshold of £20,000-£30,000/QALY.
- The key driver for cost-effectiveness was the efficacy estimates for pazopanib versus IFN which impact upon the efficacy estimates for pazopanib versus sunitinib. In particular, results were sensitive to the method used to adjust for the cross-over of patients in the pazopanib trial VEG105192.
- As discussed in the clinical section, two statistical methods have been used recently to adjust for cross-over in survival analysis in RCTs (RPSFT and IPCW). Both were applied to the OS data from VEG105192 with RPSFT estimates used for the base case. Alternative methods resulted in ICERs for pazopanib versus sunitinib of £87,496/QALY and £21,622/QALY using Cox model censoring on cross over, and IPCW estimates respectively.
- A similar pattern for comparisons of pazopanib versus IFN and BSC was observed.
- It is important to note that sunitinib was approved by NICE under the Supplementary Advice on appraising end of life medicines based on an ICER versus IFN of £54,366/QALY. In the present evaluation the ICERs for sunitinib and pazopanib versus IFN were £42,872/QALY and £27,000/QALY respectively. If afforded the same consideration pazopanib should be considered a cost effective treatment option. Similarily the base case ICER versus BSC was £25,264/QALY, therefore pazopanib is likely to be a cost effective option for patients for whom sunitinib or IFN are unsuitable.
- GSK are planning to provide a patient access scheme to the NHS that will address the difference between the list price of pazopanib and the effective price of sunitinib to the NHS under the sunitinib patient access scheme. The patient access scheme will also address the uncertainty in the comparative evidence of pazopanib versus sunitinib until the results of the ongoing head to head COMPARZ study of pazopanib versus sunitinib are available.

Pazopanib constitutes a cost-effective treatment option for the first-line treatment of advanced/metastatic RCC. However, GSK acknowledge that there is uncertainty surrounding the clinical effectiveness of pazopanib owing to the lack of an active comparator in the pazopanib pivotal trial and the requirement to make adjustments for crossover without a universally accepted methodology. Consequently GSK intend to offer a patient access scheme to the NHS that will address this uncertainty.

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 **Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.**

A separate systematic review was undertaken to identify relevant cost effectiveness studies. The search strategy used is provided in Section 9.10, Appendix 10. A supplementary search for relevant health technology appraisals was conducted. A critique of the identified evaluations can be found in section 10 of the systematic review report provided with this submission.

Description of identified studies

6.1.2 **Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

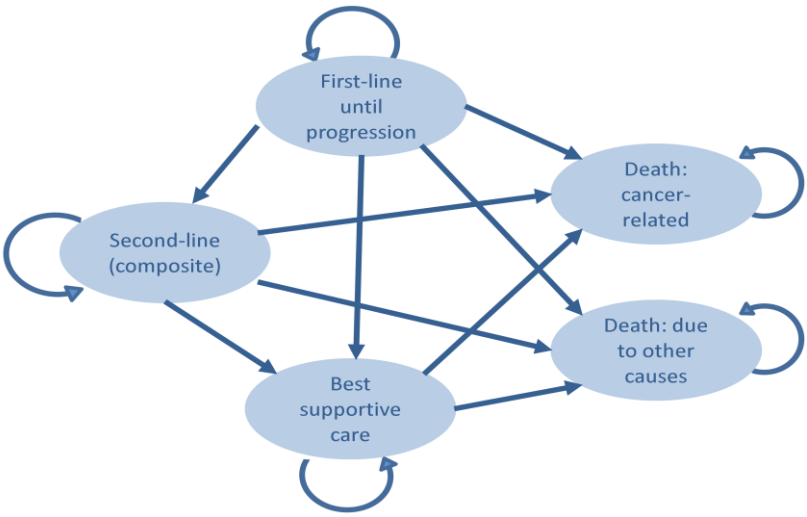
Two studies were identified which met the inclusion criteria for the review and are summarised in table 6.5. A list of excluded studies and a rationale for their exclusion is available upon request. A critical appraisal of the two included studies can be found in 9.11.

Remak 2008

Remak 2008 was a Markov model based study assessing the cost effectiveness and cost utility of sunitinib as a first-line treatment in advanced/metastatic RCC compared with interferon (IFN) and interleukin-2 (IL2) from a US societal perspective. The model followed a hypothetical cohort of 1,000 patients with advanced/metastatic RCC and documented clear-cell histology, radiographically measurable lesions, adequate organ function and ECOG performance status of 0 or 1 over the patient's lifetime (10 years).

This study reported the results and inputs of a 10-year Markov model, for which the model structure is shown in figure 6.3. In this model, patients were assumed to receive active treatment until an investigator's assessment of tumour progression was confirmed, then the patients were switched to either second-line treatment or to BSC. Cost-effectiveness and cost-utility analysis were performed and conclusions were made on the basis of ICER and ICUR. The Markov model used in the study was well defined and sensitivity analyses of model parameters were performed. A full critical appraisal of this study can be found in Appendix 9.11.

Figure 6.1: Structure of the model presented in Remak 2008



Model inputs are shown in table 6.1 and include efficacy (PFS), HRQL (EQ-5D), safety and direct medical costs including the costs of treating adverse events.

Table 6.1: Overview of model inputs in Remak 2008

Input	Remak 2008
Efficacy	Data from the second interim analysis of the pivotal phase III trial for sunitinib. Data from a randomised, multicentre, phase III study for IL2.
HRQL	The EuroQol (EQ-5D) instrument was used to measure HRQL. Outcomes were valued in QALYs in accordance with economic assessment guidelines. Utility values from a phase II trial of second-line sunitinib in advanced/metastatic RCC were used to calculate utilities during second-line treatment and palliative care.
Safety	The model incorporated the following treatment-related AEs; fatigue/asthenia stomatitis, hypertension, thrombocytopenia, neutropenia, abnormal ejection fraction, nausea/vomiting, diarrhoea, anaemia, hand-foot syndrome, and infection. Resource use based on expert opinion and published sources.
Costs	Direct medical costs included were; managing treatment-related serious AEs, diagnosis and treatment of progression, and BSC in the terminally ill. Indirect costs were not included. National average length of stay associated with each AE was based on the Agency for Healthcare Research and Quality (AHRQ) Healthcare Costs and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) database according to ICD-9 codes.

The results of this economic evaluation are shown in table 6.2. The results showed that sunitinib was both less costly and more effective than IL-2. In addition, sunitinib was more costly, but more effective than IFN, resulting in an ICER (LYs gained) of $67 215 and an ICUR of $52 593.

Table 6.2: Incremental cost-effectiveness and cost utility ratios for sunitinib versus IFN and IL-2 in the model presented in Remak 2008

Model Outcome	Deterministic mean per treatment strategy		
	Sunitinib	IFN	IL2
Cost, $	224 970	217 436	228 411
Progression free years	0.92	0.1	0.57
Life-years	2.09	1.98	1.85
QALYs	1.33	1.19	1.13
ICER – progression free years gained, $		18 611	Dominated
ICER – LYs gained, $		67 215	Dominated
ICUR, $		52 593	Dominated

ICER = Incremental cost effectiveness ratio , ICUR =Incremental cost utility ratio, IFN =Interferon alpha, IL-2 = Interleukin-2

Mickisch 2009

Mickisch 2009 presented a decision analytical model based study evaluating the costs of managing AEs of bevacizumab in combination with IFN compared to sunitinib in the first-line treatment of advanced/metastatic RCC in United Kingdom, Germany, Italy and France. The study reported the results and inputs of an Excel-based linear decision analytic model for which the model structure was not presented. Costs and consequences were measured accurately and in appropriate physical units and the study examined both costs and effects of the treatments. Incremental cost analysis was not reported in the study. All possible alternatives were explored through sensitivity analysis. A critical appraisal of this study can be found in Appendix 9.11.

Model inputs included the incidence and cost of treating adverse events. These are summarised in table 6.3.

Table 6.3: Overview of inputs into the economic evaluation

Input	Mickisch 2009
Safety	The model used the total incidence of grade 1-4 AEs reported in phase III trials in the disease setting.
Costs	Costs included the management of AEs only. UK; from a review of published literature. Germany; calculated from the diagnosis-related group (DRG) funding system catalogue (2008) and from Einheitlicher Bewertungsmaβstab catalogue (2008). Costs include medicines and staff and maintenance. France; drug costs - Banque Claude Bernard database and from Pharmacie central des Hopitaux de Paris. Laboratory tests and examinations from official tariff lists. Hospitalisation costs estimated using French DRG hospital database and Etude Nationale de Couts. Italy; report of a Delphi panel of exports from five clinical practices, from Italian national DRG tariff and from two studies.

Mickisch 2009 reported that the average cost per patient of managing all-grade and grade 3-4 AEs varied across the countries assessed in the evaluation, and that the costs were higher for sunitinib than for bevacizumab plus IFN, Table 6.4. The main cost drivers were lymphopenia, neutropenia, thrombocytopenia, leucopenia and fatigue/asthenia for sunitinib; and proteinuria, fatigue/asthenia, bleeding, anaemia and gastrointestinal perforation for bevacizumab plus IFN.

Table 6.4: All-grade AE management costs per patient (Euros) in each of the countries (Mickisch 2009)

Country	Sunitinib	Bevacizumab plus IFN	Cost saving*
UK	€2 350	€1 309	€1 041 (44%)
Germany	€2 071	€1 477	€594 (29%)
France	€5 127	€1 957	€3 170 (62%)

*cost saving of Bevacizumab plus IFN compared to sunitinib. IFN = Interferon alpha

Summary

Only two economic evaluations were identified by the systematic review, one of which was a US based study (Remak 2008), the other was conducted in multiple European countries, including the UK (Mickisch 2009). Results from the Remak study demonstrated that from a US societal perspective sunitinib dominated IL2 (i.e. it was less costly and more effective). When compared with IFN sunitinib yields both greater cost and effectiveness. Transferability of this study to the UK context might be prevented by the potential differences in unit costs, resource use, baseline risks and the perspective used in this study (effectiveness estimates may be more comparable).

The study by Mickisch *et al*., reported that the average cost per patient of managing all-grade and grade 3/4 AEs varied across the European countries, and that the costs were higher for sunitinib than for bevacizumab plus IFN. In terms of the UK, the cost of managing AEs was 44% greater with sunitinib treatment than it was with bevacizumab plus IFN treatment.

Table 6.5: Summary list of cost-effectiveness evaluations

Study	Year	Country	Summary of model	Patient population (average year)	QALY (intervention comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
(Remak 2008)	2006	US	The Markov model was developed in excel to simulate disease progression and outcomes over the lifetime (10 years) of a hypothetical cohort of 1000 patients with advanced/metastatic RCC receiving first-line treatment with (in 6-week cycles) with sunitinib compared with IFN or IL2.	Hypothetical cohort of 1000 patents	The estimated gains over IFN were 0.14 QALYs, and over IL-2 were 0.20 QALYs with sunitinib.	**Sunitinib** Drug cost (full dose): $5985/cycle Drug cost (reduced dose): $4488.75/cycle Cost of serious AEs: $160.13 **IFN** Drug cost (First cycle): $1903.10/cycle Drug cost (subsequent cycles): $2254.20/cycle Cost of serious AEs: $72.48 **IL2** Drug costs: $13 903.54 Cost of serious AEs: $312.62	Incremental cost per PFY gained for sunitinib versus IFN was $18 611, and the ICER and ICUR of sunitinib versus IFN were $67 215 per LY gained and $52 593 per QALY gained.
(Mickisch 2009)	Un-clear	United Kingdom, Germany, Italy, France	An Excel-based linear decision analytical model was developed to calculate and compare the costs of management of all grades of AEs according to standard clinical practice for bevacizumab plus IFN and sunitinib used as first-line treatment of metastatic RCC.	Not reported	Not reported	All grade AE management costs per patient for bevacizumab plus IFN arm in UK, Germany, and France were €1309, €1477, and €1957, respectively. All grade AE management costs per patient for Sunitinib arm in UK, Germany, and France were €2350, €2071, and €5127, respectively. Grade 3 – 4 AE management costs per patient for bevacizumab plus IFN and sunitinib arm in Italy were €402 and €891, respectively.	Not reported

ICER = Incremental cost-effectiveness ratio, IL-2 = Interleukin-2, QALY = Quality adjusted life years.

NICE appraisal of sunitinib in advanced/metastatic RCC

In addition to the two cost-effectiveness studies identified by the systematic review, a multiple technology appraisal for the treatment of advanced/metastatic RCC was identified that was later split into an MTA and a Single Technology Appraisal (STA) for sunitinib in the first-line treatment of advanced/metastatic RCC (TA 169). A critique of the economic model submitted by the manufacturer of sunitinib is presented in Table 72 of the systematic review report. As part of this STA, the assessment group developed a Markov model to assess the cost-effectiveness of sunitinib versus IFN, standard of care at that time. This Markov model had three distinct health states: progression free survival, progressive disease and death, and had a 10-year time horizon. Baseline efficacy data for IFN was taken from a study comparing bevacizumab plus IFN to IFN alone. Weibull curves were fitted to the Kaplan-Meier data and HRs from the sunitinib pivotal trial were applied to estimate PFS and OS survival curves for sunitinib. All data were taken from the final ITT analysis with the exception of the OS data from the IFN arm of the sunitinib trial which was from an analysis conducted in patients with no post-study therapy. Utilities used in the model were derived directly from the sunitinib trial and UK EQ-5D tariffs. Costs incorporated into the model included drug acquisition costs (modified according to dose intensity in the sunitinib RCT), monitoring costs and post-progression supportive care costs. Deterministic sensitivity analyses demonstrated that the model was sensitive to estimates of effectiveness, drug acquisition cost and health state utility inputs. The assessment group was requested to assume PFS of 1.06 and 1.75 years for IFN and sunitinib respectively and OS of 2.21 and 3.07 years, respectively. The assessment group noted concerns regarding the fit of the Weibull curves for PFS data and the fact that survival curves for OS data were estimated from different patient groups (ITT for sunitinib, no post-study treatment for IFN). Cost-effectiveness results for this analysis are presented in Table 6.6. Sunitinib was subsequently approved by NICE for use in the treatment of first-line advanced/metastatic RCC with an ICER of £54,366 under the Supplementary Advice on appraising end of life medicines.

Table 6.6: Cost effectiveness results from TA169 using the committee's preferred assumptions and the assessment groups' model.

	Sunitinib	IFN	Difference
QALYs	2.10	1.51	0.59
Total Costs	44,852	12,931	31,921
Cost/LY gained			41,729
Cost/QALY			54,366

6.1.3 **Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[13] or Philips et al. (2004)[14]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.**

[13] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[14] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

A quality assessment for each cost-effectiveness study identified is presented in section 9.11, Appendix 11.

A critical appraisal of the economic model developed by the assessment group for TA169 was not conducted. Rather, as stated above, a critique of the model provided by the manufacturer is available in the systematic review report.

6.2 De novo analysis

Patients

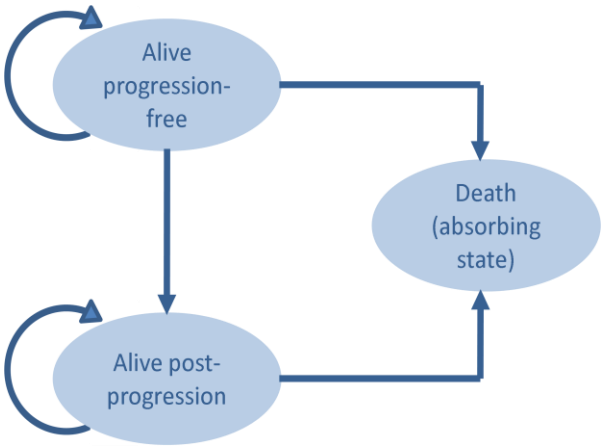
6.2.1 **What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.**

Pazopanib is likely to be granted a licence for the treatment of patients with both treatment-naïve and cytokine-pre-treated advanced/metastatic RCC consistent with the two sub-populations examined in the VEG105192 trial. For the purpose of this submission, only the cost-effectiveness of pazopanib in the treatment-naïve advanced/metastatic RCC population is examined, consistent with the scope of the appraisal.

Model structure

6.2.2 **Please provide a diagrammatical representation of the model you have chosen.**

Figure 6.2: Model schematic



The analytic model that was used projects expected clinical and economic outcomes for treatment-naïve advanced/metastatic RCC patients who are assumed to receive either pazopanib, sunitinib, IFN or BSC. The modelling approach used in this evaluation may be labelled as a "partitioned-survival" model. The model is characterized by three mutually exclusive health states ("*Alive Pre-Progression*", "*Alive Post-Progression*", and "*Dead*").

The model is similar to a Markov cohort model. However, unlike a Markov model in which transitions between health states are modelled explicitly using transition probabilities, the partitioned survival model calculates the proportion of patients in each treatment cohort that are expected to be in each health state at any time after treatment initiation based on parametric survival curves fitted to empirical data on OS and PFS over time. The proportion of patients in the progression health state at any given time is calculated as the difference between OS and PFS.

In the model, pazopanib is assumed to be administered until disease progression or death (if occurring prior to progression). Following therapy initiation, patients are 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 experience disease progression are assumed to discontinue therapy. Those who discontinue therapy are assumed to transition to an "Alive Post-Progression" health state and to reside in that state until death (a "capture" or "absorbing" state).

While residing in a particular health state, patients are assigned a corresponding cost of care as well as health-state preference weight (i.e. utility value), both of which are assumed to depend upon disease status.

6.2.3 **Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.**

The current source of OS data for pazopanib comes from an interim analysis performed with a cut-off date of 23 May 2008[15]. It was therefore necessary to use a modelling approach in order to project lifetime outcomes and costs. The partitioned survival analysis model employed in the evaluation was chosen because it permitted projection of the proportion of patients within states defined on the basis of progression and death. PFS was the primary efficacy outcome of the VEG105192 trial, and death is necessary for calculation of QALYs. A partitioned survival analysis model generates projections of both PFS and OS that are consistent with the data from the VEG105192 trial.

Partitioned survival models have been employed in recently completed technology appraisals including those of treatments for advanced/metastatic RCC [TA178 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)], and metastatic colorectal cancer (TA118 Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer), as well as in manufacturer's submissions for ongoing appraisals of lapatinib in metastatic breast cancer (STA, Lapatinib for use in women with previously treated advanced or metastatic breast cancer) and for rituximab in relapsed B-CLL (STA, Rituximab for the treatment of relapsed chronic lymphocytic leukaemia).

15 The interim analysis of OS in the VEG105192 trial was performed with a cut off date of 23 May 2008. At this point 90 events had occurred (39% of all treatment-naïve subjects). Hence, at the time of the interim analysis, 143 subjects from the treatment-naïve population were ongoing in follow- up.

Use of a model with states defined based on PFS and OS is consistent with clinical outcomes employed in oncology trials, and specifically with those employed in the VEG105192 trial. As patients are usually treated until disease progression, differences in costs and potentially HRQL between pre- and post-progression health states should be expected. Presence or absence of disease progression has been reported to be a key determinant of health-state utility (Bremner 2007; Nafees 2008; Wittenberg 2005; Ferguson 2008).Furthermore, partitioned survival models have been used in numerous prior technology assessments of cancer therapies.

It should be noted that the present cost-effectiveness evaluation is based on the understanding that currently there are no further treatment options available in the NHS after first-line treatment for advanced and/or metastatic RCC. Hence, best supportive care (BSC) will be offered to those patients with advanced/metastatic RCC who progress while receiving first-line therapy.

6.2.4 **Please define what the health states in the model are meant to capture.**

Model states are meant to capture differences in HRQL and costs for pre- and post-progression health states in this patient population. Presence or absence of disease progression is assumed to be a key determinant of HRQL and medical resource utilisation.

6.2.5 **How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.**

Prognosis is extremely poor for patients with advanced/metatstatic RCC, therefore HRQL and survival are important outcomes, both of which are captured in the model (section 2.1). In the model, treatment with pazopanib reflects underlying disease progression. Pazopanib is assumed to be administered until disease progression or death (if occurring prior to progression). Patients who experience disease progression are assumed to discontinue pazopanib therapy and receive only BSC. Presence or absence of disease progression is therefore a key determinant of HRQL and is reflected in the model by assigning different utility values to the *"Alive Pre-Progression"* and *"Alive Post-Progression"* health states. Disease progression is thus also a key determinant of medical resource utilisation.

6.2.6 **Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.**

Table 6.7: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	In the VEG105192 trial, median OS at the interim analysis was approximately 20 months. Assuming a relatively constant monthly hazard of death, approximately 99% of all patients receiving pazopanib would be dead within 10 years. Accordingly, all outcomes were evaluated over a ten-year (3653 day) timeframe, beginning with start of treatment. This timeframe approximates a lifetime projection, consistent with recommended good practice for cost-effectiveness analysis.	VEG105192
Cycle length	One day	Allows comparison of treatments with different cycle lengths and avoids the need for half-cycle correction	
Half-cycle correction	N/A	Not necessary as one day cycle length	NICE 2008
Were health effects measured in QALYs; if not, what was used?	Yes	As per reference case	NICE 2008
Discount of 3.5% for utilities and costs	Yes	As per reference case	NICE 2008
Perspective (NHS/PSS)	NHS	As per reference case	NICE 2008
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 **Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?**

The intervention (pazopanib) and comparators are implemented in the model as per the marketing authorisation and dose as stated in sections 1.3 and 1.5.

6.2.8 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

No additional treatment continuation rule has been assumed in the model, beyond the requirements of the marketing authorisation. In the economic evaluation, pazopanib therapy is assumed to continue until disease progression or death (if occurring prior to disease progression).

Patients who experience disease progression and discontinue pazopanib therapy are assumed thereafter to receive BSC, consistent with the absence of further treatment options available in the NHS after first-line treatment for advanced and/or metastatic RCC. Best efforts were employed based on clinical interviews and review of the published literature to estimate medical resource utilisation for patients receiving BSC (Sections 6.5.4 and 6.5.6).

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

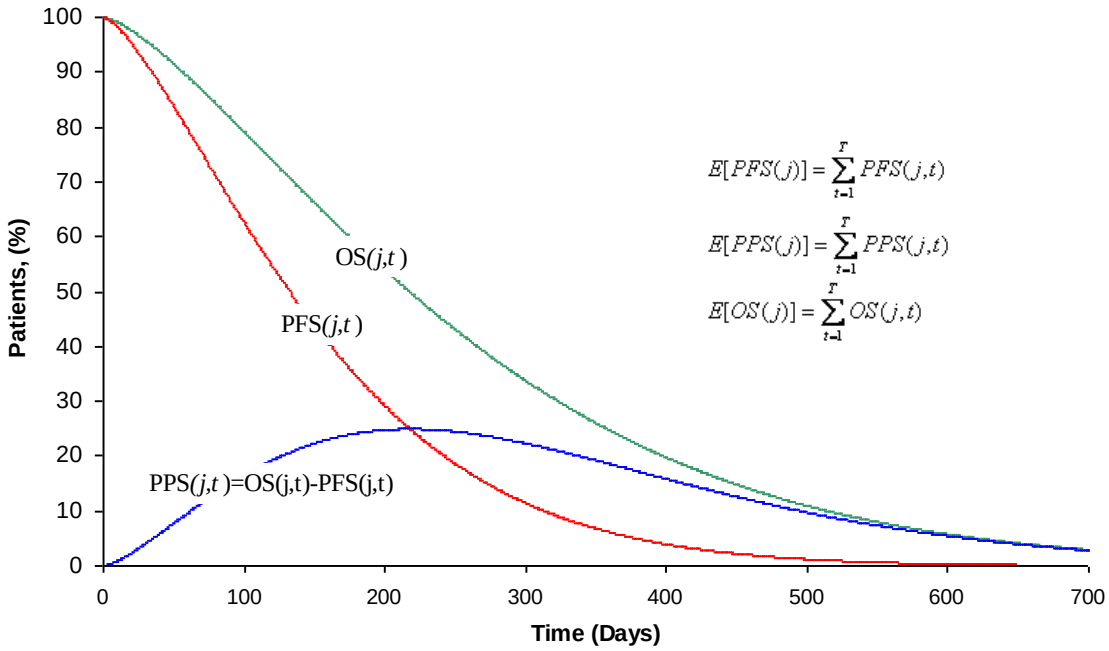
6.3.1 **Please demonstrate how the clinical data were implemented into the model.**

The clinical effectiveness data utilised by the economic model is outlined below.

PFS and OS

The proportion of patients in each treatment group that are expected to reside in each health state are based on the estimated survival functions for PFS and OS. Rather than estimating transition probabilities for use within the model an area under the curve analysis is used to estimate mean time prior to disease progression and mean survival. The difference between the two curves provides a direct estimate of the mean time alive following disease progression. Further detail is provided in Appendix 15.

Figure 6.3: Hypothetical example of the calculation of the amount of time spent in each health state.



To calculate measures of effectiveness, the proportion of patients receiving each treatment strategy that are expected to be alive and alive and progression free at each time, t, i.e. OS(t) and PFS(t), are generated by the model. In the model, time t represents days since initiation of therapy. For each strategy, the proportion of patients alive and post-progression at each time, PPS(t), is calculated by subtracting PFS(t) from OS(t). Expected (i.e. mean) PFLYs, PPLYs, and overall LYs for each strategy are calculated as the sum of PFS(t), PPS(t), and OS(t) respectively, over the modelling timeframe. Thus, for any given strategy, expected PFS and OS equal the area under the curves represented by PFS(t) and OS(t), while expected post-progression survival represents the area between the PFS and OS curves, as shown in Figure 6.3.

Estimates of *PFS[t]* and *OS[t]* for each comparator were obtained by first fitting a parametric survival function[16] to observed failure time data for one the comparators ("reference arm") and then applying to those survival functions relative hazard ratios (HRs) for each of the other comparators vs. that of the reference using the formula:

$$S_A[t] = S_B[t]^{HRAB}$$

Where $S_A[t]$ is survival for the comparator, $S_B[t]^{HR}$, is survival for the reference, and HR is the HR for the comparator vs. the reference treatment.

Parametric survival functions for PFS and OS were based on Weibull survival functions fit to the reported Kaplan-Meier survival curves for the IFN arm of the sunitinib pivotal trial (Motzer ASCO 2007; Figlin ASCO 2009; DSU / PenTAG Additional Work for NICE). The Weibull is a flexible survival function that allows for increasing or decreasing risk of events over time (Carroll 2003). Weibull survival functions take the general form below:

$$S[t] = \exp(-\lambda t^{\gamma})$$

where *S[t]* was the probability of not experiencing the event (e.g., progression or death) at time *t*.

HRs for the comparators versus the reference were obtained based on direct or indirect estimates obtained from randomized controlled trials of the comparators.

Estimated HRs for PFS and OS for pazopanib versus placebo/BSC were obtained from the VEG105192 study. Because the VEG105192 trial compared pazopanib with placebo/BSC, it was necessary to estimate HRs for PFS and OS for IFN vs. placebo/BSC in treatment-naïve patients and to combine these with estimates of the HRs for PFS and OS for pazopanib vs. placebo/BSC to obtain indirect estimates of the HRs for PFS and OS for pazopanib vs. IFN. Details of the indirect comparison and the effectiveness estimates used in the model can be found in section 5.7 and are summarised in Table 6.8.

As mentioned in the clinical sections, OS data from VEG105192 are currently immature[17] and a large proportion of patients in the placebo/BSC arm (40% at the clinical cut-off) crossed over to receive pazopanib at disease progression. The likely effect of such cross-over was to improve survival times for patients in the placebo/BSC group relative to what would have been observed had BSC patients not been allowed to cross-over. Several approaches were utilised to adjust for this cross over including the inverse probability of censoring weights (IPCW) method and the rank preserving structural failure time (RPSFT) method. The application of these two methods to adjust for cross-over in survival analysis is relatively new and there is currently no consensus on which is the most appropriate method. Therefore, it was particulary difficult to decide on which methodology to use for the base case and although the RPSFT-derived HR was used for the base case, cost-effectiveness results using IPCW-derived estimates as well as results obtained using a Cox regression model censoring on cross-over have also been provided.

The decision to use RPSFT for the base case was based on expert opinion from leading academics in this field. RPSFT was thought to be the most appropriate method to handle cross-

16 The impact of fitting alternative survival functions and/or using a different reference am was explored in sensitivity analyses

17 Final OS data is expected to be available in 3Q 2010

over in the pazopanib trial as it neither breaks randomisation nor assumes that there are no unknown confounders. Furthermore, the RPSFT technique has been considered by the Evidence Review Groups (ERGs) involved in previous NICE appraisals (sunitinib in GIST [TA 179] and everolimus in mRCC [Everolimus ACD, Feb 2010] to be the more methodologically robust for these two reasons. The main limitation of using RPSFT is the high degree of re-censoring required when applied to immature trial data; this is likely to be less of an issue when it is applied to the final OS data.

It should be noted that the HR used for OS from the sunitinib trial was not adjusted for post-study therapy in the same way as the OS data in VEG105192 and was taken from a sub-group analysis in subjects with no post-study therapy (Motzer 2009). This was based on the availability of reported HRs for OS in the sunitinib trial and is discussed further in section 5.7.4.

Table 6.8: Effectiveness estimates used in the economic model

		PFS			OS			Sources
		Est.	95%CI		Est.	95%CI		
IFN Weibul distribution	λ	0.1544			0.0700			PFS: Motzer 2007 ASCO OS: TA169/ Figlin 2008
	γ	0.8952			0.8300			
HR vs BSC	Pazopanib	0.360	0.240	0.550	0.345	0.086	0.1.276	PFS: VEGF105192 IRC Scan dates OS: VEGF105192 RPSFT model
	IFN	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	Pazopanib	0.512	0.326	0.802	0.432	0.106	1.750	Indirect comparison HR Paz vs. BSC ÷ HR IFN vs Plc
	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-Pts w/PS tx excl.)

Weibull Survival Functions for IFN and Placebo

The reference survival functions for treatment-naïve patients were estimated based on data for the IFN arm of the phase III trial of sunitinib vs. IFN. Parameters for OS for IFN (lambda=0.07, gamma=0.83) are based on estimates derived by PenTAG (assessment group) by fitting to OS data provided by Pfizer excluding patients who received non-study therapy (TA 169). These figures were validated using the Kaplan-Meier (KM) data for the analysis excluding patients who received non-study therapy as reported by Figlin at ASCO 2008. These parameters were used to approximately replicate the estimated LYs for IFN obtained by PenTAG using the Appraisal Committee (AC) preferred assumptions (~2.2 LY), which were used as the basis of the AC final decision regarding sunitinib. The placebo arm of the VEG105192 trial was not used because it was confounded by cross-over to pazopanib. While it would have been feasible to use the pazopanib arm of the VEG105192 trial as the reference, which was not affected by cross-over, the use of the "standard" or less effective treatment as the reference is conventional.

Weibull parameters for PFS were obtained by fitting data to KM curves for investigator assessed PFS for IFN patients in the sunitinib pivotal trial as reported in the Motzer 2007 ASCO presentation. Weibull parameters for PFS from the DSU/PenTAG's report using the AC's preferred assumptions were not employed because of concerns regarding the validity of these estimates. Specifically, according to the DSU/PenTAG report, PFS curves were provided by Pfizer and were based on the final ITT analysis of PFS. However, the median IRC-assessed PFS in the DSU/PenTAG's report is 20.88 months for sunitinib and 12.72 months for IFN. These contrast with figures of 11.0 months for sunitinib and 5.1 months for IFN reported in the ASCO 2007 presentation by Motzer (10.8 and 4.1 months based on investigator assessment). The estimates from ASCO 2007 are similar to those reported in the latest publication of the sunitinib vs. IFN trial (11 and 5 months respectively) (Motzer 2009). With respect to the KM curves for PFS reported in the ASCO 2007 presentation, the number of censored observations prior to the median (as indicated by tick marks on the curves) are limited, and it is not possible therefore that additional follow-up for these patients would explain an approximate doubling of median PFS for both groups. This suggests that the curves used to project PFS in the DSU's final report were in error. As a consequence, the DSU likely overestimated PFS for sunitinib and IFN, and therefore overestimated the incremental costs of sunitinib treatment which is assumed to be administered until disease progression.

Weibull survival functions for IFN for PFS were estimated (and those for OS validated),by using KM survival functions for the IFN arm of the sunitinib pivotal trial that were obtained from published reports using digitizing software.[18] The reported KM survival functions were transformed to obtain a linear relationship, as follows:

$$\ln\{-\ln(S[t])\} = \ln(\lambda) + \gamma \ln(t)$$

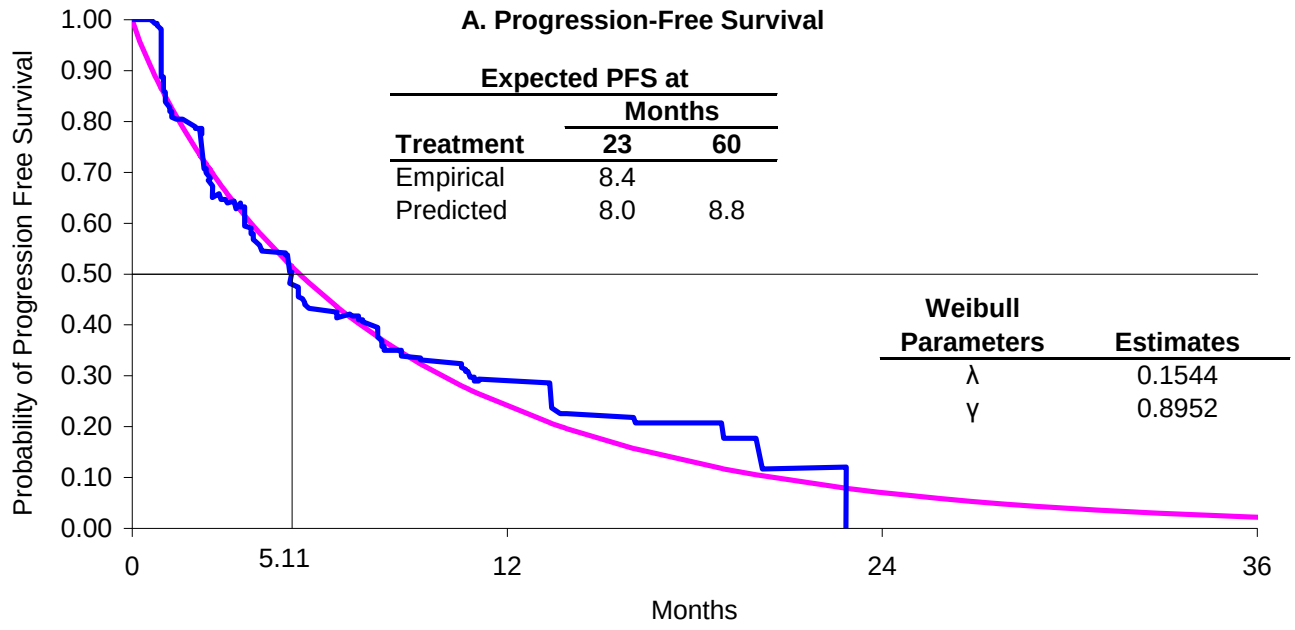
Ordinary least squares regressions were fitted with $\ln\{-\ln(S[t])\}$ as the dependent variable and $\ln(t)$ as the independent variable. The exponent of the intercept of these regressions yields λ in eq. 2; the coefficient on $\ln(t)$ yields γ. Because for values of $S[t]$ slightly less than 1, i.e. for very

18 Coordinates from the Kaplan-Meier curve were obtained at every vertical or horizontal shift in the curve. When fitting to the curve, this approach fits between the steps on the curve and gives greater weight to the early part of the curve where there were more failures.

small *t*, *-ln(S[t])* was fractionally greater than 0, and hence *ln{-ln(S[t])}* was very large and negative. Accordingly, values of *S[t]* close to one were omitted from the regression.

Actual and predicted PFS and OS for treatment-naïve patients receiving IFN are shown in Figure 6.4 and subsequent curves obtained by applying a relative HR for all comparators are shown in Figure 6.5.

Figure 6.4: Actual and predicted PFS and OS for treatment-naïve patients receiving IFN



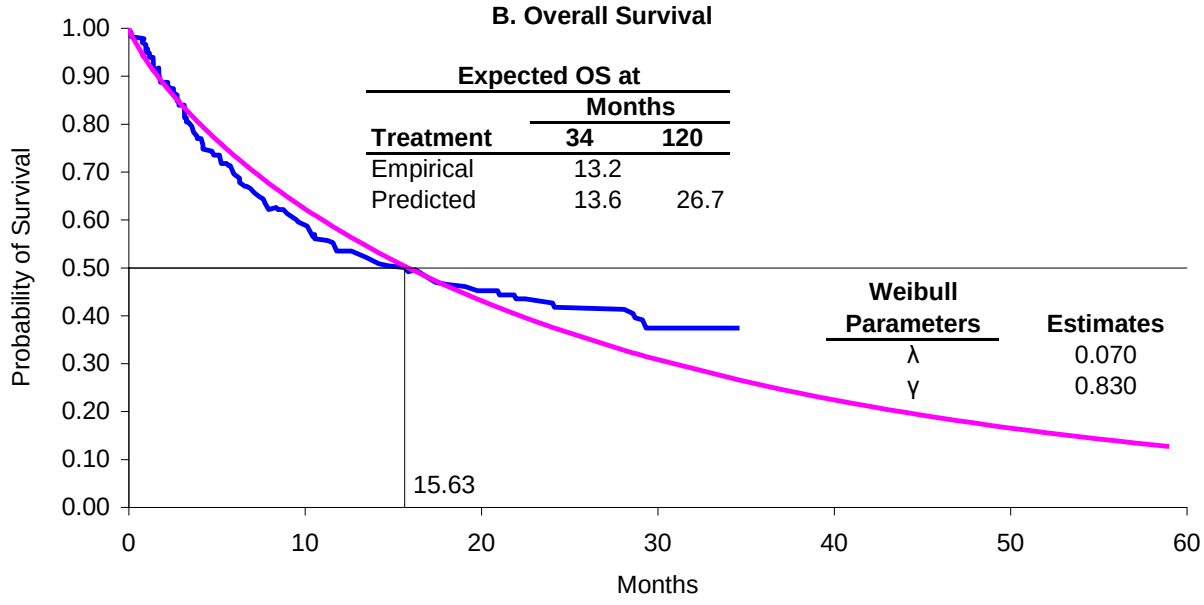
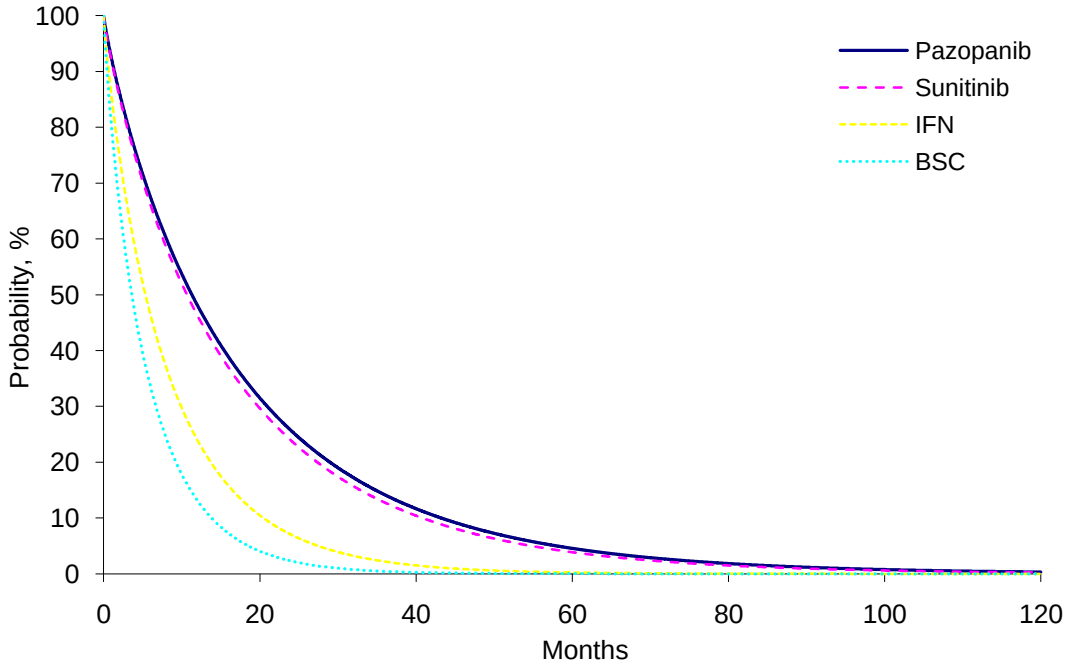
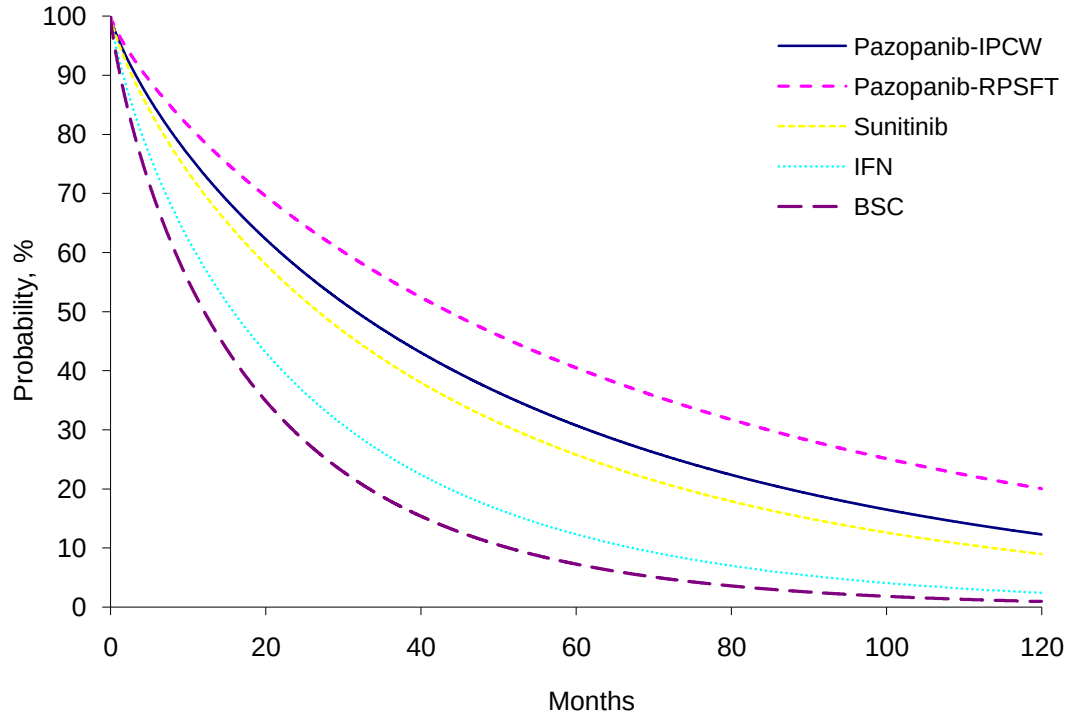


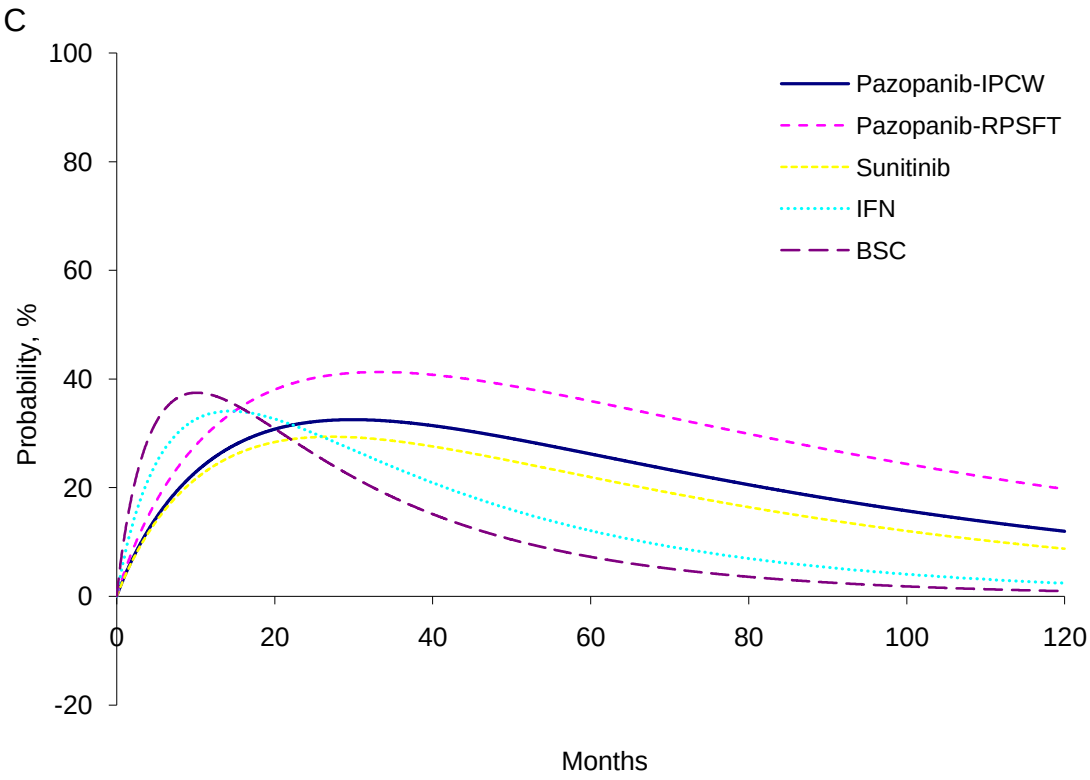
Figure 6.5: Predicted PFS (A) OS (B) and PPS (C) survival curves utilised in the economic model

A



B



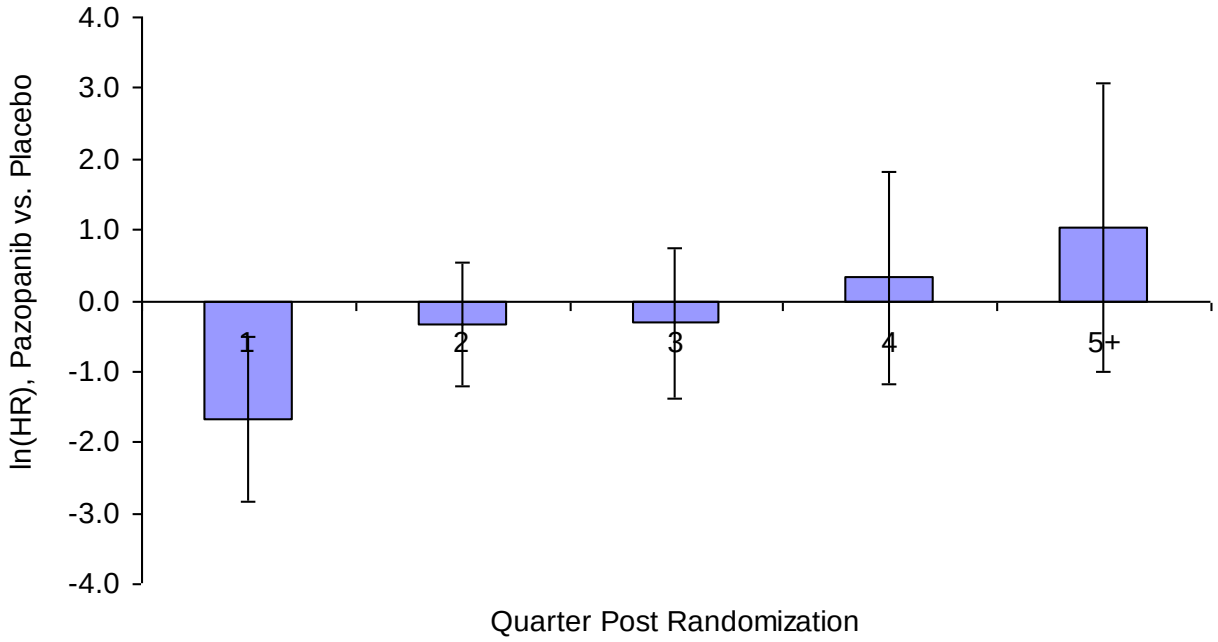


Assessment of Proportionality Assumption

The mathematical model employed in the economic evaluation does not require the assumption of proportional hazards, as independent Weibull survival functions for PFS and OS may be entered for any comparator. However, because the indirect comparison of pazopanib vs. IFN and vs. sunitinib uses HRs for PFS and OS as measures of relative effectiveness, an assumption of proportionality of hazards for PFS and OS is required.

To test the proportionality assumption for PFS and OS in VEG105192, a Cox proportional hazards regression model including covariates for treatment and the interaction of treatment and the log of failure time was run. Proportionality based on the correlation between the ranked failure time and the Schoenfeld residuals, and using the supremum test for proportional hazards based on the observed standardized score process (Ng'Andu 1998) was also tested. For OS, analyses were conducted with patients who crossed over censored at cross-over. There was no evidence to reject the proportionality assumption for PFS (all tests were not statistically significant). However, for OS all three tests provided evidence that the proportionality assumption was violated. As shown in Figure 6.6 below, the log of the HR for OS increased over time, suggesting diminishing benefit for pazopanib vs. placebo. This may have been a consequence of confounding resulting from the differential censoring of placebo patients due to cross-over to pazopanib.

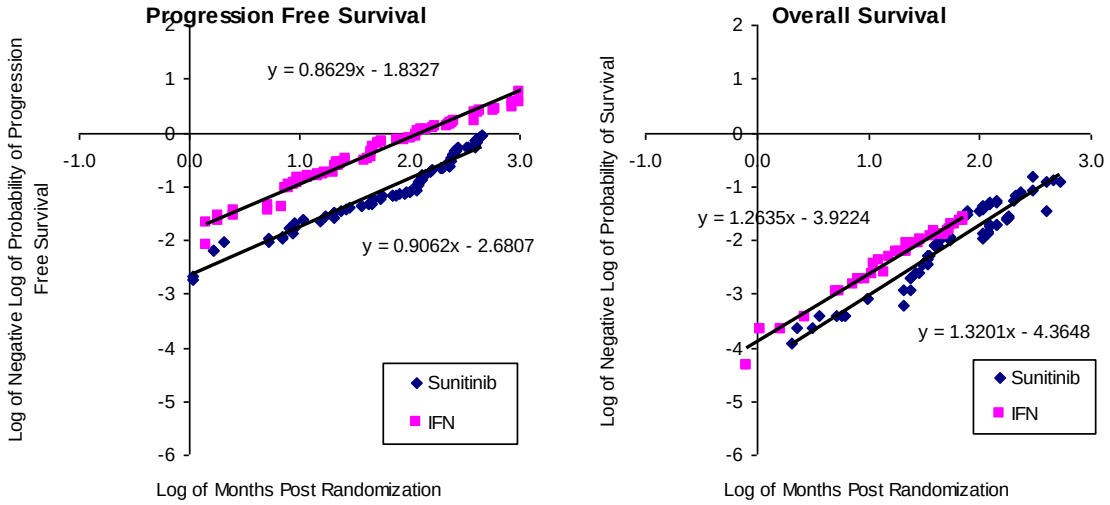
Figure 6.6: Log of Hazard Ratio for OS for pazopanib vs. placebo by quarter of follow-up in treatment-naïve patients in VEG105192



Lacking patient level data, it is not practically feasible to conduct formal statistical assessments of the proportionality of hazards for PFS and OS in the trials of the other comparators. Therefore proportionality by plotting the log of the negative log of KM estimated PFS and OS against the log of months was assessed. Assuming that PFS and OS follow a Weibull distribution, the lines fitted to these plots should be approximately parallel. Plots for sunitinib vs. IFN in treatment-naïve patients are shown in Figure 6.7. Generally, the lines for treatment and control are parallel and do not provide strong evidence for non-proportionality.

Taken as a whole, these analyses seem to suggest that use of the HR to conduct an indirect comparison of the therapies of interest is reasonable, although the assumption of a constant HR for OS for pazopanib vs. placebo in treatment-naïve patients may be confounded because of cross-over. Because the survival functions for PFS were generally complete for all trials, the bias associated with using observed HRs for PFS with non-proportional hazards is limited. Addressing the potential bias associated with non-proportionality of hazards for OS with pazopanib vs. placebo would require estimating separate HRs for different time segments which is not feasible with the existing economic model. However, a sensitivity analysis was conducted in which estimates of *PFS[t]* and *OS[t]* for pazopanib and BSC were obtained by fitting independent Weibull survival functions to observed failure time data from VEG105192 (section 6.7.7). PFS was based on the scan dates and OS was estimated controlling for cross-over using RPSFT (see Section 5.5.1.2.2). HRs for the comparators vs. BSC were obtained based on direct or indirect estimates obtained from randomized controlled trials of the comparators.

Figure 6.7: Plot of log(-log(S[t]) vs. log(t) for PFS and OS for sunitinib and IFN



Incidence of Adverse Events

Estimates of the incidence of AEs for each comparator were obtained from published results of randomised controlled trials as described above. AEs considered in the model included those that were identified prior to the conduct of the evaluation as being of particular interest based on clinical opinion (diarrhoea, nausea/vomiting, fatigue/asthenia, hypertension, heart failure, gastrointestinal (GI) perforation, palmar plantar erythrodysesthesia (PPE, hand-foot syndrome), mucositis/stomatis, and non-PPE rash) and those with a combined incidence of grade 3 and 4 events greater than or equal to 5% or with a combined incidence of all grades greater than or equal to 20%, in any arm of any RCT of any comparator. AEs were estimated separately by grade (grades 1 or 2 and grades 3 or more).

To control for differences between trials in participants and methods, and to maintain randomisation, an adjusted indirect comparison of AEs was conducted using a standard methodology (Sutton 2008). It should be noted that the indirect comparison of AEs utilised for the economic evaluation is slightly different to that presented in the clinical section (section 5.9.2.5). The differences in the incidence of AEs between pazopanib vs. IFN were calculated as the differences between the estimated differences between pazopanib vs. placebo and the estimated differences between IFN vs. placebo. Estimates of the risk differences for IFN vs. placebo were obtained by mixed treatment comparison using (i) indirect estimates from the phase II trial sorafenib vs. IFN in treatment-naive patients (Escudier 2009), as well as (ii) direct estimates from the Percy Quattro trial (Negrier 2007). AE rates in the other trials of IFN vs. placebo or inactive control were either unavailable or deemed to be not comparable with those from pivotal studies of targeted therapies and were not included. Because it was suspected that the reporting of AEs in the PERCY Quattro trial was less complete than that in the more recent trials of the targeted therapies, the risk difference was estimated based on the mixed comparison only if information on the incidence of the AE was reported in the PERCY Quattro

trial. If information on the AE was not reported in the PERCY Quattro trial, the risk difference was based on the indirect comparison only. If information on the AE was not reported in either the PERCY Quattro trial or either of the sorafenib trials, the risk difference for IFN vs. placebo was assumed to be zero. Estimates of the incidence of AEs in treatment-naïve patients are shown in Table 6.9.

Table 6.9: Incidence of adverse events in treatment-naive patients

	Grades 1 and 2								Grades 3+							
	IFN		Pazopanib		Sunitinib		Placebo		IFN		Pazopanib		Sunitinib		Placebo	
AE	Risk	SE	Risk	SE	Risk	SE	Risk	SE	Risk	SE	Risk	SE	Risk	SE	Risk	SE
Alopecia	1.1	1.1	8.3	6.3	1.1	3.0	1.1	6.1	0.0	0.5	0.0	0.5	0.0	1.2	0.0	0.5
Anemia	18.7	1.1	9.4	6.8	48.7	3.7	18.7	6.1	5.1	0.7	1.8	2.8	4.1	1.7	1.5	2.4
Anorexia / Weight loss	22.4	1.4	27.2	8.7	22.4	3.1	10.0	7.9	1.7	0.5	0.0	2.2	1.7	1.2	0.0	1.7
Asthenia / Fatigue	44.5	1.6	26.6	8.7	46.5	4.0	11.8	7.8	16.2	1.2	8.4	4.7	11.2	2.8	6.0	4.3
Bleeding	3.9	1.1	3.9	6.8	3.9	3.0	3.9	6.1	0.3	0.3	0.3	1.9	0.3	1.2	0.3	1.6
Constipation	2.9	1.1	0.0	6.8	2.9	3.0	0.0	6.1	0.3	0.4	0.7	2.0	0.3	1.2	0.3	1.7
Cough	3.6	1.1	0.0	4.9	3.6	3.0	0.0	3.9	0.0	0.5	0.0	0.6	0.0	1.2	0.0	0.6
Diarrhea	13.8	1.1	53.5	7.8	49.8	3.3	13.8	6.8	0.8	0.4	3.9	1.4	5.8	1.2	0.8	1.7
Dyspnea	8.3	1.1	0.0	4.7	8.3	3.0	0.0	4.0	1.3	0.5	0.0	1.7	1.3	1.2	0.2	1.2
Fever/Pyrexia	38.7	1.6	9.2	6.9	10.7	3.2	9.6	6.2	0.7	0.4	0.0	1.7	1.7	0.6	0.0	1.7
Flu-like symptoms / Influenza-like illness	29.0	1.5	0.9	6.9	0.0	3.2	0.9	6.2	1.5	0.4	0.0	2.0	1.5	0.8	0.0	1.7
GI perforation	0.0	1.1	0.3	6.8	0.0	3.0	0.0	1.2	0.0	0.5	0.3	2.0	0.0	1.2	0.0	0.4
Hair color changes	0.9	0.5	35.3	6.7	49.6	1.9	0.0	6.1	0.0	0.5	0.3	2.0	0.0	0.5	0.0	1.7
HFS/PPE	1.1	0.5	5.2	6.2	15.1	2.0	0.9	6.0	0.0	0.5	0.7	3.5	5.0	1.2	0.0	1.7
HF/CD/↓LVEF	0.6	0.3	0.6	6.7	23.1	1.6	1.1	6.0	0.6	0.4	1.3	2.0	4.8	1.0	0.0	3.4
Headache	12.7	1.1	13.6	6.8	8.7	2.7	0.6	6.0	0.6	0.5	0.6	2.0	1.6	0.7	0.6	1.7
Hyperglycemia	2.4	1.1	10.3	6.8	2.4	3.0	8.1	6.1	0.4	0.5	0.0	2.0	0.4	1.2	0.6	1.7
Hyperlipidemia	2.9	1.1	2.9	6.8	2.9	3.0	2.4	6.1	0.3	0.4	0.3	2.0	0.3	1.2	0.4	1.7
Hypertension	4.4	1.0	29.9	6.3	20.4	2.1	2.9	6.1	0.8	0.3	3.6	1.6	7.8	1.5	0.3	1.7
Infection	2.5	1.1	2.8	6.8	2.5	3.0	4.4	5.0	0.5	0.5	0.8	2.0	0.5	1.2	0.0	0.9
Leukopenia	13.3	1.1	42.6	6.8	32.3	3.7	2.5	6.1	1.3	0.5	1.3	2.0	4.3	1.4	0.5	1.7
Mucositis/Stomatitis	1.4	0.5	8.9	6.7	42.4	2.6	13.3	6.1	1.0	0.5	0.0	1.3	2.0	1.2	1.3	1.7
Nausea / Vomiting	21.6	1.3	34.4	8.7	41.6	3.8	1.4	6.0	1.7	0.5	1.7	2.2	6.7	1.6	0.0	1.2
Neutropenia	7.9	0.8	32.7	6.8	28.9	3.7	5.5	7.7	3.4	0.6	2.1	2.0	8.4	2.3	0.6	1.5
Pain	11.7	1.2	6.3	7.5	0.0	3.0	7.9	6.1	1.1	0.4	2.8	3.4	4.8	1.0	0.7	1.9
Peripheral edema	2.3	1.0	2.3	6.8	2.3	3.0	0.0	5.9	0.0	0.5	0.0	2.0	0.0	1.2	1.1	2.9
Proteinuria	1.9	0.8	9.8	6.7	1.9	2.9	2.3	6.1	0.0	0.5	1.4	2.0	0.0	1.2	0.0	1.7
Rash	4.4	0.8	9.2	6.7	16.4	2.4	1.9	6.0	0.6	0.4	0.9	2.6	1.6	1.0	0.0	1.7

IFN=interferon. MPA=medroxyprogesterone. HF=Heart failure. CD=Cardiac dysfunction. ↓LVEF=Reduced left ventricular ejection fraction. HFS=Hand foot syndrome. PPE=Palmar plantar erythrodeisis NR=Not reported. SE: Standard error

6.3.2 **Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.**

Risks of disease progression and death were allowed to vary over time, consistent with the Weibull survival functions as described in Section 6.3.1.

6.3.3 **Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.**

Risks of disease progression and death were allowed to vary over time, consistent with the Weibull survival functions as described in Section 6.3.1.

6.3.4 **Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?**

OS in the model was estimated directly and was not linked to PFS.

6.3.5 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[19]:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**

[19] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Two experts in the field of RCC were consulted by GSK (one from the US and one from the UK) in the development of the economic model. The experts were questioned principally regarding the appropriateness of the methods and clinical face validity of the results of the meta-analysis of trials of IFN vs. BSC as described herein. They were also queried regarding key assumptions of the model and the patterns of treatment for adverse events. Information was collected based on informal telephone interviews and e-mail correspondence. The UK expert also participated in an Advisory Board meeting in which the methods and preliminary results of the evaluation were presented (the other meeting participants were health economists and pharmacists). Questionnaires, Delphi techniques and other iterative data collation techniques were not employed.

Summary of selected values

6.3.6 **Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.**

The economic model incorporates data from a number of sources including clinical effectiveness data from RCTs, health state utility data, resource use data and cost data. Effectiveness, cost and utility model inputs can be found in table 6.10. Incidence, cost and utilities associated with adverse events can be found in appendix 16.

Table 6.10: Summary of model inputs

	Pazopanib		Sunitinib		IFN				BSC		Reference in submission
Variable	**Value**	**SE (distribution)**	**Value**	**SE (distribution)**	**Value**			**SE (distribution)**	**Value**	**SE (distribution)**	
Effectiveness											
PFS											
Lamda					0.154						
Gama					0.895						
HR vs. IFN	0.512	0.229 (log normal)	0.539	0.114 (log normal)	1.000				1.421	0.099 (log normal)	Section 5.5.1/ 5.7.6
OS											
Lamda					0.070						
Gama					0.830						
HR vs. IFN	0.432	0.714 (log normal)	0.647	0.149 (log normal)	1.000				1.251	0.087 (log normal)	Section 5.5.1/ 5.7.6
Costs											
Drug utilization											
					Dose 1	Dose 2	Dose 3				
mg per day of use	800		50		3	6	9				Section 6.5.5
days of use/cycle	7		28		3	3	3				Section 6.5.5
No. of days in cycle	7		42		7	7	7				
No. free cycles	0		1		0	0	2				
Max No. cycles					1	1	52				
RDI - daily dose	0.86		0.86		0.84	0.84	0.84				
RDI - PFS days	1		1		1	1	1				
% IV wastage					11						
Unit costs											
cost per unit	74.73		112.10		42.40						Section 6.5.5
mg/unit	800		50		10						Section 6.5.5
Administration costs per day					6.76						Section 6.5.5
Therapy initiation cost	142.00	35.50 (Log normal)	142.00	35.50 (Log normal)	142.00			35.50 (Log normal)	142.00	35.50 (Log normal)	Section 6.5.6
Pre-progression costs (per month PFS)	145.80	36.45 (Log normal)	145.80	36.45 (Log normal)	145.80			36.45 (Log normal)	145.80	36.45 (Log normal)	Section 6.5.6
Post-progression costs (per month PPS)	228.01	57.00 (Log normal)	228.01	57.00 (Log normal)	228.01			57.00 (Log normal)	228.01	57.00 (Log normal)	Section 6.5.6
Utility Values											
Pre-progression	0.70	0.01 (Beta)	0.70	0.01 (Beta)	0.70			0.01 (Beta)	0.70	0.01 (Beta)	Section 6.4.9
Post-progression	0.11		0.11		0.11				0.11		Section 6.4.9

6.3.7 **Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.**

Costs and clinical outcomes were projected beyond the end of follow-up in the VEG105192 trial by fitting Weibull survival curves to the IFN arm of the sunitinib pivotal trial and applying relative HRs for comparators, as described in Section 6.3.1.

6.3.8 **Provide a list of all assumptions in the de novo economic model and a justification for each assumption.**

Table 6.11: Assumptions in the economic model

Assumption	Justification
Pazopanib and sunitinib are administered until disease progression	This complies with marketing authorisations for both products
PFS and OS can be modelled using a Weibull distribution.	Weibull models are widely used in economic evaluations of cancer therapies. In this case the Weibull model provides a good fit to the empirical survival distribution.
It was assumed that patients who are free of progression and with no AEs have a specific mean utility (i.e. 0.70) based on the mean EQ-5D utility value among all patients in the pivotal clinical trial.	HRQL data for pre-progression were collected in the VEG105192 trial through validated tools.
Progression was assumed to be associated with a decrement in utility of 15% (i.e. post-progression utility of 0.59)	Disease progression is an important predictor of HRQL in cancer patients. Utility values for post-progression health state were consistent with that in the Remak study and the Parasuraman study (and between that suggested by results of the VEG105192 trial and the Oxford Outcomes study). Data on the effects of adverse events on utilities conditioned on progression are currently unavailable
It was assumed that utility was negatively affected by the presence of adverse events	Utility decrements for adverse events were observed in the VEG105192 trial. The durations of AEs (required to estimate the decrement in QALYs) were also estimated using data from VEG105192
Indirect treatment comparison is an appropriate method to determine relative efficacy in the absence of head to head	No head- to-head data is currently available. Performing an indirect comparison via IFN allows determination of the relative efficacy of pazopanib to sunitinib.

clinical data.	
The costs/effects of second- line therapies were not included in this analysis. Patients that progress are assumed to receive BSC post progression.	The present cost-effectiveness analysis is based on the understanding that currently there are no further treatment options available in the NHS after first-line treatment for advanced/ metastatic RCC. Hence, BSC will be offered to those patients with advanced/metastatic RCC who progress while receiving first- line therapy
10 years approximates a lifetime time horizon for advanced/metastatic RCC patients.	In the model, approximately 20% of patients receiving pazopanib, 9% of patients receiving sunitinib, 2% of patients receiving IFN, and 1% of patients receiving BSC are alive at 10 years. For IFN and BSC, the model therefore closely approximates a lifetime projection. Because of the relatively long tails of the Weibull distributions, the model would need to be run for over 20 years for OS with pazopanib to be less than 1%. These results likely underestimate mortality in the out years as they do not reflect increasing mortality from non advanced/metastatic RCC related causes. Use of 10 year time horizon was therefore both conservative and methodologically appropriate.
Only the costs of grade 3+ costs were included in the model.	The relative low cost of treating grade 1 and 2 adverse events would have minimal impact on cost-effectiveness estimates.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 **Please outline the aspects of the condition that most affect patients' quality of life.**

RCC can have a profound impact on patients' Health Related Quality of Life (HRQL) at all disease stages. Consequently clinical studies evaluating new treatment interventions for RCC are increasingly incorporating measures to assess HRQL and symptom burden as it is widely agreed that along with survival, symptom improvement is considered to be one of the primary measures of clinical benefit.[20]

A number of general cancer questionnaires have been used in different studies to evaluate RCC symptoms or HRQL from the patient perspective, including the Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM) [Bacik 2004], the Rotterdam Symptom Checklist [de Haes 1990], and the European Organization for Research and Treatment of Cancer HRQL survey (EORTC QLQ-C30; Aaronson1993). The most frequently reported symptoms among RCC patients include fatigue, weakness, pain, lack of appetite, nausea, dyspnoea, flu-like symptoms, diarrhoea, constipation, headache, and dry mouth. Results also suggest that patient HRQL is affected, particularly with respect to physical functioning, psychological impairment (depression, anxiety, and irritability), sleep, social functioning, and role activities (Harding 2007).

A recent US national survey was conducted among 37 adults with RCC and their caregivers (Harding 2007). This cross-sectional assessment reported that while RCC patients felt that their daily and leisure activities were limited by symptoms, most addressed the emotional experience more than the physical, with emphasis on depression and worry. This emotional impairment was due in large part to initial misdiagnoses and continuing symptoms. Caregiver interviews closely mirrored patient interviews with respect to physical symptoms as they related to RCC, with pain being the predominant symptom. As expected, there was more divergence between RCC

[20] Consistent with other tumours, there is some evidence linking survival and symptoms in RCC that suggests an association between tumour and symptom burden [Kim 2003, Zisman 2002, Schips 2003, Patard 2004].

patient and caregiver views with respect to the patients' emotional symptoms such as depression; although no clear patterns were apparent.

6.4.2 **Please describe how a patient's HRQL is likely to change over the course of the condition.**

Structured interviews were conducted aimed at exploring HRQL in people with advanced/metastatic RCC as part of a utility study commissioned by GlaxoSmithKline to obtain UK societal preferences for receiving newly-developed treatments for advanced/metastatic RCC (Oxford outcomes, Swinburn 2010). The structure interview guide included questions about symptoms, and different areas of HRQL such physical functioning, psychological health, usual activities etc. Clinicians reported a marked disparity between the functional status of patients with stable and progressive advanced/metastatic RCC. Those with controlled disease were reported as capable of maintaining a relatively high level of functioning with only modest physical symptoms that could be treated effectively. Individuals with progressive disease faced significantly more challenges in preserving their quality of life. Physical, social and emotional functioning can all be adversely affected and often result in some loss of independence.

HRQL data derived from clinical trials

6.4.3 **If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.**

- **Method of elicitation.**
- **Method of valuation.**
- **Point when measurements were made.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**

HRQL was assessed using EQ-5D and the EORTC-QLQ-C30 questionnaires at baseline and at Weeks 8, 16, 24, and 48, following randomization in the pivotal trial VEG105192. Analyses for the EQ-5D results were focused on EQ-5D Index and EQ-5D visual analogue scale (VAS) score as primary HRQL endpoint.

Evaluation of HRQL through the use of EQ-5D, a validated generic measure which incorporates society preference values through the use of a choice-based method (i.e. TTO), is consistent with the reference case.

Mapping

6.4.4 **If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**
- **Details of the methodology used.**
- **Details of validation of the mapping technique.**

Not appliacable.

HRQoL studies

6.4.5 **Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.**

The search for HRQL data was incorporated with the systematic searches conducted to identify relevant clinical information, and included general descriptors such as quality of life, wellbeing, quality of well being, alongside terms to identify HRQL measurement (EuroQOL) and HRQL outcomes (QALY, preferences). Please refer to 9.12, Appendix 12 for the search strategies used.

Due to the paucity of published utility data in this patient population, a health state preference study was commissioned to generate utilities for PFS and post-progression survival, and disutilities for treatment-related adverse events (i.e. anaemia, diarrhoea, fatigue, PPE, nausea, mucositis and hypertension). The study estimated utility values for advanced/metastatic RCC health using time trade off (TTO) assessments in a sample of 100 people living in the UK (Oxford Outcomes; Swinburn 2010). Health state descriptions were developed based on a review of the literature and in consultation with three clinicians and an oncology specialist nurse all with extensive experience working with patients undergoing therapy for advanced/metastatic RCC.

Additional HRQL data were obtained from studies evaluating recently approved treatments for advanced/metastatic RCC: sunitinib (Remak 2008) and temsirolimus (Parasuraman 2008).

6.4.6 **Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.**

- **Population in which health effects were measured.**
- **Information on recruitment.**
- **Interventions and comparators.**

- **Sample size.**
- **Response rates.**
- **Description of health states.**
- **Adverse events.**
- **Appropriateness of health states given condition and treatment pathway.**
- **Method of elicitation.**
- **Method of valuation.**
- **Mapping.**
- **Uncertainty around values.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**
- **Appropriateness of the study for cost-effectiveness analysis.**

Health related quality of life outcomes were reported in only three identified studies (Motzer 2009; escudier 2009; Hudes 2007 Global ARCC trial). Various HRQL tools were used in these studies and are summarised in table 6.12 below.

Table 6.12: Summary of HRQL tools used

HRQL Tool	Studies using this tool	Validation paper
FACT-Kidney Symptom Index–Disease-related Symptom (FKSI-DRS Index)	Motzer 2009	(Cella 2007b)
FACT-Kidney Symptom Index - 15 item scale (FKSI-15 Index)	Motzer 2009; Escudier 2009	(Cella 2006)
Functional assessment of cancer therapy – general scale (FACT-G)	Motzer 2009	(Lee 2004)
EQ-5D	Motzer 2009; Hudes 2007 Global ARCC trial	http://www.euroqol.org/home.html

FACT-Kidney Symptom Index–Disease-related Symptom (FKSI DRS Index)

The FACT-Kidney Symptom Index–Disease-related Symptom subscale (FKSI-DRS) is a subscale of the validated FACT-Kidney Symptom Index–15 item scale (FKSI-15) that contains nine items measuring symptoms predominantly related to kidney cancer. The FKSI-DRS score ranges from 0 (all most severe symptoms) to 36 (no symptoms). Only one study reported FKSI-DRS index (Motzer 2009). In this study, patients in sunitinib group reported higher (more favourable) FKSI-DRS scores than those in the IFN group. Overall mean difference in scores was 1.98 points (95% CI: 1.46 to 2.51) favouring the sunitinib group ($p<0.0001$).

Table 6.13: Summary of FKSI-DRS Index

Study	Intervention	N	Mean ± SD score	
			Baseline	Endpoint
Motzer 2009 (reported in Cella 2008)	IFN	356	29.55 ± 5.03	27.4 (N = 319)
	Sunitinib	373	29.74 ± 5.24	29.4 (N = 349)

IFN = interferon-α

FACT-Kidney Symptom Index - 15 item scale (FKSI-15 Index)

The FKSI-15, introduced in 2006, is a validated symptom index for kidney cancer patients containing 15 questions, each scored on a 5-point scale (0 = not at all; 4 = very much) (Cella 2006). The FKSI-15 score ranges from 0 (most severe symptoms and concerns) to 60 (no symptoms or concerns). Linked citation of Motzer 2009 i.e. Cella 2008, reported the HRQL outcomes. In this study, sunitinib was compared with IFN. Patients in sunitinib group reported higher (more favourable) FKSI-15 scores than those in the IFN group. Overall mean difference in scores was 3.27 points (95% CI: 2.36 to 4.18) favouring the sunitinib group (p<0.0001). Similar results were reported for a trial comparing sorafenib with IFN (Escudier 2009), where a clinically significant difference of 5.9 points was observed in favour of sorafenib (p = 0.015).

Table 6.14: Summary of FKSI-15 Index

Study	Intervention	N	Mean ± SD score	
			Baseline	Endpoint
Escudier 2009	IFN	92		34.6
	Sorafenib	97		40.5
Motzer 2009 (reported in Cella 2008)	IFN	356	46.1 ± 8.7	42.1 (N = 319)
	Sunitinib	373	46.45 ± 8.46	45.3 (N = 349)

IFN = interferon-α, SD = standard deviation

Functional assessment of cancer therapy – general scale (FACT-G)

FACT-G, a reliable and valid scale (Lee 2004), measures the impact of treatment on general cancer related Health Related Quality of Life (HRQL) and functioning. In a study comparing sunitinib with IFN, patients in sunitinib group reported higher (more favourable) FACT-G scores than those in the IFN group. Overall mean difference in scores was estimated to be 5.58 points (95% CI: 3.91 to 7.24) favouring the sunitinib group (p<0.0001).

Table 6.15: Summary of FACT-G

Study	Intervention	N	Mean ± SD score	
			Baseline	Endpoint
Motzer 2009 (reported in Cella 2008)	IFN	356	81.25 ± 16.04	76.8 (N = 319)
	Sunitinib	373	82.3 ± 15.2	82.3 (N = 349)

FACT-G = functional assessment of cancer therapy – general guide, IFN = Interferon alpha

EQ-5D

EQ-5D Index score is a reliable and valid tool for the assessment of HRQL (Lang 2009). The EQ-5D Index score ranges from –0.594 to 1.000, with scores of 1, 0, or less than 0 denoting that the corresponding health state is valued by the population as equivalent to full health, death, or worse than death, respectively. EQ-5D score was reported in two of the included studies.

In the study comparing sunitinib with IFN, the overall post-baseline mean treatment difference was estimated to be 0.364 points in favour of sunitinib (95% CI: 0.0109 to 0.0620, p = 0.0364). Similar results were reported for a trial comparing temsirolimus with IFN (Hudes 2007), where a significant difference of 0.098 points was observed in favour of temsirolimus (95% CI: 0.036 to 0.162, p = 0.0022).

Table 6.16: Summary of EQ-5D

Study	Intervention	N	Baseline	Endpoint
Motzer 2009 (reported in Cella 2008)	IFN	356	0.76 ± 0.23	0.73 (N = 319)
	Sunitinib	373	0.76 ± 0.23	0.762 (N = 349)
Hudes 2007 Global ARCC trial	IFN	155	Mean baseline score for all assessable patients = 0.62 (SD = 0.24)	0.49 (SE = 0.031)
	Temsirolimus	115		0.59 (SE = 0.026)

Q-VAS

The EQ-VAS is a 100-point visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state) that expresses the patient's self-perceived value for his/her health state. EQ-VAS score was reported in only one study comparing sunitinib with IFN. The overall mean treatment difference was estimated to be 4.74 points in favour of sunitinib (95% CI: 2.60 to 6.87, p<0.0001).

Table 6.17: Summary of EQ-VAS

Study	Intervention	N (BL)	Baseline	Endpoint	Comments
Motzer 2009 (reported in Cella 2008)	IFN	356	71.43 ± 19.51	68.7 (N = 319)	Least square mean reported; estimated from mixed-effects model, and the average post-baseline score were computed at approximately week 17.
	Sunitinib	373	73.8 ± 18.5	73.4 (N = 349)	

IFN = Interferon alpha.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

HRQL values reported in this submission (including those derived from studies identified in the literature search) are generally consistent with a few exceptions. First, the decrement in utility with progression in the VEG105192 trial was less than that reported in other studies. This may reflect that quality of life was not assessed routinely after progression in this trial. Conversely, the decrement in TTO utility associated with progression in the Oxford Outcomes study was substantially greater than that in studies using EQ5-D assessments. This is likely due to the nature of the descriptions of progression free and post-progression health states. The extent to which these descriptions correspond with those of actual patients has not been systematically validated.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Mean utility values for assessments during which patients in VEG105192 were and were not experiencing adverse events are shown in Table 6.18 (source: VEG105192 clinical study report). Also shown are adjusted estimates of the decrement in utility for each AE calculated by applying to the mean utility for patients without the AE the coefficients from a multivariate

logistic regression model of the impact of progression and AEs on utility values.[21] Unadjusted values should be interpreted with caution because of the possibility of confounding due to correlation of AEs with age, poor prognosis, and other factors that might be inversely correlated with HRQL. Also, the numbers of assessment for some AEs (e.g. bleeding, grade 3+ diarrhoea, flu-like symptoms) were small.

Table 6.18: EQ-5D utility values for persons with and without adverse events in VEG105192

	Unadjusted								
	With Event			Without Event			Difference		Adjusted
Adverse Events	N	Mean	SE	N	Mean	SE	Mean	SE	Difference
Anaemia	23	0.58	(0.01)	1,488	0.70	(0.01)	-0.12	(0.01)	-0.17
Bleeding	9	0.61	(0.12)	1,502	0.70	(0.01)	-0.09	(0.12)	-0.03
Diarrhoea grades 3+	nr	nr	nr	nr	nr	nr	nr	nr	-0.02
Diarrhoea all grades	293	0.76	(0.01)	1,218	0.69	(0.01)	0.07	(0.01)	-0.10
Fatigue/asthenia grades 1-2	nr	nr	nr	nr	nr	nr	nr	nr	-0.19
Fatigue/asthenia Grade 3+	207	0.59	(0.02)	1,304	0.72	(0.01)	-0.13	(0.02)	nr
Fatigue/asthenia All Grades	nr	nr	nr	nr	nr	nr	nr	nr	nr
Fever	4	0.62	(0.09)	1,507	0.70	(0.01)	-0.08	(0.10)	0.00
Flu like symptoms	4	0.71	(0.07)	1,507	0.70	(0.01)	0.01	(0.07)	-0.34
PPE syndrome	51	0.76	(0.03)	1,460	0.70	(0.01)	0.06	(0.03)	-0.05
Hypertension	248	0.72	(0.02)	1,263	0.70	(0.01)	0.02	(0.02)	-0.07
Low WBC	44	0.73	(0.04)	1,467	0.70	(0.01)	0.03	(0.04)	nr
Mucositis/stomatitis	26	0.65	(0.05)	1,485	0.70	(0.01)	-0.05	(0.05)	-0.02
Nausea/vomiting	168	0.65	(0.02)	1,343	0.71	(0.01)	-0.06	(0.02)	-0.09
Non-PPE Rash	42	0.79	(0.04)	1,469	0.70	(0.01)	0.10	(0.04)	-0.01
Thrombocytopenia	61	0.71	(0.03)	1,450	0.70	(0.01)	0.01	(0.04)	nr

Quality-of-life data used in cost-effectiveness analysis

6.4.9 **Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.**

For the model, it was assumed that patients free of progression and with no AEs have a mean utility of 0.70 based on the mean EQ-5D utility value among all patients without AEs in the VEG105192 trial. Progression was assumed to be associated with a decrement in utility of 15% (i.e. post-progression utility of 0.59), consistent with that in the Remak and Parasuraman

[21] Covariates in the model included presence vs. absence of AEs, progression, treatment group, line of treatment, age, sex, ECOG Score, Motzer risk category, metastatic sites, time since initial diagnosis, and visit week.

studies, as well as those suggested by results of the VEG105192 trial and the Oxford Outcomes study. These utilities are summarized in Table 6.19.

Table 6.19: Summary of quality-of-life values used in the cost-effectiveness analysis

State	Utility value	Confidence interval	Reference	Justification
Progression Free (no AEs)	0.70	0.68 to 0.72	VEG105192	Best available estimates
Post progression	0.59	N/A	Remak 2008 Parasuraman 2008	Best available published estimates

Utility decrements for adverse events were obtained from the VEG105192 trial as shown in Table 6.18, and those obtained from the study by Oxford Outcomes were used as a sensitivity analysis as shown in section 6.7.7.

The durations of AEs (required to estimate the decrement in QALYs) were estimated using data from VEG105192 and are reported in Table 6.20. When duration was not available for either grades 1 and 2 or 3 +, the duration was assumed to be the same for all grades. SEs for the duration of AEs were not reported and were therefore assumed to be equal to 0.25 multiplied by the mean.

Table 6.20: Mean duration of AEs (days) in VEG105192 trial

	Grades 1 and 2			Grades 3+		
Adverse Event	**N**	**Mean**	**SE**	**N**	**Mean**	**SE**
Alopecia	24	207.8	52.0	0	-	-
Anemia	16	83.9	21.0	7	35.7	8.9
Anorexia	72	134.4	33.6	5	33.0	8.3
Bleeding	15	24.9	6.2	5	15.6	3.9
Constipation	24	63.0	15.7	0	-	-
Cough	35	70.0	17.5	0	-	-
Diarrhea	156	128.9	32.2	10	29.1	7.3
Dyspnea	26	41.3	10.3	6	6.2	1.5
Fatigue / Asthenia	102	125.5	31.4	15	56.9	14.2
Fever	22	7.5	1.9	0	-	-
Flu-like Symptoms	9	15.4	3.9	0	-	-
GI Perforation	0	-	-	1	1.0	0.3
Hair color changes	108	277.6	69.4	1	252.0	63.0
PPE Syndrome	15	300.7	75.2	2	60.5	15.1
HF/CD/↓LVEF	0	-	-	1	1.0	0.3
Headache	39	56.3	14.1	0	-	-
Hyperglycemia	6	74.8	18.7	0	-	-
Hyperlipidemia	2	229.5	57.4	0	-	-
Hypertension	117	122.9	30.7	14	40.2	10.1
Infection	76	44.6	11.2	9	67.2	16.8
Leukopenia	10	313.2	78.3	0	-	-
Mucositis / Stomatitis	25	52.8	13.2	1	4.0	1.0
Nausea / Vomiting	116	84.2	21.0	11	21.5	5.4
Neutropenia	11	92.3	23.1	4	32.3	8.1

Non-PPE Rash	25	109.1	27.3	1	4.0	1.0
Pain	142	113.5	28.4	22	33.5	8.4
Peripheral Edema	6	29.7	7.4	0	-	-
Proteinuria	24	93.3	23.3	4	28.8	7.2

SEs estimated to be 0.25 x the mean.

6.4.10 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[22]:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

See section 6.3.5.

6.4.11 **Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?**

Within each health state (PFS and PPS), HRQL is assumed to be independent of treatment or other factors, but within the PFS state it is assumed to be dependent on adverse events. Estimates of the variance of utility values used for these health states were investigated through sensitivity analysis (section 6.7.7).

[22] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.4.12 **Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?**

No health effects were excluded.

6.4.13 **If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?**

Baseline quality of life was not assessed in the economic evaluation.

6.4.14 **Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.**

HRQL is assumed to differ for time in the PFS and PPS states and in response to adverse events but is otherwise assumed to be constant over time.

6.4.15 **Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.**

Values have not been amended.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 **Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.**

Costs considered in the economic model include acquisition costs for study medications, drug administration costs for those therapies requiring infusions, costs of treatment of grade 3+ adverse events (AEs), routine follow-up costs, costs of progression, and supportive care costs. Such treatment may include inpatient, day case and outpatient treatments that would fall under a variety of HRG codes. HRG codes and corresponding reference costs used in the model are described in the following sections.

6.5.2 **Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.**

There are no specific HRG or Payment by results (PbR) codes for pazopanib. All treatment strategies would incur a one-off treatment initiation cost. Subsequent administration of sunitinib or pazopanib would form part of regular disease monitoring. IFN was assumed to be self-administered by 75% of patients and administered by a district nurse visit for 25% of patients (based on assumption used in PenTAG report; TA 169).

Resource identification, measurement and valuation studies

6.5.3 **Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:**

- **country of study**
- **date of study**
- **applicability to UK clinical practice**
- **cost valuations used in study**
- **costs for use in economic analysis**
- **technology costs.**

Costs were estimated using the best available published and unpublished sources, supplemented with expert opinion and assumption as necessary and appropriate. Published sources were identified from a previous systematic review (Colosia 2008), supplemented with searches of online databases, internet searches, and hand searches of retrieved articles.

6.5.4 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[23]:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

See section 6.3.5.

Intervention and comparators' costs

6.5.5 **Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.**

Measures of costs calculated for each treatment strategy include:

- Cost of acquisition of study medications;
- Cost of administration of study medications;
- Cost of monitoring of study medications;
- Cost of treatment of adverse events (AEs);
- Other costs during PFS;
- Other costs during PPS; and

[23] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- Total costs

Unit costs for sunitinib and IFN were based on the British National Formulary (BNF 57). The list price of pazopanib has been set at parity with the sunitinib list price (calculated on a price per day basis). To estimate the costs of pazopanib, it was assumed that the cost of continuous daily treatment with pazopanib over 42 days would be equivalent to that of 42 days of intermittent dosing with sunitinib (i.e. 28 days on therapy followed by 14 days off therapy). IFN was assumed to be self-administered by 75% of patients and administered by a district nurse visit for 25% of patients (PenTAG assumption; TA 169). Unused medication from vials of IFN was assumed to be wasted. The first 42 day cycle of sunitinib was assumed to be provided free based on the sunitinib Patient Access Programme (TA 169).

Table 6.21: Medication and administration costs

Cost		Cost, £	Reference	Dose and frequency
Medication Costs	IFN 10 MIU vial	42.40	BNF	Week 1: 3MU 3x a week Week 2: 6 MU 3x a week 9MU 3x a week thereafter
	Sunitinib 50 mg capsule	112.10	BNF	50mg daily for 4 weeks followed by 2 weeks rest
	Pazopanib 800 mg tablets	74.73	N/A	800mg daily
Administration costs	IFN per district nurse visit	27.04	PSSRU (PenTAG assumption)	

Costs of study medications were adjusted using relative dose intensities reported in RCTs of the study treatments as shown in Table 6.21. Generally, the methods used to calculate these measures were not well described so it is difficult to assess their comparability. The reported mean dose intensities were similar for pazopanib (0.86) compared with sunitinib (0.86). In the model, it was assumed the dose intensity of IFN was 0.84 based on the sunitinib trial.

Table 6.22: Measures of dose intensity reported in pivotal studies of comparator treatments

Comparator	Trial	Arm	Mean	SD	Median	Range	Source/Comments
Pazopanib	VEG 105192	Pazopanib	0.86	0.36	1.00	0.0-1.00	Ratio of mean daily dose on treatment to planned daily dose
Sunitinib	Pivotal Phase III Motzer	Sunitinib	0.86	na	Na	na	Not reported in publications. From company submission to NICE as reported by PenTAG (TA169).
		IFN	0.84	na	Na	na	

Health-state costs

6.5.6 **Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.**

There is a resource use/cost associated with outpatient monitoring when patients are in the PFS health state but when patients move to the progressed state it is assumed that they will be managed by primary care. Routine monitoring and supportive care costs associated with PFS

and PPS were based on standard NHS reference costs and units of services used in the PenTAG report and are reported in Table 6.23.

Table 6.23: Assumed services and costs of monitoring during PFS and OS

	Service	Cost, £	Reference
PFS	1 consultant led outpatient attendance		
	First visit	241.00	NHS reference costs HRG WF01A
	Subsequent visits	99.00	NHS reference costs HRG WF01B
	1 CT scan per 3 months	46.80	NHS reference costs 2006 (speciality code RBD1)
	Monthly blood tests	Subsumed in OP attendance costs	
PPS	1 GP	37.45	PSSRU
	1.5 community nurse	40.56	PSSRU
	Morphine sulphate 50 mL vial per day BNF	150.00	BNF 57

PbR=Payment by Results. BNF=British National Formulary. PSSRU=Personal Social Services research Unit.

Total cost estimates are reported in Table 6.24**.** The SEs of the cost estimates were assumed to be 25% of the mean estimates.

Table 6.24: Routine follow-up and supportive care costs used in the model

	Monthly Cost, £	(SE)
Treatment initiation (one off cost)	142	(36)
Follow-up, per month pre-progression	146	(37)
Supportive care, per month post progression	228	(57)

In the model, supportive care costs were assumed to be incurred after disease progression. To maintain consistency with estimates of OS obtained from pivotal trials, costs of subsequent lines of treatment (e.g. sorafenib for patients who progress on IFN and everolimus for patients who progress on TKIs) were not considered in the model.

Adverse-event costs

6.5.7 **Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.**

Only the costs of treatment of AEs that were grade 3 or more and had an incidence of 5% or more for any treatment based on the indirect comparison were considered (see section 6.3.1). The cost per event was assumed to be independent of treatment. Treatment costs were estimated based on the PbR Tariff, Reference Costs from the Department of Health, the University of Kent Personal Social Services Research Unit, and the PenTAG report (TA 169).

Treatment algorithms included outpatient visits, medications, outpatient tests and procedures, and hospitalisations as appropriate. The unit costs of medications were based on the British National Formulary (BNF 57). Hospitalisation costs were based on the PbR Tariff. The assumed services and costs of treatment of AEs were based on expert opinion and are displayed in Table 6.25.

Table 6.25: Assumed services and costs of treating grade 3+ adverse events

AE	Service	Cost, £	Reference
Anaemia	Day Case Transfusion	441	HRG SA04F
	Short Stay Transfusion	702	HRG SA04F
Fatigue	Repeat OP Attendance Medical Oncology (consultant led)	99	HRG WF01A
Diarrhea	Short stay Admission	748	HRG FZ35C
	Loperamide 2 mg 4 per day 30 days	4	BNF 57
HFS/PPE	Repeat OP Attendance Medical Oncology (consultant led)	99	HRG WF01A
	Short Stay	845	HRG QZ17C
Hypertension	Captopril,	2	BNF 57
Nausea/Vomiting	Short Stay Admission	845	HRG FZ35C
	Metroclopramide,	1	BNF 57
Neutropenia	Day Case Transfusion	441	HRG SA04F
	Short Stay Transfusion	702	HRG SA04F
Pain	Repeat OP Attendance Medical Oncology (consultant led)	99	HRG WF01A
	Acetaminophen 500 mg, 8 per day x 30 days	4	BNF 57
	Ibuprofen 800 mg, 4 per day x 30 days	9	BNF 57
	Morphine 30 mg, 6 per day x 30 days	54	BNF 57
	Senna 8.6mg with docusate 50mg 2 per day x 30 days	7	BNF 57

The expected costs of treatment of grade 3+ AEs are reported in Table 6.26. The standard errors (SEs) of the cost estimates were assumed to be 25% of the mean estimates.

Table 6.26: Expected costs per grade 3+ adverse events

Adverse event	Expected Cost, £ (SE)
Anemia	1,143 (286)
Diarrhea	752 (188)
Fatigue/Asthenia	99 (25)
HFS/PPE	944 (236)
Hypertension	3 (1)
Nausea/Vomiting	846 (212)
Neutropenia	1143 (286)
Pain	171 (43)

HFS=Hand foot syndrome. PPE=Palmar plantar erythrodeisis.

Miscellaneous costs

6.5.8 **Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.**

No other costs were used in the model. Personal and social service costs have not been considered but are not expected to be significant and are assumed to be similar for all comparators.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 **Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.**

As stated in section 6.3.1, estimates of PFS and OS for each comparator were obtained by first fitting a parametric survival function to observed failure time data for one the comparators ("reference arm") and then applying to those survival functions relative hazard ratios (HRs) for each of the other comparators vs. that of the reference. For the base case, parametric survival functions for PFS and OS were based on Weibull survival functions fit to the reported KM survival curves for the IFN arm (i.e. reference arm) of the sunitinib trial.
Structural uncertainty has therefore been investigated with respect to a) the impact of fitting alternative survival parametric functions, and b) using a different reference treatment for calculation of PFS and OS. In addition, alternative model timeframes of 5 and 15 years were investigated.

6.6.2 **Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.**

Deterministic analysis was conducted for all variables described in section 6.3.6 and are displayed in table 6.27.

Table 6.27: Deterministic sensitivity analysis

Scenarios		Rationale
1	HR PFS pazopanib vs. IFN=0.326	**Efficacy:** The actual comparative effectiveness of pazopanib vs. IFN is a key parameter in the economic evaluation. These scenarios explore the impact of efficacy using both higher and lower limits from the CIs obtained in the indirect comparison used in the base case (pooled analysis of IFN trials).
2	HR PFS pazopanib vs. IFN =0.802	
3	HR OS pazopanib vs. IFN=0.106	
4	HR OS pazopanib vs. IFN =1.750	
5	Cost IFN admin = 0.5 x base-case	**Costs**: IFN is administered by subcutaneous injection three times per week, for a maximum of 52 weeks. These scenarios explore the impact of decreasing/increasing administration costs by 50%
6	Cost IFN admin=1.5 x base-case	
7	Cost therapy initiation=0.5 x base-case	**Costs:** other costs, including other (non-study) medications, physician visits, hospitalisation, diagnostics, and other care, during PFS and PPS are calculated by multiplying the mean cost per month of PFS and PPS respectively by expected discounted PFS and PPS respectively. These scenarios explore the impact of increasing/decreasing cost of therapy initiation and other costs by 50%
8	Cost therapy initiation=1.5 x base-case	
9	Other Cost PFS=0.5 x base-case	
10	Other Cost PFS=1.5 x base-case	

11	Other Cost PPS=0.5 x base-case	
12	Other Cost PPS=1.5 x base-case	
13	Cost of AEs=0.5 x base-case	**Costs:** The costs of treatment of AEs are calculated by multiplying the expected incidence of treatment-related AEs by the expected cost of these events. Scenarios explore the impact of potential variation in these costs (+/- 50%)
14	Cost of AEs=1.5 x base-case	
15	Incidence of AEs = lower 95% CI	**Adverse events:** The impact of adverse events are explored by varying the incidence of AEs using both the lower and upper CI.
16	Incidence of AEs = upper 95% CI	
17	Utility PFS=0.75 x base-case	**Utility values:** A key assumption in the model is the utility values used for the patient population. These scenarios explore the impact of varying utility value estimates for pre/post-progression health states
18	Utility PFS=1.75 x base-case	
19	Utility PFS=0.65	
20	Utility PFS=0.75	
21	Utility PFS and PPS for that of a healthy person (0.78), no decrement for AEs.	
22	Decrement utility w/Progression 0.5 x base-case	
23	Decrement utility w/Progression 1.5 x base-case	
24	Decrement in utility with AEs=0.5 x base-case	**Utility values:** In these scenarios the decrement in utility after experiencing adverse events (i.e. disutility) is varied
25	Decrement in utility with AEs=1.5 x base-case	
26	Duration of utility with AEs = 0.5% x base case	
27	Duration of utility with AEs = 1.5% x base case	
28	Decrement in utility with AEs from Oxford Outcomes	

29	HR for PFS and OS for pazopanib vs. IFN calculated using only the MRC RE-01 study (PFS HR=0.545, OS HR=0.460)	**Efficacy:** Because pazopanib was compared to placebo in VEG105192, the HRs for PFS and OS for pazopanib vs. IFN in treatment-naïve patients were estimated by indirect comparison using data from a pooled analysis of randomized controlled trials of IFN versus BSC (i.e. no active treatments). These scenarios explore the use of two different approaches in the indirect comparison of pazopanib versus IFN in order to assess the relative impact their inclusion/exclusion makes a) Including only the MRC RE-01 trial b) Excluding trials using vinblastine (VBL) in one of the treatment arms (Kriegmair 1995 & Pyrhonen 1999)
30	HR for PFS and OS for pazopanib vs. IFN calculated excluding the VBL studies (PFS HR=0.495, OS HR=0.400)	
31	HR for PFS for pazopanib vs. IFN adjusted to reflect % w/ECOG=0/1 in sunitinib pivotal trial (HR=0.460)	
32	HRs for OS for pazopanib vs. IFN using HR for pazopanib vs. placebo in VEG105192 without censoring on cross-over or adjustment for baseline covariates (HR=0.930)	**Efficacy**: These scenarios explore the method used to account for cross over in VEG105192
33	HRs for OS for pazopanib vs. IFN using HR for pazopanib vs. placebo in VEG105192 adjusted for cross over using a Cox model with censoring (HR= 0.6360)	
34	HRs for OS for pazopanib vs. IFN using HR for pazopanib vs. placebo in VEG105192 adjusted for cross over using IPCW (HR= 0.5630)	
35	HR for OS for sunitinib vs. IFN based on final analysis (HR=0.820)	**Efficacy:** These scenarios explore the impact of alternative OS estimates for sunitinib vs. IFN and the affect of assuming pazopanib has equivalent PFS and/or OS as sunitiinib vs. IFN.
36	HRs for PFS and OS for pazopanib vs. IFN = HRs for sunitinib vs. IFN (PFS HR=0.539, OS HR=0.647)	
37	HR for OS for pazopanib vs. IFN = HR for sunitinib vs. IFN (HR=0.647)	
38	HR for OS for pazopanib vs. IFN to make PPS equal to that of sunitinib (HR=0.629)	
39	Pazopanib arm VEG105192 as reference	**Structural:** Expected PFS and OS were estimated by fitting parametric survival curves to PFS and OS curves for IFN (from Sunitinib pivotal trial). Expected PFS and OS for other treatment comparators were then obtained by applying the estimated HRs for PFS and OS vs. IFN. These scenarios explore the use of different reference arms.
40	Independent Weibull from pazopanib arm VEG105192 used for pazopanib, independent Weibull from placebo arm VEG105192 used as reference for comparators	
41	Time Frame= 5 years	**Other**: Other scenarios explore the effect of time frame and discounting on costs and effects used in the model.

42	Time frame = 15 years	
43	Annual discount rate=0%	
44	Annual discount rate=6%	

6.6.3 **Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).**

Probabilistic sensitivity analyses were conducted by simultaneously sampling from estimated probability distributions of model parameters to obtain 1,000 sets of model input estimates. Utility estimates for the model health states were assumed to be distributed as beta random variables. Other estimates were assumed to be distributed as either normal or lognormal random variables. When SEs for model estimates were unavailable, they were assumed to be 25% of their base-case estimates. Distributions and their sources can be found in section 6.3.6.

For each simulation, the differences between pazopanib and each comparator in costs and QALYs were calculated. Ninety-five percent confidence intervals (95% CIs) for incremental costs and QALY were calculated based on the 2.5 and 97.5 percentiles of these simulations. For each comparison, simulation results on the cost-effectiveness plane and construct cost-effectiveness acceptability curves were plotted for pazopanib vs. the comparator to identify the proportion of simulations for which pazopanib would be preferred given various levels of decision-makers willingness to pay (WTP) for a QALY. Probabilistic sensitivity analyses were conducted for scenarios where different methods to adjust for cross-over in VEG105192 were used (IPCW and cox regression model censoring on cross over). These can be found in separate excel workbooks.

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.

- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

A full set of cost effectiveness results produced using alternative OS estimates for pazopanib vs. BSC (IPCW and Cox regression model censoring on cross-over) is provided in separate excel work books, including probabilistic sensitivity analyses.

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Clinical outcomes from the model

6.7.1 **For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

A comparison of effectiveness estimates used in the economic model and those reported in clinical trials can be found in table 6.28.

Table 6.28: Summary of model results compared with clinical data

	Pazopanib		Sunitinib		IFN		BSC	
Outcome Months (median)	Clinical trial result	Model result	Clinical trial result	Model result	Clinical trial result*	Model result	Clinical trial result**	Model result
PFS	11.1	11.3	11.4	10.7	4.0	5.4	2.8	5.6
PPS	8.7	32.3	15	16.1	5.0	10.4	17.2	6.5
OS	19.8†	43.6	26.4	26.8	9.0	15.8	20.0††	12.1

*from Hancock 2000. **from placebo arm of VEG150192. †interim analysis. ††not adjusted for cross over

The main discrepancies between modelled and observed results are due to the following:

- Overall survival data from VEG105192 are immature therefore it was necessary to extrapolate OS results for use in the economic model.

- Overall survival data in VEG105192 was confounded by cross-over. As discussed in section 5.3.6.1, at the time of the clinical cut-off for the interim analysis, 31 (40%) of 78 placebo-treated patients in the treatment-naive sub-population had crossed over to receive pazopanib and thus the true effect of pazopanib treatment is likely to be underestimated in the ITT analysis. Several approaches were therefore considered to

evaluate the impact of this effect on the interim OS data in VEG105192. For reasons discussed earlier, the RPSFT method was used for derivation of the HR used in the base case.

- Clinical outcomes for IFN were based on random effects meta-analysis utilising data from 5 RCTs which directly compared IFN with a non-IFN control therapy (vinblastine or medroxyprogesterone acetate) rather than solely the MRC trial (Hancock 2000) as reported in table 5.33 (section 5.7).

6.7.2 **Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.**

Not applicable.

6.7.3 **Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.**

QALYs are generated in the model based on the estimated proportion of patients in each health state (pre-progression, post-progression) on a per day basis. The proportion of patients in each health state is estimated through a proportional hazard Weibull model (see section 6.3.1).

6.7.4 **Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:**

Table 6.29: Model outputs by clinical outcomes

	Life year				QALY				Cost (£)			
Outcome	Pazopanib	Sunitinib	IFN	BSC	Pazopanib	Sunitinib	IFN	BSC	Pazopanib	Sunitinib	IFN	BSC
PFS	1.412	1.339	0.691	0.471	0.972	0.907	0.465	0.325	35,843	31,633	4,769	1,010
PPS	2.646	1.679	1.328	1.127	1.561	0.991	0.784	0.665	7,240	4,596	3,635	3,084
OS	4.058	3.018	2.020	1.598	2.533	1.898	1.249	0.990	43,082	36,228	8,404	4,094

LY, life years; QALY, quality-adjusted life year; AE, adverse events

6.7.5 **Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.**

Table 6.30: Summary of QALY gain by health state

A. Pazopanib vs. Sunitinib

Health state	Pazopanib QALY	Sunitinib QALY	Increment	% Increment
PFS	0.972	0.907	0.065	10.24
PPS	1.561	0.991	0.570	89.76
Total	2.533	1.898	0.635	100.00
QALY, quality adjusted life year				

B. Pazopanib vs. IFN

Health state	Pazopanib QALY	IFN QALY	Increment	% Increment
PFS	0.972	0.465	0.507	39.49
PPS	1.561	0.784	0.777	60.51
Total	2.533	1.249	1.284	100.00
QALY, quality adjusted life year				

C. Pazopanib vs. BSC

Health state	Pazopanib QALY	BSC QALY	Increment	% Increment
PFS	0.972	0.325	0.647	41.93
PPS	1.561	0.665	0.896	58.07
Total	2.533	0.990	1.543	100.00
QALY, quality adjusted life year				

Table 6.31: Summary of costs by health state

A. Pazopanib vs. Sunitinib

Health state	Pazopanib Costs (£)	Sunitinib Costs (£)	Increment (£)	% Increment
PFS	35,843	31,633	4,210	61.4
PPS	7,240	4,596	2,644	38.6
Total	43,082	36,228	6,854	100.0

B. Pazopanib vs. IFN

Health state	Pazopanib Costs (£)	IFN Costs (£)	Increment (£)	% Increment
PFS	35,843	4,769	31,074	89.6
PPS	7,239	3,635	3,604	10.4
Total	43,081	8,404	34,678	100.0

C. Pazopanib vs. BSC

Health state	Pazopanib Costs (£)	BSC Costs (£)	Increment (£)	% Increment
PFS	35,843	1,010	34,833	89.3
PPS	7,239	3,084	4,155	10.7
Total	43,081	4,094	38,988	100.0

Table 6.32: Summary of predicted resource use by category of cost

A. Pazopanib vs. Sunitinib

Item	Pazopaninib (£)	Sunitinib (£)	Increment (£)	% Increment
Acquisition cost	33128	28856	4271	62.3
Administration costs	0	0	0	0.0
Adverse event costs	102	292	-190	-2.8
Other pre progression costs	2613	2484	129	1.9
Other post progression costs	7240	4596	2644	38.6
Total	43082	36228	6854	100.0

B. Pazopanib vs. Sunitinib

Item	Pazopaninib (£)	IFN (£)	Increment (£)	% Increment
Acquisition cost	33128	2754	30374	87.6
Administration costs	0	532	-532	-1.5
Adverse event costs	102	132	-30	-0.1
Other pre progression costs	2613	1351	1262	3.6
Other post progression costs	7240	3635	3605	10.4
Total	43082	8404	34679	100.0

C. Pazopanib vs. BSC

Item	Pazopaninib (£)	BSC (£)	Increment (£)	% Increment
Acquisition cost	33128	0	33128	85.0
Administration costs	0	0	0	0.0
Adverse event costs	102	43	59	0.2
Other pre progression costs	2613	967	1646	4.2
Other post progression costs	7240	3084	4156	10.7
Total	43082	4094	38989	100.0

Base-case analysis

6.7.6 **Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

Table 6.33: Base case results

				vs. BSC			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	4,094	1.598	0.990				
IFN	8,404	2.020	1.249	4,310	0.421	0.259	16,650
Sunitinib	36,228	3.018	1.898	32,135	1.420	0.908	35,395
Pazopanib	43,082	4.058	2.533	38,989	2.460	1.543	25,264

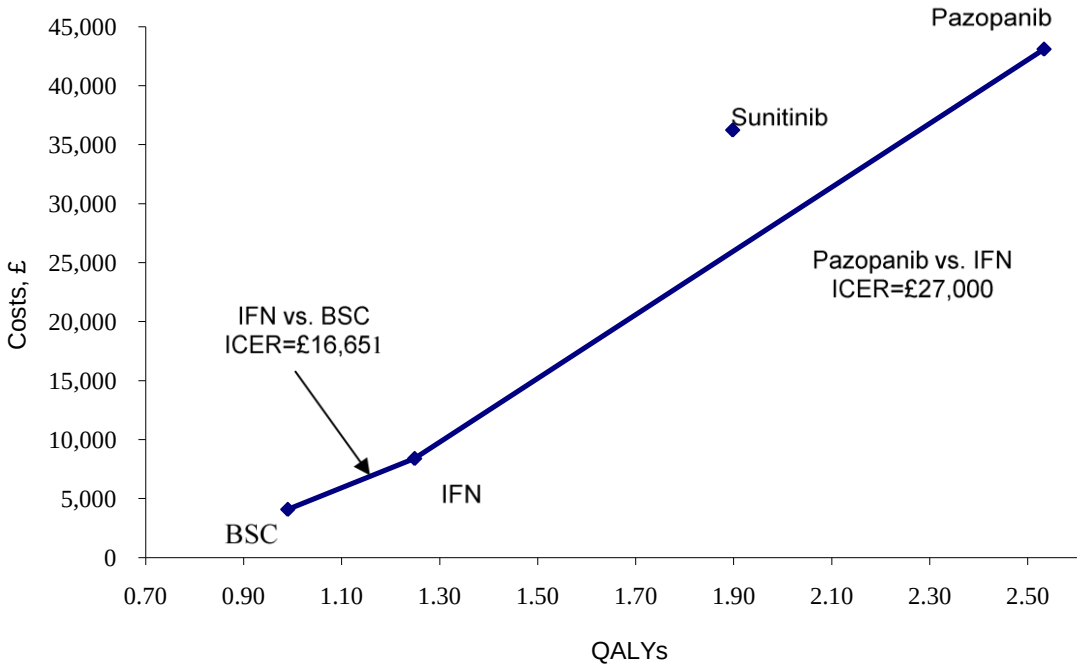
				vs. IFN			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	4,094	1.598	0.990	-4,310	-0.421	-0.259	16,650
IFN	8,404	2.020	1.249				
Sunitinib	36,228	3.018	1.898	27,825	0.999	0.649	42,872
Pazopanib	43,082	4.058	2.533	34,679	2.039	1.284	27,000

				vs. Sunitinib			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	4,094	1.598	0.990	-32,135	-1.420	-0.908	35,395
IFN	8,404	2.020	1.249	-27,825	-0.999	-0.649	42,872
Sunitinib	36,228	3.018	1.898				
Pazopanib	43,082	4.058	2.533	6,854	1.040	0.635	10,787

Table 6.34: Incremental base case results

Technology (and comparators)	Total cost	Total QALY	Incremental cost	Incremental QALY	ICERs versus baseline	Incremental analysis
BSC (baseline)	4,094	0.990	0	0		
IFN	8,404	1.249	4,310	0.259	16,650	16,650
Sunitinib	36,228	1.898	32,135	0.908	35,395	Extended domination by pazopanib
Pazopanib	43,082	2.533	38,989	1.543	25,264	27,000
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios						

Figure 6.8: Incremental cost-effectiveness analysis



Sensitivity analyses

6.7.7 **Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

Deterministic sensitivity analyses are presented in Table 6.35. A further sensitivity analysis is provided where the pazopanib aquisition cost is varied (Table 6.36).

Table 6.35: Deterministic sensitivity analyses

Scenario		Pazopanib		Difference Pazopanib vs. Sunitinib			Difference Pazopanib vs. IFN			Difference Pazopanib vs. BSC 2L		
		Costs, £	QALYs	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £
0	Base Case	43,082	2.533	6,854	0.635	10,787	34,679	1.284	27,000	38,989	1.543	25,264
1	HR PFS pazopanib vs. IFN=0.326	61,055	2.621	24,827	0.723	34,320	52,651	1.372	38,364	56,961	1.631	34,918
2	HR PFS pazopanib vs. IFN =0.802	31,063	2.474	-5,166	0.577	dominant	22,659	1.226	18,489	26,969	1.484	18,168
3	HROS pazopanib vs. IFN=0.106	50,964	4.233	14,736	2.335	6,311	42,560	2.984	14,263	46,870	3.243	14,454
4	HROS pazopanib vs. IFN =1.750	28,000	0.754	-8,229	-1.144	7,196 †	19,596	-0.494	dominated	23,906	-0.236	dominated
5	Cost IFN admin=0.5 x base-case	43,082	2.533	6,854	0.635	10,787	34,945	1.284	27,207	38,989	1.543	25,264
6	Cost IFN admin=1.5 x base-case	43,082	2.533	6,854	0.635	10,787	34,413	1.284	26,793	38,989	1.543	25,264
7	Cost therapy initiation=0.5 x base-case	43,011	2.533	6,854	0.635	10,787	34,679	1.284	27,000	38,989	1.543	25,264
8	Cost therapy initiation=1.5 x base-case	43,153	2.533	6,854	0.635	10,787	34,679	1.284	27,000	38,989	1.543	25,264
9	Other Cost PFS=0.5 x base-case	41,847	2.533	6,790	0.635	10,686	34,048	1.284	26,508	38,166	1.543	24,730
10	Other Cost PFS=1.5 x base-case	44,318	2.533	6,918	0.635	10,888	35,310	1.284	27,491	39,812	1.543	25,797
11	Other Cost PPS=0.5 x base-case	39,463	2.533	5,532	0.635	8,707	32,877	1.284	25,596	36,911	1.543	23,917
12	Other Cost PPS=1.5 x base-case	46,702	2.533	8,176	0.635	12,868	36,481	1.284	28,403	41,067	1.543	26,610
13	Cost of AEs=0.5 x base-case	43,031	2.533	6,949	0.635	10,937	34,694	1.284	27,011	38,959	1.543	25,244
14	Cost of AEs=1.5 x base-case	43,133	2.533	6,759	0.635	10,637	34,664	1.284	26,988	39,018	1.543	25,283
15	Incidence of AEs=lower 95% confidence interval	43,002	2.542	6,896	0.638	10,805	34,637	1.291	26,836	38,949	1.549	25,152
16	Incidence of AEs=upper 95% confidence interval	43,342	2.516	6,933	0.625	11,091	34,886	1.270	27,474	39,074	1.534	25,469
17	Utility PFS=0.75 x base-case	43,082	1.823	6,854	0.453	15,117	34,679	0.928	37,383	38,989	1.113	35,036
18	Utility PFS=1.75 x base-case	43,082	3.243	6,854	0.817	8,385	34,679	1.641	21,131	38,989	1.974	19,754
19	Utility PFS=0.65	43,082	2.330	6,854	0.583	11,748	34,679	1.182	29,327	38,989	1.420	27,451
20	Utility PFS=0.75	43,082	2.736	6,854	0.687	9,971	34,679	1.386	25,014	38,989	1.666	23,399
21	Utility PFS and PPS that of healthy person (0.78), no decrement for Aes	43,082	3.165	6,854	0.811	8,450	34,679	1.590	21,809	38,989	1.919	20,321
22	Decrement utility w/Progression 0.5 x base-case	43,082	2.679	6,854	0.689	9,954	34,679	1.357	25,558	38,989	1.627	23,966
23	Decrement utility w/Progression 1.5 x base-case	43,082	2.388	6,854	0.582	11,772	34,679	1.212	28,614	38,989	1.460	26,709
24	Decrement in utility with AEs=0.5 x base-case	43,082	2.541	6,854	0.629	10,905	34,679	1.283	27,024	38,989	1.549	25,170
25	Decrement in utility with AEs=1.5 x base-case	43,082	2.525	6,854	0.642	10,672	34,679	1.286	26,975	38,989	1.538	25,358
26	Duration of utility with Aes=0.5 x base-case	43,082	2.541	6,854	0.629	10,905	34,679	1.283	27,024	38,989	1.549	25,170
27	Duration of utility with Aes=1.5 x base-case	43,082	2.525	6,854	0.642	10,672	34,679	1.286	26,975	38,989	1.538	25,358

Scenario		Pazopanib		Difference Pazopanib vs.								
				Sunitinib			IFN			BSC 2L		
		Costs, £	QALYs	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £
28	Decrement in utility with AEs from Oxford Outcomes	43,082	2.507	6,854	0.635	10,801	34,679	1.266	27,393	38,989	1.524	25,586
29	HR for PFS and OS for pazopanib vs. IFN calculated using only the MRC study (PFS HR=0.545, OS HR=0.460)	40,636	2.427	4,407	0.529	8,326	32,232	1.178	27,353	36,542	1.437	25,425
30	HR for PFS and OS for pazopanib vs. IFN calculated excluding the VBL studies (PFS HR=0.495, OS HR=0.400)	44,756	2.656	8,528	0.758	11,247	36,352	1.407	25,832	40,662	1.666	24,406
31	HR for PFS for pazopanib vs. IFN adjusted to reflect % w/ECOG=0/1 in sunitinib pivotal trial (HR=0.455)	47,181	2.553	10,953	0.655	16,710	38,778	1.304	29,726	43,088	1.563	27,561
32	HRs for OS for pazopanib vs. IFN using HR for pazopanib vs. placebo in VEG105192 without censoring on cross-over or adjustment for baseline covariates (HR=0.930)	37,919	1.420	1,691	-0.478	dominated	29,515	0.171	172,598	33,825	0.430	78,689
33	HRs for OS for pazopanib vs. IFN using HR for pazopanib vs. BSC in VEG105192 adjusted for cross-over using multivariate cox model (HR=0.636)	40,354	1.945	4.126	0.047	87,496	31,951	0.696	45,894	36,261	0.955	37,968
34	HRs for OS for pazopanib vs. IFN using HR for pazopanib vs. BSC in VEG105192 adjusted for cross-over using IPCW (HR=0.5630)	41,203	2,128	4,974	0.230	21,622	32,799	0.879	37,311	37,109	1.138	32,611
35	HR for OS for sunitinib vs. IFN based on final analysis (HR=0.820)	43,082	2.533	8,410	0.971	8,662	34,679	1.284	27,000	38,989	1.543	25,264
36	HRs for PFS and OS for pazopanib vs. IFN = HRs for sunitinib vs. IFN (PFS HR=0.539, OS HR=0.647)	38,583	1.912	2,354	0.014	171,532	30,179	0.663	45,536	34,489	0.922	37,423
37	HR for OS for pazopanib vs. IFN = HR for sunitinib vs. IFN (HR=0.647)	40,237	1.920	4,009	0.022	183,674	31,833	0.671	47,452	36,143	0.930	38,876
38	HR for OS for pazopanib vs. IFN to make PPS equal to that of sunitinib (HR=0.629)	40,430	1.961	4,202	0.064	66,107	32,027	0.713	44,944	36,337	0.971	37,405
39	Pazopanib arm VEG105192 as reference	27,429	1.432	5,008	0.386	12,970	21,428	0.704	30,429	24,974	0.821	30,417
40	Independent Weibull from pazopanib arm VEG105192 used for pazopanib, independent Weibull from placebo arm VEG105192 used as reference	28,965	1.208	761	-0.865	dominated	19,522	-0.247	dominated	23,826	0.012	2,066,021

Scenario		Pazopanib		Difference Pazopanib vs.								
				Sunitinib			IFN			BSC 2L		
		Costs, £	QALYs	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £
	for comparators											
41	Time Frame=5 years	38,587	1.861	5,203	0.335	15,553	30,829	0.752	40,981	34,825	0.943	36,938
42	Time Frame=15 years	44,493	2.819	7,684	0.809	9,498	35,976	1.546	23,275	40,360	1.821	22,169
43	Annual discount rate=0%	46,343	2.858	7,579	0.755	10,038	37,452	1.508	24,831	41,960	1.803	23,274
44	Annual discount rate=5%	41,853	2.415	6,592	0.593	11,122	33,635	1.204	27,939	37,870	1.450	26,125
† Pazopanib is less costly and less effective than comparator; value represents CE of comparator vs Pazopanib												

Table 6.36: Sensitivity analysis varying the acquisition cost of pazopanib

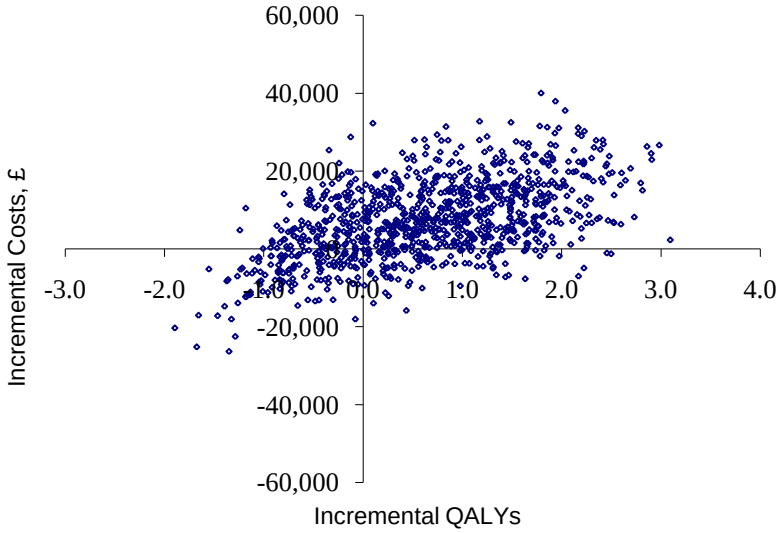
Percentage change in pazopanib unit costs	Pazopanib		Diff. Pazopanib vs.						ΔCost/ΔQALY £		
			BSC		IFN		Sunitinib		Pazopanib vs.		
	Costs £	QALYs	Costs £	QALYs	Costs £	QALYs	Costs £	QALYs	BSC	IFN	Sunitinib
0	43,082	2.533	38,989	1.543	34,679	1.284	6,854	0.635	25,264	27,000	10,787
+5%	47,739	2.533	40,645	1.543	36,335	1.284	8,510	0.635	26,337	28,289	13,394
+10%	46,395	2.533	42,302	1.543	37,992	1.284	10,167	0.635	27,410	29,579	16,001
-5%	41,429	2.533	37,335	1.543	33,025	1.284	5,201	0.635	24,192	25,712	8,185
-10%	39,771	2.533	35,677	1.543	31,367	1.284	3,543	0.635	23,118	24,421	5,575

6.7.8 **Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.**

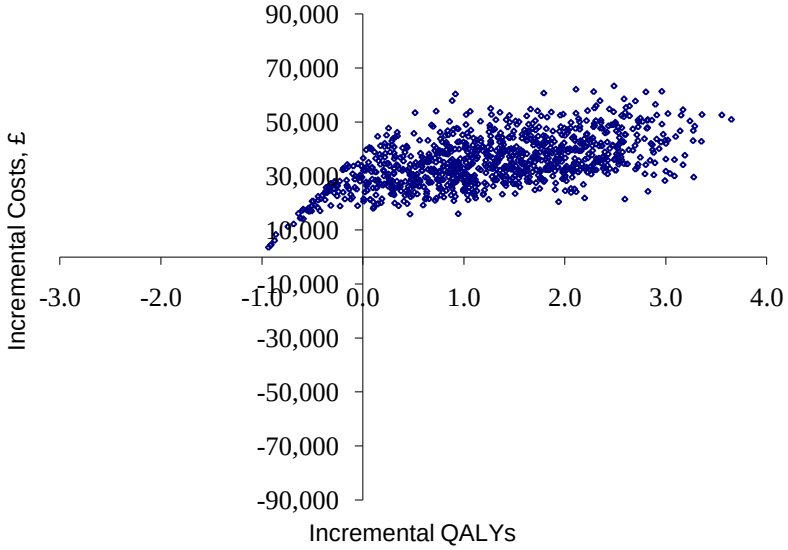
Probabilistic sensitivity analysis is presented for the base case in Figure 6.9 and the corresponding cost-effectiveness acceptability curve is shown in Figure 6.10. As deterministic sensitivity analysis suggested that the method for adjusting for cross over was a large driver of pazopanib cost-effectiveness, further probabilistic sensitivity analyses can be found in the excel work books provided where results are presented using IPCW and cox model estimates.

Figure 6.9: Scatterplot of PSA (1,000 runs) - Base case. A vs. sunitinib; B vs. IFN; C vs. BSC

A. Pazopanib vs. sunitinib



B. Pazopanib vs. IFN



C. Pazopanib vs. BSC

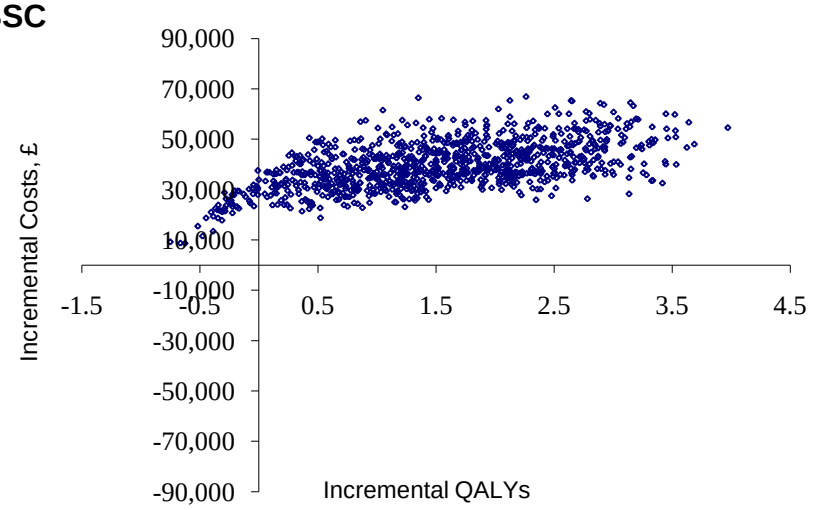
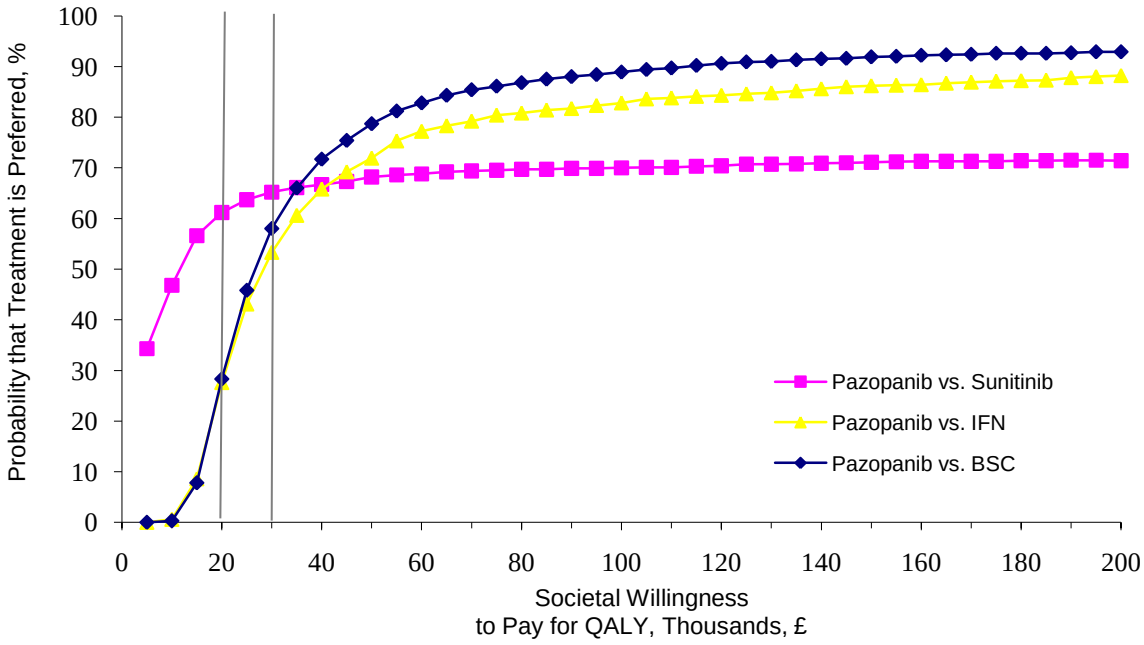


Figure 6.10: Cost-effectiveness acceptability curve – base case: pair-wise comparisons of pazopanib vs. sunitinib, pazopanib vs. IFN, and pazopanib vs. BSC



6.7.9 **Please present the results of scenario analysis. Include details of structural sensitivity analysis.**

A full set of deterministic sensitivity analyses are presented in Tables 6.34 and 6.35.

6.7.10 **What were the main findings of each of the sensitivity analyses?**

The findings of probabilistic sensitivity analysis for the base case are summarised in Table 6.37. At a QALY threshold of £20,000 and £30,000 the proabability that pazopanib is cost effective versus sunitinib was 61% and 65% respectively. The probability that pazopabinib was cost effective versus IFN or BSC was over 50% at a threshold of £30,000/QALY, and just under 30% at a threshold of £20,000/QALY.

Table 6.37: Summary of PSA results

QALY Threshold	Proabability that pazopanib is cost-effective versus comparator (%)		
	Sunitinib	IFN	BSC
£20,000	61	28	28
£30,000	65	53	58

In the majority of cases deterministic sensitivity analyses on the base case indicated that pazopanib was cost effective versus sunitinib at a threshold of £20,000-£30,000/QALY.

Sensitivity analyses where the resultant ICERs were greater than £30,000/QALY included scenarios where an alternative cross-over methodology was employed. This has been extensively explored and is discussed further in 6.7.12.

Using efficacy estimates for OS and/or PFS for pazopanib that were equivalent to those for sunitinib resulted in ICERs versus sunitinib of greater than £30,000/QALY. However as direct evidence for the comparative efficacy of sunitinib and pazopanib will not be known until the results of the head to head COMPARZ trial are available, this may be an unreliable assumption. Furthermore this assumption results in giving a greater emphasis to the differential acquisition costs of sunitinib and pazopanib, which GSK intend to address with a patient access scheme which GSK intend to address with a patient access scheme.

To explore the impact of a non-proportional hazards assumption, a sensitivity analysis where independent Weibull distributions were fitted to the pazopanib and placebo arms of VEG105192 was performed.This resulted in pazopanib being dominated by sunitinib. However, this may not be an appropriate approach as the placebo arm of VEG105192 was confounded by patients crossing over to pazopanib. As described in section 6.2 a more appropriate way to account for the potential bias would be to estimate HRs for different time periods. This was not possible with the current economic model. Moreover this non-proprtionality may not be evident in the final OS data.

Changes in monitoring costs, the cost of treating AEs and utility values had little impact on cost-effectiveness.

A similar pattern was observed for comparisons of pazopanib versus IFN and BSC suggesting that pazopanib should be considered a cost effective treatment option for patients for whom IFN and/or sunitinib are unsuitable.

6.7.12 **What are the key drivers of the cost-effectiveness results?**

The key drivers of cost-effectiveness were the efficacy estimates for pazopanib versus IFN which subsequently contribute to the relative efficacy of pazopanib and sunitinib. Specifically the model is sensitive to the method used for adjusting for cross over for OS data from VEG105192. Cost effectiveness results utilising different methods for adjusting for cross over are summarized in Table 6.38. As discussed in the clinical section, two statistical methods have been used recently to adjust for cross-over in survival analysis in RCTs (RPSFT and IPCW). RPSFT was used for the base case and varying the method for adjusting for cross-over in VEG105192 resulted in ICERs of £21,622/QALY vs. sunitinib using the IPCW-derived HR, and £87,496/QALY using the results from a Cox model censoring on cross over.

Probabilistic sensitivity analysis for results using these methods is provided in the excel workbooks attached to this submission and is summarised in Table 6.38. The probability that pazopanib is cost effective versus sunitinib is over 50% using state of the art methodology to account for crossover (IPCW and RPSFT). The probability of pazopanib being a cost effective option versus IFN and BSC appears to be influenced more significantly by the choice of cross over methodology.

Table 6.38: Cost effectiveness results using alternative cross over methodologies

Method for adjusting for cross over	Pazopanib costs (£)	Pazopanib QALYs	ICER vs. Sunitinib (£)	Probability CE at £30,000/ QALY	ICER vs. IFN (£)	Probability CE at £30,000/ QALY	ICER vs. BSC (£)	Probability CE at £30,000/ QALY
ITT	37,919	1.420	Dominated		172,598		78,869	
Cox model censored on cross over	40,354	1.945	87,496	43%	45,894	16%	37,968	26%
IPCW	41,203	2.128	21,622	55%	37,311	29%	32,611	38%
RPSFT	43,082	2.533	10,787	65%	27,000	53%	25,264	58%

6.8 Validation

6.8.1 **Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.**

Model validation was undertaken by Professor Steve Morris (University College, London). The validation process had two parts, described below.

Firstly, the reviewer examined an earlier version of the model User Guide and Draft Report to test the model for face validity. The focus in this part of the validation process was whether or not the model was consistent with the Draft Scope produced by NICE ("Single Technology Appraisal: Pazopanib for the first-line treatment of advanced and/or metastatic renal cell carcinoma"), and whether or not the methods underpinning the model and the results produced were appropriate. The latter focused on whether or not the approaches taken to model cost-effectiveness were clearly described and plausible.

The outcome of this external review can be found in appendix 17. GSK and PAI (who undertook the modelling work) responded to each comment on a point-by-point basis, highlighted in grey in the Appendix. In some cases the model or the description of the model in the User Guide and Draft Final Report was amended in the light of the comments received. In some cases the comments were noted but no further action was required or undertaken. The responses were fed back to the reviewer, who was content with the responses received.

Secondly, the external health economics reviewer examined the technical validity of the Excel workbook containing the model to try and identify any flaws in the model structure. This was undertaken by looking at all the inputs and calculations to ensure that the calculations were undertaken correctly and that cells are linked properly within the model. In addition, the reviewer went through the input worksheets in the Excel workbook, modified the input parameter values, and tested if the resulting changes to the results are as expected. No significant issues were identified, and the reviewer was content with the technical validity of the model.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

Due to limited sample size subgroup analyses were not conducted.

6.10 Interpretation of economic evidence

6.10.1 **Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?**

No published cost-effectiveness data for pazopanib was identified. However as described in section 6.5, TA169 appraised the use of sunitinib in first-line advanced/metastatic RCC. Suntinib was approved based on an ICER versus IFN of £54,366/QALY. In the current economic evaluation the equivalent ICER was £42,872/QALY. Sunitinib had an estimated 0.649 QALY gain over IFN in the present evaluation compared to a 0.59 QALY gain that was reported using the assessment group's model. Incremental costs were estimated to be £27,825 in the present evaluation and £31,921 in the assessment group's model. These estimates are broadly comparable however the differences between these results derive from several factors. The assessment group estimated PFS and OS for IFN based on the IFN arm of the pivotal study of bevacizumab, whereas the current analysis estimated PFS based on the IFN arm of the sunitinib pivotal trial. In addition, the utility estimates for PFS and PPS are higher in the assessment group's analysis than in the current analysis (0.76 vs. 0.70 and 0.68 vs. 0.59, respectively). Furthermore as discussed in section 6.2 we did not use the Appraisal Committee's preferred assumptions regarding PFS estimates.

6.10.2 **Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?**

Although the licence for pazopanib is anticipated to include treatment-naive and cytokine pre-treated patients with advanced/metastatic RCC, the treatment-naive sub-population forms the main focus of this submission in line with the scope for this appraisal. NICE have removed the planned STA for pazopanib in cytokine pre-treated patients based on the low number of patients who may be eligible to receive pazopanib second-line in the future.

6.10.3 **What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?**

Strengths

- The evaluation was consistent with the NICE critical appraisal checklist:
    - The decision problem was consistent with the NICE scope
    - Comparators included all therapies routinely used in the NHS, including technologies regarded as current best practice
    - An NHS perspective on costs was employed (PPS costs were assumed to be unaffected by the technology)

- All relevant health effects on individuals were considered (PFS, OS and AEs were assumed to comprise all relevant effects)
- A cost effectiveness analysis was employed
- The synthesis of evidence on outcomes was based on a systematic review of the literature
- QALYs were the primary measure of health benefits
- The primary source of data for measurement of HRQL was data from patients in VEG105192 trial (EQ-5D)
- Valuation of changes in HRQL were based on preference data from a representative sample of the public (e.g., EQ-5D tariffs)
- A 3.5% annual discount rate was used for costs and health effects in the calculation of cost-effectiveness
- An additional QALY was given the same weight regardless of the other characteristics of the individuals receiving the health benefit

- The cost effectiveness model was developed using established methodology that was used previously to evaluate the cost-effectiveness of sunitinib in a prior NICE technology assessment (TA 169).

- Estimates of relative effectiveness for pazopanib vs. other comparators not examined in the VEG105192 trial (IFN and sunitinib) were based on adjusted indirect comparisons consistent with NICE guidance. This methodology maintains randomization across studies and is not associated with the limitations inherent in naïve or unadjusted indirect comparisons.

- Estimates of effectiveness for all comparators were based on comprehensive systematic reviews of the literature.

- When appropriate (e.g. for IFN vs. placebo), studies results were pooled using random effects meta-analysis. The degree of heterogeneity across studies was examined using appropriate statistics (e.g., Q-statistics, I statistics).

- Goodness of fit of Weibull survival distributions used in the model was explored. Validity of proportional hazards assumption required by model was examined.

- Every effort was made to fully explore the impact of cross over on OS in VEG105192 and the most up to date methodologies were employed. Experts in the application of these methods were consulted in the conduct of the analyses. The limitations in these methods were fully described.

- Costs of services were based on NHS reference costs where appropriate.

- Pre-progression utilities were based on community based preferences derived from EQ-5D data collected directly in the VEG105192 trial. This methodology is consistent with the NICE preferred reference case.

- Extensive probabilistic and deterministic sensitivity analyses were performed.

- The model was validated internally by the developer and by an external expert. The model was checked against results reported previously in the technology assessment of sunitinib and yielded similar results when similar inputs were employed.

Limitations

Like most cost-effectiveness evaluations, the present analysis is based on a number of necessary simplifying assumptions and uses data from a variety of primary and secondary data sources, and certain limitations must therefore be recognised:

- Head-to-head comparative studies of targeted therapies in the treatment of advanced/metastatic RCC are unavailable and estimates of comparative efficacy and safety were therefore based on an adjusted indirect comparison. The 95% CIs surrounding the HR estimates for pazopanib vs. sunitinib were wide highlighting the uncertainty in the point estimates, and hence, the findings with respect to the relative cost-effectiveness must be interpreted with caution.

- Estimates of the effectiveness of IFN vs. BSC, required for the indirect comparison of pazopanib vs. IFN and pazopanib vs. Sunitinib, were based on data from five trials conducted over a period beginning in 1986 and including studies comparing IFN with MPA and IFN vs. Vinblastine and IFN plus vinblastine vs. Vinblastine alone. While it is presumed that vinblastine has no effect on outcomes in patients with mRCC, the possible of confounding must be recognized. Also, for some of these trials, the HRs for PFS or OS were not reported and were estimated based on published survival curves which may have also confounded the analysis.

- This study did not examine the cost-effectiveness of sequential therapies. Although everolimus is approved for use in patients who have failed sunitinib or sorafenib, comparative studies on different sequential therapies are not available. Consequently, costs or treatment effects of second- or third-line therapies were not incorporated in the analysis. It should be noted that a similar approach was adopted by NICE when appraising sunitinib in its first line indication[1].

- Data on costs were not collected during the trials of the study therapies and these were therefore estimated from secondary sources. The relative cost-effectiveness of pazopanib vs. sunitinib in treatment-naïve patients was sensitive to the assumed difference in incremental costs associated with disease progression. To the extent that the evaluation may have over (under) estimated these incremental costs, it may have biased our results in favour of pazopanib (sunitinib).

- Data on utility post-progression from VEGF105192 was not available and this was therefore estimated based on data from a secondary source.

- The HR for OS in VEG105192 was adjusted for cross-over using the RPSFT method which was limited by interim OS data and the degree of re-censoring required (see

[1] NICE recommendation for sunitinib is based on the understanding that currently there are no further treatment options available in the NHS after first-line treatment for advanced and/or metastatic renal cell carcinoma.

section 5.5.1.2.2). The 95% CI for the HR for OS for pazopanib vs. placebo derived by this method was wide adding uncertainty to the cost-effectiveness estimates.

- Although cross-over occurred in the sunitinib trial we were unable to apply IPCW and RPSFT methodology to sunitinib data due to a lack of patient level data. As cross-over was limited in the IFN versus BSC trials, the ICER for pazopanib vs. IFN may be more robust than the pazopanib vs. sunitinib ICER.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Clinical evidence from the head-to-head studies of pazopanib versus sunitinib, including the outcomes of the ongoing COMPARZ trial, will greatly reduce the uncertainty and improve the robustness of the economic evaluation. As stated in section 1.6, studies directly comparing these two agents in terms of efficacy and tolerability are ongoing:

- COMPARZ (VEG108844): Comparing the efficacy, safety and tolerability of pazopanib vs sunitinib. A phase III, randomised, open-label, parallel group study is ongoing to evaluate the efficacy and safety of pazopanib compared to sunitinib in subjects with locally advanced and/or metastatic RCC who have received no prior systemic therapy

- PISCES (VEG113046): Patient preference study of pazopanib versus sunitinib in advanced/metastatic RCC. A randomised, double-blind, cross-over study of pazopanib versus sunitinib in patients with locally advanced/metastatic RCC with no prior systemic therapy.

- A chart study examining treatment patterns in patients receiving angiogenesis inhibitors for advanced/metastatic RCC in the UK is also planned.

The availability of final overall survival data will alleviate some uncertainty and should result in more robust estimates when adjusting for cross-over in VEG105192 using the RPSFT method.

The sensitivity analyses presented in Section 6.7 attempt to evaluate the impact of uncertainties in the underlying data; however, it is inevitable that some uncertainty will remain. For this reason extensive PSA and deterministic analyses have been conducted to inform the decision problem.

Summary

- Pazopanib constitutes a cost-effective treatment option for the first-line treatment of advanced/metastatic RCC. However, GSK acknowledge that there is uncertainty surrounding the clinical effectiveness of pazopanib owing to the lack of an active comparator in the pazopanib pivotal trial and the requirement to make adjustments for crossover without a universally accepted methodology.

- Sunitinib was approved by NICE under the Supplementary Advice on appraising end of life medicines based on an ICER versus IFN of £54,366/QALY. In the present evaluation the ICERs for sunitinib and pazopanib versus IFN were £42,872/QALY and £27,000/QALY respectively. If afforded the same consideration pazopanib should be considered a cost effective treatment option. Similarily the base case ICER versus BSC

was £25,264/QALY, therefore pazopanib is likely to be a cost effective option for patients for whom sunitinib or IFN are unsuitable.

- GSK are planning to provide a patient access scheme to the NHS that will address the difference between the list price of pazopanib and the effective price of sunitinib to the NHS under the sunitinib patient access scheme, as well as the uncertainty in the comparative evidence of pazopanib versus sunitinib until the results of the ongoing head to head COMPARZ study of pazopanib versus sunitinib are available.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The population for England and Wales between 2010 and 2015 (see table 7.1) was estimated from 2008 based population projections from the Office for National Statistics for 2008 (ONS 2008).

The number of patients eligible for treatment with pazopanib was derived from an annual age-standardised incidence of kidney cancer in the UK of 10.1 per 100,000 across males and females (Cancer Research UK). Ninety per cent of cases of kidney cancer are renal cell carcinoma (RCC) (NICE TA 169) and 80% of these cases have clear cell histology (Harrison 2007). We have estimated that 68% of patients with clear cell renal cell carcinoma will develop advanced or metastatic disease (mRCC). This is based on the assumption that 36% of patients are diagnosed at a local stage (Cancer Research UK), that 40% of those treated for local disease relapse (Lam 2005; Motzer 2007) and that 32% of patients have advanced or metastatic disease at diagnosis (17% stage IV, 15% stage IIIb not amenable to curative surgery or radiation therapy). The remaining patients have an unknown stage at diagnosis but it has been assumed that the same percentages apply (GSK assumption). Only patients that have an ECOG PS score of 0 or 1 (68%) would be considered suitable for first-line treatment with pazopanib (NICE sunitinib costing template 2009).

The estimated number of patients with advanced/metastatic RCC eligible for first-line pazopanib treatment in England and Wales is shown in Table 7.1.

Table 7.1: Eligible patient population for first-line treatment of advanced/metastatic RCC

		Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
		2010	2011	2012	2013	2014	2015
Total population (England and Wales)		62,222,403	62,649,014	63,073,914	63,497,831	63,921,121	64,344,156
Estimated Incidence of kidney cancer in UK	10.1 per 100,000	6284	6328	6370	6413	6456	6499
90% of cases of kidney cancer are RCC	9.1 per 100,000	5606	5645	5683	5721	5759	5797
80% of cases are clear cell RCC	7.3 per 100,000	4542	4573	4604	4635	4666	4697
68% of patients develop advanced or metastatic disease	5.0 per 100,000	3111	3132	3154	3175	3196	3217
68% of patients have a ECOG score of 0 or 1 and are eligible for 1L therapy	3.4 per 100,000	2116	2130	2145	2159	2173	2188
Eligible patient population		2116	2130	2145	2159	2173	2188

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

The only targeted treatment currently approved by NICE for the first-line treatment of advanced/ metastatic RCC within the UK is sunitinib. The introduction and subsequent NICE recommendation of sunitinib in this setting resulted in the displacement of the previous standard of care – interferon-α (IFN). Recent data (IMS Oncology Analyser Q3 2009) suggest that less than 1% of advanced/metastatic RCC patients are currently receiving IFN with 81% of eligible patients receiving sunitinib. For the purpose of this budget impact assessment it is assumed that all patients eligible for first-line treatment in the UK would receive sunitinib. In reality some patients may receive alternative treatments, be entered into clinical trials, or may be deemed unsuitable for treatment due to contraindications or tolerability issues.

7.3 What assumption(s) were made about market share (when relevant)?

It is anticipated that the market share of pazopanib for the first-line treatment of advanced/ metastatic RCC will rise to 40% by 2012 (GSK assumption). This is based on pazopanib receiving positive NICE guidance in Q4 2010 and the anticipated positive results from the head-to-head COMPARZ trial in 2012. The estimated market share for pazopanib is shown in table 7.2. It has been assumed that this rise in pazopanib market share will directly displace sunitinib market share.

Table 7.2: Anticipated market share

	2010	2011	2012	2013	2014	2015
Estimated Market Share (%)	0	28	40	40	40	40

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

In addition to acquisition costs, monitoring costs and the cost of treating adverse events have been included in the assessment of budget impact. These costs have been taken from the economic model and can be found in section 6.5.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs for sunitinib and pazopanib can be found in section 6.5.

7.6 Were there any estimates of resource savings? If so, what were they?

There may be a reduction in resource use associated with the treatment of adverse avents.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The overall budget impact for the NHS of introducing pazopanib for the first-line treatment of advanced/metastatic RCC is estimated to be £2.5 million in 2011, rising to 3.7 million annually by 2015 (Table 7.3).

Table 7.3: Overall budget impact of introducing pazopanib

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
	2010	2011	2012	2013	2014	2015
1L mRCC ELIGIBLE PATIENT POPULATION						
Estimated patient numbers	2116	2130	2145	2159	2173	2188
FUTURE TREATMENT OF 1L mRCC						
Sunitinib treatment costs						
Estimated market share (%)	100	72	60	60	60	60
patient numbers	2,116	1,534	1,287	1,295	1,304	1,313
Drug acquisition cost £28,856 per course per patient	£61,059,296	£44,253,562	£37,137,672	£37,380,062	£37,622,453	£37,882,157
Monitoring costs £2,484	£5,256,144	£3,809,462	£3,196,908	£3,217,774	£3,238,639	£3,260,995
Costs of treating adverse events £292	£617,872	£447,811	£375,804	£378,257	£380,710	£383,338
Net sunitinib costs	**£66,933,312**	**£48,510,835**	**£40,710,384**	**£40,976,093**	**£41,241,802**	**£41,526,490**
Pazopanib treatment costs						
Estimated market share (%)	0	28	40	40	40	40
patient numbers	0	596	858	864	869	875
Drug acquisition cost £33,127 per course per patient	£0	£19,756,943	£28,422,966	£28,608,477	£28,793,988	£28,992,750
Monitoring costs £2,613	£0	£1,558,393	£2,241,954	£2,256,587	£2,271,220	£2,286,898
Costs of treating adverse events £102	£0	£60,833	£87,516	£88,087	£88,658	£89,270
Net pazopanib costs	**£0**	**£21,376,169**	**£30,752,436**	**£30,953,151**	**£31,153,866**	**£31,368,918**
Budget Impact (Future treatment)	**£66,933,312**	**£69,887,004**	**£71,462,820**	**£71,929,244**	**£72,395,668**	**£72,895,408**
CURRENT TREATMENT of 1L mRCC						
Sunitinib treatment costs						
Estimated market share (%)	100	100	100	100	100	100
patient numbers	2116	2130	2145	2159	2173	2188
Drug acquisition cost £28,856 per course per patient	£61,059,296	£61,463,280	£61,896,120	£62,300,104	£62,704,088	£63,136,928
Monitoring costs £2,484	£5,256,144	£5,290,920	£5,328,180	£5,362,956	£5,397,732	£5,434,992
Costs of treating adverse events £292	£617,872	£621,960	£626,340	£630,428	£634,516	£638,896
Budget impact (current treatment)	**£66,933,312**	**£67,376,160**	**£67,850,640**	**£68,293,488**	**£68,736,336**	**£69,210,816**
OVERALL BUDGET IMPACT OF INTRODUCING PAZOPANIB for 1L mRCC						
Overall Budget Impact	**£0**	**£2,510,844**	**£3,612,180**	**£3,635,756**	**£3,659,332**	**£3,684,592**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None

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9 Appendices

9.1 Appendix 1

9.1.1 Votrient (Pazopanib®) Summary of Product Characteristics (CHMP opinion version). The Summary of Product Characteristics (SPC) for the 200mg strength tablets is provided but the same SPC applies to the 400mg strength tablets.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Votrient 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- Each film-coated tablet contains 200 mg pazopanib (as hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Capsule-shaped, pink, film-coated tablet with GS JT debossed on one side.

4. CLINIC AL PARTICULARS

4.1 Therapeutic indications

Votrient is indicated for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.

4.2 Posology and method of administration

Votrient treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

Adults

The recommended dose of pazopanib is 800 mg once daily.

Dose modifications

Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of pazopanib should not exceed 800 mg.

Paediatric population

Pazopanib is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

Elderly

There are limited data of the use of pazopanib in patients aged 65 years and older. In the RCC studies of pazopanib, overall no clinically significant differences in safety of pazopanib were observed between subjects aged at least 65 years and younger subjects. Clinical experience has not identified differences in

responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal impairment

Renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites (see section 5.2). Therefore, no dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population.

Hepatic impairment

The safety and pharmacokinetics of pazopanib in patients with hepatic impairment have not been fully established (see section 4.4). Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring due to potentially increased exposure to the medicinal product. Insufficient data are available in patients with mild hepatic impairment to provide a dose adjustment recommendation but a reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (see section 5.2).

Pazopanib is contraindicated in patients with severe hepatic impairment (see section 4.3).

Method of administration

Pazopanib should be taken without food, at least one hour before or two hours after a meal (see section 5.2). Votrient film-coated tablets should be taken whole with water and not broken or crushed (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Severe hepatic impairment.

4.4 Special warnings and precautions for use

Hepatic effects

Cases of hepatic failure (including fatalities) have been reported during use of pazopanib. The safety and pharmacokinetics of pazopanib have not been fully established in patients with pre-existing hepatic impairment. Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring. A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (see section 4.2). Insufficient data are available in patients with mild hepatic impairment to provide a dose adjustment recommendation. Pazopanib is contraindicated in patients with severe hepatic impairment (see section 4.3).

In clinical studies with pazopanib, increase in serum transaminases (ALT, AST) and bilirubin were observed (see section 4.8). In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin.

Monitor serum liver tests before initiation of treatment with pazopanib and at least once every 4 weeks for the first 4 months of treatment, and as clinically indicated. Periodic monitoring should then continue after this time period.

- Patients with isolated transaminase elevations ≤ 8 X upper limit of normal (ULN) may be continued on pazopanib with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.

- Patients with transaminases of > 8 X ULN should have pazopanib interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose and measure serum liver tests weekly for 8 weeks (see section 4.2). Following reintroduction of pazopanib, if transaminase elevations > 3 X ULN recur, then pazopanib should be discontinued.

- If transaminase elevations > 3 X ULN occur concurrently with bilirubin elevations > 2 X ULN, bilirubin fractionation should be performed. If direct (conjugated) bilirubin is > 35 % of total bilirubin, pazopanib should be discontinued.

Hypertension

Blood pressure should be well controlled prior to initiating pazopanib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy (see section 4.8). Hypertension occurs early in the course of treatment (88 % occurring in first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the pazopanib dose may be reduced (see section 4.2). Temporary suspension is recommended in patients if hypertension is severe and persists despite anti-hypertensive therapy and pazopanib dose reduction. Pazopanib treatment may be resumed once hypertension is appropriately controlled.

QT prolongation and Torsade de Pointes

In clinical studies with pazopanib, events of QT prolongation and Torsade de Pointes have occurred (see section 4.8). Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrythmics or other medicinal products that may prolong QT interval and those with relevant pre-existing cardiac disease. When using pazopanib, base line and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within normal range is recommended.

Arterial thrombotic events

In clinical studies with pazopanib, myocardial infarction, ischemic stroke, and transient ischemic attack were observed (see section 4.8). Pazopanib should be used with caution in patients who are at increased risk for any of these events. A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

Haemorrhagic events

In clinical studies with pazopanib haemorrhagic events have been reported (see section 4.8). Pazopanib is not recommended in patients who had a history of haemoptysis, cerebral, or clinically significant

gastrointestinal (GI) haemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of haemorrhage.

Gastrointestinal perforations and fistula

In clinical studies with pazopanib, events of GI perforation or fistula have occurred (see section 4.8). Pazopanib should be used with caution in patients at risk for GI perforation or fistula.

Wound healing

No formal studies on the effect of pazopanib on wound healing have been conducted. Since Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgement of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.

Heart failure

The safety and pharmacokinetics of pazopanib in patients with moderate to severe heart failure has not been studied.

Hypothyroidism

In clinical studies with pazopanib, events of hypothyroidism have occurred (see section 4.8). Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of pazopanib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on pazopanib treatment. Laboratory monitoring of thyroid function should be performed periodically and managed as per standard medical practice.

Proteinuria

In clinical studies with pazopanib, proteinuria has been reported. Baseline and periodic urinanalysis during treatment is recommended and patients should be monitored for worsening proteinuria. Pazopanib should be discontinued if the patient develops Grade 4 proteinuria.

Pregnancy

Pre-clinical studies in animals have shown reproductive toxicity (see section 5.3). If pazopanib is used during pregnancy, or if the patient becomes pregnant whilst receiving pazopanib, the potential hazard to the foetus should be explained to the patient. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with pazopanib (see section 4.6).

Interactions

Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to pazopanib (see section 4.5). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BCRP should be considered.

Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to pazopanib (see section 4.5).

Concomitant administration of pazopanib with uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g. irinotecan) should be undertaken with caution since pazopanib is an inhibitor of UGT1A1.

Grapefruit juice should be avoided during treatment with pazopanib (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on pazopanib

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

CYP3A4, P-gp, BCRP Inhibitors: Pazopanib is a substrate for CYP3A4, P-gp and BCRP.

Co-administration of pazopanib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice contains an inhibitor of CYP3A4 and may also increase plasma concentrations of pazopanib.

Administration of 1,500 mg lapatinib (a substrate for and weak inhibitor of CYP3A4 and P-gp and a potent inhibitor of BCRP) with 800 mg pazopanib resulted in an approximately 50 % to 60 % increase in mean pazopanib $AUC_{(0-24)}$ and C_{max} compared to administration of 800 mg pazopanib alone. Inhibition of P-gp and/or BCRP by lapatinib likely contributed to the increased exposure to pazopanib.

Concurrent administration of a single dose of pazopanib eye drops (at a low dose of 400 µg (80 µl of 5 mg/ml)) with the strong CYP3A4 inhibitor and P-gp inhibitor, ketoconazole, in healthy volunteers resulted in a 2.2- and 1.5-fold increase in mean $AUC_{(0-t)}$ and C_{max} values, respectively. Inhibition of P-gp and/or BCRP by ketoconazole likely contributed to the increased exposure to pazopanib. At present no dosing recommendations can be made for either potent specific inhibitors of CYP3A4 or ketoconazole. Co-administration of pazopanib with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations. Co-administration with potent P-gp or BCRP inhibitors may also alter the exposure and distribution of pazopanib, including distribution into the central nervous systems (CNS).

Combination with strong CYP3A4, P-gp or BCRP inhibitors should therefore be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4, P-gp or BCRP is recommended..

CYP3A4, P-gp, BCRP Inducers: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Co-administration of pazopanib with potent P-gp or BCRP inducers may alter the exposure and distribution of pazopanib, including distribution into the CNS. Selection of an alternate concomitant medication with no or minimal enzyme or transporter induction potential is recommended.

Effects of pazopanib on other medicinal products

In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an *in vitro* human PXR assay. Clinical pharmacology studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib resulted in an increase of approximately 30 % in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33 % to 64 % in the ratio of dextrometrophan to dextrophan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 25 % and 31 % in paclitaxel AUC and C_{max}, respectively.

Based on *in vitro* IC_{50} and *in vivo* plasma C_{max} values, pazopanib metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of pazopanib towards BCRP. Furthermore, inhibition of BCRP and P-gp by pazopanib in the gastrointestinal tract cannot be excluded. Care should be taken when pazopanib is co-administered with other oral BCRP and P-gp substrates.

In vitro, pazopanib inhibited human organic anion transporting polypeptide (OATP1B1). It cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g. rosuvastatin).

Effect of food on pazopanib

Administration of pazopanib with a high fat or low fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of pazopanib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pazopanib should not be used during pregnancy unless the clinical condition of the women requires treatment with pazopanib. If pazopanib is used during pregnancy, or if the patient becomes pregnant while receiving pazopanib, the potential hazard to the foetus should be explained to the patient.

Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with pazopanib.

Breast-feeding

The safe use of pazopanib during lactation has not been established. It is not known whether pazopanib is excreted in human milk. There are no animal data on the excretion of pazopanib in animal milk. A risk to the suckling child cannot be excluded. Breast feeding should be discontinued during treatment with pazopanib.

Fertility

Animal studies indicate that male and female fertility may be affected by treatment with pazopanib (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. A detrimental effect on such activities cannot be predicted from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of pazopanib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired or weak.

4.8 Undesirable effects

Pooled data from the pivotal RCC study (VEG105192, n=290), extension study (VEG107769, n=71) and the supportive Phase II study (VEG102616, n=225) was evaluated in the overall evaluation of safety and tolerability of pazopanib (total n=586) in subjects with RCC (see section 5.1).

The most important serious adverse reactions were transient ischaemic attack, ischaemic stroke, myocardial ischaemia, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation and pulmonary, gastrointestinal and cerebral haemorrhage, all adverse reactions being reported in < 1 % of treated patients.

Fatal events that were considered possibly related to pazopanib included gastrointestinal haemorrhage, pulmonary haemorrhage/haemoptysis, abnormal hepatic function, intestinal perforation and ischemic stroke.

The most common adverse reactions (experienced by at least 10 % of the patients) of any grade included: diarrhoea, hair colour change, hypertension, nausea, fatigue, anorexia, vomiting, dysgeusia, elevated alanine aminotransferase and elevated aspartate aminotransferase.

Treatment related adverse reactions, all grades, which were reported in RCC patients are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000
not known	(cannot be estimated from the available data)

Categories have been assigned based on absolute frequencies in the clinical study data. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Table 1: Treatment-related adverse reactions reported in RCC studies (n=586)

System Organ Class	Frequency (all grades)	Adverse Reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders	Common	Thrombocytopenia	25 (4 %)	3 (< 1 %)	3 (< 1 %)
	Common	Neutropenia	17 (3 %)	4 (< 1 %)	2 (< 1 %)
	Common	Leukopenia	14 (2 %)	1 (< 1 %)	0
Endocrine disorders	Common	Hypothyroidism	23 (4 %)	0	0
Metabolism and nutrition disorders	Very common	Decreased appetite[e]	122 (21 %)	6 (1 %)	0
	Uncommon	Hypophosphataemia	4 (< 1 %)	2 (< 1 %)	0
	Uncommon	Hypomagnesaemia	3 (< 1 %)	0	0
Nervous system disorders	Very common	Dysgeusia[c]	92 (16 %)	0	0
	Common	Headache	41 (7 %)	0	0
	Common	Dizziness	19 (3 %)	0	1 (< 1 %)
	Common	Lethargy	12 (2 %)	1 (< 1 %)	0
	Common	Paraesthesia	12 (2 %)	2 (< 1 %)	0
	Uncommon	Peripheral sensory neuropathy	5 (< 1 %)	0	0
	Uncommon	Hypoaesthesia	4 (< 1 %)	0	0
	Uncommon	Transient ischaemic attack	3 (< 1 %)	2 (< 1 %)	0
	Uncommon	Cerebrovascular accident	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	Ischaemic stroke	1 (< 1 %)	0	0
Eye disorders	Uncommon	Eyelash discolouration	3 (< 1 %)	0	0
Cardiac disorders	Uncommon	Bradycardia	3 (< 1 %)	0	0
	Uncommon	Cardiac dysfunction	4 (< 1 %)	1 (< 1 %)	1 (< 1 %)
	Uncommon	Myocardial infarction	2 (< 1 %)	0	2 (< 1 %)
	Uncommon	Myocardial ischaemia	1 (< 1 %)	1 (< 1 %)	0
Vascular disorders	Very common	Hypertension	225 (38 %)	34 (6%)	0
	Common	Hot flush	11 (2 %)	0	0
	Uncommon	Flushing	5 (< 1 %)	0	0
	Uncommon	Haemorrhage	1 (< 1 %)	0	0
	Uncommon	Hypertensive crisis	1 (< 1 %)	0	1 (< 1 %)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	16 (3 %)	0	0
	Common	Dysphonia	15 (3 %)	0	0
	Uncommon	Pulmonary embolism	4 (< 1 %)	1 (< 1 %)	3 (< 1 %)
	Uncommon	Haemoptysis	3 (< 1 %)	0	0
	Uncommon	Pulmonary haemorrhage	1 (< 1 %)	0	0
	Very common	Diarrhoea	286 (49 %)	19 (3 %)	2 (< 1 %)

Gastrointestinal disorders	Very common	Nausea	161 (27 %)	3 (< 1 %)	0
	Very common	Vomiting	89 (15 %)	7 (1 %)	1 (< 1 %)
	Very common	Abdominal pain[a]	60 (10 %)	8 (1 %)	0
	Common	Dyspepsia	24 (4 %)	2 (< 1 %)	0
	Common	Stomatitis	24 (4 %)	0	0
	Common	Flatulence	20 (3 %)	0	0
	Common	Abdominal distension	15 (3 %)	0	0
	Uncommon	Mouth ulceration	4 (< 1 %)	1 (< 1 %)	0
	Uncommon	Frequent bowel movements	3 (< 1 %)	0	0
	Uncommon	Gastrointestinal haemorrhage	3 (< 1 %)	1 (< 1 %)	0
	Uncommon	Rectal haemorrhage	3 (< 1 %)	1 (< 1 %)	0
	Uncommon	Large intestine perforation	2 (< 1 %)	1 (< 1 %)	0
	Uncommon	Mouth haemorrhage	2 (< 1 %)	0	0
	Uncommon	Enterocutaneous fistula	1 (< 1 %)	0	0
	Uncommon	Haematemesis	1 (< 1 %)	0	0
	Uncommon	Haematochezia	1 (< 1 %)	0	0
	Uncommon	Haemorrhoidal haemorrhage	1 (< 1 %)	0	0
	Uncommon	Ileal perforation	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	Melaena	1 (< 1 %)	0	0
	Uncommon	Oesophageal haemorrhage	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	Pancreatitis	1 (< 1 %)	0	0
	Uncommon	Peritonitis	1 (< 1 %)	0	0
	Uncommon	Retroperitoneal haemorrhage	1 (< 1 %)	0	0
	Uncommon	Upper gastrointestinal haemorrhage	1 (< 1 %)	0	0
Hepatobiliary disorders	Common	Hepatic function abnormal	20 (3 %)	6 (1 %)	0
	Common	Hyperbilirubinaemia	18 (3 %)	2 (< 1 %)	1 (< 1 %)
	Uncommon	Hepatotoxicity	5 (< 1 %)	3 (< 1 %)	0
	Uncommon	Jaundice	2 (< 1 %)	1 (< 1 %)	0
	Uncommon	Hepatic failure	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	Hepatitis	1 (< 1 %)	1 (< 1 %)	0
Skin and subcutaneous disorders	Very common	Hair colour change	231 (39 %)	1 (< 1 %)	0
	Common	Rash	52 (9 %)	3 (< 1 %)	0
	Common	Alopecia	50 (9 %)	0	0
	Common	Palmar-plantar erythrodysaesthesia syndrome	43 (7 %)	7 (1 %)	0
	Common	Skin hypopigmentation	25 (4 %)	0	0

	Common	Erythema	15 (3 %)	0	0
	Common	Pruritus	13 (2 %)	0	0
	Common	Skin depigmentation	13 (2 %)	0	0
	Common	Dry skin	12 (2 %)	0	0
	Common	Hyperhidrosis	9 (2 %)	0	0
	Uncommon	Photosensitivity reaction	7 (1 %)	0	0
	Uncommon	Skin exfoliation	7 (1 %)	0	0
	Uncommon	Rash vesicular	3 (< 1 %)	0	0
	Uncommon	Pruritus generalised	2 (< 1 %)	1 (< 1 %)	0
	Uncommon	Rash papular	2 (< 1 %)	0	0
	Uncommon	Plantar erythema	1 (< 1 %)	0	0
	Uncommon	Rash erythematous	1 (< 1 %)	0	0
	Uncommon	Rash generalised	1 (< 1 %)	0	0
	Uncommon	Rash macular	1 (< 1 %)	0	0
	Uncommon	Rash pruritic	1 (< 1 %)	0	0
Musculoskeletal and connective tissue disorders	Common	Myalgia	15 (3 %)	2 (< 1 %)	0
	Common	Muscle spasms	12 (2 %)	0	0
Renal and urinary disorders	Common	Proteinuria	40 (7 %)	5 (< 1 %)	0
	Uncommon	Haemorrhage urinary tract	1 (< 1 %)	0	0
Reproductive system and breast disorders	Uncommon	Menorrhagia	1 (< 1 %)	0	0
	Uncommon	Metrorrhagia	1 (< 1 %)	0	0
	Uncommon	Vaginal haemorrhage	1 (< 1 %)	0	0
General disorders and administration site conditions	Very common	Fatigue	139 (24 %)	16 (3 %)	0
	Common	Asthenia	41 (7 %)	8 (1 %)	0
	Common	Mucosal inflammation	27 (5 %)	2 (< 1 %)	0
	Common	Oedema[b]	19 (3 %)	0	0
	Common	Chest pain	14 (2 %)	2 (< 1 %)	0
	Uncommon	Mucous membrane disorder	1 (< 1 %)	0	0
Investigations	Very common	Alanine aminotransferase increased	83 (14%)	28 (5 %)	4 (< 1 %)
	Very common	Aspartate aminotransferase increased	72 (12%)	17 (3 %)	3 (< 1 %)
	Common	Weight decreased	38 (6 %)	2 (< 1 %)	0
	Common	Blood creatinine increased	13 (2 %)	2 (< 1 %)	0
	Common	Blood bilirubin increased	11 (2 %)	1 (< 1 %)	1 (< 1 %)
	Common	White blood cell count decreased[d]	10 (2 %)	1 (< 1 %)	0
	Common	Lipase increased	9 (2 %)	4 (< 1 %)	1 (< 1 %)

	Common	Blood pressure increased	6 (1 %)	0	0
	Common	Blood thyroid stimulating hormone increased	6 (1 %)	0	0
	Common	Gamma-glutamyltransferase increased	6 (1 %)	1 (< 1 %)	1 (< 1 %)
	Common	Hepatic enzyme increased	6 (1 %)	2 (< 1 %)	0
	Uncommon	Aspartate aminotransferase	5 (< 1 %)	2 (< 1 %)	0
	Uncommon	Blood urea increased	5 (< 1 %)	1 (< 1 %)	0
	Uncommon	Electrocardiogram QT prolonged	5(< 1 %)	1 (< 1 %)	0
	Uncommon	Blood amylase increased	4 (< 1 %)	0	0
	Uncommon	Blood glucose decreased	4 (< 1 %)	0	0
	Uncommon	Alanine aminotransferase	3 (< 1 %)	2 (< 1 %)	0
	Uncommon	Transaminase increased	3 (< 1 %)	1 (< 1 %)	0
	Uncommon	Blood pressure diastolic increased	2 (< 1 %)	0	0
	Uncommon	Thyroid function test abnormal	2 (< 1 %)	0	0
	Uncommon	Blood pressure systolic increased	1 (< 1 %)	0	0
	Uncommon	Liver function test abnormal	1 (< 1 %)	0	0
The following terms have been combined: [a] Abdominal pain, abdominal pain upper and abdominal pain lower [b] Oedema, oedema peripheral, eye oedema, localised oedema and face oedema [c] Dysgeusia, ageusia and hypogeusia [d] White cell count decreased, neutrophil count decreased and leukocyte count decreased [e] Decreased appetite and anorexia					

4.9 Overdose

Pazopanib doses up to 2,000 mg have been evaluated in clinical studies without dose-limiting toxicity.

There is no specific antidote for overdose with pazopanib and treatment of overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Protein- kinase inhibitors, ATC code: L01XE11

Mechanism of action

Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and –β, and stem cell factor receptor (c-KIT), with IC_{50} values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose-dependently inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR-β receptors in cells. *In vivo*, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in various animal models, and the growth of multiple human tumour xenografts in mice.

Clinical studies

The safety and efficacy of pazopanib in RCC were evaluated in a randomized, double-blind, placebo-controlled multi-centre study. Patients (N= 435) with locally advanced and/or metastatic RCC were randomized to receive pazopanib 800 mg once daily or placebo. The primary objective of the study was to evaluate and compare the two treatment arms for progression-free survival (PFS) and the principle secondary endpoint is overall survival (OS). The other objectives were to evaluate the overall response rate and duration of response.

From the total of 435 patients in this study, 233 patients were treatment naïve and 202 were second line patients who received one prior IL-2 or INFα-based therapy. The performance status (ECOG) was similar between the pazopanib and placebo groups (ECOG 0: 42 % vs. 41 %, ECOG 1: 58 % vs. 59 %). The majority of patients had either favourable (39 %) or intermediate (54 %), MSKCC (Memorial Sloan Kettering Cancer Centre) / Motzer prognostic factors. All patients had clear cell histology or predominantly clear cell histology. Approximately half of all patients had 3 or more organs involved in their disease and most patients had the lung (74 %), and/or lymph nodes (54 %) as a metastatic location for disease at baseline.

A similar proportion of patients in each arm were treatment-naïve and cytokine-pre-treated (53 % and 47 % in pazopanib arm, 54 % and 46 % in placebo arm). In the cytokine-pre-treated subgroup, the majority (75 %) had received interferon based treatment.

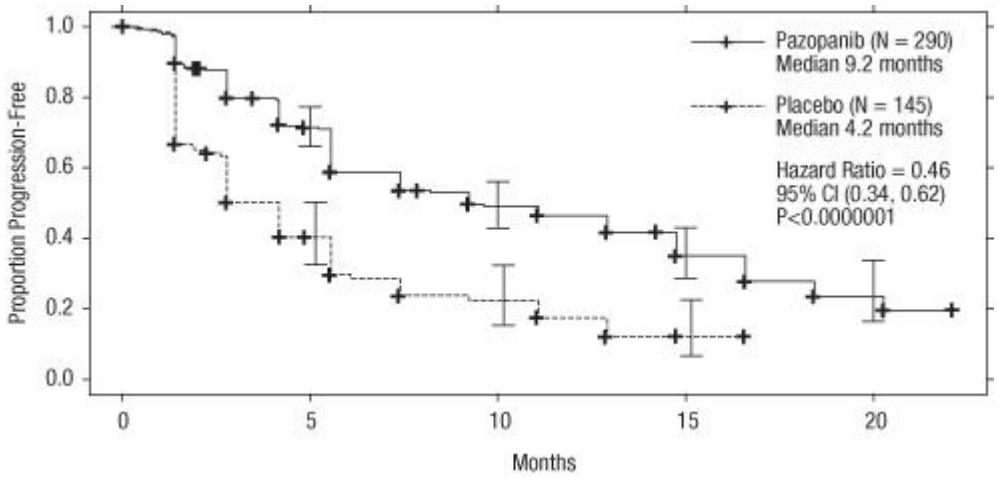
Similar proportions of patients in each arm had prior nephrectomy (89 % and 88 % in the pazopanib and placebo arms, respectively) and/or prior radiotherapy (22 % and 15 % in the pazopanib and placebo arms, respectively.
The primary analysis of the primary endpoint PFS is based on disease assessment by independent radiological review in the entire study population (treatment naïve and cytokine pre-treated).

a. Table 2: Overall efficacy results by independent assessment

Endpoints/Study Population	Pazopanib	Placebo	HR (95% CI)	P value (one-sided)
PFS Overall* ITT Median (months)	 N = 290 9.2	 N = 145 4.2	 0.46 (0.34, 0.62)	 <0.0000001
Response rate % (95% CI)	N = 290 30 (25.1,35.6)	N = 145 3 (0.5, 6.4)	 –	 <0.001

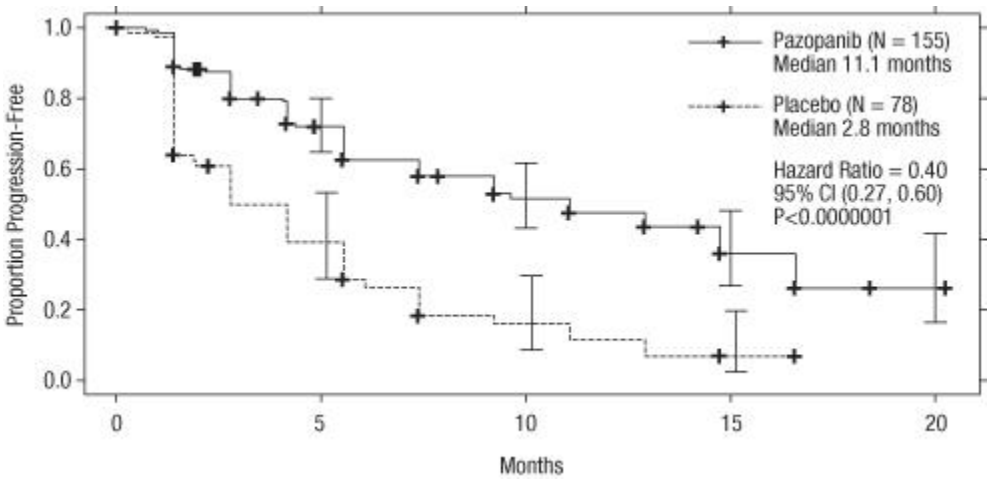
HR = Hazard ratio; ITT = Intent to treat; PFS = Progression-free survival. * - Treatment-Naïve and Cytokine Pre-treated Populations.

Figure 1: Kaplan-Meier curve for progression-free survival by independent assessment for the overall population (treatment-naïve and cytokine pre-treated populations)



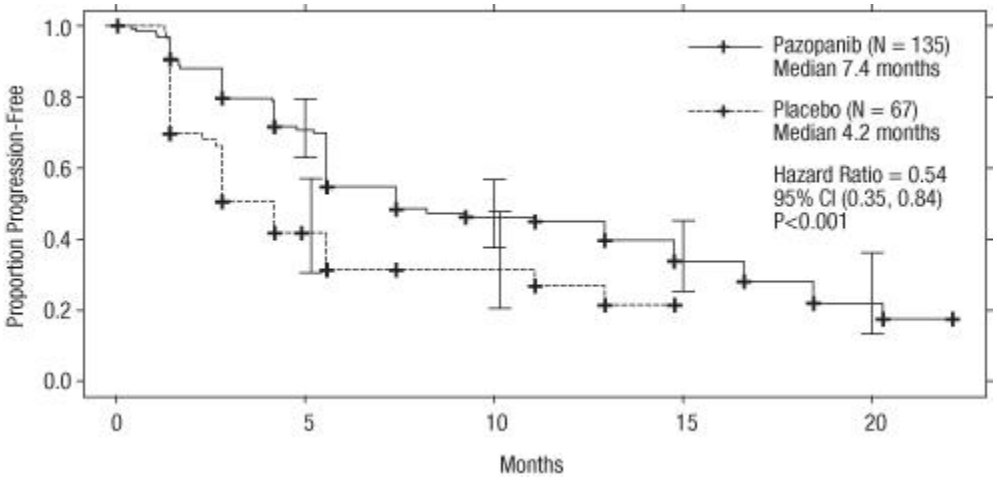
x axis; Months, y axis; Proportion Progression Free, Pazopanib ——— (N = 290) Median 9.2 months; Placebo -------- (N = 145) Median 4.2 months; Hazard Ratio = 0.46, 95 % CI (0.34, 0.62), P < 0.0000001

Figure 2: Kaplan-Meier curve for progression-free survival by independent assessment for the treatment-naïve population



x axis; Months, y axis; Proportion Progression Free, Pazopanib ——— (N = 155) Median 11.1 months; Placebo ---------- (N = 78) Median 2.8 months; Hazard Ratio = 0.40, 95 % CI (0.27, 0.60), P < 0.0000001

Figure 3: Kaplan-Meier Curve for progression-free survival by independent assessment for the cytokine pre-treated population



x axis; Months, y axis; Proportion Progression Free, Pazopanib ——— (N = 135) Median 7.4 months; Placebo ---------- (N = 67) Median 4.2 months; Hazard Ratio = 0.54, 95 % CI (0.35, 0.84), P < 0.001

For patients who responded to treatment, the median time to response was 11.9 weeks and the median duration of response was 58.7 weeks as per independent review.

At the time of the analysis for the primary endpoint, the overall survival data were not sufficiently mature.

No statistical differences were observed between treatment groups for Global Quality of Life using EORTC QLQ-C30 and EuroQoL EQ-5D.

In a Phase 2 study of 225 patients with locally recurrent or metastatic clear cell renal cell carcinoma, objective response rate was 35 % and median duration of response was 68 weeks, as per independent review. Median PFS was 11.9 months.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Votrient in all subsets of the paediatric population in Renal Cell Carcinoma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on the product every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption: Upon oral administration of a single pazopanib 800 mg dose to patients with solid tumours, maximum plasma concentration (C_{max}) of approximately 19 ± 13 µg/ml were obtained after median 3.5

hours (range 1.0-11.9 hours) and an AUC_{∞} of approximately 650 ± 500 μg.h/ml was obtained. Daily dosing results in 1.23- to 4-fold increase in AUC_T.
There was no consistent increase in AUC or C_{max} at pazopanib doses above 800 mg.

Systemic exposure to pazopanib is increased when administered with food. Administration of pazopanib with a high fat or low fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least two hours after food or at least one hour before food (see section 4.2).

Administration of a pazopanib 400 mg crushed tablet increased $AUC_{(0-72)}$ by 46 % and C_{max} by approximately 2 fold and decreased t_{max} by approximately 2 hours compared to administration of the whole tablet. These results indicate that the bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet (see section 4.2).

Distribution: Binding of pazopanib to human plasma protein *in vivo* was greater than 99 % with no concentration dependence over the range of 10-100 μg/ml. *In vitro* studies suggest that pazopanib is a substrate for P-gp and BCRP.

Biotransformation: Results from *in vitro* studies demonstrated that metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. The four principle pazopanib metabolites account for only 6 % of the exposure in plasma. One of these metabolites inhibits the proliferation of VEGF-stimulated human umbilical vein endothelial cells with a similar potency to that of pazopanib, the others are 10- to 20-fold less active. Therefore, activity of pazopanib is mainly dependent on parent pazopanib exposure.

Elimination: Pazopanib is eliminated slowly with a mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via faeces with renal elimination accounting for < 4 % of the administered dose.

Special populations

Renal impairment: Results indicate that less than 4 % of an orally administered pazopanib dose is excreted in the urine as pazopanib and metabolites. Results from population pharmacokinetic modelling (data from subjects with baseline CLCR values ranging from 30.8 ml/min to 150 ml/min) indicated that renal impairment is unlikely to have clinically relevant effect on pazopanib pharmacokinetics. No dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population (see section 4.2).

Hepatic impairment: In subjects with moderate hepatic impairment the median pazopanib C_{max} and AUC(0-6 hr) normalized to a dose of 800 mg once daily were both increased 2-fold compared to those in subjects with normal hepatic function. Based on safety, tolerability and pharmacokinetic data, the dosage of pazopanib should be reduced to 200 mg once daily in subjects with moderate hepatic impairment (see section 4.2). Data are not available in subjects with mild hepatic impairment. Pazopanib is contraindicated in patients with severe hepatic impairment (see section 4.3).

5.3 Preclinical safety data

The preclinical safety profile of pazopanib was assessed in mice, rats, rabbits and monkeys. In repeat dose studies in rodents, effects in a variety of tissues (bone, teeth, nail beds, reproductive organs, haematological tissues, kidney and pancreas) appear related to the pharmacology of VEGFR inhibition and/or disruption of VEGF signalling pathways with most effects occurring at plasma exposure levels below those observed in the clinic. Other observed effects include body weight loss, diarrhoea and/or morbidity that were either secondary to local gastrointestinal effects caused by high local mucosal medicinal product exposure (monkeys) or pharmacologic effects (rodents). Proliferative hepatic lesions (eosinophilic foci and adenoma) were seen in female mice at exposures 2.5 times human exposure based on AUC.

Reproductive, fertility and teratogenic effects

Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures more than 300-fold lower than the human exposure (based on AUC). Effects included reduced female fertility, increased pre- and post-implantation loss, early resorptions, embryo lethality, decreased foetal body weight and cardiovascular malformation. Decreased corpora lutea, increased cysts and ovarian atrophy have also been noted in rodents. In a rat male fertility study, there was no effect on mating or fertility, but decreased testicular and epididymal weights were noted with reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations observed at exposures 0.3 times human exposure based on AUC.

Genotoxicity

Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat in vivo micronucleus). A synthetic intermediate in manufacture of pazopanib, which is also present in the final drug substance in low amounts, was not mutagenic in the Ames assay but genotoxic in the mouse lymphoma assay and in vivo mouse micronucleus assay.

Carcinogenicity

Carcinogenicity studies with pazopanib have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate (type A)

Tablet coating
Hypromellose
Iron oxide red (E172)

Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with polypropylene child resistant closures containing either 30 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
Berkeley Avenue
Greenford
Middlesex
UB6 0NN
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter).

A comprehensive search strategy was designed to retrieve relevant clinical data from published literature. Details of the search strategy can be seen in section 9.2.4. The following electronic databases were searched:

Table 9.1: Databases examined for the clinical systematic review and the service provider used

Data source	Service Provider
MEDLINE	Embase.com; http://www.embase.com/
EMBASE	
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane library; http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html
Cochrane Database of Systematic Reviews (CDSR)	
Cochrane Methodology Register	
MEDLINE in process (2009 only)	PubMed; http://www.ncbi.nlm.nih.gov/sites/entrez

Searches were also carried out in www.clinicaltrials.gov and the Meta-Register (UK Clinical Trials Gateway [UKCTG] and the International Standard Randomized Controlled Trial Number [ISRCTN] Registe) to identify any ongoing studies of relevance to this review.

9.2.2 The date on which the search was conducted.

MEDLINE, EMBASE and The Cochrane Library were searched on 23 November 2009. MEDLINE in-process, www.clinicaltrials.gov and the Meta-Register were searched on 02 December 2009.

9.2.3 The date span of the search.

All the databases listed above were searched from 1980 onwards, with the exception of MEDLINE In-process which was searched for 2009 only.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategy for the identification of clinical RCT evidence was as follows:

MEDLINE and Embase

Date search run: 23 November 2009

#	Search History	Results
1.	'clinical trial'/exp	754474
2.	'randomization'/de	48076
3.	'controlled study'/de	3084530
4.	'comparative study'/de	573453
5.	'single blind procedure'/de	11501
6.	'double blind procedure'/de	92524
7.	'crossover procedure'/de	25892
8.	'placebo'/de	156832
9.	'clinical trial' OR 'clinical trials'	856289
10.	'controlled clinical trial' OR 'controlled clinical trials'	352414
11.	'randomised controlled trial' OR 'randomised controlled trial' OR 'randomised controlled trials' OR 'randomised controlled trials'	268489
12.	'randomisation' OR 'randomization'	59957
13.	Rct	5404
14.	'random allocation'	1000
15.	'randomly allocated'	12960
16.	'allocated randomly'	1589
17.	allocated NEAR/2 random	739
18.	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	152930
19.	placebo*	225692
20.	'prospective study'/de	135910
21.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	4174839
22.	'case study'/de	7268
23.	'case report'	1666932
24.	'abstract report'/de	89415
25.	'letter'/de	645194
26.	#22 OR #23 OR #24 OR #25	2270904
27.	#21 NOT #26	4066688
28.	'pazopanib'/de OR 'sunitinib'/de OR 'sorafenib'/de OR 'bevacizumab'/de OR 'temsirolimus'/de OR 'everolimus'/de OR 'interleukin 2'/de OR 'alpha interferon'/de	94250
29.	'alpha-interferon':ab,ti OR alfaferone:ab,ti OR alferon:ab,ti OR 'alpha ferone':ab,ti OR cilferon:ab,ti OR ginterferon:ab,ti OR 'interferon-alpha':ab,ti OR introma:ab,ti OR kemron:ab,ti OR leukinferon:ab,ti OR leukinferron:ab,ti OR 'leukocyte interferon':ab,ti OR 'refecon a':ab,ti OR 'referon a3':ab,ti OR sumiferon:ab,ti OR sumipheron:ab,ti OR veldona:ab,ti	10766
30.	'biotest':ab,ti OR bioleukin:ab,ti OR 'interleukin-ii':ab,ti OR 'interleukin-2':ab,ti OR 'il-2':ab,ti OR il2:ab,ti OR 'ro-236019':ab,ti OR tcgf:ab,ti OR tsf:ab,ti	56840
31.	everolimus:ab,ti OR afinitor:ab,ti OR certican:ab,ti OR 'nvp-rad-001':ab,ti OR 'rad-001':ab,ti OR 'rad 001a':ab,ti OR rad001:ab,ti OR rad001a:ab,ti OR 'sdz rad':ab,ti	853
32.	temsirolimus:ab,ti OR 'cci-779':ab,ti OR 'cell-cycle-inhibitor-779':ab,ti OR 'nsc 683864':ab,ti OR nsc683864:ab,ti OR torisel:ab,ti	402
33.	bevacizumab:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti OR 'anti-vegf':ab,ti OR 'rhumab-vegf':ab,ti	4100
34.	'bay 43-9006':ab,ti OR 'bay 439006':ab,ti OR 'bay43-9006':ab,ti OR bay439006:ab,ti OR	996

#	Search History	Results
	nexavar:ab,ti OR sorafenib:ab,ti	
35.	sunitinib:ab,ti OR sutent:ab,ti OR 'pha 2909040ad':ab,ti OR 'pha2909040ad':ab,ti OR 'su 010398':ab,ti OR 'su 011248':ab,ti OR 'su 10398':ab,ti OR su10398:ab,ti OR 'su 11248':ab,ti OR su010398:ab,ti OR 'su011248':ab,ti OR su11248:ab,ti	960
36.	armala:ab,ti OR pazopanib:ab,ti OR gw786034*:ab,ti OR (gw NEXT/1 786034*):ab,ti OR (sb NEXT/1 710468*):ab,ti OR sb710468*:ab,ti OR votrient:ab,ti	39
37.	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	121860
38.	'kidney carcinoma'/de	27437
39.	'kidney tumour'/exp	64633
40.	renal*:ab,ti OR kidney*:ab,ti OR grawit*:ab,ti OR hypernephroid*:ab,ti OR nephroid*:ab,ti	602660
41.	carcinoma*:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR adeno*:ab,ti OR tumo?r*:ab,ti OR pyelocarcinoma*:ab,ti OR metastas?s:ab,ti OR oncocytoma:ab,ti	1586263
42.	#40 AND #41	69298
43.	(metanephric NEAR/2 adeno*):ab,ti	136
44.	rcc:ab,ti OR mrcc:ab,ti OR 'm-rcc':ab,ti	5722
45.	'hypernephroma':ab,ti	1196
46.	#38 OR #39 OR #42 OR #43 OR #44 OR #45	100246
47.	#27 AND #37 AND #46	3814
48.	**#27 AND #37 AND #46 AND [1980-2010]/py**	**3884**

Cochrane

Date search run: 23 November 2009

ID	Search History	Results
#1	MeSH descriptor Interferon-alpha explode all trees	2099
#2	MeSH descriptor Interleukin-2 explode all trees	702
#3	("alpha-interferon" OR alfaferone OR alferon OR "alpha ferone" OR cilferon OR ginterferon OR "interferon-alpha" OR introma OR kemron OR leukinferon OR leukinferron OR "leukocyte interferon" OR "refecon a" OR "referon a3" OR sumiferon OR sumipheron OR veldona):ab,ti,kw	3001
#4	(biotest OR bioleukin OR "interleukin-ii" OR "interleukin-2" OR "il-2" OR il2 OR "ro-236019" OR tcgf OR tsf):ab,ti,kw	1902
#5	(everolimus OR afinitor OR certican OR "nvp-rad-001" OR "rad-001" OR "rad 001a" OR rad001 OR rad001a OR "sdz rad"):ab,ti,kw	154
#6	(temsirolimus OR "cci-779" OR "cell-cycle-inhibitor-779" OR "nsc 683864" OR nsc683864 OR torisel):ab,ti,kw	25
#7	(bevacizumab OR avastin OR "nsc 704865" OR nsc704865 OR "anti-vegf" OR "rhumab-vegf"):ab,ti,kw	236
#8	("bay 43-9006" OR "bay 439006" OR "bay43-9006" OR bay439006 OR nexavar OR sorafenib):ab,ti,kw	63
#9	(sunitinib OR sutent OR "pha 2909040ad" OR pha2909040ad OR "su 010398" OR "su 011248" OR "su 10398" OR su10398 OR "su 11248" OR su010398 OR su011248 OR su11248):ab,ti,kw	37
#10	(armala OR pazopanib OR gw786034* OR sb710468* OR votrient):ab,ti,kw	2

ID	Search History	Results
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)	5875
#12	MeSH descriptor Carcinoma, Renal Cell explode all trees	301
#13	(renal* OR kidney* OR grawit* OR hypernephroid* OR nephroid*):ab,ti,kw	24198
#14	(carcinoma* OR cancer* OR neoplasm* OR adeno* OR tumo?r* OR pyelocarcinoma* OR metastas?s OR oncocytoma):ab,ti,kw	60577
#15	(#13 AND #14)	1811
#16	(metanephric adj2 adeno*):ab,ti,kw	0
#17	(rcc OR mrcc OR "m-rcc"):ab,ti,kw	168
#18	hypernephroma:ab,ti,kw	4
#19	(#12 OR #15 OR #16 OR #17 OR #18)	1829
#20	(#11 AND #19)	334
#21	**(#11 AND #19), from 1980 to 2009 [Cochrane review, clinical trials, Method studies]**	**317**

MEDLINE in-process (2009 only)

Date search run: 2 December 2009

#15	Search ("2009/01/01"[Publication Date] : "3000"[Publication Date]) AND (#10 AND #13)	485
#14	Search #10 AND #13	5015
#13	Search #11 OR #12	200717
#12	Search ((((("Sutent"[Title/Abstract]) OR ("Votrient"[Title/Abstract])) OR ("Afinitor"[Title/Abstract])) OR ("Torisel"[Title/Abstract])) OR ("Nexavar"[Title/Abstract])	105
#11	Search (((((((("Pazopanib"[Title/Abstract]) OR ("Bevacizumab"[Title/Abstract])) OR ("Sunitinib"[Title/Abstract])) OR ("Temsirolimus"[Title/Abstract])) OR ("Interferon"[Title/Abstract])) OR ("interleukin"[Title/Abstract])) OR ("Everolimus"[Title/Abstract])) OR (Avastin)) OR (Sorafenib)	200712
#10	Search #8 OR #9	61128
#9	Search ((((("RCC"[Title/Abstract]) OR ("MRCC"[Title/Abstract])) OR ("M-RCC"[Title/Abstract])) OR ("hypernephroma"[Title/Abstract])) OR ("metanephric adenocarcinoma"[Title/Abstract])	6497
#8	Search #4 AND #7	59700
#7	Search #5 OR #6	1437992
#6	Search "oncocytoma"[Title/Abstract]	1286
#5	Search (((((((("carcinoma"[Title/Abstract]) OR ("cancer"[Title/Abstract])) OR ("neoplasm"[Title/Abstract])) OR ("adenocarcinoma"[Title/Abstract])) OR ("tumour"[Title/Abstract])) OR ("tumour"[Title/Abstract])) OR ("pyelocarcinoma"[Title/Abstract])) OR (metastasis)) OR (metastases)	1437614
#4	Search #1 OR #2 OR #3	512295
#3	Search "nephroid"[Title/Abstract]	11
#2	Search ("grawit"[Title/Abstract]) OR ("hypernephroid"[Title/Abstract])	210
#1	Search ("renal"[Title/Abstract]) OR ("kidney"[Title/Abstract])	512199

Meta-register search

Date search run: 2 December 2009

Search term: (Pazopanib OR Bevacizumab OR Sunitinib OR Temsirolimus OR Interferon OR interleukin OR Everolimus OR Sorafenib OR Avastin OR Sutent OR Nexavar OR Torisel OR Afinitor OR Votrient)

Limit: UKCTG, ISRCTN

Total retrieved: 153

Clinicaltrial.gov search

Date search run: 2 December 2009

Search term:

Search strategy	Search result
Search by Topic: Condition - Kidney Cancer	747
Advance search: Condition - renal cancer AND Interventions - Pazopanib	9
Advance search: Condition - renal cancer AND Interventions - Bevacizumab	53
Advance search: Condition - renal cancer AND Interventions - Sunitinib	93
Advance search: Condition - renal cancer AND Interventions - Temsirolimus	16
Advance search: Condition - renal cancer AND Interventions - Interferon	69
Advance search: Condition - renal cancer AND Interventions - interleukin	65
Advance search: Condition - renal cancer AND Interventions - Everolimus	21
Advance search: Condition - renal cancer AND Interventions - Sorafenib	67
Advance search: Condition - renal cell carcinoma AND Interventions - Pazopanib	9
Advance search: Condition - renal cell carcinoma AND Interventions - Bevacizumab	52
Advance search: Condition - renal cell carcinoma AND Interventions - Sunitinib	91
Advance search: Condition - renal cell carcinoma AND Interventions - Temsirolimus	16
Advance search: Condition - renal cell carcinoma AND Interventions - Interferon	68
Advance search: Condition - renal cell carcinoma AND Interventions - interleukin	65
Advance search: Condition - renal cell carcinoma AND Interventions - Everolimus	20
Advance search: Condition - renal cell carcinoma AND Interventions - Sorafenib	66

Total retrieved: 196 (after removing duplicates and potential exclusions)

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

In addition to the database searches conference searching was also conducted to ensure all relevant literature was included in the review. The following conference proceedings were hand searched from 2007 to 2009:

- American Society of Clinical Oncology (ASCO)
- ASCO-Genitourinary (ASCO-GU)
- European Society for Medical Oncology (ESMO)
- European Conference for Clinical Oncology (ECCO)

Other data sources:

- References lists in clinical trial publications identified via the database search and in systematic reviews and qualitative reviews conducted in this disease area.

In order to provide a complete understanding of the evidence for pazopanib compared with current treatments for advanced/metastatic RCC, additional sources of information

other than those identified by the systematic review were used to supplement data in section 5; unpublished data from clinical study reports (CSRs) held by GlaxoSmithKline were also included. The manufacturers of other technologies were not contacted for unpublished data.

9.2.6 The inclusion and exclusion criteria.

Table 9.2: Eligibility criteria used in search strategy for clinical evidence

	Criteria for clinical effectiveness search	Rationale
Inclusion criteria	**Population** • Age: Adults (≥ 18 years) • Gender: Any • Race: Any • Stage of disease: Locally advanced / Advanced / Metastatic / Stage III / Stage IV • Line of therapy: No prior systemic therapy (treatment-naïve)	• The patient population has been restricted to match that stated in the decision problem for pazopanib in the first-line treatment of advanced and/or metastatic RCC. • Since the current treatments for RCC are only licensed for adult patients, studies including children or adolescents were excluded.
	Interventions • Pazopanib monotherapy (or in combination with best supportive care [BSC]) • Interferon-alpha (IFN-α) monotherapy (or in combination with BSC) • Interleukin-2 (IL-2) monotherapy (or in combination with BSC) • Sunitinib monotherapy (or in combination with BSC) • Sorafenib monotherapy (or in combination with BSC) • Temsirolimus monotherapy (or in combination with BSC) • Bevacizumab in combination with IFN-α (and in combination with BSC)	• The included interventions are those which are either licensed for the first-line treatment of advanced/ metastatic RCC or for which RCT data in this setting exist. • The review was limited to studies of these agents administered as monotherapy (or with the exception of bevacizumab in combination with interferon) as per their licensed indications or as per the anticipated licence in the case of pazopanib.
	Comparator/controls • Any of the included interventions • Placebo • Best supportive care (BSC)*	• These comparators were chosen to enable both direct and indirect comparisons between the interventions of interest.
	Outcomes of interest *Efficacy:* • Overall survival (OS) • Progression-free survival (PFS) • Time to progression (TTP) • Overall response rate (ORR: Complete response [CR] + Partial response [PR]) • Proportion of patients with stable disease (SD) • Time to and duration of response • Health-related quality of life *Safety:* • Incidence and severity of all adverse events (AEs) • Withdrawals due to AEs • Withdrawals due to death • Serious adverse events (SAEs) • Incidence and severity of specific adverse events – see section 3.1.6 in the full Systematic Review report for listing	• These outcomes were chosen since they are frequently measured and reported in trials of RCC, and will enable the study question of the review to be answered.
	Study design • Randomised control trials (RCTs) with any blinding status	• RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of the interventions. Therefore only these studies were included. To enhance the

		amount of evidence, studies with double blind, single blind and open label design were included.
	Language restrictions • English only	• The restriction would not limit results substantially due to widespread data availability in English language.
	Publication timeframe • 1980 onwards for literature searches • Last 3 years for conference searching	• This restriction would not limit results substantially due the vast majority of data for cytokines and targeted therapies being reported from 1980s onwards. • Studies which are presented at conferences are usually published in full within 3 years of presentation.
Exclusion criteria	**Outcome of interest** • Studies should report an outcome of interest.	• Studies not reporting at least one outcome of interest could not feature in any analyses and were therefore excluded.
	No subgroup analysis • No subgroup analysis for disease of interest • No subgroup analysis for advanced/metastatic disease • No subgroup analysis for treatment naïve patients	• Studies not reporting outcome data specifically for the disease, disease stage and line of treatment of interest were excluded, since these studies would introduce heterogeneity into the review.

*BSC definition: no active treatment/observation/a method of care that is not a focused treatment/treatments which clinicians consider to be "placebo-equivalent" including medroxyprogresterone and vinblastine. RCC= renal cell carcinoma , RCT = Randomised control trial

Further detail regarding the inclusion criteria for the intervention and comparator and the rationale for this are provided in Table 9.3.

Table 9.3: Detail regarding the intervention and comparator inclusion criteria

Intervention	Comparator	Included?	Reasoning
Intervention list drug (e.g. Sunitinib)	BSC/Placebo	Yes	Allow us to obtain studies with common comparators which can then be indirectly compared.
Intervention list drug (e.g. Sunitinib)	Other intervention list drug (e.g. Pazopanib)	Yes	This allows direct comparison of interventions.
Intervention list drug (e.g. Sunitinib)	Non-intervention list drug (e.g. Surgery)	No	These studies do not aid in answering the study question, and would not provide useful links in indirect comparisons.
Intervention list drug + Non-intervention list drug (e.g. Sunitinib + Retinoic acid)	Non-intervention list drug (e.g. Surgery)	No	
Intervention list drug dose 1 (e.g. IFN dose 1)	Intervention list drug dose 2 (e.g. IFN dose 2)	No	
Intervention list drug A + intervention list drug B (e.g. Sunitinib + IFN)	Intervention list drug C (e.g. Pazopanib)	No	
Intervention list drug A + intervention list drug B (e.g. Sunitinib + IFN)	Intervention list drug A (e.g. Sunitinib)	No	
Intervention list drug A + non-intervention list drug (e.g. IFN + retinoic acid)	Intervention list drug B (e.g. IL-2)	No	
Intervention list drug A + non-intervention list drug (e.g. IFN + Retinoic acid)	Intervention list drug A (e.g. IFN)	No	

9.2.7 **The data abstraction strategy.**

Bibliographic details and abstracts of all citations detected by the literature search were downloaded into the Heron Systematic Review Database (SRDB), a bespoke, structured query language (SQL)-based internet database.

First pass of citations
Citations were first screened based on the abstract supplied with each citation. Each citation was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this 'first pass'; where unclear, citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded in the first pass. Full-text copies of all references that could potentially meet the eligibility criteria were also ordered at this stage.

Second pass of citations
The eligibility criteria were applied to the full-text citations. Each full-text was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Data presented in the studies still included after this stage were extracted to data extraction grids.

Extraction strategy
The final extraction grid is provided in Appendix C of the Systematic Review report. Data from trials were extracted in parallel by two independent reviewers, with reconciliation of any differences by a third independent reviewer. All reviewers were qualified with either a Masters degree in pharmacy or an equivalent related discipline, and furthermore were fully trained in conducting systematic reviews with a minimum of 1.5 to 2 years of full-time experience of systematic review work within a health economics and outcomes research organisation.

Where more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction table to avoid double counting of patients. Each publication was referenced in the table to recognize that more than one publication may have contributed to the entry.

Studies excluded during data each stage, along with rationale for exclusion are provided in a separate MS Excel document (Clinical Excluded Studies) – available on request.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 **A suggested format for the quality assessment of RCT(s) is shown below.**

Studies were assessed qualitatively and by means of a study grade and Jadad score. In addition, a qualitative assessment was conducted, using the assessment criteria as recommended by NICE. A summary of qualitative assessment of all 13 studies identified by the Systematic Review is provided in Table 9.4. The complete quality assessment for each study is provided in Table 9.5.

Methods used to generate random allocation sequence were reported in only three of the included studies and were judged as adequate; this included the AVOREN trial, CRECY trial and the VEG105192 pazopanib trial. Only five studies reported the method used for concealment of allocation sequence. All of included studies reported comparable patient

populations across interventions in the study in terms of demographic and disease characteristics at baseline. Evidence of selective reporting could not be determined for the majority of studies because of a lack of published protocol. Four studies had no evidence of selective reporting. However, since one or both OS and PFS were often measured and reported in each study this may not be an area of concern. All except one included study reported ITT analysis; however the method used to account for missing data was poorly reported. None of the studies were identified as being at a high risk of bias, so the validity of the results is not affected in each individual study. All studies were therefore included in the analyses of the review, where data availability permitted.

Table 9.4: Quality assessment results for RCTs

Study	Random-isation	Concealment grade	Baseline compar-ability	Blinding	Follow-up	Selective reporting	Analysis
Pazopanib							
VEG105192	Yes	Yes	Yes	Yes	No	No	Yes
Sunitinib							
Motzer 2009	Not clear	Not clear	Yes	Yes	No	Not clear	Yes
Sorafenib							
Escudier 2009	Not clear	Not clear	Yes	No	No	No	Yes
TARGET Study	Not clear	Not clear	Yes	Yes	No	Not clear	Yes
Bevacizumab							
AVOREN trial	Yes	Yes	Yes	Yes	Yes	Not clear	Yes
CALGB 90206	Not clear	Not clear	Yes	No	No	Not clear	Yes
Temsirolimus							
Global ARCC trial	Not clear	Not clear	Yes	No	No	No	Yes
IFN, IL-2							
Negrier 2007	Not clear	Yes	Yes	No	Not clear	No	Yes
CRECY Trial	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes
MRC RE01	Not clear	Yes	Yes	Not clear	Not clear	Not clear	Yes
Steineck 1990	Not clear	Not clear	Yes	Yes	No	Not clear	Yes
Pyrhonen 1999	Not clear	Not clear	Yes	Not clear	No	Not clear	Yes
Kriegmair 1995	Not clear	Not clear	Yes	Not clear	Yes	Not clear	No

Randomisation; Was randomisation carried out appropriately? **Concealment grade;** Was the concealment of treatment allocation adequate? **Baseline comparability;** Were the groups similar at outset in terms of prognostic factors, for example, severity of disease? **Blinding;** Were the care providers, participants and outcome assessors blind to treatment allocation? **Follow-up;** Were there any unexpected imbalances in drop-outs between groups? **Selective reporting;** Is there any evidence to suggest that the authors measured more outcomes than they reported? **Analysis;** Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Figure 1: Risk of bias plot

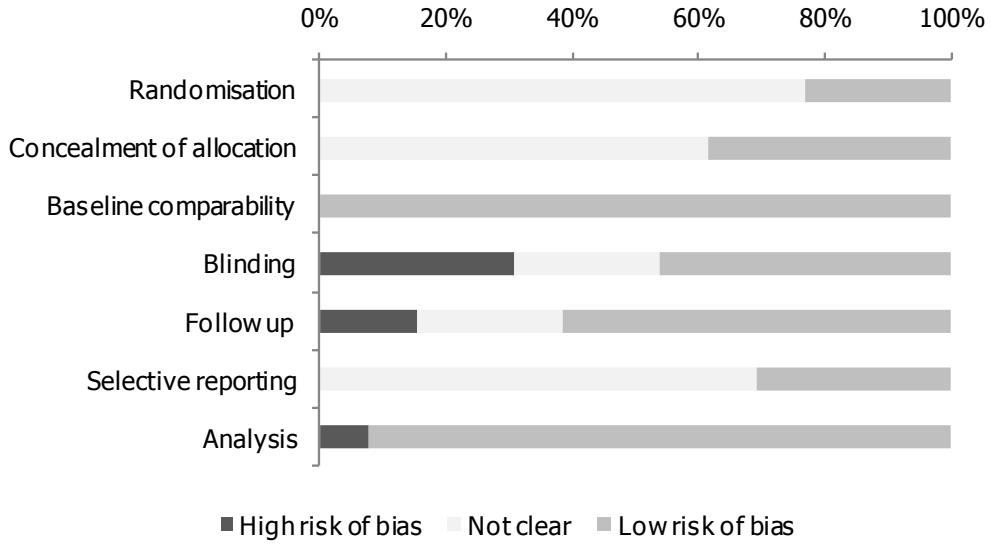


Table 9.5: Quality assessment of clinical studies identified in the systematic review

Study name	Jadad score	Allocation grade	Randomisation	Baseline characteristics	Blinding	Withdrawal	Outcome selection and reporting	Statistical analysis
VEG105192	5	A	Yes. Patients were centrally randomly assigned in a 2:1 ratio to pazopanib or placebo. Eligible patients were stratified on the basis of baseline ECOG PS (0 vs. 1), prior nephrectomy (yes vs. no), and prior systemic therapy for advanced RCC (cytokine-pretreated vs.treatment naïve) and were randomised by GSK Biomedical Data Sciences Department using GSK interactive voice response system (IVRS) called RAMOS (Registration And Medication Ordering System).	Yes. Baseline comparability was achieved between the two groups in terms of age, gender, race, histology, disease duration, organs involved, ECOG performance status and MSKCC risk category.	Yes. Adequate blinding was achieved by using matching placebo tablets. Additionally, disease assessments were conducted by independent reviewers who were also blinded to treatment assignment.	No. Reasons for withdrawal of patients were reported adequately. Patients mainly withdrew due to the following reasons: disease progression; death; AEAEs; lost to follow-up; protocol violation; patient or investigator's decision; or other reasons.	No. The authors reported all the outcomes as specified in the protocol of the study.	Yes. An ITT analysis was used for efficacy evaluation and appropriate methods were used to account for missing data.
Motzer 2009	2	B	Not Clear. Patients were randomised using permuted block design. The method of allocation concealment was not reported in the study.	Yes. The two treatment groups were similar in terms of their performance status, prior chemotherapy and histology.	Yes. An independent central review committee evaluating the radiographs was blinded to the treatment allocation. Blinding status of investigators was unclear.	No. There were no unexpected imbalances in the drop-outs between the groups. Withdrawals and reasons for all cause withdrawals were reported in the study.	Not clear.	Yes. The primary end point was analysed in all patients assigned to a study group, according to the intention-to-treat principle. Safety analyses were performed on the basis of the treatment actually received. Method of handling missing data was not reported in the study.
Escudier 2009	2	B	Not clear. Patients were randomly assigned (1:1) to sorafenib or interferon and were stratified by MSKCC classification and region.	Yes. Baseline characteristics were similar between groups in terms of histology, performance and prognostic factors.	No. This was an open-label study. However, data from independent blinded radiologic review were the primary data for determination of radiologic progression of period I.	No. Treatment discontinuations due to AEs and death were reported for both the arms.	No. The authors measured all the outcomes that were reported.	Yes. For efficacy analysis, ITT population was used. Safety population was mITT. Appropriate statistical methods were used in the study.

Study name	Jadad score	Allocation grade	Randomisation	Baseline characteristics	Blinding	Withdrawal	Outcome selection and reporting	Statistical analysis
Target Study	3	B	Not clear. Patients were stratified according to country and MSKCC prognostic score and randomly assigned to study groups in a 1:1 ratio with a block size of four.	Yes. Baseline characteristics were comparable between study groups in terms of age, weight, ECOG score etc.	Yes. This was a triple-blind study. Investigators and independent radiologists who were unaware of the study-group assignments assessed study outcomes.	No. The reasons for withdrawals were reported in the study.	Not clear	Yes. ITT and mITT approaches were used to analyse efficacy and safety data, respectively. Details of handling missing data were not reported.
AVOREN trial	4	A	Yes. Randomisation was done centrally with a block design procedure and stratified according to country and MSKCC risk group. Patient randomisation list was kept in secure location and was not available to any person directly involved in the study other than the interactive voice recognition system provider and the randomisation manager at Roche.	Yes. Authors reported that the arms were balanced with regard to baseline disease and demographic characteristics.	Yes. This was a double blind study. The method of blinding was unclear.	Yes. Reasons for withdrawals and all cause withdrawals were reported in the study.	Not clear	Yes. Primary efficacy analysis was done by intention-to treat approach. For secondary efficacy analysis patients with measurable disease at baseline were included. All patients who were randomised and exposed to study medication were included in the safety analysis. For safety analysis, patients were assigned to treatment groups on the basis of what they actually received, with patients in the placebo arm receiving one or more doses of bevacizumab being assigned to the bevacizumab arm.
CALGB 90206	2	B	Not clear. Patients were randomised according to stratified random block design. Patients were stratified by nephrectomy status and number of adverse prognostic factors. The method of allocation concealment was not reported in the study.	Yes. The two treatment groups were similar in terms of their performance status, prior chemotherapy and histology.	No. This was an open label trial.	No. There were no unexpected imbalances in the drop-outs between the groups.	Unclear. It was unclear whether the authors measured more outcomes than they reported.	Yes. Patients who discontinued treatment for reasons other than progression were observed for disease progression or death. An intention-to-treat approach was used in the analysis.
Global ARCC trial	2	B	Not Clear. Patients were randomly assigned in equal proportions, with the	Yes; The three treatment groups were well balanced on the basis of age, sex, and	No. This was an open-label trial.	No; Reasons for treatment discontinuation included disease	No; the authors reported measured outcomes only.	Yes; The primary end point was calculated on an intention-to-treat basis. An appropriate

Study name	Jadad score	Allocation grade	Randomisation	Baseline characteristics	Blinding	Withdrawal	Outcome selection and reporting	Statistical analysis
			use of permuted blocks of three, to one of three treatment groups. Method of concealment of allocation was not reported in the study.	performance-status score.		progression, AEs, symptomatic deterioration, death, patient request, other and protocol violation. A total of 19 patients were lost to follow-up.		statistical analysis was used. Details regarding handling of missing data were not reported.
Negrier 2007	1	A	Not clear. Randomization was stratified by participating centre by using a block method with a block size of 4, and it was performed centrally through a specific website.	Yes. Author has reported that only few significant differences were detected between comparison groups. More non-IFN-treated than IFN-treated patients had abdominal lymph nodes (31.2% vs. 21.8%; P = .02), and less non-IFN-treated than IFN-treated patients had elevated serum lactate dehydrogenase (LDH) levels (16.2% vs. 25.1%; P = .03). Among non-IL-2-treated patients, 73.1% had normal hemoglobin levels versus 63.8% among patients receiving IL-2 (P = .03). Comparison groups were overall considered well balanced.	No. Treatments were administered unblinded.	Not clear. Details regarding withdrawals were not reported.	No. Four additional per-protocol analyses were performed: 1) after exclusion of the 18 patients with major protocol deviation, 2) after exclusion of the 58 patients crossed over to another treatment, 3) on the 386 patients with proven clear cell renal cancer, or 4) on the 270 patients not receiving second-line treatment. All yielded results similar to those of the first analysis.	Yes. Efficacy analysis was done on ITT basis. Method of handling missing data was not reported in the study.
CRECY Trial	2	A	Yes. Randomisation was performed centrally by an interactive computerised procedure at the study data-monitoring centre. Randomisation was stratified according to centre.	Yes. Authors stated that there were no significant differences in patient characteristics among three treatment groups.	Yes. Blinded external committee reviewed treatment response.	Not clear. Number of patients and reasons for withdrawal were not reported.	Not clear	Yes. An ITT analyses was performed. Method of handling of missing data was not reported.
MRC RE01	1	A	Not clear. A minimisation method was used and patients were stratified by centre, nephrectomy	Yes. Authors stated that characteristics of patients were similar in both treatment groups.	Not clear. It was unclear whether study was blinded or not.	Not clear. The details regarding withdrawal were not reported in the study. Protocol deviations were	Not clear	Yes. An ITT analyses was performed for primary efficacy outcome. Method of handling of missing

Study name	Jadad score	Allocation grade	Randomisation	Baseline characteristics	Blinding	Withdrawal	Outcome selection and reporting	Statistical analysis
			and by whether there were single or multiple metastases. Concealment of allocation was adequate. Randomisation was by telephone call to the MRC Cancer Trials Office.			reported by the author.		data was not reported.
Steineck 1990	1	B	Not clear. Method of randomisation and allocation concealment was not reported in the study.	Yes. Baseline characteristics seem to be comparable in terms of age, gender and other demographic characteristics.	Yes. The outcome assessor (radiologist) was blinded to the treatment. Blinding status of patients and investigators was unclear.	No. Withdrawals and reasons for all cause withdrawals were not reported in the study.	Unclear. It was unclear whether the authors measured more outcomes than they reported.	Yes. An ITT analysis for efficacy and safety was carried out. For more strict evaluation of efficacy nine patients were excluded from the analysis. The exclusion of these patients did not change the proportion of responding patients.
Kriegmair 1995	1	B	Not clear. Patients were randomised in blocks of five to each treatment group. Method of concealment of allocation was unclear.	Yes. Baseline comparability was achieved between the two groups in terms of age, gender, performance status and distribution of the tumour lesions.	Not clear. Blinding of patients, investigators, statistician or outcome assessor was not reported.	Yes. There were unexpected imbalances in the drop-outs between the groups. Three patients in IFN plus vinblastine group and 10 patients in medroxyprogestrone group withdrew the informed consent.	Not clear. It is unclear whether authors measured more outcomes than they reported.	No. A PP analysis was used for efficacy and safety evaluations. Method for handling missing data was not reported.
Pyrhonen 1999	2	B	Not clear. The method of randomisation and allocation concealment was not reported.	Yes. The treatment groups were well balanced for all measured baseline demographic and disease characteristics.	Not clear. Films of patients with objective response were reviewed by a single central radiologist and the principal investigators from the two centres not treating the patient.	No. In this study, no patients were lost to follow-up at the time of this report, and follow-up of all surviving patients is continuing. The reasons for withdrawals were reported adequately.	Not clear	Yes. Data was analysed using an ITT analyses.

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

Relevant data/studies for use in the indirect comparison were identified as set out in section 9.2 for the identification of relevant RCT clinical evidence.

9.4.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter).**

The databases used to identify studies for use in the indirect comparison are the same as those detailed in section 9.2.1.

9.4.2 **The date on which the search was conducted.**

See section 9.2.2.

9.4.3 **The date span of the search.**

See section 9.2.3.

9.4.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).**

See section 9.2.4.

9.4.5 **Details of any additional searches (for example, searches of company databases [include a description of each database]).**

See section 9.2.5.

9.4.6 **The inclusion and exclusion criteria.**

See section 9.2.5.

9.4.7 **The data abstraction strategy.**

See section 9.2.7.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

Quality assessment for the seven studies used in the indirect comparison (VEG105192; Motzer 2009; MRC RE-01; Negrier 2007; Pyrhonen 1999; Steineck 1990; Kriegmair 1995) can be found in section 9.3 (Appendix 3).

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The systematic review set out only to identify randomised controlled trials (RCTs). Two non-RCTs of pazopanib are considered in section 5.8 of the main submission as supportive evidence. A phase II pazopanib study (VEG102616) was identified during the systematic review process but was excluded from the final list of included studies on the basis that its original randomised discontinuation design was amended to a single-arm open-label design following an interim analysis. The other non-RCT is VEG107769, the unblinded extension study to VEG105192 enrolling subjects on open-label pazopanib who progressed on placebo in the pivotal study. These are both GSK-sponsored studies and therefore the respective Clinical Study Reports formed the main data source.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.7.1 **Please tabulate the quality assessment of each of the non-RCTs identified.**

Quality assessment for the two non-RCTs considered in this submission is tabulated in section 5.8.1.6 of the main submission.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

Relevant data on adverse events was identified as set out in section 9.2 for the identification of relevant RCT clinical evidence.

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

9.9.1 **Please tabulate the quality assessment of each of the non-RCTs identified.**

Quality assessment for the RCTs and non-RCTs from which the adverse event data presented in this submission have been taken is presented in section 9.3 (Appendix 3) and in section 5.8.1.6, respectively.

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided:

9.10.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter).**

A comprehensive search strategy was designed to retrieve relevant economic data from published literature; details of the search strategy can be seen in 9.10.4.

Table 9.6: Databases examined for the economic systematic review and the service provider used

Data source	Service Provider
MEDLINE	Embase.com; http://www.embase.com/
EMBASE	
Cochrane Economic Evaluations Database/ NHS Economic Evaluation Database	Cochrane library; http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html
Cochrane Technology Assessments Database	
Database of Abstracts of Reviews of Effects (DARE)	

DARE = Database of Abstracts of Reviews of Effects, NHS = National Health Service

9.10.2 **The date on which the search was conducted.**

The electronic database search was conducted on 23 November 2009.

9.10.3 **The date span of the search.**

The databases were searched from 1980 onwards.

9.10.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).**

The search strategy for the identification of economic evidence was as follows:

MEDLINE and EMBASE

Date search run: 23 November 2009

#	Search History	Results
1.	'economics'/de	174965
2.	'economic aspect'/de	92015
3.	'cost'/de	45254
4.	'health care cost'/de	86127
5.	'drug cost'/de	41407
6.	'hospital cost'/de	9530
7.	'socioeconomics'/de	84286
8.	'health economics'/de	29146
9.	'pharmacoeconomics'/de	1708
10.	'fee'/exp	28062
11.	'budget'/exp	13917
12.	'economic evaluation'/exp	147273
13.	'hospital finance'/de OR 'financial management'/de	87263
14.	'health care financing'/de	9708
15.	'low cost'	15803
16.	'high cost'	5526
17.	health*care NEXT/1 cost* OR 'health care' NEXT/1 cost*	146263
18.	fiscal OR funding OR financial OR finance	264093
19.	cost NEXT/1 estimate*	1248
20.	'cost variable'	32
21.	unit NEXT/1 cost*	1228
22.	economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti	144464
23.	(cost* NEAR/3 (treat* OR therap*)):ab,ti	19388
24.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	769525
25.	'pazopanib'/de OR 'sunitinib'/de OR 'sorafenib'/de OR 'bevacizumab'/de OR 'temsirolimus'/de OR 'everolimus'/de OR 'interleukin 2'/de OR 'alpha interferon'/de	94250
26.	'alpha-interferon':ab,ti OR alfaferone:ab,ti OR alferon:ab,ti OR 'alpha ferone':ab,ti OR cilferon:ab,ti OR ginterferon:ab,ti OR 'interferon-alpha':ab,ti OR introma:ab,ti OR kemron:ab,ti OR leukinferon:ab,ti OR leukinferron:ab,ti OR 'leukocyte interferon':ab,ti OR 'refecon a':ab,ti OR 'referon a3':ab,ti OR sumiferon:ab,ti OR sumipheron:ab,ti OR veldona:ab,ti	10766
27.	'biotest':ab,ti OR bioleukin:ab,ti OR 'interleukin-ii':ab,ti OR 'interleukin-2':ab,ti OR 'il-2':ab,ti OR il2:ab,ti OR 'ro-236019':ab,ti OR tcgf:ab,ti OR tsf:ab,ti	56840
28.	everolimus:ab,ti OR afinitor:ab,ti OR certican:ab,ti OR 'nvp-rad-001':ab,ti OR 'rad-001':ab,ti OR 'rad 001a':ab,ti OR rad001:ab,ti OR rad001a:ab,ti OR 'sdz rad':ab,ti	853
29.	temsirolimus:ab,ti OR 'cci-779':ab,ti OR 'cell-cycle-inhibitor-779':ab,ti OR 'nsc 683864':ab,ti OR nsc683864:ab,ti OR torisel:ab,ti	402

#	Search History	Results
30.	bevacizumab:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti OR 'anti-vegf':ab,ti OR 'rhumab-vegf':ab,ti	4100
31.	'bay 43-9006':ab,ti OR 'bay 439006':ab,ti OR 'bay43-9006':ab,ti OR bay439006:ab,ti OR nexavar:ab,ti OR sorafenib:ab,ti	996
32.	sunitinib:ab,ti OR sutent:ab,ti OR 'pha 2909040ad':ab,ti OR 'pha2909040ad':ab,ti OR 'su 010398':ab,ti OR 'su 011248':ab,ti OR 'su 10398':ab,ti OR su10398:ab,ti OR 'su 11248':ab,ti OR su010398:ab,ti OR 'su011248':ab,ti OR su11248:ab,ti	960
33.	armala:ab,ti OR pazopanib:ab,ti OR gw786034*:ab,ti OR (gw NEXT/1 786034*):ab,ti OR (sb NEXT/1 710468*):ab,ti OR sb710468*:ab,ti	39
34.	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	121986
35.	'kidney carcinoma'/de	27437
36.	'kidney tumour'/exp	64633
37.	renal*:ab,ti OR kidney*:ab,ti OR grawit*:ab,ti OR hypernephroid*:ab,ti OR nephroid*:ab,ti	602660
38.	carcinoma*:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR adeno*:ab,ti OR tumo?r*:ab,ti OR pyelocarcinoma*:ab,ti OR metastas?s:ab,ti OR oncocytoma:ab,ti	1586263
39.	#37 AND #38	68847
40.	(metanephric NEAR/2 adeno*):ab,ti	136
41.	rcc:ab,ti OR mrcc:ab,ti OR 'm-rcc':ab,ti	5722
42.	'hypernephroma':ab,ti	1196
43.	#35 OR #36 OR #39 OR #40 OR #41 OR #42	100246
44.	#24 AND #34 AND #43	192
45.	**#24 AND #34 AND #43 AND [1980-2010]/py**	**192**

A.1.1 Cochrane

Date search run: 23 November 2009

ID	Search History	Results
#1	MeSH descriptor Interferon-alpha explode all trees	2099
#2	MeSH descriptor Interleukin-2 explode all trees	702
#3	(“alpha-interferon” OR alfaferone OR alferon OR “alpha ferone” OR cilferon OR ginterferon OR “interferon-alpha” OR introma OR kemron OR leukinferon OR leukinferron OR “leukocyte interferon” OR “refecon a” OR “referon a3” OR sumiferon OR sumipheron OR veldona):ab,ti,kw	3001
#4	(biotest OR bioleukin OR “interleukin-ii” OR “interleukin-2” OR “il-2” OR il2 OR “ro-236019” OR tcgf OR tsf):ab,ti,kw	1902
#5	(everolimus OR afinitor OR certican OR “nvp-rad-001” OR “rad-001” OR “rad 001a” OR rad001 OR rad001a OR “sdz rad”):ab,ti,kw	154
#6	(temsirolimus OR "cci-779" OR "cell-cycle-inhibitor-779" OR "nsc 683864" OR nsc683864 OR torisel):ab,ti,kw	25
#7	(bevacizumab OR avastin OR “nsc 704865” OR nsc704865 OR “anti-vegf” OR “rhumab-vegf”):ab,ti,kw	236
#8	(“bay 43-9006” OR “bay 439006” OR “bay43-9006” OR bay439006 OR nexavar OR sorafenib):ab,ti,kw	63
#9	(sunitinib OR sutent OR “pha 2909040ad” OR pha2909040ad OR “su 010398” OR “su	37

ID	Search History	Results
	011248" OR "su 10398" OR su10398 OR "su 11248" OR su010398 OR su011248 OR su11248):ab,ti,kw	
#10	(armala OR pazopanib OR gw786034* OR sb710468* OR votrient):ab,ti,kw	2
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)	5875
#12	MeSH descriptor Carcinoma, Renal Cell explode all trees	301
#13	(renal* OR kidney* OR grawit* OR hypernephroid* OR nephroid*):ab,ti,kw	24198
#14	(carcinoma* OR cancer* OR neoplasm* OR adeno* OR tumo?r* OR pyelocarcinoma* OR metastas?s OR oncocytoma):ab,ti,kw	60577
#15	(#13 AND #14)	1811
#16	(metanephric adj2 adeno*):ab,ti,kw	0
#17	(rcc OR mrcc OR "m-rcc"):ab,ti,kw	168
#18	hypernephroma:ab,ti,kw	4
#19	(#12 OR #15 OR #16 OR #17 OR #18)	1829
#20	(#11 AND #19)	334
#21	**(#14 AND #22), from 1980 to 2009 [Technology assessments, Economic evaluations]**	**14**

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

In addition to the search of literature databases, supplementary searches of published health technology appraisals were conducted for the following authorities:

- NICE
- SMC
- CADTH
- PBAC
- AWMSG

9.10.6 The inclusion and exclusion criteria.

To be included in the economic review, trials were required to meet the eligibility criteria in Table 9.7.

Table 1.7: Eligibility criteria used in search strategy for economic evidence

	Clinical effectiveness	Rationale
Inclusion criteria	**Population** • Age: Adults (≥ 18 years) • Gender: Any • Race: Any • Stage of disease: Advanced and Metastatic (stage III/IV) • Line of therapy: Treatment naïve	• The patient population has been restricted to match that stated in the decision problem for pazopanib in the first-line treatment of advanced/metastatic RCC. • Since the current treatments for RCC are licensed for adult patients, studies including children or adolescents were excluded.
	Interventions • Pazopanib monotherapy (or in combination with BSC) • IFN-α monotherapy (or in combination with BSC) • IL-2 monotherapy (or in combination with BSC) • Sunitinib monotherapy (or in combination with BSC) • Sorafenib monotherapy (or in combination with BSC) • Temsirolimus monotherapy (or in combination with BSC) • Bevacizumab in combination with IFN-α (and in combination with BSC)	• The included interventions are those which are either licensed for the first-line treatment of advanced/metastatic RCC or for which RCT data in this setting exist. • The review was limited to studies of these agents administered as monotherapy (or with the exception of bevacizumab in combination with IFN) as per their licensed indications or as per the anticipated license in the case of pazopanib.
	Comparator • Any of the included interventions • Placebo • Best supportive care*	• These comparators were chosen to enable both direct and indirect comparisons between the interventions of interest.
	Study design • Economic evaluations, including cost analyses, cost minimization analyses, cost-effectiveness analyses, cost utility analyses, utility studies.	• All economic evaluations should be considered.
	Language restrictions • English only	• The restriction would not limit results substantially due to data availability in English language.
	Publication timeframe • 1980 onwards for literature searches	• The restriction of date would not limit results substantially.
	Outcome of interest • Studies should report an outcome of interest. Outcomes of interest are: o Effectiveness and utilities o Resources o Costs o ICERs/ICs	• Studies which do not report outcomes of interest would not feature in any analyses or answer the review questions and were therefore were excluded.
Exclusion criteria	**No subgroup analysis** • No subgroup analysis for disease of interest • No subgroup analysis for advanced/metastatic disease • No subgroup analysis for treatment naïve patients	• Studies with no subgroup data for the disease, disease stage and line of treatment were not included, since these studies would introduce heterogeneity into the review.

*BSC definition: no active treatment/observation/a method of care that is not a focused treatment/treatments which clinicians consider to be "placebo-equivalent" including medroxyprogresterone and vinblastine. RCC = renal cell carcinoma

9.10.7 The database abstraction strategy.

Bibliographic details and abstracts of all citations detected by the literature search were downloaded into the Heron Systematic Review Database (SRDB), a bespoke, structured query language (SQL)-based internet database.

First pass of citations

Citations were first screened based on the abstract supplied with each citation. Each citation was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this 'first pass'; where unclear, citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded in the first pass. Full-text copies of all references that could potentially meet the eligibility criteria were also ordered at this stage.

Second pass of citations
The eligibility criteria were applied to the full-text citations. Each full-text was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Data presented in the studies still included after this stage were extracted to data extraction grids.

Extraction strategy
The final extraction grid is provided in Appendix C of the Systematic Review report. Data from trials were extracted in parallel by two independent reviewers, with reconciliation of any differences by a third independent reviewer. All reviewers were qualified with either a Masters degree in pharmacy or an equivalent related discipline, and furthermore were fully trained in conducting systematic reviews with a minimum of 1.5 to 2 years of full-time experience of systematic review work within a health economics and outcomes research organisation.

Where more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction table to avoid double counting of patients. Each publication was referenced in the table to recognize that more than one publication may have contributed to the entry. Studies excluded during data each stage, along with rationale for exclusion are provided in a separate MS Excel document (Economic Excluded Studies).

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

The two studies (Mickisch 2009 and Remak 2008) that met the inclusion criteria for the economic review were assessed qualitatively using the Drummond and Philip's checklist (Drummond 1996; Philips 2004) (Tables 9.8 and 9.9). In the study Mickisch 2009, Costs and consequences were measured accurately and in appropriate physical units and the study examined both costs and effects of the treatments. The incremental cost analysis was not done in the study. All possible alternatives were explored through sensitivity analysis in this study. Remak et al., performed cost-effectiveness and cost-utility analysis and made conclusions on the basis of ICER and ICUR. The Markov model used in the study was well defined and sensitivity analyses of model parameters were performed.

Table 9.8: Quality assessment of Mickisch 2009 study

Study:	**Mickisch 2009**	
Critical appraisal – Drummond Checklist		
	Y/N/U	**Commentary**
1. Was a well-defined question posed in answerable form?		
1.1. Did the study examine both costs and effects of the service(s) or programme(s)?	Y	The study examined both costs and effects of the treatments.
1.2. Did the study involve a comparison of alternatives?	Y	The study compared sunitinib with combination of bevacizumab and IFN-alfa.
1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Y	The viewpoint of the study was clearly stated.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?		

2.1. Were there any important alternatives omitted?	Y	There are many alternatives used in the treatment of disease in question. Only two of those were included in this analysis.
2.2. Was (should) a do-nothing alternative be considered?	N	Ethically, do-nothing alternative should not be used in cancer trials.
3. Was the effectiveness of the programme or services established?		
3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	N	The data was obtained from clinical trials.
3.2. Was effectiveness established through an overview of clinical studies?	Y	The data was obtained from clinical trials.
3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	N	Observational data was not used to establish the effectiveness of the study.
4. Were all the important and relevant costs and consequences for each alternative identified?		
4.1. Was the range wide enough for the research question at hand?	N	Only the management cost for AE were considered
4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)	N	Provider's viewpoint was considered
4.3. Were the capital costs, as well as operating costs, included?	N	Only the management cost for AE were considered
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?		
5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	N	Costs and consequences were measured accurately and in appropriate physical units.
5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	N	No such circumstances were discussed.
6. Were the cost and consequences valued credibly?		
6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements)	Y	All important sources were clearly identified.
6.2. Were market values employed for changes involving resources gained or depleted?	N	Not reported
6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?	N	Not reported
6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?	Y	The type of costs analysis was appropriate to answer the study question.
7. Were costs and consequences adjusted for differential timing?		
7.1. Were costs and consequences that occur in the future 'discounted' to their present values?	N	Not reported
7.2. Was there any justification given for the discount rate used?	N	Not reported
8. Was an incremental analysis of costs and consequences of alternatives performed?		
8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?	N	This was a simple costs analysis study. Incremental costs analysis was not done.
9. Was allowance made for uncertainty in the estimates of costs and consequences?		
9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?	Y	Appropriate statistical analyses were performed.
9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?	N	Details of sensitivity analyses were not reported.

9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?	N	The study results were not sensitive to changes in various parameters. It proved that analytic model was robust.
10. Did the presentation and discussion of study results include all issues of concern to users?		
10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	N	It was a cost study.
10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	N	Authors compared the results with those of others who investigated the same question.
10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups?	N	Generalisability of the results was not discussed.
10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?	N	Not reported
10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	N	No such discussion was reported.

Critical appraisal - Philips et al 2006

Section		Y/N/U	Commentary
Method of analysis	Is the pre-evaluation data analysis methodology based on justifiable statistical and epidemiological techniques?	N	Not reported
	Has the evidence regarding the model structure been described? Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	N	Ns such evidence was described in the study.
	Are the sources of data used to develop the structure of the model specified?	Y	All sources of data were specified.
	Are the causal relationships described by the model structure justified appropriately?	N	It was justified.
	Are the structural assumptions transparent and justified?	N	Structural assumptions were transparent.
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the evaluation?	N	Structural assumptions were reasonable given the objective and perspective.
	Do the disease states or the care pathways reflect the underlying biological process of the disease in question and the impact of interventions?	N	Not reported
	Is the cycle length defined and justified in terms of the natural history of disease?	N	Not reported
	Are transition probabilities calculated appropriately?	N	Not reported
	Has a half cycle correction been applied to both cost and outcome? If not, has this omission been justified?	N	Not reported
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	N	No such assumptions were reported.
Sensitivity analysis	Have alternative extrapolation assumptions been explored through sensitivity analysis?	Y	All possible alternatives were explored through sensitivity analysis.
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	N	Not reported

	Have the four principal types of uncertainty been addressed (methodological, structural, heterogeneity, parameters)? If not, has the omission of particular forms of uncertainty been justified?	N	Detail of methodology of sensitivity analysis was not reported.
	Have methodological uncertainties been addressed by running alternative versions of the evaluation with different methodological assumptions?	Y	Modification of basic clinical and economic assumptions (hospitalisation costs and the main cost-driving AEs) showed that the model remained stable over the entire range of plausible values for a given parameter
Author conclusions	Is there evidence that the mathematical logic of the evaluation has been tested thoroughly before use?	N	No such evidence was reported.
	If the evaluation has been calibrated against independent data, have any differences been explained and justified?	N	It was not reported.

Table 9.9: Quality assessment of Remak 2008 study

Study:	**Remak 2008**	
Critical appraisal – Drummond Checklist		
	Y/N/U	**Commentary**
1. Was a well-defined question posed in answerable form?		
1.1. Did the study examine both costs and effects of the service(s) or programme(s)?	Y	The study examined both costs and effects of treatments.
1.2. Did the study involve a comparison of alternatives?	Y	The study compared sunitinib with IL-2 and IFN.
1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Y	View point of analysis was clearly identified as US societal perspective.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?		
2.1. Were there any important alternatives omitted?	N	It seems that important alternatives were used for comparison.
2.2. Was (should) a do-nothing alternative be considered?	U	Comparison with observation or best supportive care could have been performed.
3. Was the effectiveness of the programme or services established?		
3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	U	Effectiveness of intervention was established through randomised controlled trial which may not adequately reflect routine clinical practice.
3.2. Was effectiveness established through an overview of clinical studies?	N	Data were derived from an RCT.
3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	N	Data were derived from an RCT.
4. Were all the important and relevant costs and consequences for each alternative identified?		
4.1. Was the range wide enough for the research question at hand?	N	The study adopted societal perspective however indirect cost were not included.
4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)	N	A narrow perspective was used and only direct medical costs were included. Burden of disease on family and care givers and indirect cost to society could be considered.
4.3. Were the capital costs, as well as operating costs, included?	U	Intervention is unlikely to introduce capital expenditure.
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?		

5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	N	All identified items were measured and included in analysis.
5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	U	Authors do not discuss about any circumstances which made measurement difficult.
6. Were the cost and consequences valued credibly?		
6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements)	Y	Sources of all values were clearly reported.
6.2. Were market values employed for changes involving resources gained or depleted?	Y	Market values were used for resource use and their source was clearly reported.
6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?	U	Authors do not report any circumstances were market values were absent.
6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?	Y	Cost-effectiveness and cost-utility analysis was performed.
7. Were costs and consequences adjusted for differential timing?		
7.1. Were costs and consequences that occur in the future 'discounted' to their present values?	Y	All costs and outcomes were discounted at 5% annually.
7.2. Was there any justification given for the discount rate used?	N	No justification provided for the discount rate used.
8. Was an incremental analysis of costs and consequences of alternatives performed?		
8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?	Y	Incremental costs were reported.
9. Was allowance made for uncertainty in the estimates of costs and consequences?		
9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?	Y	Statistical analyses performed were appropriate.
9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?	Y	Authors stated that one-way deterministic sensitivity analysis was conducted using extreme values (reference case estimate ± 20%).
9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?	Y	Deterministic sensitivity analyses showed the results to be sensitive to the utility values during treatment, costs of Sunitinib and cost of BSC.
10. Did the presentation and discussion of study results include all issues of concern to users?		
10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	Y	Conclusion of analysis was based on ICER and ICUR.
10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	N	Authors do not discuss the results in comparison with other studies.
10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups?	Y	Authors acknowledge that the use of clinical trial data is the major study limitation as it may not adequately reflect routine clinical practice.
10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?	N	Not discussed in detail however authors discussed about threshold limit for acceptance of cost effectiveness.
10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	N	The issue was not discussed.
Critical appraisal - Philips et al 2006		

Section		Y/N/U	Commentary
Method of analysis	Is the pre-evaluation data analysis methodology based on justifiable statistical and epidemiological techniques?	Y	Data analysis methodology is justifiable.
	Has the evidence regarding the model structure been described? Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	The structure of model was well defined.
	Are the sources of data used to develop the structure of the model specified?	Y	Data sources are well reported.
	Are the causal relationships described by the model structure justified appropriately?	Y	Casual relationship described by the model structure was justified.
	Are the structural assumptions transparent and justified?	Y	Model assumptions were clearly reported.
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the evaluation?	Y	Structural assumptions seem justified.
	Do the disease states or the care pathways reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Yes, disease states reflect the underlying biological process of the disease in question and the impact of interventions.
	Is the cycle length defined and justified in terms of the natural history of disease?	Y	Cycle length was defined and seems justified.
	Are transition probabilities calculated appropriately?	U	Cumulative survival probabilities were converted to 6-week cycle probabilities.
	Has a half cycle correction been applied to both cost and outcome? If not, has this omission been justified?	U	Authors do not report about half cycle correction.
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	U	Not applicable. Patients received therapy until disease progression after which patients were switched to second line treatment or BSC.
Sensitivity analysis	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N	Short term survival data were extrapolated to model long term outcome. Alternative techniques for this were not explored.
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	U	Not applicable. Patients received therapy until disease progression after which patients were switched to second line treatment or BSC.
	Have the four principal types of uncertainty been addressed (methodological, structural, heterogeneity, parameters)? If not, has the omission of particular forms of uncertainty been justified?	N	Sensitivity analyses of model parameters were performed.
	Have methodological uncertainties been addressed by running alternative versions of the evaluation with different methodological assumptions?	N	Different methodological assumptions were not tested in sensitivity analysis.
Author conclusions	Is there evidence that the mathematical logic of the evaluation has been tested thoroughly before use?	Y	The study employed well established Markov modelling technique.
	If the evaluation has been calibrated against independent data, have any differences been explained and justified?	N	Authors do not discuss the results in comparison with other studies.

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

See section 9.10 (Appendix 10).

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

See section 6.5.5.

9.14 Appendix 14: Report on Use of Inverse Probability of Censored Weighted (IPCW) and Rank Preserving Structural Failure Time (RPSFT) Estimates of the Effect of Pazopanib on Overall Survival in Treatment-Naive Patients in the VEG105192 Trial

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Source of funding	Funding for this research was provided to PAI, Analysis Group Inc.,

	and Dr. Robins by GSK.
Competing Interest	PAI has received research funding and consulting fees from GSK. Analysis Group Inc. has received research funding from GSK. Dr. Robbins has received consulting fees from GSK.
Acknowledgements	For reviewing and commenting on the analysis, Dr. Lee-Jen Wei, Professor of Biostatistics, Department of Biostatistics, Boston, Massachusetts, USA and Mr. Ian White, MRC Biostatistics Unit, University of Cambridge, Cambridge, UK
Date	20 December 2010

BACKGROUND AND RATIONALE

Pazopanib is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit. The VEGF105192 study was a randomized, double-blind, placebo-controlled phase III study to evaluated efficacy and safety of pazopanib monotherapy in treatment-naive and cytokine-pretreated patients with advanced renal cell carcinoma (RCC) [1]. Adult patients with measurable, locally advanced, and/or metastatic RCC were randomly assigned 2:1 to receive oral pazopanib or placebo. The primary end point was progression-free survival (PFS). Secondary end points included overall survival, tumour response rate (Response Evaluation Criteria in Solid Tumours), and safety. Radiographic assessments of tumours were independently reviewed. Of 435 patients enrolled, 233 were treatment naive (54%) and 202 were cytokine pretreated (46%). PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; P < .0001), the treatment-naive subpopulation (median PFS 11.1 v 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; P < .0001), and the cytokine-pretreated subpopulation (median PFS, 7.4 v 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; P < .001).

At the time of the cut-off date (May 23, 2008), 67 subjects (46%) in the placebo arm and 109 subjects (38%) in the pazopanib arm had died. OS appeared to be prolonged in the pazopanib arm relative to the placebo arm (HR 0.73 [95% CI, 0.53, 1.00, 99.16% CI, 0.47, 1.12; one sided p=0.020]), although, the results did not reach the prespecified O'Brien-Fleming significance level for the interim analysis. Pazopanib was associated with a 26% reduction in risk of death relative to the placebo arm in treatment-naïve subjects (HR 0.74 [95% CI, 0.47, 1.15, one-sided p=0.079]), the sample size in this subgroup was small and data were immature. A total of 70 patients randomized to receive placebo in the VEG105192 trial (48% of patients in the placebo arm) received the pazopanib upon disease progression as a consequence of participation in an extension study (VEG107769).

The likely effect of such cross-over was to increase the survival times for patients in the placebo group relative to what would have been observed had placebo patients not been allowed to cross-

over. Because a treatment strategy of initial treatment with placebo, followed by treatment with pazopanib upon disease progression, is not likely to be employed in real world clinical practice, the utility of the ITT analysis is therefore limited. An estimate of the treatment effect with pazopanib on OS in a "counterfactual" setting where survival for patients receiving pazopanib would be identical to those of patients randomized to pazopanib arm in the VEG105192 clinical trial whereas survival for those receiving placebo would be identical to that of a hypothetical cohort of patients who received placebo but who were ineligible to receive pazopanib upon disease progression is required.

Several methods have been employed for analyzing OS in randomized controlled trials in OS may be confounded by cross-over to active treatment. These include censoring patients who cross-over, or including a time-dependent covariate representing cross-over in a Cox proportional hazards regression analysis. However, these methods may be confounded by differences in between groups in time-dependent factors that are correlated with cross-over and survival. More recently, Inverse Probability of Censoring Weighed (IPCW) methods [2-4] and Rank Preserving Structural Failure Time (RPSFT) methods [5-6] have been employed to address this issue. Both these methods have been used recently to estimate the effects of everolimus on OS among patients with metastatic renal cell carcinoma who had previously failed treatment with VEGF/TKI therapy based on results from the everolimus Phase III trial [4,7].

The objective of this analysis was to evaluate the effects of pazopanib on OS among patients in the VEGF105192 trial controlling for the potential confounding effects of cross-over on survival. Because the use of pazopanib amongst cytokine-pretreated patients is likely to be limited given changes in practice patterns since the VEGF105192 trial was conducted, this analysis focused on the treatment-naïve subgroup of the VEGF105192 trial. Survival outcomes, censoring, and cross-over in these patients summarized in **Table 1**. Among treatment-naïve patients in the VEGF105192 trial (155 patients randomized to pazopanib and 78 patients randomized to placebo), 31 patients randomized to placebo (39.7%) crossed-over to open-label pazopanib after disease progression.

Table 1. Survival outcomes and cross-over among treatment-naïve patients in the VEGF105192 trial

	Pazopanib	Placebo	Total
N	155	78	233
N censored	99	44	143
Follow-up ended[24]	9	1	10
N failed (i.e., died)	56	34	90
N cross-over	0	31*	31*

* A total of 33 patients randomised to placebo crossed-over to pazopanib treatment. However, 2 of these patients have a last contact date within 1 week of their crossover date. There is no impact of crossover expected for these subjects and they have therefore not been treated as crossovers in the analyses conducted to adjust for crossover.

INVERSE PROBABILITY OF CENSORING WEIGHTED (IPCW) ANALYSIS

The IPCW method of analyzing mortality to adjust for cross-over entails the following three general steps:

(iii) **Create Panel Data**: For placebo patients, follow-up time from randomization until cross-over or end of follow-up (defined as death, withdrawal of consent, or end of study, whichever occurred first) was partitioned into intervals based on visits dates[25]. For each of these intervals, time-dependent variables that might be predictive of cross-over and mortality (e.g., ECOG performance status, occurrence of grade 3/4 adverse events (AEs), and number of weeks since disease progression) were calculated.

(iv) **Calculate Stabilized Weights**: Using the panel data created in Step 1, for each placebo patient *i* and interval (j), stabilized weights, $SW_i(j)$, were estimated. The denominator of the weights is the probability of remaining uncensored (i.e., not crossing over to pazopanib) to the end of interval (j) given baseline and time-dependent confounders. The numerator of the weights is the probability of remaining uncensored (i.e., not crossing

[24] Includes patients with loss of follow-up and who withdrew consent from the study.
[25] In VEG105192 trial, visits were scheduled at 3-week intervals from Day 1 to Week 24 and 4-week intervals from Week 24 to treatment discontinuation.

over to pazopanib) to the end of interval (j) given only baseline confounders. Estimates were obtained by fitting pooled logistic models with censoring (cross-over) as the dependent variable.

(v) **Run IPCW Cox Regression**: AHR for OS was estimated using a weighted Cox proportional hazard regression model, where patients intervals were weighted by the stabilized weights calculated in Step 2. For all patients who were randomized to pazopanib, the weight is equal to 1.0 (i.e., $SW_i(j)=1$). Placebo patients who crossed-over were censored (i.e., for placebo patients who crossed over, intervals after cross-over have a weight of zero and are therefore dropped from the model).

Each of these steps is described in greater detail below.

Step 1: Create the Panel Data

A panel data set was created with multiple intervals per patient with each interval corresponding to a patient visits beginning with randomization and ending with cross-over to pazopanib or trial censoring, defined as death, withdrawal of consent, or end of study, whichever occurred first. In VEGF1051092, visits were scheduled every three weeks until week 24 and every four weeks thereafter.[26] For each observation, baseline personal and disease characteristics, including age, gender, Motzer risk category, time since initial diagnosis, a binary variable for stage 3 or 4 disease at initial diagnosis, a variable indicating the presence of liver metastasis, and the number of metastatic disease sites were calculated. Time-dependent characteristics included ECOG performance status measured at each visit, history of grade 3/4/5 AEs, a binary variable indicating the occurrence of a grade 3/4/5 AE since last visit, time since disease progression, and a quadratic term for time since disease progression to capture non-linearity. For each visit, a binary indicator of the event (death or cross-over) was created. Patients randomized to placebo

[26] If a patient missed a scheduled visit during the clinical trial, we did not impute that visit when creating the panel data file i.e., we assumed a patient who missed a visit could not cross over at that visit. . For patients who progressed , patient-intervals were added to the panel data file at each 4-week interval during the follow-up period for overall survival assessment (i.e., between the date of progression until death, withdrawal of consent, or the study cut-off date, whichever occurred first).

who crossed over to pazopanib were censored at the visit of cross-over, and post cross-over visits were excluded from the subsequent analysis. Out of 78 patients initially randomized to the placebo arm in the treatment-naïve population, 61 patients had disease progression and 31 of these patients were IPCW-censored at the time of cross-over to pazopanib after disease progression.

Imputation Approach for Missing Values. Among treatment-naïve patients, two subjects had unknown stage of disease at initial diagnosis, 8 subjects had unknown Motzer risk category, and 19 subjects had missing dates of initial diagnosis. For these patients with missing information, we imputed the sample mean value[27] in order to keep these patients for the survival analysis of pazopanib relative to placebo. The imputation affected a total of 27 subjects (i.e., two subjects had more than one variable with missing information), representing 11.6% of the first-line treatment population.

Step 2: Calculate Stabilized Weights

Using the panel data created in Step 1, for each placebo patient *i* and interval *(j)*, an estimate of the stabilized weights $SW_i(j)$ was obtained where

$$SW(j)_i \equiv \frac{\prod_{k=0}^{j} P[C(k)_i = 0 \mid C(k-1)_i = 0, X(0)_i]}{\prod_{k=0}^{j} P[C(k)_i = 0 \mid C(k-1)_i = 0, X(0)_i, Y(k)_i]}.$$

Here:

$C(k)_i$ = an indicator function representing censoring/cross-over status at end of interval *k* (1: censored or cross-over, 0: uncensored)

$X(0)_i$ = an array of patients characteristics measured at baseline

[27] For example, 55.6% of patients with non-missing dates for their initial diagnosis were classified in the "1=less than one year" category for the regression analysis; the remaining 44.4% of patients with non-missing dates were classified in the "0=more than one year" category. Consequently, for patients with missing dates we imputed the sample mean value of 0.556 in the regression models for this categorical variable.

$Y(k)_i$ = an array of time-dependent patients characteristics measured at or prior to the beginning of interval k

$P[C(k)_i|C(k\text{-}1)_i , X(0)_i]$ = probability of remaining uncensored at end of interval *k* given uncensored at end of interval *k-1* and conditioned on baseline characteristics $X(0)_i$

$P[C(k)_i|C(k\text{-}1)_i , X(0)_i,Y(k)_i]$ = probability of remaining uncensored at end of interval *k* given uncensored at end of interval *k-1* and conditioned on baseline characteristics $X(0)_i$, and time-dependent patient characteristics $Y(k)_i$.

Specifically to estimate the numerator of the stabilized weights we fit a logistic regression (model 1) in which we modelled the probability of remaining uncensored at time (j) conditional on patient *i* baseline factors (age, sex, intermediate/poor Motzer risk category, indicator for less than one year since initial diagnosis, indicator for stage 3 or 4 disease at initial diagnosis, indicator for liver metastasis, the number of metastatic disease sites) and a time-dependent intercept. We estimated the time-dependent intercept by inserting a variable indicating the number of weeks elapsed since randomization (i.e., study week) and a quadratic term for study week. The dependent variable in the logistic model was a binary variable (1/0) indicating whether the patient had crossed over or not since last visit. We fit this model on all patient-intervals from randomization until cross-over to pazopanib or trial censoring, defined as death, withdrawal of consent, or end of study, whichever occurred first.

To estimate the denominator of the stabilized weights we fit a logistic regression (model 2) in which modelled the probability of remaining uncensored conditional on the same baseline factors and patient *i* time-dependent covariates at time (j): ECOG performance status (0 [fully active] versus 1 or higher), history of grade 3/4/5 AEs, occurrence of a grade 3/4/5 AE since last visit, time since progression, and time since progression squared. Because patients discontinued from the study upon disease progression, the time dependent data on health conditions (i.e., ECOG and AEs) was not updated after progression. Therefore, only health status at the time of progression (fixed) and time since progression (time-varying) were predictors of cross over in this model. The choice of baseline and time-dependent covariates were based on prior knowledge from the literature and goodness-of-fit statistics. We fit this second model on all patient-

intervals post-disease progression,[28] i.e., from disease progression until cross-over to pazopanib or trial censoring, defined as death, withdrawal of consent, or end of study, whichever occurred first. **Table 2** and **Table 3** present the results of the logistic regression models 1 and 2.

Table 2. Pooled logistic regression analysis on remaining uncensored conditioned on baseline factors for treatment-naïve patients in VEGF105192 trial (placebo patients [N=78], all intervals [N=825 intervals]) (Model 1)

Covariate	OR	95% CI		P
Age (Continuous variable)	1.017	0.983	1.053	0.3357
Female (Reference: Male)	0.726	0.275	1.918	0.5181
Motzer Score: Intermediate/Poor (Reference: Favourable)	0.906	0.364	2.254	0.8322
Year Since Initial Diagnosis: 0-1 (Reference: >1 year)	1.074	0.438	2.634	0.8765
Stage 3-4 at Initial Diagnosis (Reference: Stage 1-2)	1.842	0.775	4.380	0.1666
Presence of Liver Metastasis (Reference: No)	1.804	0.486	6.695	0.3779
Number of Metastatic Disease Site (Continuous variable)	1.241	0.842	1.830	0.2749
Study Week (Linear Term)	0.864	0.785	0.950	0.0027
Study Week (Square Term)	1.002	1.001	1.003	0.0071

Note: Two subjects had unknown stage of disease at initial diagnosis, 8 subjects had unknown Motzer risk category, and 19 subjects had missing dates of initial diagnosis. For these patients, we imputed the sample mean of each categorical variable in order to keep these patients for the IPCW survival analysis of pazopanib relative to placebo. The imputation affected a total of 27 subjects (two subjects had more than one variable with missing information), representing 11.6% of the first-line treatment population.

Table 3. Pooled logistic regression analysis on remaining uncensored given baseline and time-dependent factors for treatment-naïve patients in VEGF105192 trial (placebo patients [N=61 patients], post-progression intervals [N=315 intervals]) (Model 2)

Covariate	OR	95% CI		P
Age (Continuous variable)	1.022	0.985	1.062	0.2461

[28] According to the study protocol, the probability of crossing over for placebo patient-segments prior to disease progression is zero (alternatively, the probability of remaining uncensored is one). Therefore, we set the probability of being uncensored at intervals (j) to 1 for patients-intervals prior to disease progression and did not use these observations in this logistic model.

Female (Reference: Male)	1.222	0.395	3.784	0.7280
Motzer Score: Intermediate/Poor (Reference: Favourable)	2.583	0.799	8.345	0.1128
Year Since Initial Diagnosis: 0-1 (Reference: > 1 year)	1.585	0.573	4.386	0.3747
Stage 3-4 at Initial Diagnosis (Reference: Stage 1-2)	1.703	0.584	4.965	0.3292
Presence of Liver Metastasis (Reference: No)	4.487	0.898	22.416	0.0674
Number of Metastatic Disease Site (Continuous variable)	1.060	0.642	1.750	0.8192
Study Week (Linear Term)	0.924	0.826	1.034	0.1685
Study Week (Square Term)	1.001	0.999	1.003	0.1907
ECOG Status: Fully Active (Reference: Other Status)	1.330	0.470	3.765	0.5913
History of Grade 3/4 AE (Reference: No)	0.252	0.019	3.406	0.2994
Grade 3/4 AE Since Last Visit (Reference: No)	12.97	0.698	241.02	0.0856
Time Since Progression (Weeks)	0.927	0.788	1.091	0.3598
Time Since Progression Squared	1.005	0.998	1.011	0.1515

Table 4 presents summary statistics on the stabilized weights. For all patients who were randomized to pazopanib, the stabilized weights for all intervals were set to 1.0 (i.e., $SW_i(j)=1$). For patients randomized to placebo, stabilized weights for intervals prior to progression were calculated with the numerator of $SW_i(j)$ calculated using model 1 as described above and with the denominator of $SW_i(j)$ set to 1.0 (i.e., time-dependent probability of cross-over set equal to zero). Thus, these weights are all less than 1.0 For post-progression intervals for placebo patients, the numerator of $SW_i(j)$ is calculated using model 1 and the denominator is calculated using model 2. These weights may be greater than 1.0.

Table 4. Summary statistics of stabilized weights for IPCW analysis of OS among treatment-naïve patients in VEGF105192

Follow-up intervals	N	Mean	SD	Min	Max
Pazopanib patients, all intervals	2343	1.000	0.000	1.000	1.000

Placebo patients	825	0.967	0.376	0.301	5.248
Intervals before disease progression	509	0.833	0.176	0.301	0.999
Intervals after disease progression	315	1.184	0.493	0.431	5.248

Step 3: IPCW Cox Proportional Hazards Regression (Censoring at Cross-Over)

In the final step, a time-dependent Cox proportional hazards model was estimated using time-varying stabilized weights, as calculated in Step 2, to compare the overall survival between pazopanib and placebo, adjusting for baseline characteristics and confounding resulting from cross-over of placebo patients to open-label pazopanib upon disease progression. In this model, a binary variable indicating the status (0=censored; 1=death) at each person-time was used as the censoring variable and number of days since randomization was used as the survival time variable. Patients randomized to placebo who crossed over to pazopanib were censored at the visit of cross-over, and post cross-over visits were excluded from the subsequent analysis (i.e., *SWi(j)*=0). All other person-time observations were weighted by the stabilized weights calculated in step 2. A binary indicator of randomization arm (pazopanib relative to placebo) and baseline covariates used in the IPCW modelling were added in the Cox model. **Table 5** presents the results of the IPCW-adjusted Cox proportional hazards model.

Table 5. IPCW-adjusted Cox proportional hazards regression analysis for OS among treatment-naïve patients in VEGF105192 trial (Pazopanib: N=155; Placebo: N=78)

Covariate	HR	95% CI		P
Pazopanib (Reference: Placebo)	0.450	0.280	0.721	0.0009
Age (Continuous variable)	0.995	0.974	1.018	0.6831
Female (Reference: Male)	1.774	1.106	2.846	0.0175
Motzer Score: Intermediate/Poor (Reference: Favourable)	1.770	1.047	2.992	0.0331
Year Since Initial Diagnosis: 0-1 (Reference: >1 year)	2.223	1.263	3.915	0.0056
Stage 3-4 at Initial Diagnosis (Reference: Stage 1-2)	1.333	0.686	2.590	0.3957
Presence of Liver Metastasis (Reference: No)	1.094	0.640	1.871	0.7420
No. of Metastatic Disease Site (Continuous variable)	1.456	1.208	1.755	<.0001

These results based on the treatment-naive population, adjusting for the cross-over 40% of placebo patients using the IPCW approach, indicates that treatment with pazopanib was associated with significant reduction in the risk of mortality of approximately 55% (HR: 0.450; 95%CI: 0.280-0.721; p-value=0.0009), compared to placebo.

RANK PRESERVING STRUCTURAL FAILURE TIME METHOD

The RPSFT method is based on an accelerated failure time (AFT) model which uses a structural assumption of time-proportionality (instead of a proportional hazards assumption as in the Cox model). A simple version of an RPSFT model specifies that U_i, the lifetime of the i^{th} individual, had that individual, possibly contrary to fact, never received treatment, can be described by the following relationship:

$$U_i = \int_0^{T_i} \exp\{\psi^* D_i(x)\}\, dx$$

Where

ψ^* is an unknown parameter representing the causal effect of treatment on survival time

$D_i(t)$ is an indicator for whether patient i received treatment at time t

Note that $\psi^* = 0$ implies no effect of treatment on survival whereas $\psi^* < 1$ implies that continuous treatment would <u>*increase*</u> life by a factor of $\exp(-\psi^*)$, and $\psi^* > 1$ implies that continuous treatment would <u>*decrease*</u> life by a factor of $\exp(-\psi^*)$.

Note that the RPSFT method is based on intention-to-treat population to avoid potential pitfalls and biases that may be introduced by methods that adjust for post-randomization time-dependent covariates. The RPSFT method maintains the original randomized group definitions and thus

preserves the validity of between-group comparisons and therefore is said to produce "randomization-based effect estimators".

The RPSFT approach employed here consisted of the following steps:

1. Obtain an estimate of the effect of exposure to the active treatment on survival time, ψ^*, as described below.

2. Estimate the HR for OS for randomization to pazopanib vs. randomization to placebo with no cross-over to pazopanib by fitting a Cox proportional hazards regression model to the pazopanib failure times as observed in the VEG105192 trial and re-censored adjusted failure times for placebo patients based on the estimate of $\exp(\psi^*)$

Two separate RPSFT analyses were performed. In the first, there was no adjustment for baseline patient characteristics. In the second, adjustments were made for baseline patient characteristics, including age, gender, Motzer risk category, time since initial diagnosis, stage 3 or 4 disease at initial diagnosis, presence of liver metastasis, and number of metastatic disease sites as well as the patient theoretical maximum follow-up time as defined by time from patient's randomization date to the final data cut-off date (May 23, 2008). In adjusted analyses, missing values were imputed using the same methods as were employed in the IPCW analysis.

Step 1: Estimation of ψ^*

To estimate the true parameter ψ^*, a grid of parameter values $\rangle \psi_{k=0 to 160} \langle$ was created, where ψ_k ranged from -2 to 2 in 0.025 increments. For each patient i, C_i, was defined as the difference between the date of the end of follow-up (May 23d 2008) and individual's randomization date. For patients who dropped out of the study prior to the end of follow-up (2 in the placebo arm and 15 in the pazopanib arm) Q_i was defined as the time to actual censoring

For each patient i and each ψ an adjusted follow-up time $U_i(\psi)$ and censoring time $C_i(\psi)$ were calculated. $U_i(\psi)$ was calculated by adjusting each patient's exposure to the active treatment (if any) by $\exp(\psi)$:

$$U_i(\psi) = \begin{cases} \exp(\psi) \cdot T_i^{\text{exposed}} + T_i^{\text{unexposed}}, \text{ for active treatment patients} \\ T_i^{\text{Follow-up}}, \text{ for placebo patients who never crossed over} \\ T_i^{\text{Cross-over}} + \exp(\psi) \cdot T_i^{\text{exposed}}, \text{ for placebo patients who crossed over} \\ \text{missing, for patients who were censored only at the end of follow-up} \end{cases},$$

where

$T_i^{exposed}$ was the cumulative duration of the follow-up when a patient was exposed to the active treatment,

$T_i^{unexposed}$ was the cumulative duration of the follow-up when a patient was not exposed to the active treatment,

$T_i^{Cross-over}$ was the time to cross-over for placebo patients and

$T_i^{Follow-up}$ was the time to death or censoring due to withdrawal from the study.

$C_i(\psi)$ was defined as $\exp(\psi) \cdot C_i$, for values of ψ that implied a beneficial effect of treatment on overall survival, and C_i, for other values of ψ

$$C_i(\psi) = \begin{cases} C_i, \text{ for } \psi \geq 0 \\ \exp(\psi) \cdot C_i, \text{ for } \psi < 0 \end{cases}.$$

The adjusted event time, $X_i(\psi)$, was defined as

$$X_i(\psi) = \begin{cases} \min[U_i(\psi), C_i(\psi)], \text{ for } U_i(\psi) \neq \text{missing} \\ C_i(\psi), \text{ for } U_i(\psi) = \text{missing} \end{cases}.$$

The censoring flag $\Delta_i(\psi)$ was defined as

$$\Delta_i(\psi) = \begin{cases} 0, \text{ if } X_i(\psi) = C_i(\psi) \text{ or } Q_i < C_i \text{ [29]} \\ 1, \text{ otherwise} \end{cases}$$

All patients with $\Delta_i(\psi) = 1$ died. However for nonzero ψ, some deaths have $\Delta_i(\psi) = 0$, i.e., they are treated in the analysis as artificially censored. This is needed to insure an unbiased estimate of the true parameter ψ^*.

Our estimate of ψ^* ($\hat{\psi}^*$) is the value of ψ that results in equivalence of OS for the two treatment arms. Therefore, for each ψ_k, a Cox proportional hazards regression model was estimated and associated score test calculated to test the null hypothesis of no difference in OS between treatment arms, with time to failure defined as $X_i(\psi_k)$, censoring indicator defined as $\Delta_i(\psi_k)$, and with treatment arm as a dependent variable. The value of ψ_k that yielded the largest p-value was defined to be our point estimate of ψ^* (i.e., $\hat{\psi}^*$). As a secondary analysis, the Cox model was also fit with baseline covariates added. Confidence intervals for $\hat{\psi}^*$ were obtained by repeating the analysis on 1000 bootstrap samples of the data. Unadjusted and adjusted estimates of ψ^* along with corresponding confidence intervals and p-values are reported in **Table 6**.

[29] In principle subjects who dropped out of the study should be ignored in the analysis and all other patients should be used to represent the drop outs in the study by estimating an IPCW weight. However, because the number of subjects who dropped out was small the above approach was expected to produce little bias and was relatively simple to implement within the limited time available for the analysis. However because of the differential rate of drop out the sensitivity of the model to this method will be examined in future analyses.

Table 6. Estimated causal rate ratio (ψ*) for OS for pazopanib among treatment-naïve patients in VEGF105192 trial (Pazopanib: N=155; Placebo: N=78)

	Not Adjusted for Patient Characteristics	Adjusted for Patient Characteristics
$\hat{\psi}^*$	-1.500	-1.725
Standard error $\hat{\psi}^*$	0.678	0.426
95%CI	-2.571 to 0.354	-2.500 to -0.900
exp($\hat{\psi}^*$)	0.223	0.178
95%CI	0.076 to 1.425	0.082 to 0.407

Step 2: Estimation of the HR for OS

Kaplan Meier curves and HRs for OS based on Cox proportional hazards regression were estimated using the observed event times and the observed censoring indicators for each patient in the active treatment arm. For patients in the placebo arm, the adjusted event times $X_i(\psi^*)$ and censoring indicators $\Delta_i(\psi^*)$, were employed, with ψ^* based on our point estimate ($\hat{\psi}^*$), except that , for $\psi<0$, we redefined $C_i(\psi)$, as

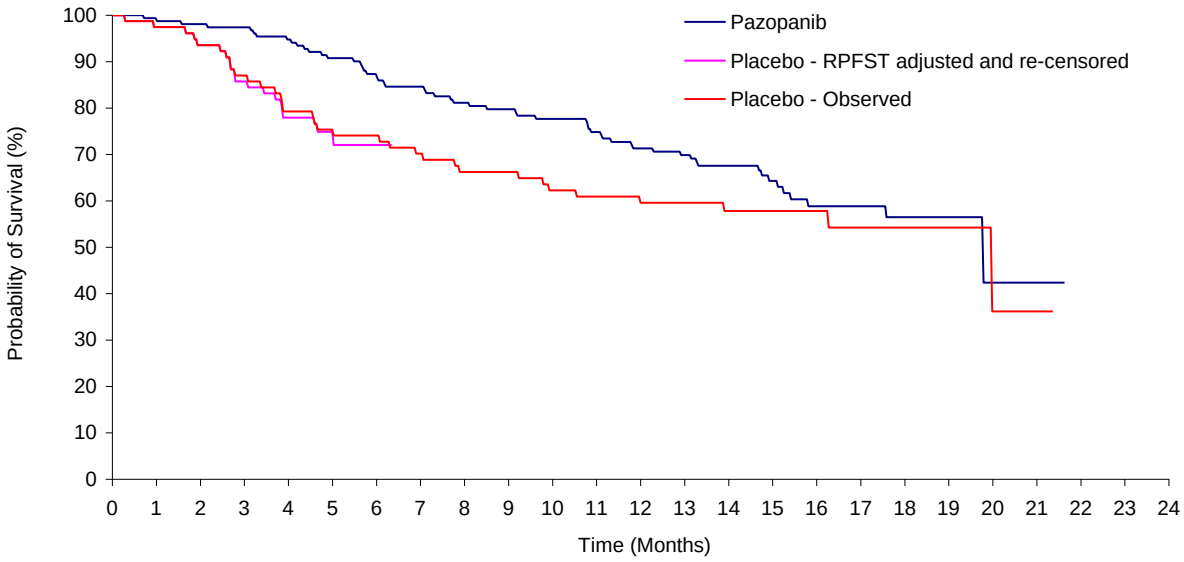
$$C_i^*(\psi^*) = XO_{\min} + (C_i - XO_{\min}) \cdot \exp(\psi^*) .$$

Here XO_{min} is the minimum time to cross over observed in the trial (51 days). This redefinition of $C_i(\psi)$ increases the amount of uncensored person time in the placebo arm without introducing bias.

Kaplan-Meier plots of observed failure times for active treatment patients and adjusted re-censored failure times for placebo patients are reported in **Figures 1** (unadjusted) and **2** (adjusted based on Cox model with baseline covariates).

Figure 1. Kaplan-Meier plot of observed survival times (months) for pazopanib patients and observed and RPSFT adjusted and re-censored survival times for placebo patients

based on univariate RPSFT model, treatment-naïve patients in VEGF105192 trial (pazopanib: N=155; placebo: N=78)



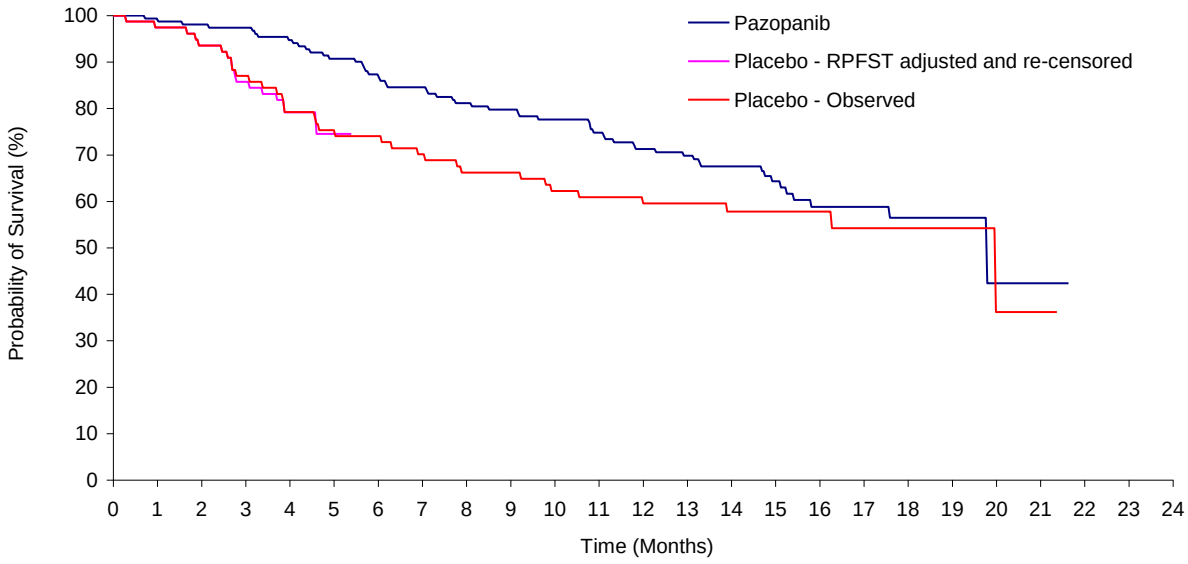
No. at risk									
Pazopanib	155	146	127	114	101	51	19	2	0
Placebo									
Observed	78	67	57	50	45	25	7	1	0
Adjusted	78	66	2	0	0	0	0	0	0

The Cox model estimates and bootstrap standard errors for the HR for OS for pazopanib vs. placebo both with and without adjustment for baseline covariates are given in **Table 7**. Results of the unadjusted RPSFT analysis suggest that compared with placebo treatment and no cross-over to pazopanib, treatment with pazopanib reduces the risk of death by 65.5% (HR=0.345, 95%CI 0.086 to 1.276), although this difference is not statistically significant (confidence interval spans 1.0). Results for the adjusted analysis are more favourable (HR=0.206, 95%CI 0.54 to 0.593)

Table 7. Cox proportional hazards regression analysis for OS for among treatment-naïve patients in VEGF105192 using RPSFT adjusted and re-censored failure times for placebo patients (Pazopanib: N=155; Placebo: N=78)

Model/Covariate	HR	95%CI	
Not Adjusted for Patient Characteristics			
Pazopanib (Reference: Placebo)	0.345	0.086	1.276
Adjusted for Patient Characteristics			
Pazopanib (Reference: Placebo)	0.206	0.054	0.593
C_i	1.000	0.995	1.004
Age (Continuous variable)	0.991	0.963	1.017
Female (Reference: Male)	1.512	0.845	2.842
Motzer Risk Score: Intermediate/Poor (Reference: Favourable)	1.332	0.755	2.507
Time Since Initial Diagnosis 0-1 year(Reference: >1 year)	2.757	1.452	6.148
Stage 3-4 at Initial Diagnosis (Reference: Stage 1-2)	1.309	0.577	3.552
Presence of Liver Metastasis (Reference: No)	1.081	0.563	2.173
Number of Metastatic Disease Site Continuous variable)	1.600	1.272	2.046

Figure 2. Kaplan-Meier plot of observed survival times (months) for pazopanib patients and observed and RPFST adjusted and re-censored survival times for placebo patients based on multivariate RPSFT model, treatment-naïve patients in VEGF105192 trial (pazopanib: N=155; placebo: N=78)



No. at risk									
Pazopanib	155	146	127	114	101	51	19	2	0
Placebo									
Observed	78	67	57	50	45	25	7	1	0
Adjusted	78	66	0	0	0	0	0	0	0

DISCUSSION

The objective of this analysis was to estimate of the effect treatment with pazopanib vs. placebo, measured in terms of a HR, on OS in a setting where survival for patients receiving pazopanib would be identical to those of patients randomized to pazopanib in the treatment-naïve subgroup of the VEG105192 trial, whereas survival for those receiving placebo would be identical to that for a hypothetical cohort of patients otherwise similar to those who received placebo in the treatment-naïve subgroup of the VEG105192 trial, but who were ineligible to receive pazopanib upon disease progression. Using the IPCW method, the HR for OS for pazopanib vs. placebo is 0.450 (95%CI 0.280 – 0.721, p=0.0009). The univariate HR for OS for pazopanib vs. placebo using the RPSFT method is 0.345 (95%CI 0.086 to 1.276). The multivariate RPSFT HR for OS for pazopanib vs. placebo is 0.206 (95%CI 0.054 to 0.593). These results compare with HRs for OS for pazopanib vs. placebo of 0.752 based on an unadjusted ITT analysis, 0.524 based on a

multivariate adjusted ITT analysis, 0.683 based a unadjusted Cox regression analysis with censoring of placebo patients at the time of cross-over, and 0.508 based on an adjusted Cox regression analysis with censoring of placebo patients at the time of cross-over and including baseline patient characteristics as covariates, 0.684 with cross-over as a time-dependent covariate, and 0.517 with cross-over as a time-dependent covariate and including baseline patient characteristics as covariates (**Table 8**).

Table 8. Alternative estimates of HR for OS for pazopanib vs. placebo in treatment-naïve patients in VEGF105192 (Pazopanib: N=155; Placebo: N=78)

	HR	95%CI		P
ITT				
Unadjusted	0.752	0.491	1.153	0.1909
Adjusted	0.524	0.336	0.817	0.0043
Censoring at cross-over				
Unadjusted	0.683	0.426	1.093	0.1123
Adjusted	0.508	0.312	0.825	0.0062
Cross-over as time-dependent covariate				
Unadjusted	0.684	0.428	1.095	0.1137
Adjusted	0.517	0.319	0.837	0.0073
IPCW	0.45	0.28	0.721	0.0009
RPSFT				
Unadjusted	0.345	0.086	1.276	na
Adjusted	0.206	0.054	0.593	na

Limitations of these analyses should be noted. Because of time constraints, these analyses only controlled for cross-over from placebo to pazopanib and did not control for receipt of other post-study anti-cancer therapy in the placebo or pazopanib groups. Among all patients in the VEGF105192 trial (including cytokine pre-treated patients), 13% of placebo patients and 27% of pazopanib patients received post-study anti-cancer agents other than pazopanib. Sorafenib, sunitinib, and IFN were the other anti-cancer therapies most frequently received in both groups. To the extent that more pazopanib patients received other post-study therapies than placebo patients, results presented here might be biased in favour of pazopanib.

The results of the IPCW analyses are limited by the lack of information on time-varying clinical and other factors that might be predictive of cross-over and OS. In particular, ECOG performance status, history of grade 3/4/5 AEs, and ongoing grade 3/4/5 AE up to time of progression, and time since progression and time since progression squared were the only characteristics available as time-dependent covariates. Data on Motzer risk score, presence of liver metastasis, and number of metastatic disease sites were not available after disease progression and therefore could not be used in estimation of the denominator for the stabilized weights. The extent to which this may have biased our findings is unknown.

The results of the RPSFT are limited by the high degree of re-censoring in the placebo group, which was required to ensure an unbiased estimate of ψ^*. The analysis is therefore heavily weighed toward the early follow-up period (approximately 200 days in the multivariate analysis) which may not be representative of treatment effects over the entire un-recensored follow-up period. The high degree of recensoring also affects statistical power to estimate a lower confidence limit for our estimates of ψ^* and the HR for pazopanib vs. placebo. Specifically, for some bootstrap samples biologically implausible values of ψ^*, are obtained and the model lacks sufficient power to reject these values. This method may have greater utility when updated survival data become available (expected in April 2010) as an additional 2 years of follow-up will be available and results may be less affected by re-censoring

It should be noted that the relative risk reductions (RRR) for OS for treatment-naïve patients obtained from the RPSFT method (unadjusted RRR=65.5%; adjusted RRR=75.4%) are substantially greater than that reported for PFS based on ITT analysis (RRR=60%) [7]. This results appears to conflict with results of a recent meta-analysis that examined the association between treatment effects on disease progression endpoints (predominantly PFS) and treatment effects on OS in trials of treatments for metastatic renal cell carcinoma [8]. This study reported that, in trial that did not allow for treatment crossover upon progression, the RRR for OS is projected to be 0.54 times that of the RRR in the TDP (95%CI 0.21 to 0.86). There are at least three possible explanations for this apparent conflict.

First, this may simply reflect the high degree of uncertainty associated with RPSFT estimates of the HR for mortality with pazopanib vs. placebo. The CI for the HR based on the univariate RPSFT method is much wider than that for the HR for PFS based on the ITT analysis (HR, 0.40; 95% CI, 0.27 to 0.60). Indeed, the upper limit of the CI for the PFS HR excludes the null value of 1.0. In contrast, the upper confidence limit for the RPSFT mortality hazard ratio is 1.276 which exceeds the upper limit of 1.5 for the ITT mortality HR, as predicted by theory. (The theory of RPSFT estimation guarantees that CI for the ITT mortality HR will be contained within the CI for RPSFT mortality HR; this guarantee is a consequence of the fact that under the null hypothesis of no effect on mortality the RPSFTM analysis preserves the alpha level). Thus, accounting for sampling variability (as summarized in our confidence limits) the results of our RPSFTM analysis are consistent with the aforementioned meta-analysis results.

Second, as noted above, the results of the RPSFT are limited by the high degree of re-censoring in the placebo group, which was required to ensure an unbiased estimate of ψ. The analysis is therefore heavily weighed toward the early follow-up period. Indeed, as can be seen from the red Kaplan Meier curve in Figure 2, all placebo patients have been artificially censored in the RPSFTM analysis after 200 days and the Kaplan-Meier curves for the adjusted and recensored survival times for placebo patients are virtually identical to the observed failure times. The ITT HR based on unadjusted Cox regression with all patients censored after 200 days of follow-up (which is less contaminated by cross-over of placebo patients than is the average ITT HR over the full follow-up period of 680 day) is 0.476 (95%CI 0.265 -0.854). These results suggest that the principal driver of the RPSFT adjustment is the censoring of placebo patients after cross-over.

Third, if one believes that the effect of the drug declines with calendar time due to the development of resistance in an increasing fraction of patients, the RPSFT method on which we based our analysis is misspecified, and our estimate 0.345 of the average mortality HR over the first 200 days is biased due to model misspecification. Specifically the RPSFT model that we fit assumes that the effect of one day of exposure to pazopanib is to increase survival by the same

proportionate amount, regardless of when that exposure occurred. If the proportionate effect of a day of exposure in fact changes with time, a more elaborate model may be required.

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9.15 Appendix 15: Technical explanation of survival function calculations

To calculate measures of effectiveness, the proportion of patients receiving each treatment strategy (j) that is expected to be alive at each time (t) (i.e., overall survival, [OS(j,t)]), and alive and progression-free at each time (i.e., progression-free survival, [PFS(j,t)]), are generated by the model. In the model, time t represents days since initiation of therapy. For each strategy, the proportion of patients alive and post-progression at each time (post-progression survival, [PPS(j,t)]) is calculated by subtracting PFS(j,t) from OS(j,t). .

Expected (i.e., mean) PFLYs, PPLYs, and overall LYs for each strategy, (E[PFS(j)], E[PPS(j)], and E[OS(j)], respectively) are calculated as the sum of PFS(j,t), PPS(j,t), and OS(j,t) over the modelling timeframe, T, as follows:

$$E[PFS\ (j)] = \sum_{t=1}^{T} PFS\ (j,t) \qquad (1)$$

$$E[PPS\ (j)] = \sum_{t=1}^{T} PPS\ (j,t) \qquad (2)$$

$$E[OS\ (j)] = \sum_{t=1}^{T} OS\ (j,t) \qquad (3)$$

Thus, for any given strategy, E[PFS(j)] and E[OS(j)] equal the area under the curves represented by PFS(j,t) and OS(j,t), while E[PPS(j)] represents the area between the PFS(j) and OS(j) curves, as shown in Figure 6.4.10.

Discounted expected PFLYs, PPLYs and overall LYs (E[PFS(j)]′, and E[PPS(j)′, E[OS(j)]′, respectively), given the annual discount rate for effectiveness measures (re), are calculated as follows:

$$E[PFS\ (j)]' = \sum_{t=1}^{T} \frac{PFS\ (j,t)}{(1 + r_e/365)^{t-1}} \qquad (4)$$

$$E[PPS\ (j)]' = \sum_{t=1}^{T} \frac{PPS\ (j,t)}{(1 + r_e/365)^{t-1}} \qquad (5)$$

$$E[OS\ (j)]' = \sum_{t=1}^{T} \frac{OS\ (j,t)}{(1 + r_e/365)^{t-1}} \qquad (6)$$

Expected QALYs for each treatment, E[QALY(j)], are calculated by multiplying E[PFS(j)] and E[PPS(j)] by corresponding estimates of utility for pre- and post-progression survival time (UPFS(j) and UPPS(j), respectively) and summing, i.e.:

$$E[QALY\ (j)] = E[PFS\ (j)] \times U_{PFS}\ (j) + E[PPS\ (j)] \times U_{PPS}\ (j) \qquad (7)$$

Discounted expected QALYs for each strategy (E[QALY(j)′) are calculated as follows:

$$E[QALY\ (j)] = E[PFS\ (j)]' \times U_{PFS}\ (j) + E[PPS\ (j)]' \times U_{PPS}\ (j) \qquad (8)$$

The model thus assumes that utilities are invariant with respect to time since therapy initiation, and are conditional only on progression status.

The model also calculates the expected difference between strategies in these outcomes, e.g.:

$$\Delta E[QALY\ ]_{1vs\,2} = E[QALY\ (1) - E[QALY\ (2)] \qquad (9)$$

Where j=1 represents the pazopanib strategy and j=2, BSC strategy

PFS and OS for patients receiving pazopanib were obtained by fitting Weibull survival functions to the patient failure time data for patients in the Hx-CD20-406 trial (by group)The Weibull function takes the general form below

$$S(t) = e^{-\lambda t^{\gamma}} \qquad (10)$$

where

λ (lambda) is scale parameter

γ (gamma) is shape parameter

Weibull survival functions were estimated using Accelerated Failure Time (AFT) models, a class of regression models in which the log of failure time is assumed to be linear function of a set of covariates plus a scaled disturbance term, using SAS PROC LIFEREG [Allison 1995; Kalbfleisch and Prentice 1980]. The distribution and scaling of the disturbance term determine the form of the survival function. Note that AFT formulation of the Weibull is somewhat different than that described above. The AFT formulation is as follows:

$$S(t) = \exp\{-[te^{-\alpha}]^{1/\sigma}\} \qquad (11)$$

where S(t) is the proportion of person in who have not experienced the event (e.g., progression or death) at time t and α is an intercept term. The parameters of the AFT Weibull can be transformed to obtain those of the traditional Weibull as follows[30]

$\gamma=1/\sigma.$ (12)

$\lambda=\exp(-\alpha/\sigma)$ (13)

[30] The SE of $\gamma = SE(\sigma)/\sigma^2$. The SE of λ is an exponential function of α and σ; it's SE and was therefore derived by bootstrapping.

9.16 Appendix 16: Summary of adverse event model inputs

Summary of adverse event inputs

		Pazopanib			Sunitinib			IFN			BSC			Re st
Adverse Event		**Value**	**Distribution**	**SE**	**Value**	**Distribution**	**SE**	**Value**	**Distribution**	**SE**	**Value**	**Distribution**	**SE**	
Anaemia G1&2	Incidence	9%	Lognormal	7%	49%	Lognormal	4%	19%	Lognormal	1%	4%	Lognormal	1%	Se
	Duration (per event, days)	83.9	Lognormal	21	83.9	Lognormal	21	83.9	Lognormal	21	83.9	Lognormal	21	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.081	Normal	0.02	0.081	Normal	0.02	0.081	Normal	0.02	0.048	Normal	0.012	Se
Asthenia/Fatigue G1&2	Incidence	27%	Lognormal	9%	47%	Lognormal	4%	45%	Lognormal	2%	20%	Lognormal	2%	Se
	Duration (per event, days)	125.5	Lognormal	31.4	125.5	Lognormal	31.4	125.5	Lognormal	31.4	125.5	Lognormal	31.4	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.046	Normal	0.011	0.046	Normal	0.011	0.046	Normal	0.011	0.028	Normal	0.007	
Bleeding G1&2	Incidence	4%	Lognormal	7%	4%	Lognormal	3%	4%	Lognormal	1%	0%	No	1%	Se
	Duration (per event, days)	24.9	Lognormal	6.2	24.9	Lognormal	6.2	24.9	Lognormal	6.2	24.9	Lognormal	6.2	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.012	Normal	0.003	0.012	Normal	0.003	0.012	Normal	0.003	0.007	Normal	0.002	
Diarrhoea G1&2	Incidence	54%	Lognormal	8%	50%	Lognormal	3%	14%	Lognormal	1%	11%	Lognormal	1%	Se
	Duration (per event, days)	128.9	Lognormal	32.2	128.9	Lognormal	32.2	128.9	Lognormal	32.2	128.9	Lognormal	32.2	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.007	Normal	0.002	0.007	Normal	0.002	0.007	Normal	0.002	0.004	Normal	0.001	
Fever/Pyrexia G1&2	Incidence	9%	Lognormal	7%	11%	Lognormal	3%	39%	Lognormal	2%	2%	Lognormal	1%	Se
	Duration (per event, days)	7.5	Lognormal	1.9	7.5	Lognormal	1.9	7.5	Lognormal	1.9	7.5	Lognormal	1.9	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.001	Normal	0.0002	0.001	Normal	0.0002	0.001	Normal	0.0002	0.0005	Normal	1E-04	
Flu-like symptoms G1&2	Incidence	1%	Lognormal	7%	0%	No	3%	29%	Lognormal	2%	1%	Lognormal	1%	Se

	Duration (per event, days)	15.4	Lognormal	3.9	15.4	Lognormal	3.9	15.4	Lognormal	3.9	15.4	Lognormal	3.9	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.157	Normal	0.039	0.157	Normal	0.039	0.157	Normal	0.039	0.097	Normal	0.024	
HFS/PPE G1&2	Incidence	5%	Lognormal	6%	15%	Lognormal	2%	1%	Lognormal	1%	2%	Lognormal	1%	Se
	Duration (per event, days)	300.7	Lognormal	75.2	300.7	Lognormal	75.2	300.7	Lognormal	75.2	300.7	Lognormal	75.2	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.025	Normal	0.006	0.025	Normal	0.006	0.025	Normal	0.006	0.014	Normal	0.003	
Hypertension G1&2	Incidence	30%	Lognormal	6%	20%	Lognormal	2%	4%	Lognormal	1%	2%	Lognormal	1%	Se
	Duration (per event, days)	122.9	Lognormal	30.7	122.9	Lognormal	30.7	122.9	Lognormal	30.7	122.9	Lognormal	30.7	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.028	Normal	0.007	0.028	Normal	0.007	0.028	Normal	0.007	0.016	Normal	0.004	
Mucositis/Stomatitis G1&2	Incidence	9%	Lognormal	7%	42%	Lognormal	3%	1%	Lognormal	1%	1%	Lognormal	1%	Se
	Duration (per event, days)	52.8	Lognormal	13.2	52.8	Lognormal	13.2	52.8	Lognormal	13.2	52.8	Lognormal	13.2	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.007	Normal	0.002	0.007	Normal	0.002	0.007	Normal	0.002	0.004	Normal	0.001	
Nausea/Vomiting G1&2	Incidence	34%	Lognormal	9%	42%	Lognormal	4%	22%	Lognormal	1%	24%	Lognormal	2%	Se
	Duration (per event, days)	84.2	Lognormal	21	84.2	Lognormal	21	84.2	Lognormal	21	84.2	Lognormal	21	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.04	Normal	0.01	0.04	Normal	0.01	0.04	Normal	0.01	0.023	Normal	0.006	
Rash G1&2	Incidence	9%	Lognormal	7%	16%	Lognormal	2%	4%	Lognormal	1%	8%	Lognormal	1%	Se
	Duration (per event, days)	109.1	Lognormal	27.3	109.1	Lognormal	27.3	109.1	Lognormal	27.3	109.1	Lognormal	27.3	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.005	Normal	0.001	0.005	Normal	0.001	0.005	Normal	0.001	0.003	Normal	0.001	
Anaemia G3p	Incidence	2%	Lognormal	3%	4%	Lognormal	2%	5%	Lognormal	1%	0%	Lognormal	0%	Se
	Duration (per event, days)	35.7	Lognormal	8.9	35.7	Lognormal	8.9	35.7	Lognormal	8.9	35.7	Lognormal	8.9	Se
	Cost per event	1143	Lognormal	285.75	1143	Lognormal	285.75	1143	Lognormal	285.75	1143	Lognormal	285.8	S
	Utility decrement per event	0.081	Normal	0.02	0.081	Normal	0.02	0.081	Normal	0.02	0.048	Normal	0.012	

Asthenia/Fatigue G3	Incidence	8%	Lognormal	5%	11%	Lognormal	3%	16%	Lognormal	1%	3%	Lognormal	1%	Se
	Duration (per event, days)	56.9	Lognormal	14.2	56.9	Lognormal	14.2	56.9	Lognormal	14.2	56.9	Lognormal	14.2	Se
	Cost per event	99	Lognormal	24.75	99	Lognormal	24.75	99	Lognormal	24.75	99	Lognormal	24.75	Se
	Utility decrement per event	0.102	Normal	0.026	0.102	Normal	0.026	0.102	Normal	0.026	0.063	Normal	0.016	
Cough G3	Incidence	0%	No	1%	0%	No	1%	0%	No	1%	0%	Lognormal	0%	Se
	Duration (per event, days)	70	Lognormal	17.5	70	Lognormal	17.5	70	Lognormal	17.5	70	Lognormal	17.5	Se
	Cost per event		No			No			No			No		
	Utility decrement per event		No			No			No			No		
Diarrhoea G3	Incidence	4%	Lognormal	1%	6%	Lognormal	1%	1%	Lognormal	0%	1%	Lognormal	0%	Se
	Duration (per event, days)	29.1	Lognormal	7.3	29.1	Lognormal	7.3	29.1	Lognormal	7.3	29.1	Lognormal	7.3	Se
	Cost per event	752.24	Lognormal	188.06	752.24	Lognormal	188.06	752.24	Lognormal	188.06	752.24	Lognormal	188.1	Se
	Utility decrement per event	0.007	Normal	0.002	0.007	Normal	0.002	0.007	Normal	0.002	0.004	Normal	0.001	
Dyspnoea G3	Incidence	0%	No	2%	1%	Lognormal	1%	1%	Lognormal	1%	2%	Lognormal	1%	Se
	Duration (per event, days)	6.2	Lognormal	1.5	6.2	Lognormal	1.5	6.2	Lognormal	1.5	6.2	Lognormal	1.5	Se
	Cost per event		No			No			No			No		
	Utility decrement per event		No			No			No			No		
Fever/Pyrexia G3	Incidence	0%	No	2%	2%	Lognormal	1%	1%	Lognormal	0%	0%	No	0%	Se
	Duration (per event, days)	7.5	Lognormal	1.9	7.5	Lognormal	1.9	7.5	Lognormal	1.9	7.5	Lognormal	1.9	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.001	Normal	0.0002	0.001	Normal	0.0002	0.001	Normal	0.0002	0.0005	Normal	1E-04	
Flu-like symptoms G3	Incidence	0%	No	2%	2%	Lognormal	1%	2%	Lognormal	0%	0%	No	0%	Se
	Duration (per event, days)	15.4	Lognormal	3.9	15.4	Lognormal	3.9	15.4	Lognormal	3.9	15.4	Lognormal	3.9	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.157	Normal	0.039	0.157	Normal	0.039	0.157	Normal	0.039	0.097	Normal	0.024	
GI perforation G3	Incidence	0%	Lognormal	2%	0%	No	1%	0%	No	1%	0%	No	0%	Se
	Duration (per event, days)	1	Lognormal	0.3	1	Lognormal	0.3	1	Lognormal	0.3	1	Lognormal	0.3	Se
	Cost per event		No			No			No			No		

	Utility decrement per event		No			No			No			No		
HFS/PPE G3	Incidence	1%	Lognormal	4%	5%	Lognormal	1%	0%	No	1%	0%	No	0%	Se
	Duration (per event, days)	60.5	Lognormal	15.1	60.5	Lognormal	15.1	60.5	Lognormal	15.1	60.5	Lognormal	15.1	Se
	Cost per event	944	Lognormal	236	944	Lognormal	236	944	Lognormal	236	944	Lognormal	236	S
	Utility decrement per event	0.025	Normal	0.006	0.025	Normal	0.006	0.025	Normal	0.006	0.014	Normal	0.003	
HF/CD/↓LVEF G3	Incidence	1%	Lognormal	2%	5%	Lognormal	1%	1%	Lognormal	0%	0%	No	0%	Se
	Duration (per event, days)	1	Lognormal	0.3	1	Lognormal	0.3	1	Lognormal	0.3	1	Lognormal	0.3	Se
	Cost per event		No			No			No			No		
	Utility decrement per event		No			No			No			No		
Headache G3p	Incidence	1%	Lognormal	2%	2%	Lognormal	1%	1%	Lognormal	1%	0%	Lognormal	0%	Se
	Duration (per event, days)	56.3	Lognormal	14.1	56.3	Lognormal	14.1	56.3	Lognormal	14.1	56.3	Lognormal	14.1	Se
	Cost per event		No			No			No			No		
	Utility decrement per event		No			No			No			No		
Hypertension G3p	Incidence	4%	Lognormal	2%	8%	Lognormal	2%	1%	Lognormal	0%	1%	Lognormal	0%	Se
	Duration (per event, days)	40.2	Lognormal	10.1	40.2	Lognormal	10.1	40.2	Lognormal	10.1	40.2	Lognormal	10.1	Se
	Cost per event	2.48	Lognormal	0.62	2.48	Lognormal	0.62	2.48	Lognormal	0.62	2.48	Lognormal	0.62	S
	Utility decrement per event	0.028	Normal	0.007	0.028	Normal	0.007	0.028	Normal	0.007	0.016	Normal	0.004	
Infection G3p	Incidence	1%	Lognormal	2%	1%	Lognormal	1%	1%	Lognormal	1%	0%	No	0%	Se
	Duration (per event, days)	67.2	Lognormal	16.8	67.2	Lognormal	16.8	67.2	Lognormal	16.8	67.2	Lognormal	16.8	Se
	Cost per event		No			No			No			No		
	Utility decrement per event		No			No			No			No		
Leukopenia G3p	Incidence	1%	Lognormal	2%	4%	Lognormal	1%	1%	Lognormal	1%	0%	No	0%	Se
	Duration (per event, days)	313.2	Lognormal	78.3	313.2	Lognormal	78.3	313.2	Lognormal	78.3	313.2	Lognormal	78.3	Se
	Cost per event		No			No			No			No		
	Utility decrement per event		No			No			No			No		
Mucositis/Stomatitis G3p	Incidence	0%	No	1%	2%	Lognormal	1%	1%	Lognormal	1%	0%	No	0%	Se
	Duration (per event, days)	4	Lognormal	1	4	Lognormal	1	4	Lognormal	1	4	Lognormal	1	Se

	Cost per event		No			No			No			No		
	Utility decrement per event	0.007	Normal	0.002	0.007	Normal	0.002	0.007	Normal	0.002	0.004	Normal	0.001	
Nausea/Vomiting G3p	Incidence	2%	Lognormal	2%	7%	Lognormal	2%	2%	Lognormal	1%	2%	Lognormal	1%	Se
	Duration (per event, days)	21.5	Lognormal	5.4	21.5	Lognormal	5.4	21.5	Lognormal	5.4	21.5	Lognormal	5.4	Se
	Cost per event	845.93	Lognormal	211.48	845.93	Lognormal	211.48	845.93	Lognormal	211.48	845.93	Lognormal	211.5	S
	Utility decrement per event	0.04	Normal	0.01	0.04	Normal	0.01	0.04	Normal	0.01	0.023	Normal	0.006	
Neutropenia G3p	Incidence	2%	Lognormal	2%	8%	Lognormal	2%	3%	Lognormal	1%	0%	No	0%	Se
	Duration (per event, days)	32.3	Lognormal	8.1	32.3	Lognormal	8.1	32.3	Lognormal	8.1	32.3	Lognormal	8.1	Se
	Cost per event	1143	Lognormal	285.75	1143	Lognormal	285.75	1143	Lognormal	285.75	1143	Lognormal	285.8	S
	Utility decrement per event		No			No			No			No		
Pain G3p	Incidence	3%	Lognormal	3%	5%	Lognormal	1%	1%	Lognormal	0%	5%	Lognormal	1%	Se
	Duration (per event, days)	33.5	Lognormal	8.4	33.5	Lognormal	8.4	33.5	Lognormal	8.4	33.5	Lognormal	8.4	Se
	Cost per event	171.14	Lognormal	42.79	171.14	Lognormal	42.79	171.14	Lognormal	42.79	171.14	Lognormal	42.79	S
	Utility decrement per event		No			No			No			No		
Proteinuria G3p	Incidence	1%	Lognormal	2%	0%	No	1%	0%	No	1%	0%	No	0%	Se
	Duration (per event, days)	28.8	Lognormal	7.2	28.8	Lognormal	7.2	28.8	Lognormal	7.2	28.8	Lognormal	7.2	Se
	Cost per event		No			No			No			No		
	Utility decrement per event		No			No			No			No		
Rash G3p	Incidence	1%	Lognormal	3%	2%	Lognormal	1%	1%	Lognormal	0%	0%	Lognormal	0%	Se
	Duration (per event, days)	4	Lognormal	1	4	Lognormal	1	4	Lognormal	1	4	Lognormal	1	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.005	Normal	0.001	0.005	Normal	0.001	0.005	Normal	0.001	0.003	Normal	0.001	
Bleeding G3p	Incidence	0%	Lognormal	2%	0%	Lognormal	1%	0%	Lognormal	0%	0%	No	0%	Se
	Duration (per event, days)	15.6	Lognormal	3.9	15.6	Lognormal	3.9	15.6	Lognormal	3.9	15.6	Lognormal	3.9	Se
	Cost per event		No			No			No			No		
	Utility decrement per event	0.012	Normal	0.003	0.012	Normal	0.003	0.012	Normal	0.003	0.007	Normal	0.002	

9.17 Appendix 17: Validation of economic model

Comments on: "Evaluation of the Cost-Effectiveness of Pazopanib for Treatment of Advanced Renal Cell Carcinoma from the UK National Health System Perspective (Report version 2.1)"

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3 March 2010

The following comments pertain to a comparison of the Report with the Draft Scope produced by NICE ("Single Technology Appraisal: Pazopanib for the first-line treatment of advanced and/or metastatic renal cell carcinoma").

1. The patient population as specified in the scope is "Patients with locally advanced and/or metastatic clear-cell renal cell carcinoma who have received no prior systemic therapy". The CE model considers two populations (see section 4.2 of the Report): patients that have received no prior systemic treatment for locally advanced or metastatic RCC (treatment-naive population); and, patients that have received one prior cytokine-based systemic treatment for locally advanced or metastatic RCC (cytokine-pretreated population). The first of these appears to be consistent with the Draft Scope, the second does not. Ought the analysis of the second population be omitted? If not, what is the rationale for retaining it? I am not convinced that the fact that this was one of the sub-groups in the GSK pivotal trial is sufficient justification.

RESPONSE: The analysis of the cytokine-pretreated group has been eliminated.

2. The comparators as specific in the Draft Scope are sunitinib and best supportive care (BSC). In the CE model, among treatment naïve patients IFN is also a comparator; among cytokine-pretreated patients sorafenib is a comparator and sunitinib is not (see section 4.3). What is the rationale for adding IFN to the analysis of treatment naïve patients? Why is sorafenib included as a comparator among cytokine-pretreated patients and sunitinib is not? Possibly the latter does not matter if this patient population falls outwith the scope anyway and so will be dropped. I note from the Report (section 4.3) that sorafenib was requested as a comparator by GSK.

RESPONSE: While sunitinib was approved by NICE for the first-line treatment of advanced/metastatic RCC under NICE Supplementary Advice regarding end of life treatments, the advice states that treatments approved following application of the advice will not necessarily be regarded as standard comparators for future appraisals of new treatments introduced for the

same condition. As this appraisal of pazopanib follows closely behind that of sunitinib, we believe that pazopanib should too be considered under this guidance relative to IFN-α.

3. The economic analysis section of the Draft Scope indicates that the CE model should be consistent with the NICE Reference Case. It might be a good idea to include a table at the start of the Report listing all the elements of the Reference Case and how the analysis conforms to these. This is commonly what the NICE Review Team does.

RESPONSE: A table listing elements of the Reference Case will be added.

4. The time frame as specified in the Draft Scope should be "sufficiently long to reflect any differences in costs or outcomes between the technologies being compared." The CE model has a 10-year time horizon because "approximately 99% of all patients receiving pazopanib would be dead within 10 years" (section 4.5). What proportion of the patients receiving the comparators would also be alive at this time point? Is it the same negligible quantity? Given that sunitinib is more effective in treatment-naïve patients (see Table 22) I wonder if not. In which case, is the time horizon appropriate?

RESPONSE: Based on preliminary analyses, it was projected that virtually all patients receiving pazopanib would be dead after 10 years. Since OS with pazopanib was projected to be greater than with sunitinib, IFN, or BSC, a similarly small proportion were projected to be alive for the comparators. Based on the final estimates of OS, approximately 20% of pazopanib patients, 9% of sunitinib patients, 2.5% of IFN patients, and 1% of BSC patients are projected to be alive at 10 years. Because of the substantial uncertainty regarding the projected survival curves beyond 10 years, we did not extend the timeframe further. Our estimates of cost-effectiveness of pazopanib may therefore be conservative.

5. The perspective for evaluating costs in the Draft Scope is "NHS and Personal Social Services" (PSS). The perspective in the CE model is "the UK healthcare system" (section 4.4). This seems to omit PSS costs. This may not be a problem because commonly PSS costs are small and therefore CE analyses can focus on the NHS costs. It appears that this is what has been done here. If so, this is probably ok, but it would be good to provide some reassurance that the PSS costs are negligible and are equal between the comparators. How is hospice care included, for example?

RESPONSE: It is correct that an NHS perspective was employed and the PSS costs were not considered. Hospice costs were not considered in the model. As mRCC is ultimately fatal for all patients, these costs are not likely to differ materially across comparators. Differences in expected time to death (on the order of a few months), and therefore discounting, are not likely sufficient to materially impact discounted costs.

6. Under "Other considerations" the Draft Scope indicates that "If evidence allows subgroups by resected versus unresected primary tumour will be considered." As far as I can see there is not a subgroup analysis of this kind in the CE model. Given that Pazopanib is probably

at best borderline cost-effective would it be worth trying to run an analysis on these sub-groups?

RESPONSE: Because of limited sample size, subgroup analyses were not conducted

7. Related to this, are there any additional sub-groups that should be considered for which an a priori clinical or cost-effectiveness case might be made. The Draft Scope does seem to allow for this.

RESPONSE: Because of limited sample size, subgroup analyses were not conducted

The following comments pertain to the Report.

8. Section 4.6.2. Other than the comment above about PSS costs, the costs components included in the analysis look fine to me.

RESPONSE: See above

9. Section 5.1. The broad approach to survival estimation looks fine to me, i.e., model survival in a common reference comparator, then apply a comparator-specific hazard ratio, then test the model assumptions.

RESPONSE: None required

10. Section 5.1.1.2. In accounting for the crossover from placebo to Pazopanib my reading is that the CE model "estimated the HR for OS with patients in the placebo group who crossed-over censored at the date of cross-over." This approach seems sensible to me; it means that survival estimates for placebo patients are not inflated by including those who crossed over to receive Pazopanib, and that survival estimates for Pazopanib patients are not deflated by the potentially lower values among the placebo patients who crossed over but did not receive Pazopanib for the full treatment period. However, would a better alternative approach be to rerun the models in Table 4 but without censoring any patients and then include a covariate in the multivariate adjustment for whether or not the patient crossed over (or, control for the time at which they crossed over if this varied by patient)? Is this feasible with the data available? If so, the advantage of doing it this way is that you will not be throwing away any data.

RESPONSE: The approach for controlling for cross-over in the analysis of OS has been modified.

11. Section 5.1. Is there a section describing how the relative survival of Pazopanib versus sunitinib were computed?

RESPONSE: The HR for pazopanib vs. sunitinib was not calculated explicitly in the report. In the submission document, it was calculated using methods of adjusted indirect comparison based on the estimated HRs for pazopanib vs. IFN and sunitinb vs. IFN.

12. Section 5.1 (or below this in the results section). It would be informative to see the final base case survival curves for all the comparators in the CE model. Could they be presented in a single figure? It would also be helpful to see a breakdown by PFS and PPS. This is related to my comment above about the time horizon in the model.

RESPONSE: The submission document includes a graph with the projected PFS and OS curves for all comparators on the same chart. The empirical distributions are not shown because it would suggest a naïve indirect comparison. A figure with PPS over time has been added as well

13. Section 5.2. As I understand it, the incidence of AEs reported in Tables 8 and 9 are estimated using adjusted indirect comparisons of trial estimates. Given that, on the basis of this, the incidence of AEs associated with Pazopanib appear to be relatively low compared with sunitinib, my concern is that that approach taken is in some way biased in favour of Pazopanib. It might be helpful to report the actual incidences in the pivotal study as well (e.g., in an appendix). If these are also relatively low compared with the estimated figures then this would be reassuring.

RESPONSE: The actual incidence estimates are included in the submission

14. Section 5.3. How were costs inflated to 2009/10 values?

RESPONSE: All costs were adjusted to 2009/10 values where appropriate using the Hospital and Community Services Prices Index (Curtis 2008).

15. Section 5.3.1. Presumably an "estimate" of the cost of Pazopanib will not be used in the final model? I assume that by the time of the submission to NICE GSK will know the actual price they are going to charge for Pazopanib?

RESPONSE: The final proposed price will be used in the final submission

16. Section 5.3.1. How will Pazopanib (and the other medications) be administered? This needs to be explicitly stated in the text and justified. Will it involve additional contacts with the NHS, or is it part of regular disease monitoring? Does this have additional cost implications? If so, these ought to be included. If not, this ought to be explicitly stated in the text and justified too.

RESPONSE: It is assumed that oral medications will not require additional contacts for administration. It is assumed that administration of IFN will require a nurse visit in 25% of administrations.

17. Section 5.3.1. What is the duration of therapy (as opposed to the time horizon of the model? Is it lifetime, or the progression-free period, or something else? Please state this

explicitly here. What was the duration of therapy in the pivotal trial? Presumably what is being modelled is the same as that, otherwise the effects cannot be calculated based on these data? Should the duration of therapy be varied in a sensitivity analysis? Might this make Pazopanib look better value for money?

RESPONSE: Consistent with the clinical data, pazopanib and sunitinib were assumed to be administered until disease progression; IFN was assumed to be administered until progression or 52 weeks maximum. Costs of therapy are further adjusted by relative dose intensities obtained from the trials. This will be stated clearly in the submission.

18. Section 5.3.2. I think that more detail is required about the assumed services and costs of treatment of AEs, presented in Table 12. On the one hand higher costs of treating AEs will work *in favour of* Pazopanib in a comparison with sunitinib, since the incidence of AEs appears to be in average higher with sunitinib. On the other hand higher costs of treating AEs will work against Pazopanib in a comparison with BSC.

RESPONSE: The table lists for all services the HRG code and corresponding reference cost. It is not clear what additional detail is required. In sensitivity analyses, the model is relative insensitive to 50% increases or decreases in the costs of AEs.

19. Section 5.3.3. How were the costs in Table 15 calculated? Presumably they were based on the figures in Table 14 in some way, but it is not clear.

RESPONSE: It is not clear which table you are referring (we may be looking at a different version of the report). If referring to "Expected costs per grade 3+ adverse events" this was calculated by summing costs in table above.

20. Section 5.4. The calculation of the utility values seems comprehensive and plausible to me. My only criticism is based on the final figures reported in Table 20. My reading of these is that, assuming no AEs, health-related quality of life does not decline in the PFS period, nor does it decline in the PPS period. Is this realistic? I can think of two reasons why it might not be. First, EQ-5D scores will decline with age and the time period of the model is 10 years. So, irrespective of progression I would think that health-related quality of life will decline during the time horizon of the model. Second, as patients get close to death I think that their health-related quality of life will decline rapidly. Given that the comparators in the CE model result in different durations in PFS and PPS states, then I think that the rate of decline might have a differential effect on QALYs associated with the comparators. In my view this is an important issue, because when NICE are considering an intervention that is borderline CE then they take a number of considerations into account, and they explicitly state that robustness of the method for computing the health-related quality of life values will be one of these.

RESPONSE: It is true that utilities may vary over time. However, the PFS period is relatively short and data on the decline in utilities during the PPS period are unavailable. The approach we used is consistent with that used in the evaluation of sunitinib in mRCC.

21. Section 6.2. Will a sensitivity analysis be undertaken to investigate the impact of changes in the drug acquisition cost of Pazopanib? Is this in Appendix II? Maybe it ought to feature more prominently in the Report? A summary figure plotting CE against Pazopanib drug acquisition cost would be nice.

RESPONSE: A sensitivity analyses was undertaken evaluating the effect of different discounts to sunitinib as well as various patient access schemes for pazopanib (in appendix)

22. Section 8.1.1. Please provide some intuition as to why Pazopanib has lower discounted QALYs than sunitinib (Table 22). Is it due to it having a worse HR versus the reference in the indirect comparison of effectiveness?

RESPONSE: This was because the HR for OS for pazopanib vs. IFN was higher than that for sunitinib vs. IFN. This has been changed in the final submission.

23. Section 8.1.1. It is possible from the figures in Table 22 to calculate a crude estimate of mean utility score associated with each comparator. I did this for treatment-naïve patients only. Using either the discounted or the discounted figures if you divide the QALY estimates by the LY estimates this gives you a crude approximation of the mean utility score associated with each comparator. When I do this I note that Pazopanib has the highest value. My interpretation of this is that the model calculates that health-related quality of life is higher with Pazopanib than with any of the other comparators. Why might this finding arise? If the reason is uncontroversial, then it might be worth pointing this out in the text.

RESPONSE: The higher mean utility for pazopanib is due to the fact that the HR for PFS is lower than the HR for OS, therefore the proportion of OS that is PFS is greater with pazopanib than the other comparators. Because PFS has a greater utility than PPS, this results in a higher mean utility for pazopanib. The lower incidence of some AEs may also contribute to this difference although this is probably minor.

24. Section 8.1.2. In my view the PSA looks fine. My interpretation of it all, summarized by Figure 10, is that Pazopanib is unlikely to be the preferred choice on cost-effectiveness grounds. This would appear to be the case even if IFN was removed as a comparator (see above).

RESPONSE: The results are changed in the submission.

25. Section 8.1.2.1. Table 24. It would be helpful to add the base case estimates to the top row of the table.

RESPONSE: Agreed.

26. Section 8.1.2.1. Table 24. Please point out in the text why the CE of Pazopanib versus sunitib (say) changes when the HR for Pazopanib versus INF changes. Is it due somehow to the indirect comparison?

RESPONSE: Yes, it is due to the nature of the indirect comparison.

Related procedures for evidence submission

9.15 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be

no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

9.16 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It

is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information

that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

9.17 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).