Pazopanib for the first line treatment of patients with advanced and/or metastatic renal cell carcinoma: A Single Technology Appraisal

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Contributions of authors

Mary Kilonzo conducted the critique of the manufacturer's economic evaluation, supervised by Luke Vale. Jenni Hislop and Graham Mowatt critiqued the manufacturer's submission of effectiveness evidence. Donald Bissett and Sam McClinton provided clinical advice and drafted the background and critique of the manufacturer's decision problem. Andrew Elders critiqued the statistical methods used. Cynthia Fraser conducted the literature searches and critiqued the methods used for identifying relevant literature. All authors commented on drafts of the report.

SUMMARY

Scope of the submission

The submitted evidence related to the use of pazopanib for the first-line treatment of patients with advanced and/or metastatic renal cell carcinoma who have received no prior systemic therapy, compared with sunitinib, immunotherapy (interferon-α (IFN), interleukin-2) or best supportive care. Within the economic model pazopanib was compared with best supportive care, or first line treatment with IFN or sunitinib.

Summary of submitted clinical effectiveness evidence

Evidence on pazopanib came primarily from the treatment-naïve sub-population of a phase III randomised controlled trial (VEG105192) comparing pazopanib with placebo. Two non-randomised studies reporting pazopanib (VEG102616, VEG107769) were provided as supportive evidence. The relative effectiveness of pazopanib versus comparator treatments was based on a (random effects) indirect comparison involving pazopanib (one study, n=233), sunitinib (one study, n=750) and IFN (five studies, n=1014). It was assumed that medroxyprogesterone (MPA) and vinblastine would have no impact on progression-free survival or overall survival and were therefore equivalent to placebo. Four IFN studies used MPA as a comparator while two used vinblastine either as a comparator or in addition to the IFN intervention.

Efficacy

For progression-free survival (PFS), in the VEG105192 study there was a statistically significant longer survival for pazopanib compared with placebo (as assessed by independent review committee, 23 May 2008 cut-off) (median 11.1 versus 2.8 months, hazard Ratio (HR) 0.40, 95% confidence interval (CI) 0.27 to 0.60). Alternative data (HR of 0.36 (95% CI 0.24 to 0.55)), based on actual scan dates rather than scheduled visits, were used in the economic model.) Directly comparative data comparing sunitinib with IFN reported a statistically significant longer survival for sunitinib (median 11 versus 5 months, HR 0.539, 95% CI 0.451 to 0.643). Data from the indirect comparison suggested that pazopanib had a greater survival than IFN (HR 0.512, 95% CI 0.326 to 0.802) but provided no evidence of any difference compared with sunitinib (HR 0.949, 95% CI 0.575 to 1.568).

With regard to overall survival, at the 15 March 2010 cut-off for study VEG105192, 64% (n=99) of patients in the pazopanib arm and 63% (n=49) of patients in the placebo arm had died and a total of 51% (n=40) of placebo patients had crossed over to receive pazopanib. Although data were provided on an intention to treat basis, cross-over between therapies made such data difficult to interpret. The manufacturer's preferred statistical method to calculate

overall survival, taking cross-over into account, was a rank preserved structural failure time (RPSFT) analysis (weighted but unadjusted for baseline characteristics). There was no evidence of any statistically significant difference between pazopanib and best supportive care (HR 0.501, 95% CI 0.136 to 2.348). For the comparison of sunitinib with IFN there was no evidence of a statistically significant difference between the groups (HR 0.821, 95% CI 0.673 to 1.001). These data were not used in the economic model, which used an exploratory analysis in the subset of patients who did not receive any post study cancer treatment (HR 0.647 (95% CI 0.483 to 0.870)). In the indirect comparison there was no statistically significant difference between pazopanib versus IFN (HR 0.627, 95% CI 0.173 to 2.269) or between pazopanib versus sunitinib (HR 0.969, 95% CI 0.359 to 2.608).

In study VEG105192 overall response rate was higher for pazopanib (32%, 49/155) compared with placebo (4%, 3/78), p<0.001 (as assessed by independent review committee). For the comparison of sunitinib with IFN the response rate for sunitinib (47%, 176/375) was higher than that for IFN (12%, 46/375), p<001) (as assessed by investigators).

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

Safety

At the 23 May 2008 cut-off 91% (141/155) of pazopanib patients had experienced an adverse event, of which 87% (n=135) were related to study medication, 37% (n=57) were grade 3 and 6% (n=9) were grade 4. In the placebo group the rates were 74% (58/78), 37% (n=29), 13% (n=10) and 6% (n=5), respectively. Treatment-related adverse events reported by > 20% of patients in the pazopanib arm included diarrhoea (39%), hypertension (38%), hair colour changes (38%), nausea (22%) and in terms of laboratory abnormalities alanine transaminase (ALT) increased (21%). Specific adverse events highlighted by the manufacturer in the pazopanib-treated arm included arterial thrombotic events (4%), congestive heart failure (1%) and haematological events, with any grade cytopenias ranging from 25% for anaemia to 38% for leukopenia in terms of toxicity grade increase from baseline. Treatment-related adverse events reported by > 20% of sunitinib patients included diarrhoea (61%), fatigue (54%),

nausea (52%), dysgeusia (46%), anorexia (34%), dyspepsia (31%), vomiting (31%), hypertension (30%), stomatitis (30%), hand-foot syndrome (29%), skin discolouration (27%), mucosal inflammation (26%), rash (24%) and dry skin (21%). Laboratory abnormalities ranged from 20% for increased total bilirubin to 78% for leukopenia.

The indirect comparison (via IFN data) of specific adverse events (all grades) for pazopanib relative to sunitinib showed generally lower rates for pazopanib, although these were statistically significant only for fatigue (HR 0.21, 95% CI 0.06 to 0.77). Rates for alopecia (HR 3.63, 95% CI 0.05 to 253.99) and hypertension (HR 2.69, 95% CI 0.11 to 63.56) were on average lower for sunitinib but the difference was not statistically significant.

Summary of submitted cost-effectiveness evidence

The manufacturer submitted a de novo model analysing the cost-effectiveness of pazopanib for treatment-naïve patients. The model compares pazopanib against IFN, sunitinib and best supportive care. The model was described by the manufacturer as a "partitioned survival" model characterised by three mutually exclusive health states: Alive pre-progression, Alive post-progression and Dead. Most of the effectiveness data were based on the pivotal study VEG105192 but relative effectiveness data were based upon the random effects indirect comparison.

Based upon the work presented in an addendum to the initial submission and including a 12.5% discount for pazopanib, sunitinib was extendedly dominated by a combination of pazopanib and IFN. As a consequence the incremental cost per QALY for pazopanib versus IFN was £38,925. The results were not greatly altered over the range of univariate deterministic sensitivity analyses conducted by the manufacturer but pairwise probabilistic sensitivity analyses suggested that given a threshold value of £30,000 there is a 54% probability that pazopanib was preferred to sunitinib, 40% chance against IFN and 47% chance against best supportive care.

The ERG conducted multi-way sensitivity analyses and showed that for some combinations of changes the ICER associated with pazopanib could be increased above £50,000. The ERG also considered the impact of changes in the hazard ratios and showed that if the HR for overall survival for pazopanib was greater than 0.75 then the ICER against sunitinib would be approximately £58,000. The relevance of this is that the confidence interval surrounding this hazard ratio was very wide. The ERG also conducted a four-way probabilistic comparison which showed that below a threshold of £20,000 best supportive care was likely to be cost-effective.

The main drivers of the cost-effectiveness results were the drug costs and the hazard ratios. There are concerns about the methods used to derive the overall survival hazards ratio and the ERG has noted limitations in the approach used.

Commentary on the robustness of submitted evidence

Seven RCTs of variable quality formed the basis for the manufacturer's submission. It was unclear from most study reports whether randomisation had been carried out appropriately and in four it was unclear whether allocation concealment was adequate. However, the participants within all studies were comparable at baseline and six studies undertook an intention to treat analysis. Blinding of care providers, participants or outcome assessors was undertaken in three studies, was unclear in three and was not undertaken in one study. In four studies there were no imbalances in drop-outs, in two this was not clear while one study was considered to have imbalances in drop-outs. Duration of follow-up ranged from 27.3 to 242.67 weeks (reported as mean or median) across four studies and was unclear in three studies. Although the ERG identified a few additional reports that might have been considered potentially relevant there was no evidence that any data of consequence had been omitted from the submission.

Strengths

- The level of evidence included in the submission was RCTs (other than two non-randomised studies reporting pazopanib that were included as supportive evidence) and as such was of reasonable quality.
- Within the manufacturer's definition of the decision problem, no evidence of consequence appears to have been omitted.
- The RPSFT method used to deal with cross-over of placebo-treated patients to pazopanib in study VEG105192 was an appropriate method to use (but see comment below).
- The manufacturer attempted to provide an informative estimate of the relative effectiveness and safety of pazopanib by means of a formal indirect comparison with studies reporting sunitinib and IFN.

Weaknesses

- The quantity of evidence was limited - a few studies met the inclusion criteria.
- No RCTs were identified that directly compared pazopanib with sunitinib.
- There were concerns with some aspects of the RPSFT analysis. The timing of the final analysis meant that the data may not be mature enough for an effect size to be estimated with sufficient accuracy, given that the chosen statistical method is sensitive to the

maturity of the data. The method of weighting used may not be the most appropriate given the lack of an adequately developed weighted RPSFT methodology required to analyse the data robustly.

- The method of RPSFT advocated by the manufacturer may not be the most appropriate given the lack of an adequately developed weighted RPSFT methodology.
- There was uncertainty surrounding the estimates reported by the indirect comparison, relating to the data used to derive the hazard ratios used to estimate relative effectiveness and hence cost-effectiveness.

Areas of uncertainty

Although the RPSFT technique used to deal with cross-over is an appropriate one to use, the specific method of RPSFT used in the original submission (unweighted) was different to that used for the longer-term data reported in the addendum (weighted). Also, the RPSFT method does have some disadvantages, for example it is heavily weighted towards the early follow-up period and the analysis only controlled for cross-over from placebo to pazopanib and not receipt of other post-study anti-cancer therapies.

There was uncertainty surrounding the estimates reported by the indirect comparison, relating to the data used to derive the hazard ratios used to estimate relative effectiveness. While the pazopanib and sunitinib studies limited inclusion to participants with ECOG performance status 0 or 1, three of the IFN studies contained some participants with ECOG performance status 2 (i.e. a worse prognosis). This might make the relative performance of pazopanib and sunitinib against IFN appear better than it actually is. However there is no directly comparative evidence on the effect of pazopanib, sunitinib or interferon-α in subgroups of patients defined on the basis of performance status. For the indirect comparison the manufacturer assumed that MPA and vinblastine would have no impact on progression-free survival or overall survival and could therefore be considered as palliative treatment equivalent to placebo. However, although the response rate to both MPA and vinblastine is low, it is not zero.

The manufacturer concentrated on presenting a series of one-way sensitivity analyses which demonstrated that the cost-effectiveness results are not greatly altered by univariate changes. They did not consider the joint impact of changes in several parameters simultaneously. Furthermore, given the imprecise and potentially biased estimates of survival the deterministic analyses fail to fully illustrate the degree of uncertainty that exists.

Key issues

- There is short term evidence of efficacy of pazopanib for the treatment of advanced and/or metastatic renal cell carcinoma in patients who have not undergone previous systemic therapy.
- The available evidence suggests that pazopanib has similar efficacy to sunitinib.
- Although pazopanib appears to be a relatively safe treatment for advanced and/or metastatic renal cell carcinoma it is associated with a variety of adverse events which appear to occur at a lower rate than for sunitinib.
- There is no robust evidence on the long term safety or efficacy of pazopanib.
- There is no robust evidence on the effectiveness of pazopanib compared with other relevant comparators.
- The RPSFT method used to deal with cross-over of placebo-treated patients to pazopanib in study VEG105192 is a recently developed method that is continuing to undergo further development.
- Only a few studies informed the indirect comparison and there is uncertainty surrounding the estimates generated by it.
- On average in the manufacturer's analyses pazopanib was associated with an ICER in excess of just over £38,000.
- Plausible changes in estimates used could increase the ICER for pazopanib to above £50,000. However, point estimates of cost-effectiveness do not adequately reflect the uncertainty caused by a potentially inappropriate method of estimating hazard ratios.
- An ongoing RCT comparing pazopanib with sunitinib (VEG108844, COMPARZ) will report in 2012.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
ECCO	European CanCer Organisation
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC-GU	European Organisation for Research and Treatment of Cancer-Genito-Urinary
ERG	Evidence Review Group
FACT-G	Functional assessment of cancer therapy – general scale
HFS	Hand foot syndrome
HIF	Hypoxia inducible factor
HR	Hazard ratio
HRQOL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFN	Interferon-α
IPCW	Inverse probability of censoring weighted
ITT	Intention to treat
LY	Life year
MMRM	Mixed-model repeated measures
MRC RE01	Medical Research Council RE01 trial
MSKCC	Memorial Sloan-Kettering Cancer Center
MU	Million units
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PbR	Payment by Results
PenTAG	Peninsula Technology Assessment Group

PFS	Progression-free survival
PICO	Patient/population, intervention, comparison, outcome
PPE	Palmar-plantar erythrodysaesthesia
PPS	Post progression survival
PS	Performance status
QALY	Quality adjusted life year
QOL	Quality of life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RPSFT	Rank preserved structural failure time
SE	Standard error
SG	Standard gamble
SMC	Scottish Medicines Consortium
SWOG	Southwest Oncology Group
TCC	Transitional cell carcinoma
TNM	Tumour Node Metastasis
TTO	Time trade off
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	Von Hippel-Lindau
WTP	Willingness to pay

1 INTRODUCTION TO THE ERG REPORT

The remit of the evidence review group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. Evidence has been submitted to NICE by GlaxoSmithKline (GSK) UK. The information considered by the ERG related to an initial submission and a later revised submission. The initial submission consisted of: a main submission report, clinical study reports, a systematic review report, and an economic model. In addition to these data GSK provided a response to points for clarification requested by the ERG. The revised submission consisted of an addendum to the main submission, a study report, a Patient Access Scheme (PAS) submission and a revised and updated economic model. In addition to these data GSK provided a response to further points for clarification requested by the ERG relating specifically to the revised submission. The ERG also conducted further economic modelling to explore the impact of uncertainties surrounding the cost-effectiveness results.

The submitted evidence related to the use of pazopanib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. Within the economic model pazopanib has been compared with best supportive care, or first line treatment with interferon-α or sunitinib.

2 BACKGROUND

Kidney cancer caused 3,848 deaths in the UK in 2008. It is the seventh most common cancer in men, 5165 new cases were diagnosed in 2007. This compares with 3,063 new cases in women, giving a male: female ratio of 5:3. There are very few cases of kidney cancer in early adulthood, but from age 40 the rates begin to rise steeply. The highest rates in both sexes are in the over 75's.[1]

In adults in the UK almost 90% of malignant kidney tumours arise in the renal parenchyma, whilst a further 5% arise in the renal pelvis and 5% in the ureter. Cancers of the renal parenchyma are also known as renal cell carcinomas (RCC). There are five subgroups of RCCs: conventional (clear cell, also called non-papillary), which account for 75-80% of RCC tumours; papillary (chromophilic) accounting for 10-15%; and chromophobe, collecting duct carcinoma and unclassified renal cell carcinoma which together make up the remainder of RCC tumours. Prognostic differences among these subtypes have been demonstrated in relatively large studies. A study by Cheville and colleagues (N = 2385) reported 5-year survival rates of 68.9%, 87.4%, and 86.7% for clear cell, papillary, and chromophobe renal cell carcinoma, respectively.[2] After stratifying for disease stage[3] and nuclear grade[4] the clear cell subtype had a significantly worse prognosis than papillary and chromophobe renal cell carcinoma ($p < 0.001$), but there was no evidence of a statistically significant difference between papillary and chromophobe renal cell carcinoma. Tumours in the renal pelvis consist mainly of transitional cell carcinomas (TCC).

Increases in kidney cancer incidence have been reported in many different countries around the world. Undoubtedly some of this increase is attributable to the extensive use of imaging methods, such as ultrasound and computed tomography (CT) of the abdomen, which frequently leads to the incidental detection of asymptomatic disease. In the 1970s and 1980s, malignancy was found incidentally in only 10-20% of patients. This percentage has increased to 35-50% in the last 15 years.[5,6] Based on retrospective analyses, it appears that incidentally discovered renal tumours are generally smaller than symptomatic tumours, have a lower stage, and are associated with higher rates of disease-free and overall survival. It is not yet clear whether the prolonged survival following treatment of incidental renal cell carcinoma is attributable to detection of the tumour at an earlier TNM stage or an intrinsically more indolent behaviour in these tumours. Some studies support the former although Tsui and colleagues suggest the latter.[7] Given that smoking and obesity are major risk factors for kidney cancer, future trends in its incidence can be expected to mirror changes in these, with a

relative increase in women compared with men as the sex ratio of smokers approaches 1:1, and the prevalence of obesity worsens.

The optimum treatment of kidney cancer is largely determined by the stage at which the disease presents. 40-50% of kidney cancers are diagnosed when localised, but around one third present with distant metastases. Most patients who present with organ-confined disease undergo surgical removal of the cancer (radical nephrectomy). Advanced kidney cancer is defined as either locally advanced disease which is unresectable (by virtue of direct invasion of adjacent organs or regional spread to retroperitoneal lymph nodes) or metastatic disease. For some patients with metastatic disease a nephrectomy is a useful therapeutic procedure, particularly when the primary tumour is causing pain and bleeding, and the volume of metastatic disease is relatively small e.g. asymptomatic pulmonary nodules. Two prospective randomised studies have evaluated the role of nephrectomy in patients with metastatic renal cell carcinoma. The Southwest Oncology Group (SWOG) study randomised 246 patients (241 eligible) with metastatic renal cell carcinoma and resectable renal cell carcinoma to radical nephrectomy followed by IFN, or IFN alone.[8] Despite the fact that response rates were similar in both groups, overall survival was 3 months longer in patients who received combination therapy (mean survival 11 months v 8 months). This improvement was seen consistently across all stratifying factors, including measurable disease, performance status, and site of metastasis. The EORTC-GU study also showed a significant improvement in the time to progression and survival favouring combination therapy (median survival 17 months v 7 months).[9] The benefits of nephrectomy in patients with extensive metastatic disease (e.g. liver, bone, brain) or poor performance status are limited and surgical intervention may not be indicated prior to systemic treatment.[10]

Survival from kidney cancer is heavily dependent on the stage of disease at diagnosis. Patients with small cancers localised to the kidney have 5 year survival rates of 80-90% after surgical removal of the cancer. However 40-50% of patients relapse after nephrectomy, the risk increasing with tumour size and spread to regional lymph nodes. Preoperative CT scan appears insufficiently accurate in detecting lymph node metastases. Less than one-half of enlarged nodes are histologically positive.[11] In addition extensive lymph node dissection at the time of radical tumour nephrectomy does not improve survival.[12] This cancer has a high propensity for blood-borne spread, and these relapses are explained by microscopic metastatic disease present at the time of nephrectomy for apparently "early disease".

The prognosis for metastatic kidney cancer is poor, with around 10% still alive at five years. It is resistant to conventional cytotoxics. However this is a heterogeneous group of patients

and the disease can be unpredictable in its behaviour. Occasional cases of spontaneous regression occur, and more frequently periods of stable disease are observed without treatment. In an interesting phase II study conducted in the UK, in which patients were followed until they had clear signs of progression and were then treated with IFN, five of 73 patients (7%) had a spontaneous complete or partial remission.[13] Four of the patients (12%) remained in remission without signs of progression for 12 months. It should be noted that this study involved a select group of patients who had a better prognosis than most patients with metastatic renal cell carcinoma and were referred to an experienced tertiary treatment centre. Similarly disease-free intervals of many years can be followed by relapse and death from metastatic disease.

Such observations led to interest in immunotherapy for this cancer. Until 2009 the only licensed treatments available to NHS patients with metastatic kidney cancer were IFN and interleukin-2. The benefits of these are believed to be modest (further information is presented in Chapter 4). The MRC RE01 study compared IFN with medroxyprogesterone acetate (MPA) (a progestogen commonly used as an appetite stimulant but with only minor antitumour activity in this disease) in patients with advanced and metastatic kidney cancer.[14] The objective response rate was 14% with IFN and 2% with hormone therapy. The median survival time was 9 months versus 6 months, and two year survival 22% versus 13%. It should be noted that more than 40% of the participants in this study had not undergone nephrectomy, and around a quarter had Eastern Cooperative Oncology Group (ECOG) performance status 2. ECOG performance status ranges from 0 to 5 as follows:

0 Fully active, able to carry on all pre-disease performance without restriction;
1 Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature;
2 Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours;
3 Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours;
4 Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair;
5 Dead.

More recently the results of the MRC RE04 study comparing interferon-α with the combination of interferon, interleukin-2, and fluorouracil have been published.[15] The response rate to the combination was higher (21% versus 14%), but the median survival time was identical (18.6 months versus 18.8 months), and the 3 year survival rate similar (26% versus 30%). The improved survival rate in RE04 compared with RE01 is probably simply

due to patient selection, 90% of those entered into the second study having had a cytoreductive nephrectomy, and all had ECOG performance status 0 or 1.

Prior to 2009, patients who did not respond to immunotherapy or progressed after treatment was discontinued were either treated symptomatically or offered treatment within clinical trials of novel agents. Patients with poor performance status from the outset were frequently offered only palliative care.

A number of prognostic factors have been established in patients with advanced disease over the last three decades, and these include grade of tumour (Fuhrman grading system is the most widely accepted), performance status, haemoglobin, hypercalcaemia, nephrectomy and length of time between nephrectomy and relapse with metastatic disease.

Von Hippel-Lindau (VHL) syndrome is inherited as an autosomal dominant condition which predisposes to clear cell carcinoma of the kidney. The VHL gene is a tumour suppressor gene, loss/mutation of which leads to activation of hypoxia inducible factor (HIF). One of HIF's effects is the over-expression of vascular endothelial growth factor (VEGF), which drives tumour angiogenesis. It has been found that inactivation of VHL occurs in the majority of clear cell carcinomas of the kidney, but not in non-clear cell variants. These observations have led to the development of targeted therapies directed against VEGF and its receptor (VEGFR).

Although several targeted therapies have shown benefit in advanced kidney cancer and are licensed for use as first or second line treatments (sunitinib, sorafinib, temsirolimus, everolimus, and bevacizumab in combination with interferon), only sunitinib is currently approved by NICE.[16] Approval in 2009 was based on follow-up data from a study in 750 patients with advanced/metastatic renal cell cancer (either pure clear cell or containing clear cell elements) and with good performance status (ECOG 0 or 1). Patients were randomised to receive either sunitinib 50 mg daily (six week cycles, four weeks on, two weeks rest) or interferon-α injections.[17] The response rates were considerably different, 31% versus 6% in favour of the targeted therapy. Many of the patients in the interferon arm went on to receive sunitinib after disease progression on interferon. Despite this, mature data from this study showed a survival benefit, with final overall median survival 26.4 months in the sunitinib arm and 21.8 months in the IFN arm. When patients who had crossed over from interferon to sunitinib after disease progression were excluded from the analysis, the median overall survival was 28.1 months for the 193 participants in the sunitinib arm and 14.1 months for the 162 participants in the IFN arm. The role of surgery in patients treated with these targeted agents is still unclear.

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of the epidemiology, pathology, and natural history of kidney cancer is clear and accurate. It should be acknowledged however that the prognostic factors which were well established in the era of immunotherapy for renal cell cancer have yet to be confirmed with targeted therapy. For example, the importance of nephrectomy in the presence of widespread metastatic disease is unclear, and indeed is being tested in clinical trials.

2.2 Critique of manufacturer's overview of current service provision

The overview of current service provision is largely accurate. Most patients with kidney cancer are diagnosed with localised disease, and the majority of these are dealt with surgically. These patients are followed up by urologists with regular imaging, so that the majority of the 40% who relapse should be picked up with relatively small volume disease and good performance status.

With regards to the patients who are diagnosed with metastatic disease at presentation, the overview suggests that most undergo nephrectomy before proceeding with treatment with sunitinib. There is a group of patients who present with widespread metastatic disease and an asymptomatic primary kidney cancer, who are treated with sunitinib initially without nephrectomy. Most of the studies of targeted therapy for advanced clear cell carcinoma of the kidney include around 10% of patients who have not had nephrectomy, and in some studies this has been as high as one third of patients.[18]

The overview correctly states that since 2009 the number of patients treated with immunotherapy, in particular interferon-α, has fallen dramatically. Indeed first-line therapy with interferon for metastatic renal cell carcinoma has essentially ceased in the UK. Sunitinib has been adopted as standard therapy for good performance status patients with advanced/metastatic clear cell carcinoma of the kidney throughout the UK. In the absence of alternative targeted therapies to be used after progression on sunitinib, selected patients will be offered second line therapy with interferon-α (e.g. patients with metastatic disease in the lung but no other organs, previous nephrectomy, and a long disease-free interval).

Sunitinib therapy is currently prescribed only by oncologists, but the overview correctly describes a variety of local approaches to treatment monitoring and management of toxicities. Monitoring of haematological and biochemical indices, as well as blood pressure monitoring and treatment of hypertension, is commonly shared with the patient's general practitioner/practice nurse. Nurse led clinics, specifically focusing on kidney cancer, have helped ensure safe and effective monitoring of these patients in larger centres.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

In general the estimated numbers of patients seem as accurate as national cancer statistics will permit. The estimate that 32% of patients with kidney cancer have unknown staging (Cancer Research UK) is unexplained, but the assumption that a third of these have metastatic disease seems reasonable. Similarly the proportions of patients with each variant of renal cell cancer are widely accepted.

Estimation of the population of patients with good performance status and advanced/metastatic disease is challenging, and could vary considerably across the UK, for example influenced by deprivation index. Within the MRC RE01 study 20% of the sample had performance status 2 or worse, and undoubtedly other patients with poor performance status were excluded from study entry by their clinicians. The manufacturer's estimate of 32% ineligible for treatment because of performance status therefore is again reasonable. However it should be noted that in the expanded access programme for sunitinib in kidney cancer, 13% of patients had performance status 2 or worse, and still appeared to benefit from treatment, with acceptable toxicity.[19] It is likely that clinicians will use sunitinib (and pazopanib) in some patients with performance status worse than 1, so that the number of patients to be treated may be somewhat higher than estimated.

3.2 Intervention

Pazopanib's mechanism of action is clearly outlined, with emphasis on differences between it and sunitinib. The common toxicities of both agents are described. It is hypothesised that some of the toxicities which lead to impairment of quality of life and dose reduction of sunitinib may occur less frequently with the novel tyrosine kinase inhibitor, because it inhibits a different spectrum of tyrosine kinases.

It should be noted that all members of this group of targeted anticancer agents are associated with life-threatening events in a small number of patients. Not surprisingly, by interfering with angiogenesis, haemorrhage can result, particularly within tumour. However arterial thrombotic events (cardiac and cerebrovascular) also occur in around 3% of patients treated with sunitinib or pazopanib.[20,21] Similarly, large bowel perforation is a rare but serious consequence of inhibition of VEGFR tyrosine kinase.

3.3 Comparators

Sunitinib is correctly identified by the manufacturer as an appropriate comparator. However since no head-to-head data for pazopanib versus sunitinib are currently available, the manufacturer presents an indirect comparison via interferon-α (IFN) and placebo/best supportive care (BSC) for the comparative clinical and economic evaluations in this appraisal. Interferon-α (IFN) may also be thought of as a valid comparator, although as noted in Chapter 2 its use in the NHS has dramatically declined recently and thus its relevance to the NHS is questionable. This should be noted as a point for consideration when interpreting the manufacturer's cost-effectiveness results summarised in Chapter 5 and the ERGs further analyses reported in Chapter 6.

The validity of using indirect comparisons as a surrogate for data from a head-to-head trial of pazopanib versus sunitinib may lead to unreliable estimates of effectiveness and cost-effectiveness and hence is questionable. However, the ERG notes that robust studies directly comparing pazopanib with sunitinib are currently unavailable. An ongoing head-to-head study of pazopanib versus sunitinib (VEG108844 [COMPARZ] and sub-study VEG113078 will address uncertainty in the comparative efficacy of the two agents in the first-line treatment of advanced renal cell cancer, with a final study report due in the second quarter of 2012.

3.4 Outcomes

These are appropriate and inclusive.

3.5 Time frame

Given the reliance on the indirect comparison, current analyses must be treated cautiously. Ideally, the assessment would be based upon the results of at least one of the head-to-head comparative studies against sunitinib.

3.6 Other relevant factors

The manufacturer notes that sunitinib was approved by NICE under the supplementary advice on appraising end of life medicines and argues that, given the same consideration, pazopanib should also be considered as a cost-effective option for this patient population.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturer's search strategy and comment on whether the search strategy was appropriate

Details of the literature searches undertaken on 23rd November and 2nd December 2009 are reported in Appendix 2 of the manufacturer's initial submission document and Appendix B of the accompanying systematic review. MEDLINE, EMBASE, MEDLINE In process and, from the Cochrane Library, CENTRAL, CDSR and the Cochrane Methodology Register (CMR) were searched for reports of clinical data. It is unclear why CMR – a register of methodological studies – was included. Conversely, DARE – the Database of Abstracts of Reviews of Effects – would have been appropriate to have been included in the Cochrane Library search.

These searches were supplemented by hand searching of the major oncology conference abstracts (ASCO, ESMP, ECCO) from 2007-9 and for details of ongoing studies, Clinical Trials.gov and Current Controlled Trials registers were searched.

While other databases such as Science Citation Index, CINAHL and Biosis would have been appropriate to search, the included sources were the main ones and as such are likely to have provided adequate coverage of the literature.

The search strategies that were used are reproduced in full in the appendices and therefore should be reproducible. However, the MEDLINE and EMBASE searches were run on the Embase.com interface to which the ERG has no access. The subject headings used were EMTREE terms and it is unclear how these mapped to MeSH terms for the MEDLINE search. The ERG tried to replicate the search using the OVID interface with the same textword terms and Emtree terms but with the addition of appropriate MeSH terms for the MEDLINE segment of the search. A larger number of hits were retrieved (5000 as opposed to 3884) however it is unknown whether this was due to differences in searching MEDLINE or differences in the completeness of de-duplication between the two interfaces. Searches in the other databases were replicable.

The search strategies for clinical effectiveness were appropriately constructed with the use of subject terms and text words that related to renal cancer and the drugs under consideration. An additional facet of the search was added to the MEDLINE/EMBASE search to restrict the retrieval to RCTs. However, the scope of the systematic review was wider than is detailed in

the statement of decision problem (Chapter 4 of the manufacturer's initial submission document), including terms relating to drugs which were not part of this appraisal. No separate searches were undertaken to identify adverse events.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

The inclusion criteria used in the study selection for the manufacturer's submission are tabulated in Table 4.1. In terms of study design, the systematic review was limited to RCTs (of any blinding status). However, the manufacturer's submission also includes outcome data for non-randomised studies reporting pazopanib, but has not considered non-randomised evidence for comparator treatments, thereby potentially introducing a bias in favour of pazopanib.

The manufacturer's submission also excludes from the indirect comparison one RCT comparing interferon-α with interleukin-2 (CRECY trial) by Negrier and colleagues[22] on the basis that it did not contain a non-active control arm to provide a 'bridge' to the VEG105192 study, thereby preventing its inclusion in the indirect comparison. When the ERG queried why interleukin-2 was listed as one of the comparators in the final scope document but not in the manufacturer's Statement of the decision problem addressed in the submission (p33, manufacturer's submission) (ERG clarification query A8), the manufacturer responded that this was because interleukin-2 did not have a licence in the UK.

The publication timeframe included studies published from 1980 onwards, as the manufacturer considered that this "would not limit results substantially due to the vast majority of data for cytokines and targeted therapies being reported from 1980s onwards". The ERG considers this a reasonable approach to take.

Although it is not explicitly stated in the final scope document that interferon-α and interleukin-2 are the only immunotherapy options to be considered, these are the two that are listed. However, no alternative examples of immunotherapy options were listed in the consultee and commentator comments on the final remit and draft scope. Our clinical advisers indicated that although there are many other immunotherapy options, none are in routine clinical practice in the UK.

For best supportive care, the decision problem of the manufacturer's submission notes this to be the comparator arm of the VEG105192 trial (i.e. the placebo arm of the trial), although placebo is listed separately from best supportive care as a comparator in the eligibility criteria.

In the absence of available data on best supportive care for the population of interest, the ERG considers it reasonable to use placebo trial data as a proxy measure.

As noted above, data from two non-randomised studies reporting outcomes for pazopanib were included in the manufacturer's submission. The justification for including these studies in the submission was that they provide "relevant supportive data for pazopanib in the patient population under consideration". One of these studies (VEG107769) was an open-label extension study which provided access to pazopanib at 800mg/day to those randomised to placebo in the included study VEG105192. The other, VEG102616 was initially designed as a randomised study comparing pazopanib at 800mg/day with placebo. However, the majority of participants (170/225) were not randomised in practice. A planned interim analysis demonstrated a 38% response rate, and, based on this and the recommendation of the independent data monitoring committee, randomisation was halted and all continuing patients were treated with pazopanib on an open-label basis. Data from these trials were not included in the economic model.

Table 4.1 Inclusion and exclusion criteria used in manufacturer's submission

Inclusion criteria	**Population**	• Aged ≥ 18 years • Any gender • Any race • Has locally advanced/advanced/metastatic/stage III/stage IV disease • No prior systemic therapy (treatment-naive)
	Intervention	• Pazopanib monotherapy (or in combination with best supportive care) • Interferon-α monotherapy (or in combination with best supportive care) • Interleukin-2 monotherapy (or in combination with best supportive care • Sunitinib monotherapy (or in combination with best supportive care
	Comparators	• Any of the included interventions • Placebo • Best supportive care
	Outcomes	Efficacy: • Overall survival • Progression free survival • Time to progression • Overall response rate (Complete + Partial Response) • Proportion of patients with stable disease • Time to response • Duration of response • Health-related quality of life Safety • Incidence and severity of adverse events • Withdrawals due to adverse events • Withdrawals due to death • Serious adverse events • Incidence and severity of specific adverse events
	Study design	• RCTs (any blinding status)
	Language restrictions	• English only
	Publication timeframe	• 1980 onwards (full-text) • Most recent 3 years (conference abstracts)
Exclusion criteria	**No outcome of interest specified**	All included studies should report an outcome of interest
	No separate analysis of: -disease of interest (RCC) -advanced/metastatic disease -treatment naïve patients	Studies should report data for treatment-naive patients with advanced/metastatic renal cell carcinoma.

Source: manufacturer's submission.

4.1.3 Table of identified studies

The manufacturer identified eight randomised controlled trials (RCTs) with published data reporting the interventions or comparators as listed in the scope document. Table 4.2

summarises the characteristics of the studies. One study (VEG105192) reported pazopanib versus placebo, one[17] reported sunitinib versus interferon-α, and six reported interferon-α, comparing it with either medroxyprogesterone (MPA),[23-26] vinblastine,[27] or interleukin-2.[28] One study involving pazopanib compared with sunitinib is ongoing (VEG108844 [COMPARZ]) and one is planned to start shortly (VEG113046 [PISCES]).

Table 4.2 Table of identified studies

Study, links with other studies, design, follow-up	N, population,	Intervention, duration	Publication status
VEG105192[21,29-31] RCT Follow-up: Median duration of follow-up at the 23 May 2008 clinical cut-off: pazopanib 62.6 weeks, placebo 58.6 weeks	233 treatment-naive participants (out of 435 in total) Locally advanced or metastatic, clear cell/predominantly clear cell renal cell carcinoma Age ≥18 years old ECOG PS ≤1	A) Pazopanib at 800mg/day B) Placebo Randomisation from April 2006 – study is ongoing	Published
Motzer 2009[17,28,32-47] RCT Follow-up: Unclear	750 participants Metastatic renal cell carcinoma with a clear cell histological component Age ≥18 years old, ECOG PS ≤1	A) Sunitinib 50mg/day (4 weeks on, 2 weeks off treatment) B) Interferon alpha at a dose of 9 MU, three times per week Randomisation carried out August 2004 – August 2005	Published
Negrier 2007[25,48] RCT Follow-up: Median 126.53 weeks (range 0 to 236.6)	492 participants Progressive metastatic renal cell carcinoma with > 1 metastatic organ site and a performance status of KPS≥80%, or 1 metastatic organ site and a performance status of KPS 80% Age ≥18 years old	A) Interferon alpha at a dose of 9 MU, three times per week B) Interleukin 2 at a dose of 9 MU bid C) Interleukin 2 as above + interferon alpha at a dose of 3 MU three times per week D) MPA (“BSC”) Randomisation carried out January 2000 – July 2004	Published
MRC RE01[14,23,49-51] RCT Follow-up: Median 242.67 weeks	350 participants Metastatic renal cell carcinoma WHO PS of 0 to 2	A) IFN at a dose of 10 MU, three times per week B) MPA (“BSC”) Randomisation carried out February 1992 – November 1997	Published
Steineck 1990[26] RCT	60 participants Locally	A) IFN at a dose of 10-50 MU/m^2, three	Published

Study, links with other studies, design, follow-up	N, population,	Intervention, duration	Publication status
Follow-up: Unclear	recurrent/metastatic adenocarcinoma of the kidney. Patients with previous irradiation of the disease or excision of metastases. Age 18 – 70 years old	times per week B) MPA ("BSC") Randomisation carried out January 1983 – September 1985	
Kriegmair 1995[24] RCT Follow-up: IFN+vinblastine group: mean 39 weeks, range 4.33 to 104); MPA group (mean 27.3 weeks, range 4.33 to 95.33)	89 participants Patients with nephrectomy and progressive renal cell carcinoma with dimensionally measurable tumour lesion WHO performance status of ≥2	A) IFN alpha at a dose of 8 MU x3 per week, plus 0.1mg/kg vinblastine administered every three weeks B) MPA ("BSC") Not reported when randomisation carried out	Published
Pyrhonen 1999[27,52] RCT Follow-up: Unclear	160 participants Advanced renal cell carcinoma KPS >50% (ECOG status of 0-2) Age ≤75 years	A) IFN alpha at a dose of 18 MU three times per week, plus 0.1mg/kg vinblastine administered every three weeks. B) Vinblastine at a dose of 0.1 mg/kg x3 per week Randomisation carried out April 1988 – October 1994	Published
Negrier 1998 CRECY Trial[22,53] RCT Follow-up: Median 169 weeks	425 participants Progressive renal cell carcinoma ECOG status of <2 Age 18 to 65 years	A) Interleukin-2 at a dose of 18 MU(per m^2 body surface area)/per day B) Interferon alpha at a dose of 18 MU three times per week Randomisation carried out March 1992 – July 1995	Published
Ongoing studies			
VEG108844 (COMPARZ)[54] RCT	838 (target) Locally advanced and/or metastatic, treatment-naive renal cell carcinoma	A) Pazopanib B) Sunitinib Ongoing	2nd Quarter 2012
VEG113046 (PISCES)[55] RCT	160 (target) Locally advanced/metastatic treatment-naive renal cell carcinoma	A) Pazopanib B) Sunitinib Manufacturer submission states 'planned to start shortly'	Date for availability of study report not given

Source: manufacturer's submission.

4.1.4 Relevant studies not included in the manufacturer's submission

Although the ERG identified a few additional reports that might have been considered potentially relevant there was no evidence that any data of consequence had been omitted from the submission. Details of the additional work undertaken by the ERG in an attempt to identify additional potentially relevant studies not included in the manufacturer's submission are reported in Chapter 6 (Additional work undertaken).

4.1.5 Description and critique of the manufacturer's approach to validity assessment

The manufacturer used three different instruments to assess the methodological quality of the included RCTs: a 7-item minimum criteria checklist suggested by NICE in section 5.4.1 of their specification for manufacturer/sponsor submission of evidence, a scale assessing the adequacy of concealment and the Jadad score.[56]

The criteria suggested by NICE cover the following aspects of methodological quality: sequence generation, allocation concealment, baseline comparability, blinding, drop-outs, outcome reporting bias and whether an intention to treat analysis was undertaken. The adequacy of concealment scale used was the same as the scale used by the Cochrane Collaboration for assessing the quality of RCTs included in Cochrane reviews (now superseded by the risk of bias tool) and grades adequacy of concealment as A (adequate), B (unclear), C (inadequate) or D (not used). The Jadad checklist contains five questions covering whether the study was randomised, adequacy of randomisation methods, whether the study was described as double-blind, adequacy of blinding, and whether a description of withdrawals and drop outs was given. One point is scored for each positive answer and points subtracted if randomisation or blinding methods were judged to be obviously flawed.

It was unclear from the manufacturer's main submission and systematic review document whether study quality was assessed independently by two reviewers.

The results of the assessment against the NICE criteria with respect to VEG105192 were reported in the text of the submission document while the results of the quality assessment for all of the included RCTs for each of the instruments used were reported as an appendix (Appendix 3) to the main submission document and also as an appendix (Appendix E) of the separate systematic review document.

The ERG considered the quality assessment tools used to be appropriate for appraising RCTs. However it is unclear why all three were used as there is overlap between them. In terms of the scale assessing adequacy of allocation concealment (A to D), adequacy of allocation

concealment is also covered by the second item on the NICE criteria 'Was the concealment of treatment allocation adequate?' The second item on the Jadad scale 'Were the randomisation methods used adequate?' is similar to the first item on the NICE checklist 'Was randomisation carried out appropriately?', while the third item on the Jadad scale 'Were blinding methods adequate?' is similar to the fourth item on the NICE checklist 'Were the care providers, participants and outcome assessors blind to treatment allocation?'

Table 4.3 summarises the results of the various checklists for the seven studies that were included in the manufacturer's indirect comparison: the VEG105192 study reporting pazopanib, the study by Motzer and colleagues[17] reporting sunitinib and the five studies reporting IFN.[23-27] These studies formed the basis of the manufacturer's submission.

As assessed against the NICE criteria, of the seven studies included in the indirect comparison, only VEG105192 was considered as having randomisation carried out appropriately, while allocation concealment was considered adequate for VEG105192, Negrier and colleagues[25] and the MRC RE01 study.[23] All studies were judged to have achieved baseline comparability between groups. Blinding of care providers, participants and outcome assessors was judged to have been carried out in the VEG105192, Motzer[17] and Steineck[26] studies. Only the study by Kriegmair and colleagues[24] was judged to have had an unexpected imbalance in drop-outs between groups, while only the VEG105192 and Negrier[25] studies were considered not to have been affected by selective reporting bias. All studies apart from Kriegmair and colleagues[24] were considered to have included an intention-to-treat analysis.

Only the VEG105192 study was given the maximum 5 points on the Jadad scale, with the remaining studies allocated either 2 points or 1 point. As only the overall summary score was reported for each study, it was unclear for those studies allocated less than 5 points which specific aspects of the Jadad instrument were considered not to have been met.

Table 4.3 Summary of manufacturer's quality assessment of the seven studies included in the indirect comparison

Study id	Jadad score	Allocation grade	Randomisation carried out appropriately	Allocation concealment adequate	Baseline comparability	Blinding	Imbalances in drop-outs	Selective outcome reporting	ITT analysis included
Pazopanib									
VEG105192	5	A	Yes	Yes	Yes	Yes	No	No	Yes
Sunitinib									
Motzer 2009[17]	2	B	Not clear	Not clear	Yes	Yes	No	Not clear	Yes
IFN									
Negrier 2007[25]	1	A	Not clear	Yes	Yes	No	Not clear	No	Yes
MRC RE01[23]	1	A	Not clear	Yes	Yes	Not clear	Not clear	Not clear	Yes
Steineck 1990[3]	1	B	Not clear	Not clear	Yes	Yes	No	Not clear	Yes
Pyrhonen 1999[27]	1	B	Not clear	Not clear	Yes	Not clear	No	Not clear	Yes
Kriegmair 1995[24]	2	B	Not clear	Not clear	Yes	Not clear	Yes	Not clear	No

Source: manufacturer's submission, appendices, Table 9.4 and Table 9.5.

4.1.6 Description and critique of the manufacturer's outcome selection

The primary outcome measure used in the manufacturer's submission was progression-free survival. The secondary outcome of overall survival was also used to inform the economic model. These were reported as continuous outcomes (e.g. median survival) with 95% confidence intervals (CIs) or ranges, or as hazard ratios for the difference between treatments being considered (with 95% CIs), or both.

The ERG considers these outcome measures to be well accepted and widely used for cancer treatments. In some instances, (particularly for VEG105192) the reporting of medians alongside interquartile ranges rather than ranges, would have provided a more accurate description of outcomes.

Additional efficacy outcomes reported were response to treatment (complete response, partial response, stable disease or progressive disease), as well as time to response and duration of response. The ERG considers response to be a well accepted outcome measure, and notes the difficulties faced by the manufacturer in compiling response data with regard to the different definitions of response used by the RECIST and WHO criteria.[57,58] The ERG also notes that different response data for both independent review committee and investigator assessment of response were provided, and that stable disease was included in response where it had been maintained for six months. The manufacturer also contacted the authors of the included sunitinib trial to determine how response was measured in that trial.

In the pazopanib study (VEG105192) quality of life was reported using the EQ-5D utility score, EQ-5D-VAS score and EORTC-QLQ C-30 score. Quality of life in the sunitinib study was reported using the EQ-5D utility score, EQ-5D-VAS and also the FACT – Kidney Symptom Index – Disease-related Symptom (FKSI-DRS Index), FACT – Kidney Symptom Index – 15 item scale (FKSI-15 Index) and Functional Assessment of Cancer Therapy – General scale (FACT-G) to report disease specific quality of life measures.[33-36,59] The ERG considers the EQ-5D to be a well accepted tool for measuring quality of life outcomes and the disease-specific instruments that were used to be appropriate.

Adverse events were well reported (although sometimes provided in separate tables not in the systematic review or manufacturer's submission). Pre-specified specific adverse events were reported and adverse events were also reported by class of event, for example gastrointestinal disorders.

4.1.7 Description and critique of the statistical approach used

The manufacturer conducted a randomised controlled trial to evaluate the effectiveness of pazopanib versus placebo in treatment-naïve and cytokine pre-treated sub-populations. The primary outcome was progression-free survival (PFS) and secondary outcomes were overall survival (OS), tumour response and health-related quality of life. Final analyses were conducted on all outcomes, other than OS, for which an interim analysis was reported based on a cut-off date of 23 May 2008 and then a final analysis based on a cut-off date of 15 March 2010.

The study was designed to provide 90% power to detect a 100% improvement in progression-free survival in the treatment-naïve sub-population assuming a 2:1 randomisation ratio in favour of pazopanib. For the overall study, this required 180 PFS events (90 in each sub-population) and 287 deaths (66%), although the study was not powered to detect differences in OS in the sub-populations. In the treatment-naïve population, there were 233 patients in the trial, of whom 94 had had disease progression within 6 months of randomisation at the time of the final PFS analysis cut-off date. At the time of the final OS analysis (cut-off 15 March 2010), 290 patients (66.7%) had died including 148 (63.5%) in the treatment-naïve population.

For overall survival, intention-to-treat analyses were conducted using Kaplan-Meier methods[60] and Cox proportional hazard models.[61] However, the trial was designed so that if patients in the placebo arm had disease progression, they could cross-over to receive pazopanib (51% of placebo patients did cross over). Patients in both arms were also potentially treated with additional anti-cancer therapies other than pazopanib following disease progression. Much of the statistical analysis therefore focused on methods which adjust for cross-over in order to attempt to correct biases that can occur as a result of these factors.

The Kaplan-Meier analysis, unadjusted for cross-over, did not control for any potential confounders other than baseline ECOG performance status. In this analysis, the hazard ratio was estimated using the Pike method[62] which is a non-parametric estimator based on the logrank test that does not require proportional hazards to be assumed. The Pike estimator is known to underestimate effect sizes for hazard ratios greater than approximately three,[63] although this potential for bias should not apply to the hazard ratios reported in the results of this trial, which are generally smaller.

The Cox regression analysis unadjusted for crossover presented univariate and multivariate results, with the latter adjusted for selected baseline characteristics (age, gender, Memorial Sloan-Kettering Cancer Centre (MSKCC) score, years since diagnosis, stage at diagnosis, presence and number of metastases). (The MSKCC score categorises patients into 3 risk groups (favourable, intermediate and poor) based on five factors, including performance status and presence/absence of prior nephrectomy.) These baseline variables were used across the analyses (including the alternative analyses described later in this section) with the rationale for their use stated as being based on prior literature and goodness-of-fit statistics (although no goodness-of-fit statistics or sources were provided).

In addition to the ITT analyses, the following methods of estimating the hazard ratio for overall survival by adjusting for cross-over were explored:

1. Kaplan-Meier and Cox analyses with censoring at the time of cross-over
2. Cox analysis with cross-over as a time-dependent covariate
3. Inverse probability censoring weighting (IPCW) analysis.[64]
4. Rank preserved structural failure time (RPSFT) analysis.[65]

The first two approaches are simply minor modifications to established methods of survival analysis. Censoring at the time of cross-over involved measuring survival from randomisation to the time of cross-over to pazopanib or switch to another anti-cancer therapy, with all other patients having survival measured from randomisation to death or last contact. In the interim analysis (cut-off 23 May 2008), Kaplan-Meier estimates were presented using the same method used for the unadjusted analysis except that additional censoring was applied to cross-over patients. This analysis was presented in the interim analysis but not in the final analysis (cut-off 15 March 2010) reported in the addendum to the initial submission, although univariate and multivariate Cox models were presented in both analyses. The manufacturer acknowledges that this approach is limited by the fact that subjects could have died soon after cross-over and that because of disease progression the health status of those who were censored is likely to be worse than those who were not censored. The Cox proportional hazard analysis with cross-over as a time-dependent covariate was the same as the original Cox analysis with univariate and multivariate results presented, except that an additional binary variable as an indicator of cross-over was added as the time-dependent covariate.

The other two methods presented by the manufacturer for adjusting for cross-over are more sophisticated techniques and have been developed relatively recently. The first of these was IPCW analysis, where patients who did cross over are censored, but stabilised weights are

assigned to placebo patients remaining at risk with the purpose of controlling not only for those patients but also for the patients censored due to cross-over. For each placebo patient, stabilised weights were calculated for a set of timepoints (at each scheduled visit which in this case was every three weeks for the first six months and less frequently thereafter). Two logistic regression models are performed for each timepoint with censoring as the dependent variable. The first model was fitted with the same baseline characteristics as the original Cox analysis with terms added for the number of study weeks elapsed and the second model was fitted with baseline and time-dependent covariates. The weights were calculated as the predictive value from the first model divided by the predictive value from the second. The time-dependent covariates were ECOG status, history and occurrence of grade, progression, time since progression and number of anti-cancer therapies approved/reimbursed in the patient's country. The hazard ratio was derived from a Cox model using the stabilised weights, adjusting for baseline characteristics. Confidence intervals for the hazard ratio were calculated using the bootstrap method[66] with 1000 re-samples to account for the variability generated from the stabilised weight estimation.

The final method presented for adjusting for cross-over was RPSFT analysis. This is where an adjustment is made to the survival time of each patient who crossed over with the purpose of correcting their actual survival to reflect what their survival would have been had they not crossed over to the active treatment. In its simple form, a weight is applied to the length of time spent on active treatment for patients in both arms and added to the unadjusted length of time not on active treatment, such that the mean overall survival estimates in both arms are equal, i.e. hypothetical estimates as if all patients in both arms spent no time on the active treatment. This approach allows not just for placebo patients who cross-over, but also for patients randomised to the active treatment who spend some or all of their time not on the active treatment.

In the RPSFT analyses for this study, the weight (or causal rate ratio) was expressed as the exponential of an unknown parameter, Ψ^* (or psi). Using a grid estimation method, the true parameter was approximated to be the value such that the distributions of adjusted event times were equivalent for both arms of the trial, with the distributions being derived as follows. A broad range of potential values for the parameter was assessed, reported as being uniformly distributed in increments of 0.025 from -2.5 to +2.5 (although the results show ranges from -4 to +3). For each value, adjusted follow-up times were calculated so that the time on pazopanib was weighted and added to the actual time to crossover for placebo patients or the actual time unexposed to pazopanib for those randomised to the treatment arm (as per the simple form of the analysis). Failure times for placebo patients who did not cross-over were

not adjusted. Censoring times were adjusted with the same weight for parameter values that would not indicate a beneficial effect of pazopanib (i.e. negative values of Ψ^*). The adjusted event times were calculated as the shorter of either the adjusted failure time or the adjusted censoring time. For patients missing from this analysis, i.e. those censored only at the end of follow-up, the adjusted event time was defined as their censoring time. Adjusted censoring indicators were also derived with patients being censored unless their adjusted event time was the same as their adjusted censoring time or unless, for subjects who dropped out of the study, their actual censoring time was less than their observed censoring time.

The distributions of event times for both arms were then compared by testing each candidate parameter value with an unweighted log-rank test in a univariate Cox analysis with adjusted event times and censoring indicators with treatment arm as the dependent variable. The value of the parameter with the largest p-value was considered to be associated with the least dissimilarity between the distributions. The model was repeated to adjust for baseline covariates. A recently developed methodology was employed to use locally efficient weighted log-rank tests in order to obtain p-values based on optimal weights, with the intention of accounting for potential bias caused by the fact that, after a certain amount of time, the number of patients in the placebo arm on pazopanib was greater than the number in the treatment arm on pazopanib (this happened in the treatment-naïve population after 400 days). This weighted analysis was carried out on the univariate model. Once the RPSFT causal rate ratios were estimated, hazard ratios were determined from Cox regression models with observed event times and censoring indicators in the pazopanib arm and adjusted event times and censoring indicators in the placebo arm. The hazard ratio from the weighted RPSFT analysis, unadjusted for baseline, was used in the base case economic model.

Unlike all the other analyses that attempted to correct for crossover bias, the weighted RPSFT model did not adjust for baseline covariates. An algorithm has been developed so that adjusted estimates can be generated from weighted analyses, but the model in its current state is reported to be unstable and future research is required. Adjusting for baseline covariates reduced the hazard ratios in all the Cox regression analyses and in the unweighted RPSFT analysis, so if the same pattern were to be observed in the weighted RPSFT analysis, the hazard ratio would be lower.

A limitation of the RPSFT parameter estimation method is that the distribution of p-values from the log-rank tests can be multimodal and therefore it is not always possible to determine the causal rate ratio in the absence of a unique highest p-value. The unweighted unadjusted

analysis for treatment-naïve patients is an example of this, with three distinct values where the associated p-value was very close to its maximum possible value of one.

The manufacturer proposed two alternative methods for calculating the confidence interval of psi (and by implication the causal rate ratio, exp(psi)) - by bootstrapping and by inversion of test statistics. For the latter, the upper 95% limit is described as being the largest parameter value for which the p-value is greater than 0.05. The upper limits of the confidence intervals obtained by bootstrapping are higher (i.e. more conservative) compared with the inversion of the test statistic, e.g. in the weighted RPSFT analysis, the upper 95% limit is stated as being 2.775 with bootstrapping and -0.05 for the inversion of the test statistic. There is generally a large amount of imprecision around the parameter estimates (although less so using the inversion of the test statistic method) and also a large difference between the methods for calculating confidence intervals.

A key concern is the derivation of the causal rate ratio for the weighted unadjusted analysis, the results of which were used in the base case economic analysis. The p-value distribution is bimodal with both peaks very close to 1 and potential point estimates at Ψ^*=-2.225 (reported) and Ψ^*=+2.7 (approximated from p-value distribution plot). This appears inconsistent with the unweighted unadjusted analysis which was treated as inapplicable as it had no clearly unique maximum p-value. Moreover, an assumption appears to have been made in favour of pazopanib as the value used to derive the hazard ratio is the negative value, with the other potential point estimate being described as a distinct peak far from the point estimate. There does not appear to be a justification for including the results of this analysis, nor is there a convincing rationale for choosing one point estimate over the other.

Despite concerns over the approach to weighting, RPSFT analysis is an appropriate method to use in this study, particularly as it has the advantage over other methods of producing randomisation-based effect estimators which maintain the validity of between-group comparisons and is not biased by post-randomisation time-dependent covariates. However, the RPSFT method is heavily weighted towards the early follow-up period and the analysis only controlled for cross-over from placebo to pazopanib and not receipt of other post-study anti-cancer therapies, which may be important as there was an imbalance between the groups with more pazopanib patients (24%) receiving other anti-cancer therapies (excluding pazopanib) compared with placebo patients (12%). If placebo patients who took pazopanib along with an additional treatment were also considered, the proportion of placebo patients would be 22% with little or no resulting bias. RPSFT is likely to be a suitable method in this context, but the type of RPSFT analysis used may not have been the most appropriate. For

example, further refinement of the weighted analysis is required, particularly as it was reported that the model used may not have been correctly specified as one of the three optimal weights was not included in the estimation. It may have been more appropriate, therefore, to base the cost-effectiveness analysis on an unweighted RPSFT analysis.

Overall, the manufacturer has presented a set of analyses which comprehensively cover the range of methodologies available to adjust for cross-over. However, care should be taken when assessing trials that have used relatively new methods as there is no consensus on the best approach to use and these methods still require further development. In this particular analysis, the results used for the base case economic model utilise a new methodology for which its use in an application is still to be peer-reviewed and published. The method therefore remains a theoretical exposition not yet proved to be of practical value. Also, the derivation of a plausible causal rate ratio (from an estimate of psi) may be, in certain circumstances, impossible or open to interpretation potentially leading to a large underestimation or overestimation of the hazard ratio.

4.1.8 Summary statement of the manufacturer's approach

The manufacturer's inclusion criteria were limited to RCTs, resulting in a smaller evidence base but higher level of evidence than if non-randomised studies had also been included. The manufacturer introduced an element of bias in favour of pazopanib by selectively including non-randomised studies reporting pazopanib as supporting evidence in their submission. The methodological quality of the included studies was comprehensively assessed using three different instruments.

The manufacturer's statement of the decision problem was mostly similar to the final scope issued by NICE. Interleukin-2 was included as a comparator in the final scope document but not in the manufacturer's statement of the decision problem addressed in the submission. When the ERG queried this the manufacturer responded to say that this was because interleukin-2 did not have a licence in the UK.

A problematic issue concerning the reporting of overall survival in the VEG105192 study was which statistical method was most appropriate to deal with the effect of the high level of placebo-treated patients who crossed over to receive pazopanib. The manufacturer explored various options, including Kaplan-Meier analysis censoring cross-over patients at time of cross-over, Cox regression analysis considering cross-over as time-dependent covariate, inverse probability of censoring weighted (IPCW) analysis, and rank preserved structural failure time (RPSFT) analysis. The manufacturer used the RPSFT approach, citing as

justification the fact that the ERG involved in a previous NICE appraisal (TA 179) had concluded that this represented a methodologically robust approach to adjust for cross-over. The data for overall survival for VEG105192 in the manufacturer's original submission were immature (cut-off 23 May 2008) and longer term-data (cut-off 15 March 2010) were subsequently provided in an addendum to the submission. However the specific method of RPSFT used in the original submission (unweighted) was different to that used for the longer-term data reported in the addendum (weighted).

No data were identified directly comparing pazopanib with interferon-α or sunitinib. Therefore in order to provide information on the relative efficacy of pazopanib in relation to comparator treatments, the manufacturer conducted an indirect comparison of pazopanib to interferon-α and the main comparator of interest, sunitinib. The patient populations in the studies included in the indirect comparison were broadly similar. The sunitinib study contained a higher percentage of patients with ECOG 0 and a lower percentage with ECOG 1 performance status compared with VEG105192. While neither the pazopanib nor sunitinib studies contained patients with ECOG performance status 2, this was not the case for some of the studies reporting interferon-α. The comparator for some interferon-α studies was MPA and for others was vinblastine. The manufacturer assumed that MPA and vinblastine could be considered as palliative treatment equivalent to placebo with best supportive care. However the response rate to both MPA and vinblastine is low but not zero, and both have significant toxicities. The manufacturer undertook a number of sensitivity analyses around the indirect comparison, including using the hazard ratio for overall survival in VEG105192 adjusted using the weighted RPSFT method but varying the inclusion of IFN trials, using the HR for VEG05192 adjusted for cross-over using the IPCW method, using the HR for overall survival for VEG105192 in subjects with no post-study therapy, using the HR for overall survival for VEG105192 censored on cross-over and using the HR for overall survival for VEG 105192 from ITT analysis.

4.2 Summary of the submitted evidence

4.2.1 Summary of the results

A. *Efficacy*

A1. Subject disposition and baseline information

For pazopanib, the manufacturer reported efficacy outcomes for treatment-naïve patients in one randomised controlled trial (VEG105192) which compared pazopanib with placebo in both cytokine pre-treated and treatment-naive patients with advanced/metastatic renal cell carcinoma.

Table 5.10 in the manufacturer's addendum to the initial submission gives a summary of subject disposition at the most recent follow-up period. This table has since been updated in the supplementary evidence provided by GSK in Table 1.1 of the addendum for the intention-to-treat population and is provided below (Table 4.4).

Table 4.4 Summary of subject disposition, VEG105192, ITT treatment-naïve population, 15 March 2010 cut-off

	Pazopanib (treatment-naive) N=155	**Placebo (treatment-naive) N=78**
Subjects' status:		
Died	99 (64%)	49 (63%)
Ongoing (still on study treatment)	14 (9%)	0 (0%)
Discontinued study treatment	141 (91%)	78 (100%)
Reasons for discontinuation		
Disease progression	92 (58%)	62 (79%)
Adverse event	20 (13%)	5 (6%)
Subject decided to withdraw	7 (5%)	1 (1%)
Death	6 (4%)	6 (8%)
Other	7 (5%)	2 (3%)
Investigator decision	6 (4%)	1 (1%)
Lost to follow-up	2 (1%)	1 (1%)
Protocol violation	1 (<1%)	0 (0%)

Source: addendum to manufacturer's submission, 20 July 2010.

Comparator data for sunitinib were taken from the randomised phase III trial in which 750 treatment-naïve patients with metastatic clear cell renal cell carcinoma were randomised to either sunitinib at a dose of 50mg/day (on a dosing schedule of four weeks on followed by two weeks off the drug), or IFN 2a, provided on non-consecutive days, thrice weekly, (starting with a 3 million unit (MU) dose during the first week, 6 MU dose the following week and 9 MU dose thereafter)[17] (see Table 4.5).

Comparator data for interferon alpha came from five trials where this treatment was an intervention. One of these trials[25] also contained a treatment arm for interleukin-2. The systematic review document provided alongside the manufacturer's submission also contains a trial comparing interferon-α with interleukin-2, but it should be noted that data from this trial are not included in the original submission document or the addendum and were not included in the indirect analysis because "a non-immunotherapy control arm was not used in this study" (manufacturer's submission p82).

Table 4.5 Interferon-α, interleukin-2 and control treatments used

Study	Treatment 1	Dose
Interferon alpha		
Motzer 2009[17]	IFN 2a	9 MU x3 per week (escalated to this dose by week 3) on non-consecutive days
Negrier 2007[25]	IFN 2a	9 MU x3 per week
Hancock 2000 (MRC RE01)[23]	IFN	10 MU x3 per week
Steineck 1990[26]	IFN 2a	Between 10MU x3 per week and 50MU x3 per week
Pyrhonen 1999[27]	IFN 2a plus vinblastine	18 MU x3 per week (escalated to this dose by week 2)
Kriegmair 1995[24]	IFN plus vinblastine	8 MU x3 per week, plus 0.1mg/kg vinblastine administered every three weeks.
Interleukin 2		
Negrier 2007[25]	Interleukin 2	9 MU x2 per day (with a specified 4 week dosing schedule including some rest days and days of x1 dose per day)
Best Supportive Care		
Negrier 2007[25]	Medroxyprogesterone acetate	200mg/day
MRC RE01[23]	Medroxyprogesterone acetate	300mg/day
Steineck 1990[26]	Medroxyprogesterone acetate	1,000mg x3 per week for 5 weeks, then 1000mg/day thereafter
Pyrhonen 1999[27]	Vinblastine	0.1 mg/kg x3 per week
Kriegmair 1995[24]	Vinblastine	500mg/week

Characteristics of included studies are reported in the submission, and available data for progression free survival, time to progression, overall survival, response rate, time to response and duration of response, are provided in the systematic review document. With regard to the main submission document and addendum, these treatments were primarily discussed in relation to deriving an appropriate method of directly comparing pazopanib and sunitinib. As a result, hazard ratios for both overall survival and progression free survival are either taken directly from these studies (where reported), or inferred. The hazard ratios were then pooled using a random effects meta-analysis to provide an overall estimate of both progression free survival and overall survival. This enabled an estimate of the effectiveness (in the form of a hazard ratio) to be derived for pazopanib against interferon-α, and subsequently allowing the drug to be directly compared with the hazard ratio for the effectiveness of sunitinib against interferon-α, as reported for the phase III randomised controlled trial.

Table 4.6 shows the baseline characteristics for the studies that were included in the manufacturer's indirect comparison. The studies were broadly similar in terms of the age of the patients. In both arms of the study by Motzer and colleagues,[17] compared with study VEG105192, a higher percentage of patients were ECOG performance status 0 (62% and 61% versus 41% and 42%) while a lower percentage were ECOG performance status 1 (38% and 39% versus 59% and 58%). The VEG105192 study and the study by Motzer and colleagues[17] excluded patients with ECOG 2 performance status, while such patients were included in three of the IFN studies: MRC RE01 (IFN 24%, BSC 27%);[23] Pyrhonen (IFN+BSC 18%, BSC 21%);[27] Kriegmair (IFN 32%, BSC 36%),[24] while the study by Negrier and colleagues[25] did not report ECOG performance status.

In the study by Motzer and colleagues[17] all patients had clear cell histology, compared with 87% of pazopanib patients and 89% of placebo patients in the VEG105192 study, while none of the other studies reported this information. A higher percentage of patients in both arms of the study by Motzer and colleagues[17] had undergone previous nephrectomy compared with those in VEG105192 (91% and 89% versus 84% and 83%). The percentage of patients who had undergone nephrectomy ranged from 83% (VEG105192, placebo arm) to 100% (Kriegmair and colleagues, both arms).[24]

In response to a clarification query (A23) the manufacturer reported that for VEG105192, of the 28 subjects from the UK, seven were treatment-naïve, of whom 5 were randomised to pazopanib and two to placebo, with all having undergone nephrectomy.

Table 4.6 Baseline characteristics of participants in the RCTs included in the indirect comparison

	VEG105192		Motzer 2009[17]		Negrier 2007[25]			MRC RE01[23]		Steineck 1990[26]		Pyrhonen 1999[27]		Kriegmair 1995[24]	
Intervention	**Paz**	**Pla**	**Sun**	**IFN**	**IL-2**	**IFN**	**MPA**	**IFN**	**MPA**	**IFN**	**MPA**	**IFN+VBL**	**VBL**	**IFN+VBL**	**MPA**
N	155	78	375	375	125	122	123	167	168	30	30	79	81	44	45
Age (yrs)	59 (28-82)	62 (25-81)	62 (27-87)	59 (34-85)	61 (33-80)					63 (39-73)	62 (40-77)	60 (30-74)	62 (39-77)	62 (44-78)	66 (47-79)
Male (%)	68	74	71	72	75			72	65	70	80	65	63	64	69
Disease duration (yrs)	0.66	0.71								0.73	0.57	0.20	0.18		
ECOG 0	63 (41)	33 (42)	231 (62)	229 (61)	35			44 (26)	43 (26)			12 (15)	15 (19)		
ECOG 1	92 (59)	45 (58)	144 (38)	146 (39)	65			83 (50)	80 (48)			53 (67)	49 (61)		
ECOG 2								39 (24)	45 (27)			14 (18)	17 (21)	14 (32)	16 (36)
MSKCC 0 (favourable)	56 (36)	31 (40)	143 (38)	121 (32)											
MSKCC 1-2 (intermediate)	87 (56)	40 (51)	209 (56)	212 (57)											
MSKCC ≥ 3 (poor)	6 (4)	5 (6)	23 (6)	25 (7)											
Histology															
Clear cell	135 (87)	69 (89)	375 (100)	375 (100)											
Papillary															
Other								96 (58)	96 (57)						
Previous nephrectomy	130 (84)	65 (83)	340 (91)	335 (89)	96							71 (90)	71 (88)	44 (100)	45 (100)
Previous radiation therapy			53 (14)	54 (14)	25							6 (8)	12 (15)	0	0
No metastases sites															
1	23 (15)	10 (13)	55 (15)	72 (19)				28 (17)	26 (16)						
2	46 (30)	25 (32)	106 (28)	112 (30)											
≥ 3	86 (56)	43 (55)	214 (57)	191 (51)											

Source: manufacturer's systematic review.

Notes:

1. Percentages reported in the systematic review table to one or more decimal points have been rounded.
2. Dichotomous outcomes are reported as n (%) and continuous as median (range) unless otherwise specified.
3. Kriegmair 1995, age is mean.
4. IFN, interferon-α; IL-2, Interleukin 2; MPA, medroxyprogesterone; VBL, vinblastine; MSKCC, Memorial Sloan-Kettering Cancer Centre; ECOG, Eastern Cooperative Oncology Group.
5. In the study by Negrier and colleagues, in addition to the arms shown, 122 patients were randomly assigned to IL-2+IFN, making the total number of patients 492. However this arm was not used by the manufacturer on the grounds that this intervention was not included in the scope.
6. For the MRC RE01 study, 350 patients were registered to enter the trial, of whom 174 were randomly assigned to interferon-α and 176 to MPA. However recruitment of patients stopped in November 1997 as a result of data presented to the data monitoring committee in October 1997, with the committee recommending closure of the trial. When the trial closed a total of 335 patients had been entered, 167 randomly assigned to the interferon-α arm and 168 to the MPA arm.

A2. Progression-free survival

The primary efficacy endpoint in the manufacturer's submission was progression-free survival (for details of the statistical approach used see section 4.1.7). Results for the treatment-naïve population are shown in Table 4.7.

Table 4.7 Progression-free survival, VEG105192 study, 23 May 2008 cut-off

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

Source: manufacturer's submission.

Notes:

1. IRC, independent review committee; ITT, intention to treat.

For the comparators, progression-free survival data are available in the systematic review for the sunitinib study by Motzer and colleagues[17] and two of the interferon-α studies included in the manufacturer's submission[23,25] (see Table 4.8). In addition, one further interferon-α trial reported time to progression.[27] This was reported separately in the systematic review, but not in the main manufacturer's submission.

Table 4.8 Progression-free survival for comparator interventions

Study	Intervention	Median PFS (95% CI)	HR (95%CI)	p-value for HR
Motzer 2009[17]	Sunitinib	11 months (11 to 13 months)	0.539 (0.451 to 0.643)	p<0.001
	IFN	5 months (4 to 6 months)		
Negrier 2007[25]	IFN	3.4 months (3 to 5.6 months)		
	IL-2	3.4 months (2.9 to 5.8 months)		
	"BSC"	3 months (2.9 to 3.6 months)		
MRC RE01[23]	IFN		0.66 (0.53 to 0.82)	p<0.001
	"BSC"			
Pyrhonen 1999[27]	IFN + "BSC"	3 months		
	"BSC"	2.08 months		

Source: manufacturer's systematic review.

A3. Overall survival

Final overall survival data for the treatment-naive study population were provided in the addendum to the manufacturer's submission, dated 20 July 2010. This was because more recent data (15 March 2010 cut-off) were available following the original manufacturer's submission (which had used interim overall survival data from a 23 May 2008 cut-off). For the treatment-naïve, intention-to-treat population, overall survival, unadjusted for crossover, was 22.9 months (95% CI 17.6 to 25.4 months) for pazopanib patients, and 23.5 months (95% CI 12.0 to 34.3 months) for placebo patients. Ninety-nine (64%) pazopanib patients had died by the time of the data cut-off (15th March 2010), compared with 49 (63%) of placebo

patients. The hazard ratio for overall survival was 1.01 (95% CI 0.72 to 1.42), with a resulting p value of p=0.525.

Additional overall survival analyses were provided to adjust for baseline characteristics (but not crossover) or to censor upon crossover or receipt of other therapies. The manufacturer also provided overall survival outcomes using methods adjusting for crossover (IPCW and RPSFT adjusted models). For adjusted analyses, baseline factors accounted for were:

- Age (continuous variable)
- Gender (female/male)
- MSKCC risk score (intermediate – poor / favourable)
- Years since diagnosis (<1 year/≥1 year)
- Stage of disease (stage III or IV/stage I or II)
- Presence of liver metastases (yes/no)
- Number of metastatic sites (continuous variable)

Analysis of overall survival amongst those who received no post-study therapy (e.g. crossover to VEG107769) was also provided. In total 117 patients randomised to pazopanib and 29 patients randomised to placebo did not receive post-study therapy. The Kaplan-Meier estimate for median overall survival was 21.7 months (95% CI 15.4 to 26.9 months) in the pazopanib arm, compared with 3.9 months (95% CI 2.7 to 6.3 months) in the placebo arm.

Of those patients receiving no post-study therapy, 71 (69%) pazopanib patients, and 23 (79%) of placebo patients had since died, while 14 pazopanib patients were still receiving the treatment they were randomised to, compared with none of the placebo patients. Excluding all those still on study therapy, median overall survival was estimated at 17.0 months (95% CI 12.3 to 22.9 months) for pazopanib patients, compared with 3.9 months (95% CI 2.7 to 6.3 months) for placebo patients. Of all those patients receiving no post-study therapy, the number of participants eligible who chose not to receive it was 78 (66.7%) in the pazopanib arm and 19 (65.5%) in the placebo arm. For this particular group of patients, median overall survival was estimated to be 20.4 months (95% CI 15.8 to 24.9 months) in the pazopanib arm, and 5.0 months (95% CI 3.8 to 7.1 months) in the placebo arm.

The results of these analyses for pazopanib versus placebo treatment are reproduced in Table 4.9.

Table 4.9 Summary of final overall survival results for treatment-naïve population in VEG105192, 15 March 2010 cut-off

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

Source: addendum to manufacturer's submission, 20 July 2010.

Notes:

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

For the comparators, overall survival data are available in the systematic review for the sunitinib study[17] and four of the interferon-α studies included in the manufacturer's submission[23-25,27] (see Table 4.10).

Table 4.10 Overall survival for comparator interventions

Study	Intervention	Median OS (95% CI)	HR (95% CI)	p value for HR	OS rate at 1 year	OS rate at 2 years	OS rate at endpoint
Motzer 2009[17]	Sunitinib	26.4 months (23, 32.9)	0.821 (0.673 to 1.001)	p=0.051			
	IFN	21.8 months (17.9, 26.9)					
Negrier 2007[25]	IFN	15.2 months (12.8, 19.9)					
	IL-2	15.3 months (13.3, 20)					
	"BSC"	14.9 months (11.7, 19.2)					
MRC RE01[23]	IFN	9 months	0.75 (0.53, 0.82)	p=0.013	43% (75)	22% (38)	
	"BSC"	6+ months			32% (56)	13% (23)	
Pyrhonen 1999[27]	IFN + "BSC"	15.6 months			55.7% (44)		4.1% (3)
	"BSC"	8.72 months			38.3% (31)		0% (0)
Kriegmair 1995[24]	IFN + "BSC"					18% (8)	
	"BSC"					16% (7)	

These data provide the basis for the indirect comparison which populates the economic model. A summary of the data used in the indirect comparison, and the results of the indirect comparison and sensitivity analyses, are listed in Tables 4.11 and 4.12 below. Figures highlighted in bold and italics denote data used in the economic model.

Table 4.11 List of hazard ratios used in the indirect comparison

Comparison	Source	HR (95% CI)	P value	Sources
Progression-free survival				
Pazopanib vs "BSC"	***VEG105192***	***0.36 (0.24 to 0.55)***	***p<0.001***	***VEG105192***
Sunitinib vs IFN	***Motzer 2009[17]***	***0.539 (0.451 to 0.643)***	***p<0.001***	***Motzer 2009***
IFN vs "BSC"	MRC RE01[23]	0.66 (0.53 to 0.82)	p<0.001	MRC RE01
IFN vs "BSC"	Negrier 2007[25]	0.88 (0.63 to 1.24)		Derived
IFN + "BSC" vs "BSC"	Pyrhonen 1999[27]	0.61 (0.41 to 0.93)		Derived
IFN vs BSC	***Pooled estimate***	***0.704 (0.580 to 0.854)***		***Derived***
Overall survival				
Pazopanib vs "BSC"	***VEG105192***	***0.501 (0.140 – 2.350)***	***p=0.548***	***VEG105192 addendum***
Sunitinib vs IFN	***Motzer 2009[17]***	***0.647 (0.483 – 0.870)***	***p=0.003***	[not reported in systematic review]
IFN vs "BSC"	MRC RE01[23]	0.75 (0.66 to 0.94)		Recalculated CIs
IFN vs "BSC"	Negrier 2007[25]	0.98 (0.72 to 1.31)		Derived
IFN + "BSC" vs "BSC"	Pyrhonen 1999[27]	0.65 (0.47 to 0.91)		Derived (Cochrane)
IFN + "BSC" vs "BSC"	Kriegmair 1995[24]	0.67 (0.37 to 1.22)		Derived (Cochrane)
IFN vs BSC	Steineck 1990[26]	1.05 (0.64 to 1.72)		Derived (Cochrane)
IFN vs BSC	***Pooled estimate***	***0.799 (0.674 to 0.948)***		***Derived***

The pooled hazard ratios for interferon alpha compared with best supportive care were used in the indirect comparison, along with hazard ratios for sunitinib compared with interferon alpha from the study by Motzer and colleagues,[17] and pazopanib compared with best supportive care from the VEG105192 trial reported in the manufacturer's submission. The results of the indirect comparison are reported in Table 4.12.

Table 4.12 Results of the indirect comparison with sensitivity analyses

Comparison	HR	95% CI	Analysis
Progression Free Survival			
Pazopanib vs IFN	***0.512***	***0.326 – 0.802***	***Base Case***
Pazopanib vs IFN	0.545	0.344 – 0.865	Using MRC RE01 only for IFN results
Pazopanib vs IFN	0.495	0.313 – 0.783	Using only BSC data using MPA comparator
Pazopanib vs sunitinib	0.949	0.575 – 1.568	Base Case
Pazopanib vs sunitinib	1.012	0.606 – 1.689	Using MRC RE01 only for IFN results
Pazopanib vs sunitinib	0.918	0.551 – 1.530	Using only BSC data using MPA comparator
Overall Survival			
Pazopanib vs IFN	***0.627***	***0.173 – 2.269***	***Base Case***
Pazopanib vs IFN	0.668	0.183 – 2.437	Using MRC RE01 only for IFN results
Pazopanib vs IFN	0.580	0.160 – 2.110	Using only BSC data using MPA comparator
Pazopanib vs IFN	0.803	0.327 – 1.971	Using IPCW-adjusted method for OS – Pooled IFN data
Pazopanib vs IFN	0.856	0.345 – 2.124	Using IPCW-adjusted methods for OS – MRC RE01 only for IFN
Pazopanib vs IFN	0.744	0.301 – 1.836	Using IPCW-adjusted methods for OS – BSC data from MPA comparators
Pazopanib vs IFN	0.476	0.245 – 0.924	Patients with no post study therapy – Pooled IFN data
Pazopanib vs IFN	0.507	0.257 – 1.000	Patients with no post study therapy – MRC RE01 only for IFN
Pazopanib vs IFN	0.440	0.225 – 0.863	Patients with no post study therapy - BSC data from MPA comparators
Pazopanib vs IFN	0.801	0.475 – 1.352	Patients censored on crossover – Pooled IFN data
Pazopanib vs IFN	0.854	0.496 – 1.468	Patients censored on crossover – MRC RE01 only data for IFN
Pazopanib vs IFN	0.741	0.435 – 1.265	Patients censored on crossover – BSC data from MPA comparators only
Pazopanib vs IFN	1.264	0.865 – 1.847	ITT analysis – Pooled IFN data
Pazopanib vs IFN	1.347	0.898 – 2.020	ITT analysis – MRC RE01 only data for IFN
Pazopanib vs IFN	1.170	0.789 – 1.735	ITT analysis – BSC data from MPA comparators only
Pazopanib vs sunitinib	0.969	0.359 – 2.608	Base Case
Pazopanib vs sunitinib	1.032	0.379 – 2.801	Using MRC RE01 only for IFN results
Pazopanib vs sunitinib	0.897	0.330 -2.425	Using only BSC data using MPA comparator
Pazopanib vs sunitinib	1.242	0.678 – 2.266	Using IPCW-adjusted method for OS – Pooled IFN data

Comparison	HR	95% CI	Analysis
Pazopanib vs sunitinib	1.323	0.714 – 2.442	Using IPCW-adjusted methods for OS – MRC RE01 only for IFN
Pazopanib vs sunitinib	1.149	0.624 – 2.110	Using IPCW-adjusted methods for OS – BSC data from MPA comparators
Pazopanib vs sunitinib	0.735	0.507 – 1.062	Patients with no post study therapy – Pooled IFN data
Pazopanib vs sunitinib	0.783	0.532 – 1.149	Patients with no post study therapy – MRC RE01 only for IFN
Pazopanib vs sunitinib	0.683	0.465 – 0.991	Patients with no post study therapy - BSC data from MPA comparators
Pazopanib vs sunitinib	1.238	0.983 – 1.553	Patients censored on crossover – Pooled IFN data
Pazopanib vs sunitinib	1.319	1.027 – 1.687	Patients censored on crossover – MRC RE01 only data for IFN
Pazopanib vs sunitinib	1.145	0.900 – 1.453	Patients censored on crossover – BSC data from MPA comparators only
Pazopanib vs sunitinib	1.953	1.791 – 2.123	ITT analysis – Pooled IFN data
Pazopanib vs sunitinib	2.081	1.859 – 2.322	ITT analysis – MRC RE01 only data for IFN
Pazopanib vs sunitinib	2.081	1.859 – 2.322	ITT analysis – BSC data from MPA comparators only

A4. Other outcomes reported in the manufacturer's submission - Response

Response to pazopanib was assessed by independent review committee and by trial investigators. Stable disease was first defined as stable disease lasting for a minimum of 12 weeks, but the overall response rate was calculated as including only those showing a complete or partial response. For response assessed by independent review committee, the total number showing either complete or partial response on pazopanib was 49 out of 155 participants (32%, 95% CI 24.3 to 38.9%), compared with 3 out of 78 participants on placebo (4%, 95% CI -0.42 to 8.12%). For response assessed by investigators, the total number showing either complete or partial response on pazopanib was 60 out of 155 participants (39%, 95% CI 31.0 to 46.4%), compared with 5 of 78 participants on placebo (6%, 95% CI 1.0 to 11.8%).

However, when stable disease was then defined as lasting for six months, participants showing stable disease for this long were included in the overall response rate (along with complete and partial responders). For response assessed by independent review committee, the total number showing either complete or partial response, or stable disease lasting at least 6 months on pazopanib was 76 out of 155 participants (49%, 95% CI 41.2 to 56.9%),

compared with 9 out of 78 placebo participants (12%, 95% CI 4.4 to 18.6%). For response assessed by investigators, the total number showing either complete or partial response or stable disease lasting at least 6 months on pazopanib was 83 out of 155 (54%, 95% CI 45.7 to 61.4%) compared with 19 out of 78 placebo participants (24%, 95% CI 14.8 to 33.9%).

For those showing a response (excluding those with stable disease), the median time to response was 11.6 weeks (95% CI 6.4 to 12.3 weeks) for pazopanib patients and 23.6 weeks (95% CI 18.1 to 24.1 weeks) for placebo patients, as assessed by independent review committee. For investigator assessed median time to response, this was 11.6 weeks (95% CI 6.7 to 12.3 weeks) for pazopanib participants and 26.1 weeks (95% CI 12.3 to 32.1 weeks) for placebo patients.

Median duration of response as calculated by independent review committee was 58.7 weeks (95% CI 44.9 to 66.1 weeks) for pazopanib patients, but was not calculable for placebo patients. For investigator assessed median duration of response, for pazopanib patients this was 67.7 weeks (95% CI not calculable) and 27.9 weeks for placebo patients (95% CI 14.1 to 32.7 weeks).

Response rates for the comparators are provided in the systematic review document, as assessed by an independent review committee, for the sunitinib trial,[17] and as assessed by investigators for the sunitinib trial and all five included interferon-α studies included in the manufacturer's submission. However, it is important to note that the criteria used for assessment of response were RECIST for sunitinib, but the WHO criteria for all interferon alpha studies. The different criteria are summarised on page 68 of the manufacturer's systematic review document.

Table 4.13 shows the response results reported for the comparator interventions included in the manufacturer's indirect comparison. Duration of response was reported for the sunitinib trial[17] and two of the interferon-α trials.[24,27] For the sunitinib trial median duration of response was 12 months (95% CI 10 to 14 months) for those in the treatment arm, compared with 10 months (95% CI 8 to 17 months) for those in the interferon-α arm.

For the interferon alpha studies, duration of response is reported separately for those showing a complete, and those showing a partial response. In the study by Pyrhonen and colleagues,[27]for those randomised to interferon-α plus "best supportive care", median duration of response was 6.23 months (range: 2.77 months to 64.89 months) for those achieving a complete response (7 patients), and 5.54 months (range: 4.16 months to 14.55

months) for those achieving a partial response (6 patients). For those randomised to "best supportive care" only, median duration of response was reported as being "23.08+ months" for one patient who achieved a complete response, and "5.54 months" for one patient who achieved a partial response.

In the study by Kriegmair and colleagues,[24] responses only occurred within the interferon-α plus "BSC" arm. For complete responders (4 participants), mean duration of response was 10.8 months (range: 4 to 16 months), while it was 11.6 months (range: 7 to 20 months) for those achieving partial response (five participants).

A5. VEG105192 subgroup analyses

The scope document stated that if the evidence allowed, the following subgroup analyses should be considered: (i) resected versus unresected primary tumour, (ii) clear cell component versus no clear cell component and (iii) performance status. However the manufacturer argued that the evidence available from the VEG105192 study did not allow these subgroups to be considered. In terms of (i) they stated that most patients (89%) in the trial had undergone a nephrectomy and therefore the unresected group was too small for interpretable results. For (ii), all patients in the trial were required to have clear cell (90%) or predominantly clear cell histology and no patients were included without a clear cell component, therefore an analysis of no clear cell component was not possible and for (iii) analysis was not conducted for the treatment-naïve sub-population because the resulting subgroups were too small for interpretable results.

While the ERG accepted the manufacturer's rationale for not undertaking the above subgroup analyses it nevertheless requested these data where available for completeness of information (ERG clarification query A12). The manufacturer provided information on response rates for these subgroups, other than for clear cell/no clear cell histology for the reasons outlined above. The response rate (complete response plus partial response) in the pazopanib group for patients with a nephrectomy was 33% (43/130) compared with 24% (6/25) for those without nephrectomy. The response rate in the pazopanib group for patients with ECOG performance status 0 was 37% (23/63) compared with 28% (26/92) for ECOG 1.

Table 4.13 Response results for comparator interventions

Study	Intervention	Overall Response % (n)	Complete Response % (n)	Partial Response % (n)	Stable Disease % (n)
Assessment by independent review committee					
Motzer 2009[17]	Sunitinib	31.61% (49)	0% (0)	31.61% (49)	36.13% (56)
	IFN	3.85% (3)	0% (0)	3.85% (3)	39.74% (31)
Assessment by investigator					
Motzer 2009[17]	Sunitinib	38.71% (60)	2.93% (11)	44.0% (165)	40.0% (150)
	IFN	6.41% (5)	1.07% (4)	11.2% (42)	53.87% (202)
Negrier 207[25]	IFN	8.20% (10)	2.46% (3)	5.74% (7)	18.85% (23)
	IL-2	4.00% (5)	0% (0)	4.00% (5)	20.80% (26)
	"BSC"	1.63% (2)	0.81% (1)	0.81% (1)	14.63% (18)
MRC RE01[23]	IFN	6.32% (11)	1.15% (2)	5.17% (9)	12.64% (22)
	"BSC"	2.27% (4)	0% (0)	2.27% (4)	8.52% (15)
Pyrhonen 1999[27]	IFN + "BSC"	16.46% (13)	8.86% (7)	7.59% (6)	39.24% (31)
	"BSC"	2.47% (2)	1.23% (1)	1.23% (1)	43.21% (35)
Kriegmair 1995[24]	IFN + "BSC"	20.45% (9)	9.09% (4)	11.36% (5)	25.00% (11)
	"BSC"	0% (0)	0% (0)	0% (0)	Not reported
Steineck 1990[26]	IFN	6.67% (2)	3.33% (1)	3.33% (1)	13.33% (4)
	"BSC"	3.33% (1)	3.33% (1)	0% (0)	10.00% (3)

Source: manufacturer's systematic review.

B. *Safety*

B1. Treatment duration

The manufacturer's submission reports a summary of exposure to pazopanib (Table 5.52) which has since been updated in Table 1.2 of the addendum to the manufacturer's original submission. When dose interruptions were not accounted for, median duration of treatment was 7.4 months (range 0 to 41 months) for pazopanib participants compared with 4.2 months (range: 0 to 24 months) for those on placebo treatment. The mean daily dose (with dose interruptions included) was 680.6mg (SD: 219.22) for those receiving pazopanib, and 778.0mg (SD: 102.95) for those receiving placebo (response to ERG clarification query A5 on the additional data submitted by the manufacturer in August 2010).

When dose interruptions were accounted for, median treatment duration did not change for placebo patients, but was reduced to 7.1 months (range: 0 to 41 months) for pazopanib patients. The mean daily dose was 704.2mg (SD: 182.03) for those receiving pazopanib, and 784.3mg (SD: 76.07) for those on placebo.

The proportion of participants still receiving treatment at specific timepoints is detailed below in Table 4.14. The addendum to the manufacturer's submission notes that in the pazopanib arm, 38% of treatment naïve participants remained on pazopanib for more than 12 months but this is an error, as 44 participants, out of 155 randomised to pazopanib, is actually 28%.

Table 4.14 Treatment duration, VEG105192 treatment-naïve safety population, 15 March 2010 cut-off

	<3 months	**3-6 months**	**6-12 months**	**>12+ months**
Not accounting for dose interruptions				
Pazopanib	38 (25%)	34 (22%)	39 (25%)	44 (28%)
Placebo	35 (45%)	15 (19%)	13 (17%)	15 (19%)
Accounting for dose interruptions				
Pazopanib	36 (23%)	34 (22%)	39 (25%)	46 (30%)
Placebo	35 (45%)	15 (19%)	13 (17%)	15 (19%)

The updated summary of subject disposition (Table 1.1 in the addendum) indicates that 20 pazopanib randomised participants, and 5 placebo-randomised participants withdrew due to adverse events. However, further safety data were not updated from the data provided in the manufacturer's original submission, although the difference is an increase of one additional withdrawal from the pazopanib arm of the trial (as the original number of withdrawals from this arm was 19).

B2. Summary of adverse events for study VEG105192

Table 4.15 summarises the adverse events for the treatment-naïve population in study VEG105192. In total, 141 (91%) of the 155 pazopanib randomised patients reported adverse events, compared with 58 (74%) of the 78 placebo patients. Adverse events 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%). The proportions of patients experiencing an adverse event 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. Serious adverse events 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 serious adverse event in patients receiving pazopanib (n=4, 3%). Serious arterial/thrombotic events (including myocardial infarction/ischaemia) and serious hepatic abnormalities were each reported in three (2%) of pazopanib-treated patients.

The manufacturer also pooled adverse event data across the VEG105192, VEG102616 and VEG107769 studies (not shown), stating that the overall safety profile of pazopanib across the three studies was similar to that reported by the VEG105192 study.

Table 4.15 Summary of adverse events for study VEG105192, 23 May 2008 cut-off

	Pazopanib (n=155)	**Placebo (n=78)**
Any adverse event	141 (91%)	58 (74%)
Adverse event related to study medication	135 (87%)	29 (37%)
Grade 3 adverse event	57 (37%	10 (13%)
Grade 4 adverse event	9 (6%)	5 (6%)
Adverse event leading to permanent discontinuation of study medication	19 (12%)	5 (6%)
Adverse event leading to dose reduction	36 (23%)	3 (4%)
Adverse event leading to dose interruption	57 (37%)	4 (5%)
Serious adverse event	33 (21%)	13 (17%)

Notes:

1. A serious adverse event was defined in the VEG105192 clinical study report (CSR) as [redacted]

[redacted]

B3. Death (VEG105192)

At the 23 May 2008 cut-off, 56 patients (36%) in the pazopanib arm and 34 patients (44%) in the placebo arm had died. There were six deaths (3.9%) resulting from adverse events in the pazopanib arm (due to bronchopneumonia, dyspnoea, haemoptysis, gastric haemorrhage, abnormal hepatic function and ischaemic stroke) and two (2.6%) in the placebo arm (due to lower respiratory tract infection and asthenia). At the 15 March 2010 cut-off, 99 patients (64%) in the pazopanib arm and 49 patients (63%) in the placebo arm had died.

B4. Treatment-related adverse events (VEG105192)

Most adverse events were considered to be treatment-related in the pazopanib arm compared with the placebo arm (87% versus 37%), see Table 4.16. Treatment-related adverse events and serious adverse events grouped by class are shown in Table 4.17. Specific treatment-related adverse events reported by > 20% of patients in the pazopanib arm included diarrhoea (39%), hypertension (38%), hair colour changes (38%), nausea (22%) and ALT increased (21%). Forty-four pazopanib arm patients (28%) experienced a grade 3 drug-related event, of which ALT increased was the most frequently reported (9% of patients).

Table 4.16 Study VEG105192 treatment-related adverse events and serious adverse events grouped by class

	Pazopanib (n=155) n (%)		Placebo (n=78) n (%)	
	Any event	**Serious events**	**Any event**	**Serious events**
All events	135 (87)	16 (10)	29 (37)	1 (1)
Gastrointestinal disorders	86 (55)	7 (5)	14 (18)	
Skin and subcutaneous tissue disorders	74 (48)		3 (4)	
Vascular disorders	62 (40)		7 (9)	
Investigations	58 (37)	1 (<1)	3 (4)	
General disorders and administration site conditions	48 (31)		5 (6)	
Metabolism and nutrition disorders	33 (21)		6 (8)	
Nervous system disorders	24 (15)		3 (4)	
Blood and lymphatic system disorders	16 (10)	1 (<1)	0	
Hepatobiliary disorders	11 (7)	3 (2)	2 (3)	
Renal and urinary disorders	13 (8)		0	
Respiratory, thoracic and mediastinal disorders	11 (7)		2 (3)	
Musculoskeletal and connective tissue disorders	11 (7)		0	
Endocrine disorders	8 (5)		0	
Psychiatric disorders	5 (3)		1 (1)	
Cardiac disorders	4 (3)	1 (<1)	0	
Eye disorders	2 (1)		1 (1)	
Infections and infestations	2 (1)		1 (1)	
Injury, poisoning and procedural complications	3 (2)	1 (<1)	0	
Reproductive system and breast disorders	3 (2)		0	

Source: manufacturer's response to clarification queries.

Notes:

1. The class of event to which the placebo group serious adverse event belonged was not reported in the response to clarification queries.

Table 4.17 On-therapy adverse events reported for ≥5% subjects in pazopanib arm related to investigational product, 23 May 2008 cut-off

	Pazopanib (n=155) n (%)			Placebo (n=78) n (%)		
	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
Diarrhoea	60 (39)	4 (3)	1 (<1)	4 (5)	0	0
Hypertension	59 (38)	5 (3)	0	7 (9)	0	0
Hair colour changes	59 (38)	1 (<1)	0	1 (1)	0	0
Nausea	34 (22)	2 (1)	0	4 (5)	0	0
ALT increased	33 (21)	14 (9)	1 (<1)	0	0	0
AST increased	29 (19)	7 (5)	1 (<1)	0	0	0
Anorexia	26 (17)	2 (1)	0	0	0	0
Vomiting	26 (17)	4 (3)	1 (<1)	3 (4)	0	0
Fatigue	22 (14)	1 (<1)	0	0	0	0
Asthenia	18 (12)	4 (3)	0	0	0	0
Alopecia	13 (8)	0	0	0	0	0
Abdominal pain	13 (8)	3 (2)	0	0	0	0
Weight decreased	12 (8)	0	0	0	0	0
Dysgeusia	11 (7)	0	0	1 (1)	0	0
Proteinuria	10 (6)	0	0	0	0	0
Rash	10 (6)	0	0	0	0	0
Headache	9 (6)	0	0	0	0	0
Skin de-pigmentation	9 (6)	0	0	0	0	0
Hypothroidism	8 (5)	0	0	0	0	0
Thrombocyopenia	8 (5)	2 (1)	0	0	0	0
Abdominal pain upper	7 (5)	0	0	1 (1)		
Abdominal distension	7 (5)	0	0	0	0	0
Neutropenia	7 (5)	2 (1)	0	0	0	0

Source: manufacturer's submission.

Notes:

1. Any adverse event includes grade 5 (fatal) events.
2. ALT, alanine aminotransferase; AST, aspartate aminotransferase (AST).

B5. Specific adverse events highlighted by the manufacturer (VEG105192)

The manufacturer highlighted adverse events relating to cardiac and vascular events and haematological events in study VEG105192. In the treatment-naïve 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. Congestive heart failure was observed in two patients (1%) in the pazopanib arm compared with none in the placebo arm.

In the pazopanib arm, any grade cytopenias ranged from 25% (n=37) for anaemia to 38% (n=57) for leukopenia, compared with, for the placebo arm, 4% (n=3) for both leukopenia and neutropenia to 32% (n=25) for anaemia. In the pazopanib arm, grade 3 events ranged from <1% (n=1) for both thrombocytopenia and anaemia to 7% (n=5) for lymphocytopenia, while in the placebo arm 1% (n=1) experienced lymphocytopenia and 1% (n=1) experienced anaemia. In the pazopanib arm < 1% (n=1) and in the placebo arm 1% (n=1) experienced anaemia as a grade 4 event.

B6. Adverse events in comparator interventions included in the indirect comparison

Table 4.18 shows a summary of specific adverse events, grouped by class, experienced at any grade by patients randomised to each intervention. This information was reported by VEG105192, the study by Motzer and colleagues[17] reporting sunitinib versus IFN, and the study by Steineck and colleagues[26] reporting IFN versus best supportive care. Rates for most events were higher for sunitinib patients compared with pazopanib patients, other than for abdominal pain, fever and headache, which were similar, while pazopanib patients experienced a higher rate of hair colour change (38.7% versus 20%) and hypertension (39.4% versus 30%). Rates higher than 10% are shown with cells shaded grey in the table.

Table 4.18 Specific adverse events grouped by class

Adverse events by class		VEG105192 %		Motzer 2009 %		Steineck 1990 %	
		Paz	Pla	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		
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		

Adverse events by class		VEG105192 %		Motzer 2009 %		Steineck 1990 %	
		Paz	Pla	Sun	IFN	IFN	BSC
	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		

Source: manufacturer's submission

Notes:

1. No adverse event data for specific adverse events (any grade) were reported by Negrier 2007, MRC RE01, Kriegmair 1995 and Pyrhonen 1999.[23-25,27]
2. Paz, pazopanib; Sun, sunitinib; IFN, interferon alpha; BSC, best supportive care; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4.19 shows a summary of specific grade 3/4 adverse events for patients randomised to each intervention. This information was reported by VEG105192, Motzer and colleagues,[17] Negrier and colleagues,[25] MRC RE01,[23] Kriegmair and colleagues[24] and Pyrhonen and colleagues.[27] Rates were less than 5% for most grade 3/4 events. Rates higher than 10% are shown with cells shaded grey in the table.

Table 4.19 Specific grade 3/4 adverse events experienced by randomised patients

Study id	VEG105192		Motzer 2009[17]		Negrier 2007[25]			MRC RE01[23]		Kriegmair 1995[24]		Pyrhonen 1999[27]	
	Paz	Pla	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
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		

Study id	VEG105192		Motzer 2009[17]		Negrier 2007[25]			MRC RE01[23]		Kriegmair 1995[24]		Pyrhonen 1999[27]	
	Paz	Pla	Sun	IFN	IFN	IL-2	BSC	IFN	BSC	IFN + BSC	BSC	IFN + BSC	BSC
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									

Source: manufacturer's submission.

Notes:

1. ALT, alanine aminotransferase; AST, aspartate aminotransferase.
2. * = on-therapy adverse events regardless of relationship to investigational product.
3. No adverse event data for specific grade 3/4 adverse events reported for Steineck 1990.
4. Cells shaded in grey show adverse events with rates > 10%.

B7. Treatment discontinuations, dose reductions and dose interruptions

Table 4.20 shows rates of treatment discontinuation, dose reductions and dose interruptions. Data for treatment discontinuation due to adverse events were reported. For study VEG105192 data for dose reductions and interruptions due to adverse events were reported, for Motzer and colleagues[17] data for dose interruptions due to adverse events were reported, while for the other studies it was unclear whether the data reported were due to adverse events. Rates of treatment discontinuation were higher for sunitinib patients compared with pazopanib patients (18.7% versus 11.0%) while rates of dose interruptions were similar (36.8% versus 38.1% respectively). In the VEG105192 study, pazopanib arm, the most common adverse events leading to (i) treatment discontinuation were diarrhoea (3%) and adverse events associated with liver function/enzyme abnormalities (2.6%), (ii) dose reductions were hypertension (n=12, 8%) and ALT increased (n=7, 5%) and (iii) dose interruptions were ALT increased (n=14, 9%), AST increased (n=12, 8%) and diarrhoea (n=9, 6%).

Table 4.20 Treatment discontinuations, dose reductions and dose interruptions due to adverse events

Study id	Intervention and comparator	Number evaluable	Treatment discontinuations	Dose reductions n (%)	Dose interruptions n (%)
VEG105192	Pazopanib	155	17 (11.0)	36 (23.2)	57 (36.8)
	Placebo	78	4 (5.1)	3 (3.8)	4 (5.1)
Motzer 2009[17]	Sunitinib	375	70 (18.7)	188 (50.1)	143 (38.1)
	IFN	375	86 (22.9)	101 (26.9)	120 (32.0)
MRC RE01[23]	IFN	167		40 (24.0)	
	BSC	168		12 (7.1)	
Pyrhonen 1999[27]	IFN+BSC	79	5 (6.3)	42 (53.2)	
	BSC	81	0 (0)		
Kriegmair 1995[24]	IFN+BSC	41		11 (26.8)	15 (36.6)
	BSC				

Source: manufacturer's systematic review document.

B8. Indirect comparison of adverse events for pazopanib versus sunitinib

Table 4.21 shows the results of the manufacturer's indirect analyses of pazopanib relative to sunitinib, via the IFN study by Steineck and colleagues[26] for specific adverse events (all grades). The direction of effect favoured pazopanib over sunitinib for most of the outcomes shown in the table, although the results were statistically significant only for fatigue. The

direction of effect for alopecia and hypertension favoured sunitinib over pazopanib but neither was statistically significant.

Table 4.21 Indirect comparison of adverse events for pazopanib versus sunitinib

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

Source: manufacturer's submission.

Notes:

1. PPE, Palmar-plantar erythrodysesthesia syndrome.

B9. Adverse events reported by comparator studies but not extracted by the manufacturer

In response to a clarification query (C11) enquiring whether all adverse events reported by included studies were included within the groupings in Table 36 of the systematic review (Specific AEs experienced by randomised patients (across all grades)) the manufacturer provided details of adverse events that were reported by comparator studies but that were not data extracted. These are listed in Appendix 2.

C. Health-related quality of life

C1. Overview

Only two studies reported health-related quality of life (HRQoL), VEG105192 reporting pazopanib versus placebo and the study by Motzer and colleagues[17] reporting sunitinib versus interferon-α. In VEG105192, HRQoL was measured using the EORTC QLQ-C30 Global Health Status score (Table 4.22), EQ-5D (Table 4.23) and EQ-5D-VAS (Table 4.24). Motzer and colleagues[17] measured HRQoL with EQ-5D and EQ-5D-VAS (Table 4.25), the FACT-Kidney Symptom Index-Disease-related Symptom (FKSI-DRS) Index, FACT-Kidney Symptom Index – 15 item scale (FKSI-15 Index), and the Functional Assessment of Cancer Therapy – General Scale (FACT-G)

In VEG105192, HRQoL was measured using the EORTC QLQ-C30 Global Health Status score, EQ-5D and EQ-5D-VAS at the 6th, 12th, 18th, 24th and 48th week. Additional data were provided by the manufacturer following clarification queries, including baseline figures for EQ-5D utility and VAS scores. This additional information notes that the analysis method was analysis of covariance adjusted for baseline score using mixed-model repeated measures (MMRM) with intercept, time, treatment, baseline score by time interaction and treatment by time interaction as fixed effects and time treated as a repeated variable within subject. As a result, differences in mean utility scores for the EQ-5D data as calculated from Table 13.1001 of the clarification responses, do not match those provided in Table 5.26 of the manufacturer's initial submission, as these have been adjusted.

C2. EORTC-QLQ-C30

The EORTC QLQ-C30 is a 30-item self-reporting questionnaire developed to assess the quality of life of cancer patients. In VEG105192, the EORTC-QLQ-C30 score showed no statistical difference between pazopanib and placebo arms at each assessment time point.

C3 EQ-5D

The EQ-5D index score ranges from -0.594 to 1.000, with scores of 1, 0, or less than 0 equivalent to the health states of full health, death, or worse than death, respectively. In the pazopanib study (VEG105192) results from a MMRM analysis for change from baseline showed no statistical difference in EQ-5D score between pazopanib and placebo patients at each assessment point. In the study comparing sunitinib with IFN, the overall post-baseline mean treatment difference was statistically significant in favour of sunitinib.

C4. EQ-5D-VAS

The EQ-5D-VAS is a 100-point visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). In the pazopanib study (VEG105192) results from a MMRM analysis for change from baseline showed no statistical difference in EQ-5D-VAS score between pazopanib and placebo patients at each assessment point. For the sunitinib study, baseline scores and the mean differences between treatments were reported (derived from the difference in endpoint scores which were derived as a least squares means calculated during the 17th week of the trial).[35] In this study, comparing sunitinib with interferon-α, the EQ-5D-VAS score was statistically significantly higher for sunitinib.

C5. FACT

The FKSI-DRS Index contains nine items measuring symptoms predominantly related to kidney cancer, with a score ranging from 0 (all most severe symptoms) to 36 (no symptoms). The FKSI-15 is a validated symptom index for kidney cancer patients containing 15 questions. The FKSI-15 score ranges from 0 (most severe symptoms and concerns) to 60 (no symptoms or concerns). The FACT-G scale measures the impact of treatment on general cancer related Health Related Quality of Life (HRQoL) and functioning. For the study comparing sunitinib with interferon-α, the scores for each of these three scales showed a statistically significant difference in favour of the sunitinib group. Results using these instruments are reported on pages 74-75 of the systematic review document.

Table 4.22 EORTC-QLQ-C-30 Global health status/quality of life, VEG105192

	6	**12**	**18**	**24**	**48**
Pazopanib (n)	133	118	100	87	45
Mean score					
Mean difference since baseline	-3.6	-2.8	-3.6	-0.7	-0.4
Adjusted mean difference since baseline	-5.03	-3.91	-4.25	-2.25	-0.79
Placebo (n)	59	44	34	27	15
Mean score					
Mean difference since baseline	-4.1	-3.8	-2.2	-1.9	-4.4
Adjusted mean difference since baseline	-2.75	-3.58	-1.31	-1.12	-1.59
Difference					
Mean difference in utility between pazopanib and placebo since baseline	0.5	1	-1.4	1.2	4
Mean adjusted difference in utility between pazopanib and placebo since baseline (95% CI)	-2.28 (-7.859, 3.299)	-0.33 (-6.231, 5.573)	-2.95 (-9.401, 3.510)	-1.12 (-7.870, 5.622)	0.80 (-7.404, 9.014)
p value for difference in adjusted utility between pazopanib and placebo since baseline	0.421	0.913	0.369	0.742	0.845

Table 4.23 EQ-5D – Utility score, VEG105192

	Baseline	**6**	**12**	**18**	**24**	**48**
Pazopanib (n)	154	138 (137)	121 (120)	103 (102)	89 (88)	46 (46)
Mean score	0.691	0.672	0.668	0.698	0.695	0.779
Mean difference since baseline		-0.019	-0.023	0.007	0.004	0.088
Adjusted mean difference since baseline		-0.037	-0.044	-0.017	-0.023	0.020
Placebo (n)	76	67 (65)	47 (45)	34 (34)	28 (28)	14 (14)
Mean score	0.720	0.716	0.723	0.783	0.764	0.778
Mean difference since baseline		0.004	-0.003	0.063	0.044	0.058
Adjusted mean difference since baseline		-0.027	-0.034	-0.020	-0.015	-0.006
Difference						
Mean difference in utility between pazopanib and placebo since baseline		-0.023	-0.020	-0.056	-0.040	0.030
Mean adjusted difference in utility between pazopanib and placebo since baseline (95% CI)		-0.010 (-0.081, 0.061)	-0.010 (-0.080, 0.061)	0.003 (-0.067, 0.073)	-0.008 (-0.094, 0.079)	0.026 (-0.059, 0.111)
p value for difference in adjusted utility between pazopanib and placebo since baseline		0.784	0.789	0.930	0.861	0.548

Notes:

1. Pazopanib and placebo rows. Numbers not in parentheses are those given in the response to ERG clarification query A10. Numbers in parentheses are those given in Table 5.26 of the manufacturer's submission.

Table 4.24 EQ-5D – VAS score, VEG105192

	Baseline	**6**	**12**	**18**	**24**	**48**
Pazopanib (n)	153	134 (132)	118 (117)	101 (100)	87 (86)	45 (45)
Mean score	65.1	64.5	68.5	68.4	71.2	73.2
Mean difference since baseline		-0.6	3.4	3.3	6.1	8.1
Adjusted mean difference since baseline		-2.58	-0.40	-0.66	0.95	3.78
Placebo (n)	74	63 (59)	45 (43)	34 (33)	27 (27)	14 (14)
Mean score	65.4	65.6	65.8	67.7	71.2	71.2
Mean difference since baseline		0.2	0.4	2.3	5.8	5.8
Adjusted mean difference since baseline		-2.81	-3.57	-1.78	0.89	1.82
Mean difference in utility between pazopanib and placebo since baseline		-0.8	3	1	0.3	2.3
Mean adjusted difference in utility between pazopanib and placebo since baseline (95% CI)		0.23 (-5.160, 5.626)	3.17 (-3.394, 9.741)	1.12 (-5.159, 7.398)	0.06 (-6.036, 6.153)	1.96 (-7.656, 11.572)
p value for difference in adjusted utility between pazopanib and placebo since baseline		0.932	0.342	0.725	0.985	0.685

Notes:

1. Pazopanib and placebo rows. Numbers not in parentheses are those given in the response to ERG clarification query A10. Numbers in parentheses are those given in Table 5.26 of the manufacturer's submission.

Table 4.25 EQ-5D utility scores and EQ-5D-VAS scores, sunitinib study

Study	Treatment	Baseline Score	Endpoint score	Difference (95% CI)	p-value for the difference
EQ-5D Index	Sunitinib	0.76 (SD: 0.23)	0.762	0.0364 (0.0109 – 0.0620)	p=0.0052
	IFN	0.76 (SD: 0.23)	0.725		
EQ-5D-VAS	Sunitinib	73.8 (SD: 18.50)	73.4	4.74 (2.60 to 6.87)	p<0.001
	IFN	71.43 (SD: 19.51)	68.7		

4.2.2 Critique of submitted evidence synthesis

Quality of reporting in the manufacturer's submission

The manufacturer submitted a substantial amount of evidence on the efficacy and safety of pazopanib in the form of the submission document, the clinical study report for VEG105192 and the systematic review document, and the addendum containing updated overall survival data. A great deal of effort has clearly gone into providing data on the efficacy and safety of pazopanib.

However, in compiling data for each outcome, it was sometimes necessary to collect data from each of these sources in order to capture the full extent of the treatment effect, as summary statistics provided in the submission were sometimes selective, although in searching multiple sources provided by the manufacturer there were sometimes discrepancies in the numbers being used (the quality of life data provided for the EQ-5D is one example where the numbers included differ from the clinical study report documents and the manufacturer's submission).

In other cases, it was difficult to draw conclusions from data reported in the submission documents because so much information had been gathered by the manufacturer on particular outcomes that these were reported in a variety of ways. For example, for response data two sets of analyses were reported. In one, response was undertaken by independent review and in the other it was assessed by investigators. In each analyses stable disease was defined in two ways (requiring a minimum of 12 weeks stable disease or requiring a minimum of six months stable disease) and under its first definition it was not included in the "overall response rate" but under its second definition it was included in the "overall response rate".

The result is a range of response rates for pazopanib depending on the reported method preferred.

The methods were generally well reported, but in some cases the manufacturer had not fully described the methods used to calculate particular outcomes. This was most notable for the method for adjusting for baseline EQ-5D scores, and also the indirect comparison method (page 98 of the manufacturer's submission), the inference of hazard ratios for interferon-α studies where these data had not been reported (page 96 of the manufacturer's submission) and the recalculation of confidence intervals around hazard ratios (page 96).

Quality of the manufacturer's systematic review

The ERG assessed the clinical effectiveness part of the manufacturer's submission for its methodological quality as a systematic review using the questions contained in CRD report 4 (Table 4.26). Overall, the methodological quality of the manufacturer's systematic review was good.

Table 4.26 Quality assessment (CRD criteria) of the manufacturer's review

CRD Quality Item	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes • Inclusion and exclusion criteria for primary studies are reported.
2. Is there evidence of a substantial effort to search for all relevant research?	Partially • Only RCTs were included. • Only English language studies included.
3. Is the validity of included studies adequately assessed?	Yes • All included RCTs were assessed using three separate instruments.
4. Are sufficient details of the individual studies presented?	Yes • Characteristics of all included studies were reported in detail.
5. Are the primary studies summarised appropriately?	Yes • Results of all primary studies summarised for efficacy, safety and health-related quality of life.

Representativeness of participants in trials to UK renal cell carcinoma patients

The VEG105192 study is a multicentre, international study (23 countries including the UK). Of the treatment-naïve-population (n=233), seven patients were from the UK (five randomised to pazopanib, two to placebo).

For the comparator interventions reporting interferon-α included in the indirect comparison, one (the MRC RE-01 study) took place in the UK, while the others took place in France,[25] Sweden,[26] Finland[27] and Germany.[24] The study by Motzer and colleagues[17] reporting sunitinib versus interferon-α was a multicentre, international study (11 countries including the UK) but it did not report how many patients were from the UK.

Efficacy and safety of pazopanib

The efficacy of pazopanib relative to sunitinib has been established based on a number of assumptions. First, there is the assumption that placebo, MPA and vinblastine all constitute best supportive care. The manufacturer stated that consistent with data from controlled trials and based on discussions with practising oncologists specialising in renal cell cancer, it was assumed that MPA and vinblastine would have no impact on progression-free survival and overall survival in this population and should therefore be considered as palliative treatment equivalent to placebo with best supportive care. However the ERG considers that the response rate to both MPA and vinblastine is low but not zero, with both having significant toxicities, therefore whether they really are equivalent to placebo with best supportive care is debatable.

In the indirect comparison the manufacturer used a pooled result from the interferon-α trials, with some trials using different doses (ranging from 9 million to 20 million units three times per week), with the assumption that the dose of interferon alpha would not affect the results. Although this may be the case and there is no clear dose-response relationship for interferon-α there are clear dose-related toxicities which could influence the duration of therapy/tolerability.

The data provided for comparator treatments were selective and not all the evidence from these trials has been taken into account. In addition, the manufacturer made reference to non-randomised pazopanib studies in the submission.

In terms of the methods used to derive efficacy results for pazopanib, the method used for overall survival differs slightly from progression free survival, as the addendum used a different method to update overall survival than the original submission. While the argument

for modifying this method may have been statistically justifiable, it does affect the results. However, the revised RPSFT methodology (based on weighted log-rank tests) does yield a higher hazard ratio than the unweighted method, so the change in methodology has not necessarily been favourable to pazopanib. Also, results from analyses using both methodologies (i.e. weighted and unweighted) are reported.

The manufacturer has used a hazard ratio for sunitinib vs interferon alpha for patients with no post-study therapy. Hazard ratios for pazopanib patients with no post study therapy were available, but the RPSFT methods were used instead.

4.2.3 Summary

The ERG's main concerns with regard to the clinical effectiveness part of the manufacturer's submission were:

- Potentially relevant studies may have been excluded by the manufacturer based on their definition of what could and could not be included in terms of 'best supportive care' and their approach to studies reporting interleukin-2.
- The RPSFT method used to deal with cross-over of placebo-treated patients to pazopanib in VEG105192 is novel and still under development.
- The method of RPSFT used to report the interim overall survival data was different to that used to report the final overall survival data.
- In the systematic review, in the indirect comparison, progression-free survival for interferon-α was reported for only the MRC RE01 study, while in the manufacturer's submission, it was reported for three studies.
- As the RPSFT method provided the overall survival data for VEG105192 for the indirect comparison, and only a small number of studies were included in the indirect comparison, its results should be interpreted with caution.

5 ECONOMIC EVALUATION

As part of the manufacturer submission a de novo economic evaluation was performed to assess the cost-effectiveness of pazopanib versus sunitinib, interferon-α (IFN) and best supportive care (BSC) in patients with advanced/metastatic RCC in the UK.

5.1 Overview of the manufacturer's economic evaluation

The manufacturer's economic evaluation included:

- A systematic review they had undertaken to identify relevant cost-effectiveness and cost-utility studies. A critique of the identified evaluations was included in section 10 of the systematic review provided as part of the initial submission.
- A report of the de novo economic evaluation conducted by GlaxoSmithKline (P150-213 of the manufacturer's initial submission document). In the initial submission the manufacturer indicated that pazopanib was likely to be granted a licence for treatment of patients who were either treatment naïve or had cytokine pre-treated advanced/metastatic RCC. This is consistent with the two subpopulations examined in the main clinical trial. In their submission only the cost-effectiveness of pazopanib used in a treatment naïve population was examined (p 150, manufacturer's initial submission document).
- A description of the model including a model schematic can be found on pages 150 and 151 of the manufacturer's initial submission document. Tables of the summary key features of the analysis and assumptions made in the economic model can be found on pages 153 and 171 respectively of this document. Costs are estimated using the best available published and unpublished sources, supplemented with expert opinion and assumptions as necessary and appropriate. Published sources were identified from a previous systematic review, supplemented with searches of online databases, internet searches and hand searches of retrieved articles.
- Results of the analysis are provided in Section 6.7 of the manufacturer's initial submission document. The base case analysis results are presented on pages 193-198 and the sensitivity analysis on pages 199-207. None of the identified subgroup analyses were performed due to limited sample sizes.
- As part of the initial submission the manufacturer provided a Microsoft Excel based electronic copy of the model used.
- Additional information was submitted by the manufacturer in the form of an addendum to the initial submission, a PAS and a revised and updated economic model.

- The addendum presented the final overall survival (OS) data conducted with a clinical cut-off date of 15 March 2010 together with associated analyses adjusting for the effects of post study therapy and the results of a revised and updated economic analysis.

[redacted]

- The revised and refined economic model taking into account potential rebates for pazopanib and revised estimates of the hazard ratios for pazopanib based upon more mature data that has become available since the preparation on the initial submission.

The ERG requested a number of points for clarification from GlaxoSmithKline on their initial submission. Presented below are the following points that are still relevant following submission of the revised analysis contained in the addendum:

- A request for a summary of model inputs.
- A detailed explanation of how the cost of pazopanib was generated.
- Clarification as to how consistent the five year survival with metastatic disease of 9.5% which is quoted in the submission is with the model predictions.
- Details on the patient groups used to estimate the EQ-5D scores.
- Clarification on the likelihood that patients who progress will discontinue pazopanib therapy
- Clarification of why an assumption of immediate cessation of treatment following progression was judged to be sufficiently realistic.
- Clarification of how long a patient would be monitored before a decision that progression had occurred is made.
- Clarification as to how would the results of the economic evaluation have changed had the data from VEG105192 been used as the reference treatment for the Weibull survival functions.

There were also specific details sought on the parameter values used in the model.

The following section focuses on the manufacturer's submission (Pazopanib (Votrient) for the first line treatment of patients with advanced renal cell carcinoma (RCC) using updated results contained in the revised submission (including the addendum and model) and the PAS where appropriate.

5.2 Cost-effectiveness analysis methods

As noted above, evidence on cost-effectiveness came from two sources, a systematic review of extant analyses and a de novo model. The manufacturer provided details on the systematic review they performed to identify any cost-effectiveness or cost-utility studies from the published literature (Section 6.1 of the manufacturer's initial submission).

The manufacturer undertook separate searches on 23rd November to identify relevant cost-effectiveness studies and these are detailed in full in Appendix 10 of the manufacturer's report and Appendix B of the systematic review. MEDLINE, EMBASE, MEDLINE In process and, from the Cochrane Library, the HTA database and NEED were searched for reports of cost-effectiveness studies relating to renal cancer.

These searches were supplemented by searching for health technology appraisals undertaken by five HTA organisations (NICE, AWMSG and SMC from the UK and CADTH (Canada) and PBAC (Australia)). It is not stated how this selection was made.

The MEDLINE and EMBASE searches were appropriately constructed using subject terms and text words. Once again, a broader list of drugs was included in the strategy. The ERG did not have access to the platform used by the manufacturer (Embase.com) so could not replicate the searches. The search of the Cochrane Library used the same search strategy as that used for clinical effectiveness but was restricted to the appropriate HTA and economic databases.

The manufacturer states that searches were undertaken for HRQoL studies but it is unclear how this was undertaken. Section 6.4.5 of the submission states that the search was incorporated into the clinical effectiveness search with the use of terms relating to general quality of life descriptors and HRQoL measurement and referring the reader to Appendix 12. Appendix 12, in turn, refers the reader to Appendix 10 which details the cost-effectiveness searches. However, neither the clinical effectiveness nor cost-effectiveness published searches includes HRQoL terms.

The eligibility criteria for inclusion were specified based on standard PICO criteria, study design, language of publication, and publication time frame. The exclusion criteria included: lack of subgroup analysis for the disease of interest or advanced metastatic disease or treatment naïve patients. Studies with no subgroup data from the disease, disease stage and line of treatment were not included, since they would introduce heterogeneity into the review

(Table 9.7 manufacturer submission). These were used to identify studies to be included in the economic evidence (Appendix 10).

The manufacturer's modelling approach was described as a "partitioned survival" model (Section 6.2.2 of the initial submission document). The model was characterised by three mutually exclusive health states: Alive pre-progression, Alive post-progression and Dead. The difference between the manufacturer's model and a Markov model was that the partition survival model calculated the proportion of patients in each treatment arm at any time after treatment initiation using parametric survival curves fitted to empirical data on overall survival and progression free survival over time. The proportion of patients in the 'Alive post progression' health state at any given time was calculated as the difference between overall survival and progression-free survival.

5.2.1 Natural history

Although the manufacturer anticipates that pazopanib will be granted a licence for the treatment of naïve and cytokine-pre treated advanced/metastatic RCC they focused on patients with treatment-naïve advanced/metastatic RCC, consistent with the scope of the appraisal. In the model pazopanib was assumed to be administered until disease progression or death (if occurring prior to progression). Their analysis was based on the understanding that there are currently no other further treatment options available in the NHS after the first line treatment for advanced and or metastatic RCC who progress while receiving first line therapy (i.e. once progression occurs patients cease active treatment and receive best supportive care).

5.2.2 Treatment effectiveness

In the model the underlying effectiveness of treatments is assessed compared with the effectiveness of IFN, which was taken to be the baseline comparator. 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 (manufacturer's submission).

Estimates of *PFS[t]* and *OS[t]* for each comparator were obtained by first fitting a parametric survival function[1] 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 hazard ratio 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.[39,43,67] The Weibull is a flexible survival function that allows for increasing or decreasing risk of events over time.[68] 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*.

The methods for assessing the relative effectiveness of pazopanib are described and critiqued in detail in Section 4.1.7 and a summary of the evidence is provided in Section 4.2.1, A2 & A3. In brief, (HRs for PFS and OS) were obtained from an RCT identified by the manufacturer (VEG105192). As there were no direct comparisons of pazopanib with the active comparators, 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. Table 4.9 in Chapter 4 reports the effectiveness estimates available and those used in the economic model.

As noted in Chapter 4, several methods were used to estimate hazard ratios and a key concern is the derivation of the causal rate ratio for the weighted unadjusted analysis used in the base case analysis. These concerns are expanded upon in Section 4.1.7 but briefly the statistical model does not appear to have a single likeliest and plausible value and where a choice has been made it has been made in favour of pazopanib. An alternative interpretation would have in some circumstances resulted in a hazard ratio greater than one. Nevertheless, the statistical critique suggests that despite concerns over the approach to weighting, RPSFT analysis is an appropriate method to use in this study, particularly as it has the advantage over other

1 The impact of fitting alternative survival functions and/or using a different reference arm was explored in sensitivity analyses.

methods of producing randomisation-based effect estimators which maintain the validity of between-group comparisons and is not biased by post-randomisation time-dependent covariates. The statistical critique goes on to note however that the RPSFT method is heavily weighted towards the early follow-up period and the analysis did not control for the use of other post-study anti-cancer therapies which was twice as common amongst pazopanib patients compared with placebo patients. Arguably the type of RPSFT analysis used may not have been the most appropriate and further refinement of the weighted analysis is required.

Incidence of adverse events

The manufacturer obtained estimates of the incidence of adverse events (AEs) for each comparator from published results of RCTs. 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/stomatitis, 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. Although AEs were presented separately by grade (grades 1 or 2 and grades 3 or more) the estimates for incidence and duration for each specific AE were the same. Estimates of the standard errors (SEs) of the durations of AEs were not available at the time of the submission. Clarification was sought from the manufacturer who stated that the assumption that SE=0.25 x mean was arbitrary, and consistent with a normal random variable with 95% CI ~equal to +/- 50% of the mean. This is likely a conservative (i.e., wide) range (e.g., if the SD of a random variable is equal to the mean (coefficient of variation [CV]=1.0), an SE = 0.25 x mean implies that the number of subjects upon which the estimate was based was <20; if the CV=2.0, the implied N is <20). The model results were not sensitive to the AE duration so this did not likely materially impact the PSA findings.

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 for indirect and mixed treatment comparison for technology assessment.[69] It was noted that the indirect comparison of AEs utilised for the economic evaluation was slightly different to that presented in the clinical section (Section 5 of the manufacturer's initial submission document). 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,[70] as well as (ii) direct estimates from the Percy Quattro trial.[25]

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.[25] If information on the AE was not reported in the PERCY Quattro trial,[25] the risk difference was based on the indirect comparison only. If information on the AE was not reported in either the PERCY Quattro trial[25] or the sorafenib trial,[70] 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 of the manufacturer's submission document.

5.2.3 Health related quality of life

Health related quality of life measures were derived from the pivotal trial VEG105192 using the EQ-5D questionnaire administered at weeks 8, 16, 24 and 48 of follow-up. For the model, the utility value for progression-free survival without adverse events was based on the mean EQ-5D utility value for patients who did not suffer an AE in the VEG105192 trial. Post progression free survival was obtained from the Remak 2008[71] and Parasuraman 2008[72] studies evaluating recently approved treatments for advanced/metastatic RCC as they were considered to be consistent with those suggested by results of the VEG105192 trial and the Oxford Outcomes study (Table 5.1). These values were used for all the interventions in the model.

Table 5.1 Summary of quality of life values used in the cost-effectiveness analysis

State	Utility value	Confidence interval	Source
Progression Free (no AEs)	0.70	0.68 to 0.72	VEG105192
Post progression	0.59	N/A	Remak 2008[71] Parasuraman 2008[72]

Source: manufacturer's submission.

Utility decrements for adverse events were also obtained from the VEG105192 trial. The manufacturer stated that 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 such as 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 of the general UK population.[73] Members of the public were recruited from four locations around the UK (London, Birmingham, Oxford and Leamington Spa) through advertisements in local newspapers, word-of-mouth and a database of existing willing survey participants. All interviews were conducted by trained interviewers in suitable private locations. Care was taken to ensure that the nature of the interview was fully explained to participants and written informed consent was obtained prior to the interview commencing. The utility decrements for adverse events were used in a sensitivity analysis.

The durations of AEs (required to estimate the decrement in QALYs) were estimated using data from VEG105192. When duration was not available by grade of complication it was assumed that the duration was the same for all grades. Standard errors or the duration of AEs were not reported and were assumed to be equal to 0.25 of the mean value. Further clarification was sought from the manufacturer about these values and details of the updated data (reproduction from the points of clarification document, initially Table 6.18 in the manufacturer's submission) can be found in Table 5.2 below.

Table 5.2 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+									-0.02
Diarrhoea All grades	293	0.76	(0.01)	1,218	0.69	(0.01)	0.07	(0.01)	
Fatigue/asthenia Grades 1-2									-0.10
Fatigue/asthenia Grade 3+									-0.19
Fatigue/asthenia All grades	207	0.59	(0.02)	1,304	0.72	(0.01)	-0.13	(0.02)	
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)	
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)	

Source: manufacturer's response to ERG clarification queries.

Resources and costs

Details of resource identification, measurement and valuation are found in Section 6.5 of the manufacturer's initial submission. Costs considered in the economic model included acquisition costs for study medications; drug administration costs for those therapies requiring infusions, costs of treatment of grade 3+ AEs (this appeared to be restricted to costs incurred in a hospital setting for example OP attendances and day case services such as transfusion); routine follow-up costs; costs of progression; and supportive care costs. Supportive care costs included inpatient, day case and outpatient treatments. Administration of pazopanib and sunitinib was assumed to 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 the

remainder (these proportions were based upon assumptions used in a previous NICE technology appraisal evaluation report by PenTAG[67]). It was stated by the manufacturer that costs were estimated using the best available published and unpublished sources, supplemented with expert opinion and assumption as deemed necessary and appropriate. Published sources were identified from a previous systematic review,[74] supplemented with searches of online databases, internet searches, and hand searches of retrieved articles.

Unit costs for sunitinib and IFN were based on the British National Formulary (BNF 57).[75] The manufacturer stated that 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). GSK propose that the current price of pazopanib incorporates a discount of 12.5% from the current list price in order to provide pazopanib at an equivalent price to sunitinib (including the sunitinib patient access scheme). Assuming 11 months median PFS for sunitinib, a patient would receive 8 cycles of treatment, the first cycle of which would be provided free. This equates to a discount of 12.5%. Details of the unit costs used within the model are described in Table 5.3.

Table 5.3 Medication and administration costs

	Cost £	Reference
IFN 10 MIU vial	42.40	BNF[75]
Administration of IFN per district nurse visit	27.04	PSSRU (PenTAG assumption)[67]
Sunitinib 50 mg capsule	112.10	BNF[75]
Pazopanib 800 mg tablets	65.39	N/A

Source: manufacturer's submission.

The revised economic model submitted as part of the additional data incorporates a 12.5% straight discount from the pazopanib list price (£74.73)

From the time of publishing of positive NICE guidance for pazopanib in first line advanced RCC, GSK will provide pazopanib to the NHS at a cost which is equivalent to the effective cost of sunitinib to the NHS (including the sunitinib PAS), but without additional administrative burden. This will be achieved through list price parity and a straight discount at the point of invoice.

[redacted]

[redacted]

Costs of study medications were adjusted using relative dose intensities reported in RCTs of the study treatments. For example in the model it was assumed that the mean dosage of pazopanib was 0.86 so 688mg per day per patient. Therefore, the cost of pazopanib per day was £56.24. A similar dose intensity was used for sunitinib with a rate of 0.84 for IFN (Table 5.4). The manufacturer stated that the methods used to calculate these measures were not well described so it is difficult to assess their comparability.

Table 5.4 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 (NICE TA169).[67]
		IFN	0.84	Na	Na	Na	

Source: manufacturer's submission.

Notes:

1. Na, not available.

Health state costs consisted of resource use cost associated with outpatient monitoring when patients are in the PFS health state. When patients move to the progressed state it is assumed that they will be managed in primary care. Routine monitoring and supportive care costs associated with PFS and PPS were based on standard NHS reference costs[76] and units of services used were based upon those reported in the PenTAG report[67] (Table 5.5).

Table 5.5 Assumed services and costs of monitoring during PFS and OS

Health State	Service	Cost (£)	Reference
Progression Free Survival	First consultant led outpatient visit	241.00	NHS reference costs HRG WF01A
	Subsequent consultant led 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 costs	
Post Progression Survival	1 GP visit	37.45	PSSRU
	1.5 community nurse visit	40.56	PSSRU
	Morphine sulphate 50 mL vial per day BNF	150.00	BNF 57
BNF British National Formulary, HRG Health related group, PSSRU Personal Social Services research Unit.			

Source: manufacturer's submission.

Further clarification was sought from the manufacturer on how the total cost estimates reported in Table 5.6 were derived. The standard errors (SEs) of the cost estimates were assumed to be 25% of the mean estimates. The cost in each month is equal to the visit cost plus 1/3 the cost of the scan (£140.4/3=£46.80). The cost in the first month is therefore £241+£46.80 = £287.80. The cost in subsequent months is £99+£46.80=£145.80. To avoid double counting, treatment initiation (one-off) costs are calculated as the first month costs minus the subsequent month costs (£287.80-£145.80=£142).

Table 5.6 Routine follow-up and supportive 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

Source: manufacturer's submission.

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 tyrosine kinase inhibitors (TKIs)) were not considered in the model.

Adverse events

For adverse events the cost per event was assumed to be independent of treatment (Table 5.7). Treatment costs were estimated based on the PbR Tariff,[76] Reference Costs from the Department of Health, the University of Kent Personal Social Services Research Unit,[77] and the PenTAG report (TA 169).[67] 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 treating 3+ adverse events were based on expert opinion

Table 5.7 Assumed services and costs of treatment of grade 3+ AEs

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
Diarrhoea	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

Source: manufacturer's submission.

5.2.4 Discounting

A 3.5% annual discount rate was used for costs and health effects in the calculation of cost-effectiveness in accordance with NICE guidelines.

5.2.5 Sensitivity analyses

Both deterministic and probabilistic sensitivity analyses were performed. Details of the deterministic analyses performed can be found in Table 6.27 in Section 6.6.2 of the manufacturer's initial submission and Table 2.11 of the addendum to the submission.

Table 5.8 provides brief explanations of the sensitivity analyses conducted (their results are further considered in Section 5.2.8 of the ERG report). Sensitivity analysis using independent Weibull from the pazopanib arm of VEG105192 was used as reference for comparators performed in the initial submission but was not repeated in the addendum.

Effectiveness of pazopanib

The description for this analysis is provided in Table 5.8. In VEG105192 pazopanib was compared to placebo and in order to get a HR for PFS and OS for pazopanib vs. IFN in treatment-naïve patients an indirect comparison using data from a pooled analysis of RCTs of IFN versus BSC (i.e. no active treatments) was used. These scenarios explored 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,[24] Pyrhonen 1999[27])

Further sensitivity analysis on clinical effectiveness data explored the impact of alternative OS estimates for sunitinib vs. IFN and the effect of assuming pazopanib has equivalent PFS and/or OS as sunitinib vs. IFN (36-38 in Table 5.8).

Costs

In the sensitivity analyses exploring the administration costs of IFN costs were increased or decreased by 50%. No justification was given for the choice of this value. Similarly, the sensitivity analysis around other costs involved increasing/decreasing the cost of therapy initiation and other costs by 50%. Again, no justification for this value was stated.

Impact of adverse events

The range of values explored in the sensitivity analysis of adverse events represented plausible upper and lower bounds of estimates as provided by the confidence intervals surrounding the point estimates of incidence. The impact of adverse events was explored by varying the incidence of AEs using both the lower and upper confidence interval of their incidence.

Utility values

Two sets of sensitivity analyses were performed on utility values. The first explored the impact of varying utility value estimates for pre/and post-progression health states for example by increasing or decreasing the PFS utility. The justification for these changes was not stated. The second set of sensitivity analysis included exploring the impact of the decrement in utility after experiencing adverse events. No justification for these changes was given.

Structural

There is uncertainty surrounding how expected PFS and OS were estimated for IFN as these values were estimated by fitting parametric curves from the Sunitinib pivotal trial. Sensitivity analyses were performed using estimates from VEG105192 study.

Other

Other sensitivity analyses were performed to explore the effect of time frame and discounting. The alternative time frames considered were 5 and 15 years. Alternative annual discount rates were 0 and 6%.

Table 5.8 Deterministic sensitivity analysis

	Scenario	Description
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 impacts 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	

	Scenario	Description
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 randomised 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,[24] Pyrhonen 1999[27]).
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)	

	Scenario	Description
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 sunitinib 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%	

Source: manufacturer's submission.

Probabilistic sensitivity analysis

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 variables. When standard errors 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 of the manufacturer's initial submission.

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 upon the 2.5 and 97.5 percentiles of these simulations.

For each comparison, the simulations were plotted on a cost-effectiveness plane and as a series of pair-wise cost-effectiveness acceptability curves of pazopanib vs. a comparator. 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).

5.2.6 Results

The manufacturer provided a full set of cost-effectiveness results produced using different OS estimates versus BSC (IPCW and Cox regression model censoring on cross-over) in separate Microsoft Excel spreadsheets. In the addendum the manufacturer first presented the results using the list price for pazopanib as per their previous submission and then results incorporating a 12.5% discount. The discount forms part of a proposed patient access scheme and these results were also presented within the PAS submitted alongside the addendum. Cost-effectiveness results with no discount and with 12.5% discount are presented in Tables 2.8 and 2.10 (manufacturer's addendum). In this document these results are provided in Table 5.9 (without discount) and Table 5.10 (with 12.5% discount).

Table 5.9 Incremental base case results without discount

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline	Incremental analysis
BSC	4,085	0.987				
IFN	8,379	1.249	4,294	0.262	16,395	16,396
Sunitinib	36,179	1.898	27,799	0.649	35,231	42,832
Pazopanib	40,441	1.966	4,263	0.068	37,126	62,414
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios						

Source: manufacturer's response to clarification queries.

Table 5.10 Incremental base case results with 12.5% discount

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline	Incremental analysis
BSC	4,085	0.987				
IFN	8,379	1.249	4,294	0.262	16,395	16,395
Sunitinib	36,179	1.898	27,799	0.649	35,231	extendedly dominated by pazopanib
Pazopanib	36,301	1.966	122	0.068	32,898	38,925
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios						

Source: addendum to manufacturer's submission.

Sensitivity analysis results

Effectiveness

The results of the cost-effectiveness analyses, using alternative methods of adjusting for cross-over in VEG105192 and also incorporating a 12.5% discount are displayed in Table 5.11. Deterministic sensitivity analysis suggested that the method for adjusting for cross-over was a large driver of pazopanib cost-effectiveness. In the majority of cases the manufacturer reported that deterministic sensitivity analyses around the base case indicated that pazopanib was cost-effective versus sunitinib at a threshold of £20,000-£30,000/QALY.

As noted above the ERG considers that there is doubt about whether the RPSFT weighted unadjusted analysis is the best basis for the cost-effectiveness analysis. The analyses underpinning estimates of hazard ratios used in the economic model has not (and currently cannot) take into account baseline covariates. Hence the estimates provided may not provide

accurate estimates of the relative effectiveness of pazopanib. It is unclear what the impact of this uncertainty is on hazard rates and it could plausibly result in changes that improve or worsen the cost-effectiveness of pazopanib.

Table 5.11 Summary of cost-effectiveness estimates for all final overall survival analyses incorporating a 12.5% discount from list price of pazopanib (reproduction of Table 2.11 in addendum)

Final OS analysis	HR vs. IFN	Pazopanib			ICER (£/QALY) vs.		
		Costs	LYs	QALYs	Sunitinib	IFN	BSC
ITT	1.264	£32,099	1.581	1.071	£4,936†	Dominated	£322,237
Cox Model censored on cross-over on receipt of other anticancer therapy	0.801	£34,676	2.503	1.616	£5,327†	£71,648	£48,638
IPCW	0.803	£34,661	2.497	1.613	£5,139†	£72,274	£48,877
RPSFT weighted unadjusted*	**0.627**	**£36,301**	**3.097**	**1.966**	**£1,790**	**£38,925**	**£32,898**
RPSFT unweighted adjusted	0.388	£39,689	4.335	2.697	£4,394	£21,625	£20,824
No post-study therapy	0.476	£38,241	3.806	2.385	£4,238	£26,293	£24,438

* Base case analysis

†Comparator is more costly and more effective than pazopanib. Ratio is cost-effectiveness of comparator vs. Pazopanib

Source: addendum to manufacturer's submission.

Sensitivity analyses 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 (£39,634 for IFN and £33,051 for BSC). 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, the relevance of the assumption is unclear. Furthermore this assumption results in giving a greater emphasis to the differential acquisition costs of sunitinib and pazopanib, [redacted]

[redacted]

Table 5.12 [redacted]

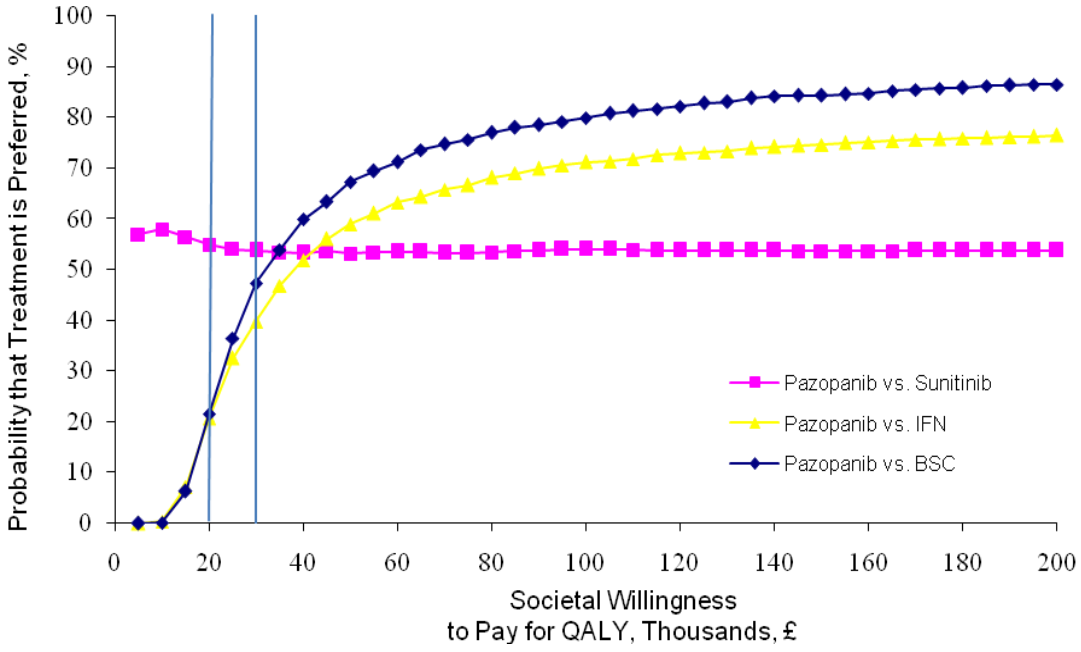
Source: manufacturer's patient access scheme document.

Probabilistic sensitivity analyses

Results of probabilistic sensitivity analyses incorporating a 12.5% discount are summarised in Table 2.13 (addendum to the initial submission) and displayed on the cost-effectiveness planes in Figures 2.6a-c) of that document. Acceptability curves for pair-wise comparisons of pazopanib vs. sunitinib, pazopanib vs. IFN, and pazopanib vs. BSC are shown in Figure 2.7, reproduced below as Figure 5.1. Acceptability curves for an incremental (i.e. multi-way) comparison of pazopanib, sunitinib, IFN, and BSC are shown in Figure 6.3 and 6.4 in this document.

The manufacturer indicated that the results of these analyses suggested that there was a high degree of uncertainty regarding the incremental costs and benefits of pazopanib vs. sunitinib. There was relatively less uncertainty regarding the incremental costs and benefits of pazopanib vs. IFN or BSC. In the pair-wise comparisons, given a threshold value of cost-effectiveness of £30,000 per QALY, there is a 54% probability that pazopanib is preferred to sunitinib, a 40% probability that pazopanib is preferred to IFN, and a 47% probability that pazopanib is preferred to BSC. In the incremental analysis (i.e., multi-way comparison), given a threshold of £30,000 per QALY, there is a 41% probability that pazopanib is preferred, a 6% probability that sunitinib is preferred, a 48% probability that IFN is preferred, and a 6% probability that BSC is preferred. Changes in monitoring costs, the cost of treating adverse events and utility values had little impact on cost-effectiveness. A similar pattern was observed for comparisons of pazopanib versus IFN and BSC.

Figure 5.1. Cost-effectiveness acceptability curve – weighted RPSFT (+12.5% discount) pair-wise comparisons



Source: addendum to manufacturer's submission.

5.3 Critical appraisal of the manufacturer's submitted economic evaluation

5.3.1 Critical appraisal of economic evaluation methods

The manufacturer's submission has been critically appraised, as outlined in Tables 5.13 and 5.14. The methods used by the manufacturer have also been compared with the criteria set out in the reference case.[78]

Table 5.13 Critical appraisal of manufacturer submission economic evaluation methods

Item	Critical appraisal	Reviewer comment
Is there a well defined question?	Yes	The economic model and submission assessed the cost-effectiveness of pazopanib for the first line treatment of patients with advance renal cell carcinoma.
Is there a comprehensive description of alternatives?	Yes	The analytic model estimates clinical and economic outcomes for treatment-naïve advanced/metastatic RCC patients who are assumed to receive either pazopanib, sunitinib, IFN or BSC.
Is the perspective of the analysis clearly stated?	Yes	The manufacturer stated that the analysis was performed from the perspective of the NHS and PSS.
Is the perspective employed appropriate?	Unsure	Although the perspective was stated as being that of the NHS and PSS there is no evidence of costs falling on PSS.
Has the correct patient group/population of interest been clearly stated?	Yes	Treatment-naïve advanced/metastatic RCC population is considered consistent with the scope of the appraisal.
Is the correct comparator used?	Yes	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. 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. 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 used to inform the economic evaluation. This might be uncertain as it assumes the population and common treatments are the same.
Is the study type reasonable?	Yes	Although RCT data are used these studies are not ideal for the evaluation. Post progression survival is estimated rather than measured and an indirect comparison of relative effectiveness of treatments is conducted. The type of analysis may be reasonable

		given the data available but a judgement is needed as to whether it is sufficient to inform a decision.
Is the effectiveness of the intervention established?	Partly	As 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. As highlighted in section 4.1.7 the comparison of the original submission and revised analysis without the discount illustrate the degree of uncertainty that using immature data had on handling cross-over.
Has a lifetime horizon been used for analysis (has a shorter time horizon been justified)?	Partly	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. However there maybe concern that this time horizon may overestimate survival given that the median age at prognosis is 60-65 (Pg 20 of manufacturer's submission).
Are the costs and consequences consistent with the perspective employed?	Yes	Costs are attributable to an NHS perspective and a budget impact statement supports this. Consequences are measured in QALYs which is recommended practice.
Is differential timing considered?	Yes	As per reference case
Is incremental analysis performed?	Yes	Results were presented as ICERs although in many analyses the manufacturer has chosen to present a series of pair-wise ICERs rather than a single complete incremental analysis
Is sensitivity analysis undertaken and presented clearly?	Partly	A number of one-way sensitivity analyses were conducted and a two-way sensitivity analysis was conducted and presented in the manufacturer's submission. However hardly any multi-way analysis was undertaken. The manufacturer did not provide justification for some of the estimates used in the sensitivity analysis.

Table 5.14 Comparison of economics submission with NICE reference case

Nice reference case requirement		**Reviewer comment**
Decision problem	As per scope developed by NICE	√ included patients only treatment naïve advanced /metastatic RCC population
Comparator	Alternative therapies routinely used in the NHS UK	√ Sunitinib, IFN and BSC
Perspective on costs	NHS and PSS	X Only NHS
Perspective on outcomes	All health effects on individuals	√
Type of economic evaluation	Cost-effectiveness analysis	√
Synthesis of evidence on outcomes	Based on systematic review	√ Single RCT for comparison of pazopanib with placebo, Indirect comparison with IFN and sunitinib
Measure of health benefits	QALYs	√
Description of health states for QALY calculations	Use of standardised and validated generic measure	√ EQ-5D from pazopanib trial
Method of preference elicitation for health state values	Choice based method e.g. standard gamble time trade off	√
Source of preference data	Representative of UK public	√
Discount rate	3.5% for costs and health effects	√
√indicates "clear", X indicates "concerns", and ? indicates "uncertain/unknown"		

As a general point, the updated model presented was usable; however there were a large number of data sheets which were traceable but also quite cumbersome. This made it difficult to trace the origin of certain figures. Also there appeared to be a lot of duplication of data.

5.4 Modelling methods

Table 5.15 presents a detailed summary review of the pazopanib manufacturer's submission against the criteria set out by Philips and colleagues.[79]

Table 5.15 Critical appraisal checklist of the GSK economic evaluation for pazopanib versus sunitinib, interferon-α and BSC in first line treatment of patients with advanced/metastatic RCC

Dimension of quality		**Comments**
Structure		
Structure of decision problem/objective	√	Cost-effectiveness modelling of pazopanib versus sunitinib, IFN and BSC as first line treatment of patients with advanced renal cell carcinoma.
Statement of scope/perspective	√	Perspective stated as NHS and PSS but only NHS perspective presented. Model was consistent with the perspective. Scope of model was stated and justification given. Outcomes of the model were consistent with the perspective, scope and overall objective.
Rationale for structure	√	The modelling labelled as a "partitioned survival" model was based on three mutually exclusive health states: Alive pre progression; alive post progress and dead. The model calculated the proportion of patients in each treatment cohort that were expected to be in each health state at any time after initiation.
Structural assumptions	√	The main model assumptions were stated. Weibull survival functions estimated from data for IFN arm of the phase III trial of sunitinib were fitted. The model assumes immediate cessation of treatment on progression.
Strategies/comparators	√	Pazopanib was compared with sunitinib, IFN and best supportive care. Indirect comparisons were carried out with IFN as the reference.
Model type	√	The model used was based on survival curves which have been frequently used in this type decision problem. However, there are concerns about the data as indicated in section 4.1.7.
Time horizon	√	The model time horizon is the anticipated lifetime of patients with this condition.
Disease states/pathways	√	The disease states include alive pre-progression, alive post progression and dead take into account the biological progression of disease and are widely accepted for this decision problem.
Cycle length	√	The cycle length of one day allows comparison of treatments with different cycle lengths and avoids the need for half cycle correction. The choice of cycle length and the model structure imply that a clinical decision about progression is made on a daily basis. In reality patients who progress would need to wait until a monitoring visit to cease treatment. This may result in a small bias in favour of the more costly treatment, in this case pazopanib.

Dimension of quality		Comments
Data		
Data identification	√	Data identification methods are described.
Pre-model data analysis	√	Details on data for calculating the costs of administration, routine follow-up, diagnostic tests BSC, Sunitinib, IFN death and treating adverse events have been provided. In some instances the manufacturer opted for simplicity and assumed that the costs of routine follow-up and supportive care are the same for all interventions.
Baseline data	√	Estimated HRs for PFS and OS for pazopanib versus placebo/BSC were obtained from the VEG105192 study. As indicated the data were immature and many patients crossed over from the placebo/BSC arm to receive pazopanib at disease progression. Several approaches were used to adjust for this cross-over. Literature currently indicates that there is no consensus on the most appropriate method and the uncertainty around these estimates has been addressed in sensitivity analysis. Concerns on the methods have been highlighted in section 4.1.7 of this document (Description and critique of the statistical approach used).
Treatment effects	√	As indicated above the estimates for HRs varied based on the alternative mechanisms to handle the cross-over of patients from placebo to active treatment. There are concerns about the methods used as they are relatively new (see above).
Quality of life weights (utilities)	√	Although there were estimates in the VEG105192 trial for treatment naïve patients the manufacturer opted to use a value based on all patients without AEs. This value was used for all interventions in the model. Although these estimates were varied in the sensitivity analysis it was always assumed to be similar for all interventions. The manufacturer's justification for using these estimates (PFS and PPS) was that they were the best available estimates. There is need for further work to be carried out to get better estimates.
Data incorporation	√	Data included in the model were not always well described and further clarification had to be sought on how these data were derived. For example the estimates for initiation and progression free survival. Also there were some errors in some of the data as indicated in the section on cell calculations.
Assessment of uncertainty	√	Several one way sensitivity analyses were performed. Only one analysis involved more than one parameter. It is anticipated that there will be instances when several parameters could change so more multi-way analyses could have been performed.

Dimension of quality		Comments
Methodological	X	GSK have only used a single type of model. As noted below uncertainty in the ideal method of estimating HR has been considered.
Structural	√	Structural uncertainties such as the use of alternative HRs have been modelled. However, two of the methods presented by the manufacturer for adjusting for cross-over are more sophisticated techniques and have been developed relatively recently, and as indicated by the manufacturer there is still not consensus on which of these is the most appropriate (see section 4.1.7).
Heterogeneity	√	GSK did not model any subgroups due to low amount of data available. This appears reasonable.
Parameter	√	Extensive one way sensitivity analyses have been performed. Multi-way sensitivity analysis should have been performed.
Consistency		
Internal consistency	√	The model was validated internally by the developer and by an external expert.
External consistency	√	The results of the model were checked against results reported previously in the technology assessment of sunitinib and yielded similar results when similar inputs were employed. However, it was not clear if the results had been compared to those of other models of metastatic RCC. The initial version of the model presented to the ERG included all the comparators in the sunitinib assessment.
√ indicates "clear", X indicates "concerns", and? indicates "uncertain/unknown" Checklist structure from Phillips 2006.[79]		

5.4.1 Modelling approach/model structure

Type of model used, is it justified for the purpose?

The submission used a model based approach to estimate cost-effectiveness. The model used survival analysis and employed clinical effectiveness data from a randomised controlled trial and other sources to model survival and disease progression over time. The modelling approach used in this evaluation was labelled as a "partitioned-survival" model. The model is characterized by three mutually exclusive health states ("*Alive Pre-Progression*", "*Alive Post-Progression*", and "*Dead*"). Adverse events are modelled as part of these states rather than separate states. This seems appropriate given the decision problem and the data available.

Rationale of the structure

The rationale for using the partitioned survival analysis model was that 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 generated projections of both PFS and OS that are consistent with the data from the VEG105192 trial. The submission also indicated that partitioned survival models have been employed in recently completed technology appraisals including those of treatments for advanced/metastatic RCC. The time horizon appears appropriate but it may overestimate survival as the median age of prognosis (as stated on pg 20 of submission) is 60-65 years. The choice of a cycle length of one day allows for flexibility but a consequence of this time horizon and the simple model structure is that it makes the assumption that progression once it occurs is instantly recognised and treatment is stopped. In terms of health state utilities it may be reasonable to assume that quality of life falls when progression occurs. However, in terms of costs it might be expected that treatment would only be stopped once a clinical diagnosis of progression has been made. Hence there may be some delay between progression occurring and progression being clinically identified and treatment stopped. The impact of this will depend upon the time between progression and the clinical identification of progression. It would be expected that the more costly the treatment and the longer the interval then the greater the impact would be on the cost-effectiveness of that more costly treatment.

Duration of treatment

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 (see comment above about the impact this assumption and the cycle length have on cost). 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 costs. With respect to utilities, progression is reflected in the model by assigning different utility values to the *"Alive Pre-Progression"* and *"Alive Post-Progression"* health states. This seems reasonable.

5.4.2 Data

Data identification

A clear description of the source of effectiveness data was provided. In all cases the data in the model appeared to match the data in the submission report apart from a few errors i.e. 0.05% discount rate which slightly favours pazopanib.

Further issues in relation to model cell calculations

The calculations behind the model are not transparent. As mentioned before, the model has been developed using Visual Basic software and although some aspects of the analysis are presented in Microsoft Excel it is not always easy to establish the exact nature of calculations and the parameters used in the final analyses.

Costs

The results of the cost-effectiveness analysis indicated that the adverse events did not greatly impact on the overall cost of the interventions. This could be attributed to the fact that very few of the adverse events (only type 3+) had costs attached to them.

The second issue noted in the cost-effectiveness results was that the main cost driver was the cost of the drugs. As noted above adverse events did not contribute much to the cost and for the base case analysis both other pre and post progression cost were only about a fifth of the total pazopanib and sunitinib costs. The impact of the cost attached to interventions is illustrated by Table 5.16 comparing the total cost and ICER results with and without the 12.5% discount.

Table 5.16 Comparison of ICERS

Intervention	**Without 12.5% discount**		**With 12.5% discount**	
	Cost (£)	***ICER***	***Cost (£)***	***ICER***
BSC	4,085		4,085	
IFN	8,379	16,396	8,379	16,395
Sunitinib	36,179	42,832	36,179	extendedly dominated by pazopanib
Pazopanib	40,441	62,414	36,301	38,925

One of the assumptions in the model was that when patients move to the progressed state they would be managed in primary care. A clinical expert member of the group indicated that this is not the normal practice in the UK setting. Since patients are managed in secondary care which may be more expensive this assumption will make interventions that spend less time in PPS more likely to be cost effective.

When deciding on the cost of pazopanib the manufacturer stated that the [redacted] Assuming that the HR data for OS suggest that there may be no differences between pazopanib and IFN, that is HR>1 for overall survival (strictly speaking

there is no evidence of a difference and the confidence interval for this estimate is very wide) the total cost of pazopanib is £34,647 and the drug acquisition cost is £27,476. On the other hand the total cost of sunitinib is £36,179 and the drug acquisition cost is £28,856. [redacted]

Quality of life/Utilities

Are utilities incorporated into the model appropriate? Are the methods used to derive utility weights justified?

The utilities incorporated in the model are appropriate as they have been estimated using the recommendations from NICE. Although it was reported that additional HRQL data were obtained from studies evaluating recently approved treatments for advanced/metastatic RCC namely sunitinib and temsirolimus, these data were not used in the analysis. There were data identified from Motzer[17] and Hudes[18] and again these data were not included in the analysis. It should be noted that results of Hudes and colleagues' study published in 2010 reported health states based on patients with poor prognosis therefore these data should be treated with caution.[80]

GSK commissioned a utility study[73] to obtain UK societal preferences for newly developed treatments for advanced/metastatic RCC and these data were used to inform the decrements in utility when patients experienced adverse events. One hundred members of the general public rated the states using the time trade-off (TTO) methodology to determine health state utility. The authors stated that the participants represented a reasonable match to UK residents as described by national census data.[81] The results indicated that the 'stable with no adverse events' state had the highest utility value, and the 'progressive' state the lowest. Utility values for adverse events states corresponded with their severity grading. Further data were requested for the estimation of EQ-5D utility values for persons with and without adverse events in the VEG105192 as those included in the submission looked at all the patients in the trial (not only the treatment naïve population). Although the values differed slightly they were mainly similar to those used in the model. These data could have been used in the sensitivity analysis but were not.

The manufacturer submission highlighted the fact that decrements in utility with progression in the VEG105192 trial was less than that reported in other studies. This was attributed to the fact that quality of life was not routinely assessed after progression in the trial. The results of the study commissioned by GSK were substantially greater than those in studies using EQ-5D assessments. They indicated that the results of the study could have been greatly influenced

by the nature of descriptions of progression free and post progression health states and that the extent to which these descriptions correspond with those of actual patients has not been systematically validated.

Data incorporation

Is the process of data incorporation transparent?

The process of data incorporation into the model was not always clear and transparent as the macro underpinning the analyses was written in Visual Basic.

5.5 Comment on validity of results presented with reference to methodology used

Apart from the issues highlighted above, the results appear valid in terms of the methods used. Most of the model analyses performed could be replicated, however this was not true for all sensitivity analyses. These are summarised in Table 5.17 below. More detailed information can be found in Table 1 in Appendix 3.

The methods section indicated that for the first set of sensitivity analyses around the HR for both PFS and OS would use the low and high confidence intervals. When the cells in the "MainInputs" worksheet relating to these data were altered (cell F12 and F22) the results differed from those presented in the updated final submission. The data in the results section had not been altered to reflect the updated estimates for OS. Further discrepancies were found in the results presented for duration of utilities with AEs in the "SEInputs" worksheet that relate to this (too many cells to name). Further discrepancies were also identified in analyses relating to efficacy such as HR for PFS and OS for pazopanib vs. IFN calculated using only the MRC study (PFS HR=0.545, OS HR=0.460; HR for PFS and OS for pazopanib vs. IFN calculated excluding the VBL studies (PFS HR=0.495, OS HR=0.400); and HR for PFS for pazopanib vs. IFN adjusted to reflect percentage w/ECOG=0/1 in sunitinib pivotal trial (HR=0.455). The analyses were redone using cells F12 and F22 in the "MainInputs" worksheet.

The manufacturer stated that 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. The results (ICERs) of the structural analysis relating to independent Weibull from pazopanib arm VEG105192 used for pazopanib, independent Weibull from placebo arm VEG105192 used as reference for comparators were not reported in the addendum.

Table 5.17 Deterministic sensitivity analysis

	Pazopanib		Difference pazopanib vs. Sunitinib			IFN			BSC		
	Costs, £	QALYs	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £
Base Case	36,301	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
HR PFS pazopanib vs. IFN=0.326	51,928	2.054	15750	0.156	100,775	43,549	0.805	54,077	47,843	1.067	44,829
HR PFS pazopanib vs. IFN =0.802	25,849	1.898	-10,329	0.009	dominant	17,470	0.658	26,531	21,764	0.920	23,646
HROS pazopanib vs. IFN=0.173	44,677	3.772	8,498	1.874	4,534	36,297	2.523	14,384	40,592	2.785	14,573
HROS pazopanib vs. IFN =2.269	18,432	0.576	-17.747	-1.527	13,220 †	10,052	-0.774	dominated	14,347	-0.476	dominated
Duration of utility with AEs=0.5 x base-case	36,301	1.974	122	0.061	1,990	27,921	0.716	38,988	32,216	0.983	32,757
Duration of utility with AEs=1.5 x base-case	36,301	1.958	122	0.075	1,626	27,921	0.718	38,861	32,216	0.975	33,041
HR for PFS and OS for pazopanib vs. IFN calculated using only the MRC study (PFS HR=0.545, OS HR=0.460)	36,745	1.898	566	0.529	1,070	28,366	1.178	24,071	32,660	1,440	22,675
HR for PFS and OS for pazopanib vs. IFN calculated excluding the VBL studies (PFS HR=0.495, OS HR=0.400)	40,457	2.656	4,278	0.758	5,643	32,077	1.407	22,795	36,372	1.669	21,790
HR for PFS for pazopanib vs. IFN adjusted to reflect % w/ECOG=0/1 in sunitinib pivotal trial (HR=0.455)	39,865	1.986	3,686	0.088	41,717	31,485	0.737	42,699	35,780	0.999	35,804

5.6 Summary of uncertainties and issues

Were methodological, structural, heterogeneity and parameter uncertainties addressed?

One major concern with structural uncertainty was with the HRs used to estimate the cost-effectiveness and in particular with the way the cross-over data were handled as indicated in section 4.1.7. In the initial manufacturer submission the base case analysis was based on the estimates from the model using RPSFT to adjust for cross-over and pooled IFN trials. In the updated analysis (addendum) the method used for adjusting for cross-over was weighted RPSFT unadjusted. As indicated in the manufacturer submission the optimal method for cross-over/switch in survival analysis remains an area of academic debate and all available approaches have their strengths and limitations. Data in Table 5.14 above indicate that the results were sensitive to the method of extrapolation used. Overall, the manufacturer has presented a set of analyses which comprehensively covers the range of methodologies available to adjust for cross-over. However, care should be taken when assessing trials that have used relatively new methods as there is no consensus on the best approach to use and these methods still require further development.

The other issue relates to the assumption that as soon as someone progressed they stopped treatment. In practice, it is unlikely that this will take place immediately they progress as the patient will only know the status of their disease when they have their next review, which may not be at the exact time they progress. This assumption may create a small bias in favour of the more costly treatments such as, for example, pazopanib.

There is also some uncertainty around the utility estimates used. The estimate used by the manufacturer was based on the EQ-5D utility value among all patients without AEs in the VEG105192 trial. This value was also assumed to be similar for all interventions.

6 ADDITIONAL WORK UNDERTAKEN

6.1 Independent literature searches to identify additional studies

Because it had not been possible to replicate the main MEDLINE and EMBASE searches, the ERG undertook independent searches of MEDLINE, EMBASE and the Cochrane Library and restricted the search to the interventions included in the scope of the appraisal i.e. pazopanib, sunitinib, interferon-α, interleukin-2 and best supportive care. The structure of the clinical effectiveness search was similar to the manufacturer's published search. The cost-effectiveness search strategy was incorporated in a wider search, designed to identify relevant economic models as well as HRQoL data. The details are provided in Appendix 1.

6.1.1 Comparing results from additional studies and those in the submission

By comparing the abstracts available from the independent literature searches undertaken, with those undertaken by the manufacturer, an additional 12 papers were found.[21,29,36,59,82-89] However, as these independent literature searches were conducted more recently than the final search date for the manufacturer's systematic review (23rd November 2009), at least four of these papers (33.3%), published in 2010, could not have been found by the manufacturer because they were published after the manufacturer's final search date.[21,84-86]

For pazopanib, three papers were identified that the manufacturer had not listed as sources for pazopanib data, although they all related to the VEG105192 trial. However, two of these papers were published more recently than the manufacturer's final search date, although they were referenced elsewhere in the manufacturer's submission[21,86] The remaining study was referenced as a source for the VEG105192 trial in the systematic review provided by the manufacturer but not in the manufacturer's submission itself.[29]

For sunitinib, eight additional papers were identified that the manufacturer had not listed as sources for sunitinib data. All of these related to the included trial comparing sunitinib with interferon-α.[17] Two were published more recently than the manufacturer's final search date.[84,85]

For immunotherapy options, aside from the interleukin-2 study that was included by the manufacturer but not used in the indirect comparison,[22] one additional study comparing two different doses of interferon-α was found meeting the inclusion criteria,[89] as interferon-α was listed as one of the interventions in the inclusion criteria (see page 42 of the manufacturer's submission), and the inclusion criteria also stated that "any of the included interventions" could also be considered as comparators.

For the pazopanib and sunitinib papers referred to in this section, the effect of the manufacturer not having identified/included these papers is likely to be negligible, as the trials were still identified by the manufacturer and recent data are available for both trials from other (i.e. identified) sources.

For the immunotherapy studies the effect of the manufacturer not having identified the study by Tannir and colleagues[89] is unclear, as none of the identified interferon-α studies had an intervention or comparator arm containing treatment with the same dose of interferon-α as contained in either arm of this study. As there were no significant differences in overall survival or progression-free survival between the different doses of interferon, this could vindicate the manufacturer's decision to pool the data from the included interferon-α studies in the indirect comparison. On the other hand, the fact that significant differences were found in this study in terms of patient tolerability and quality of life outcomes depending on the dose of interferon-α given, confirmed advice provided to the ERG from clinical advisers (personal communication, Donald Bissett, NHS Grampian, 2010). This suggests that, in the interferon-α studies included in the indirect comparison, the effect of this treatment may have been overestimated compared to best supportive care.

6.2 Screening studies included in the systematic review against inclusion criteria

We screened full-text papers and abstracts available for each of the included trials listed in the systematic review against that listed in the manufacturer's submission. The included pazopanib trial met the inclusion criteria. However, although outcomes were reported for the treatment naïve population in the manufacturer's submission for the included pazopanib trial [VEG105192], the trial included cytokine pre-treated patients as well, although baseline characteristics of the treatment naïve population were similar to that of the overall trial population.

The included immunotherapy studies were more varied. Two did not mention age, even though the inclusion criteria stated participants had to be aged 18 years or older[23,24] and one mentioned only that participants had to be younger than 75 years old.[27] In terms of disease progression, four studies (including the study by Negrier and colleagues[22] which was unused in the indirect comparison) mentioned metastatic disease[22,23,25,26] although in the case of the study by Steineck and colleagues[26] those with locally recurrent disease were also included. The remaining studies mentioned "advanced"[27] or "progressive"[24] disease.

One of the immunotherapy studies indicated that participants were treatment naïve,[25] while another[26] indicated that prior irradiation of the disease or excision of metastases was acceptable. Tumour nephrectomy was required in one study[24] and permitted in another.[26]

The ERG was concerned by the inclusion of immunotherapy studies using a definition of best supportive care within the inclusion criteria that differed from the original definition used whereby best supportive care was stated to be "treatment administered with intent to maximise quality of life without a specific antineoplastic regimen"[Submission p28] This was then defined in the inclusion criteria it as "no active treatment/observation/a method of care that is not a focused treatment/treatments which clinicians consider to be 'placebo-equivalent' including medroxyprogesterone acetate and vinblastine". This enabled them to include comparator arms with medroxyprogesterone or vinblastine in all the included interferon-α studies.[23-27] The ERG considers that vinblastine and medroxyprogesterone may not have significantly different efficacy from best supportive care, but the tolerability of these treatments may differ from best supportive care. The effect of assuming that these treatments equate to best supportive care may underestimate the effect of best supportive care treatment in the indirect comparison and consequently, the economic model.

Performance status and histology of participants were not factors for the inclusion criteria, although there was also variation in whether or not studies mentioned these characteristics, the methods used to define them (for example measurement of performance status used either WHO or KPS criteria) and cut-offs used. For example, the study by Pyrhonen and colleagues required participants to have an ECOG status between zero and two, whereas the pazopanib and sunitinib studies excluded participants with an ECOG status greater than one.

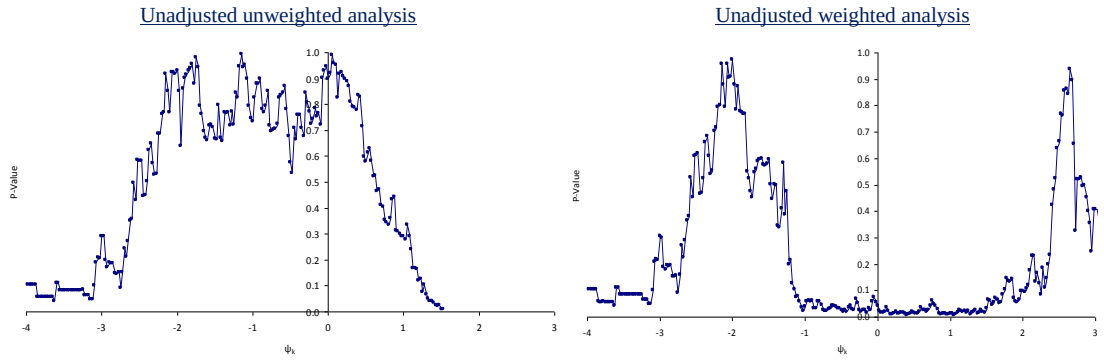
6.3 Consideration of alternative methods of estimating hazard ratios

The review of the clinical effectiveness data highlights concerns with the weighted unadjusted RPSFT results for overall survival being used for the base case analysis. However, the value of using a weighted RPSFT analysis is acknowledged and there is therefore some merit in considering the potential impact that a robust weighted analysis could have on the results, particularly with a model adjusted for baseline covariates, for which the methodology is still in development.

One approach is to consider the impact of weighing by comparing the unweighted analyses with the weighted analyses when the models were unadjusted for baseline. This could not be done by comparing hazard ratios because the unadjusted unweighted analysis model was not completed, but it is possible to examine the p-value distribution plots from the log-rank tests

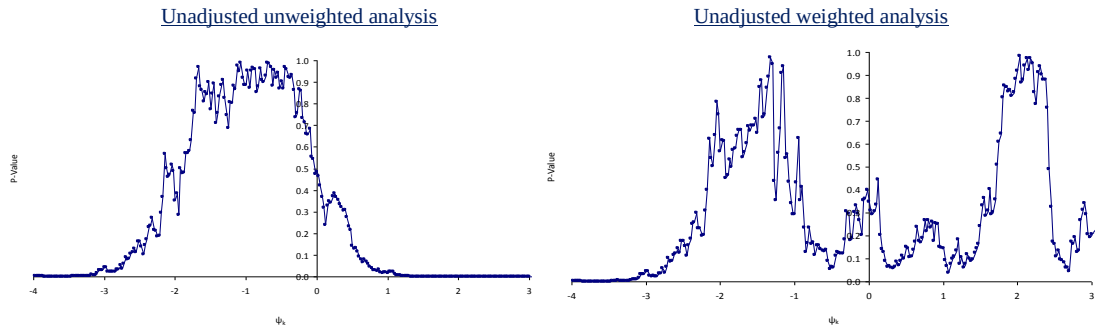
in the RPSFT analyses. An important part of this approach is to determine which parameter value has the highest p-value, which requires the plot of the distribution to have a unique peak. In the unadjusted analyses of treatment-naïve patients, weighting had the effect of changing the p-value distribution from multimodal (-1.75, -1.15 and 0.05) to bimodal (-2.225 and approximately +2.7). This is shown in the following plots in Figures 6.1 to 6.3 taken from manufacturer's Study Report v 1.0 "*Inverse Probability of Censoring Weighted and Rank Preserving Structural Failure Time Estimates of the Effect of Pazopanib on Overall Survival in Treatment-Naïve Patients in the VEG105192 Trial: Analysis Based on Updated Survival Data*".

Figure 6.1 VEG105192, treatment-naïve patients, unadjusted unweighted analysis and unadjusted weighted analysis



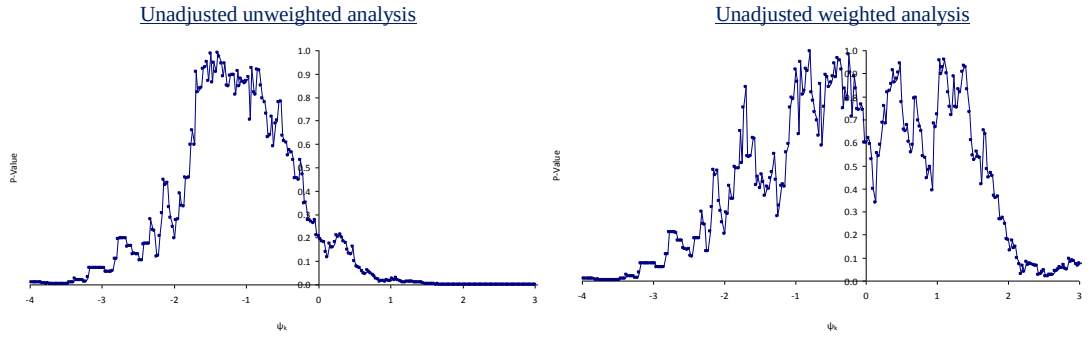
A similar pattern can be observed in the analyses of all patients (modes changing from between approximately -2 and 0 to approximately -1.4 and +2) (Figure 6.2).

Figure 6.2 VEG105192, all patients, unadjusted unweighted analysis and unadjusted weighted analysis



In the analyses of cytokine pre-treated patients, weighting had the effect of changing the p-value distribution from unimodal (approximately -1.7) to multimodal (between approximately -1 and +1.5) (Figure 6.3).

Figure 6.3 VEG105192, cytokine pre-treated patients, unadjusted unweighted analysis and unadjusted weighted analysis



From these observations, there appears to be two general effects on the results of using locally efficient weights. First, there may be a shift to a higher causal rate ratio compared with unweighted analyses, which reduces the benefit attributable to pazopanib. In other words, using a weighted analysis may result in data being used that could mean a result less favourable to pazopanib. However, despite an overall pattern, this shift is not always in a clearly upward direction, particularly when the distribution is divergent so a certain amount of uncertainty exists with regard to the direction of change. This means it is not clear whether using a hypothetical ideal method of accounting for cross-over would increase or decrease the relative effectiveness of pazopanib. The second effect is that p-value distributions as a result of weighting do not appear to have unique peaks, based on the evidence from the analysis of this study. This creates uncertainty as to the magnitude of any potential effect of weighting the analysis. Overall, it seems clear that weighting does have an impact on the hazard ratio, but it is difficult to establish the direction and magnitude of this effect.

The analysis which underpins the estimates of hazard ratios used in the economic model has not (and cannot currently) take into account baseline covariates and hence may not provide accurate estimates of the relative effectiveness of pazopanib. It is unclear what the impact of this uncertainty is on hazard rates and it could plausibly result in changes that improve or worsen the cost-effectiveness of pazopanib. As such, the ERG has refrained from conducting anything other than illustrative analyses to show the impact of different hazard ratios on cost-effectiveness. It is unclear to the ERG the extent to which any of these analyses is more worthy of consideration.

6.4 Additional cost-effectiveness sensitivity analyses conducted by the ERG

A number of further sensitivity analyses have been conducted by the ERG on the pazopanib model to explore the impact on the cost-effectiveness results of uncertainties raised in Chapter 5 of this report. These analyses have been conducted on the revised model submitted with the

addendum to the initial submission but allowing the 12.5% discount on the list price of pazopanib. Details of all changes made to the model to achieve these results and the results of the pair-wise comparisons can be found in Table 2 in Appendix 3.

6.4.1 Cost estimates

As the manufacturer mainly performed univariate sensitivity analysis on costs multi-way sensitivity analyses were performed around the cost estimates by increasing and decreasing the costs associated with initiation, administration, other costs of PFS, PPS and adverse events by 50% (Table 6.1). The 50% changes were made with no other justification than this was the magnitude of the changes made by the manufacturer, who themselves did not justify these changes. However, they are illustrative of the cumulative impact of changes in cost.

Table 6.1 Multi-way sensitivity analysis: costs*

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline
Base case analysis					
BSC	4,085	0.987			
IFN	8,379	1.249	4,294	0.262	16,395
Sunitinib	36,179	1.898	27,799	0.649	Extendedly dominated
Pazopanib	36,301	1.966	122	0.068	38,925
Increase in costs					
BSC	6,127	0.987			
IFN	10,926	1.249	4,799	0.262	18,321
Sunitinib	39,840	1.898	28,913	0.649	Extendedly dominated
Pazopanib	39,958	1.966	118	0.068	40,472
Decrease in costs					
BSC	2,042	0.987			
IFN	5,833	1.249	3,790	0.262	14,469
Sunitinib	32,517	1.898	26,685	0.649	Extendedly dominated
Pazopanib	32,644	1.966	127	0.068	37,377
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios					

* Incremental cost and QALYs versus the next most costly option. The ICER is relative to the next non-dominated or extendedly dominated option. This process has been repeated in all subsequent tables.

This analysis indicates again the lack of sensitivity of the results to changes in cost other than pazopanib and sunitinib. Although the ICER for pazopanib compared with IFN resulted in very modest changes, sunitinib remained extendedly dominated by a combination of pazopanib and IFN.

6.4.2 Utility estimates

Multi-way sensitivity analyses were also performed around the utility estimates: reducing the PFS utility by 75%, reducing the utility decrement for progression by 50% and reducing the duration of utility with AEs by 50% (Table 6.2). Further analysis was performed increasing the PFS utility by 25%, increasing the utility decrement for progression by 50% and increasing the duration of utility with adverse events by 50%. These changes again mirrored the changes considered by the manufacturer in their univariate sensitivity analyses.

Table 6.2 Multi-way sensitivity analysis: utilities

	Total cost (£)	**Total QALYs**	**Incremental cost (£)**	**Incremental QALY**	**ICERs versus baseline**
Base case					
BSC	4,085	0.987			
IFN	8,379	1.249	4,294	0.262	16,395
Sunitinib	36,179	1.898	27,799	0.649	Extendedly dominated
Pazopanib	36,301	1.966	122	0.068	38,925
Decrease in utilities					
BSC	4,085	0.773			
IFN	8,379	0.978	4,294	0.205	20,981
Sunitinib	36,179	1.477	27,799	0.499	Extendedly dominated
Pazopanib	36,301	1.525	122	0.048	51,026
Increase in utilities					
BSC	4,085	1.201			
IFN	8,379	1.520	4,294	0.319	13,455
Sunitinib	36,179	2.319	27,799	0.799	Extendedly dominated
Pazopanib	36,301	2.407	122	0.089	31,463
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios					

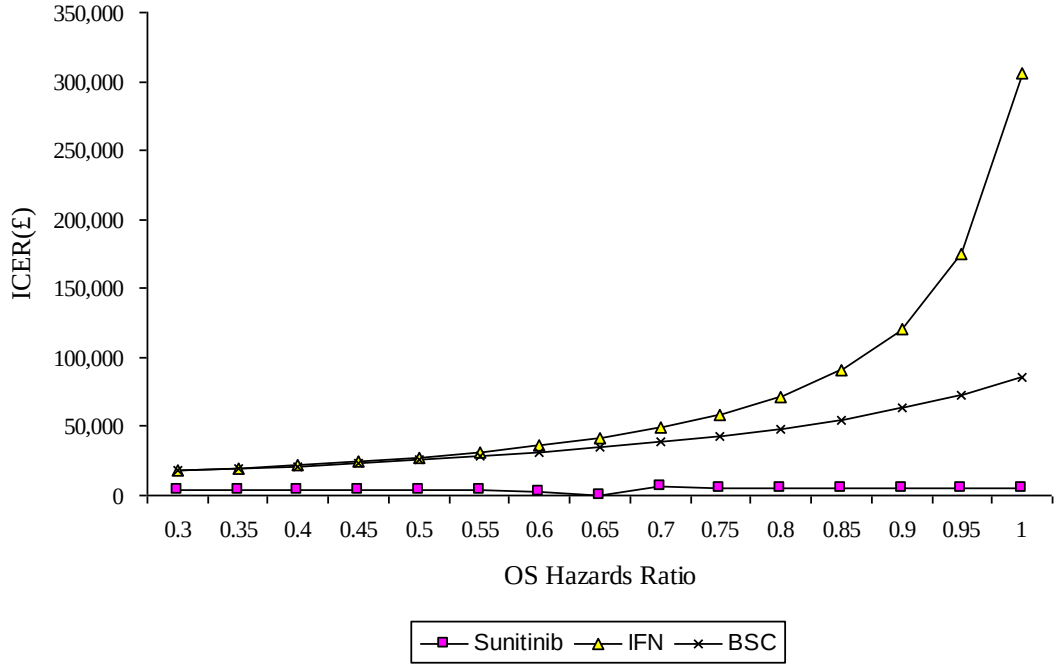
Reducing utilities resulted in the ICER for pazopanib compared to IFN while increasing to above £50,000 the utilities reduced the ICER (although it was still above £30,000.

6.4.3 HR for pazopanib

The analysis underpinning estimates of hazard ratios used in the economic model has not (and cannot currently) take into account baseline covariates and hence may not provide accurate estimates of the relative effectiveness of pazopanib. It is unclear what the impact of this uncertainty is on hazard ratios and it could plausibly result in changes that improve or worsen the cost-effectiveness of pazopanib. As such the ERG has refrained from conducting anything other than illustrative analyses to show the impact of different hazard ratios on cost-effective. It is unclear to the ERG the extent to which any of these analyses is more worthy of consideration.

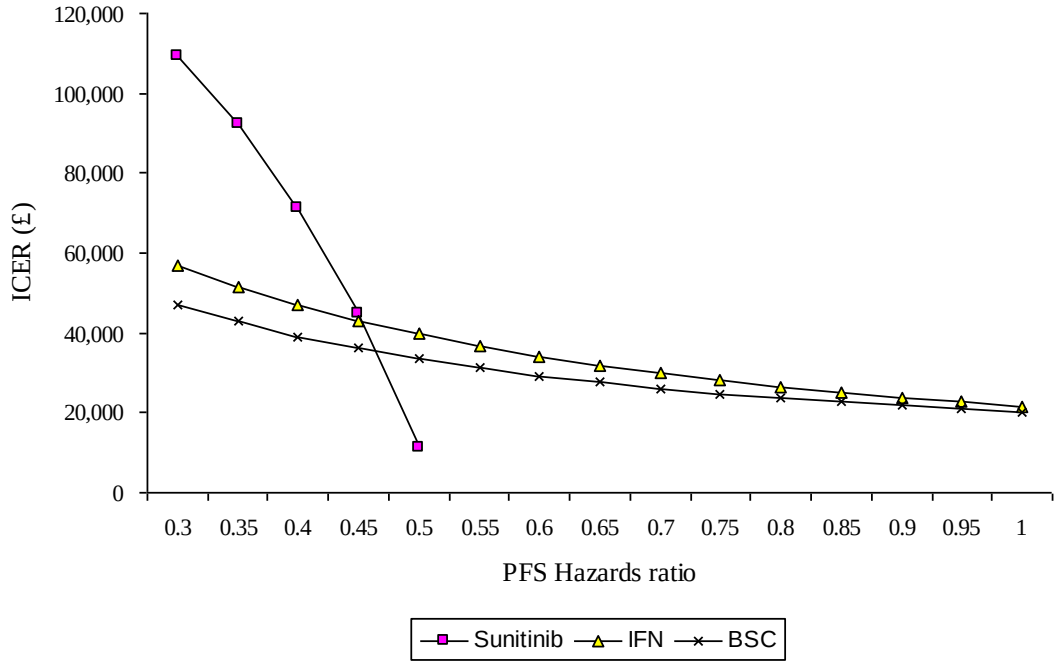
One-way sensitivity analysis was performed around the PFS and OS estimates. This was done by varying the HR estimates for pazopanib from 0.3 to 1 by 0.05 increments (Figure 6.4). These represented the range of values for this hazard ratio.

Figure 6.4 Incremental cost-effectiveness vs sunitinib, IFN and BSC as the pazopanib OS hazards ratio changes



The results of the ICERs were sensitive to the OS hazard ratios as indicated in Figure 6.4. For both IFN and BSC the ICER increased as the hazard ratio increased. However, for sunitinib the ICER decreased as the hazard ratio increased until it reached 0.65, at which point pazopanib dominated sunitinib. As the values increase from 0.65 the ICER value represents the cost-effectiveness of sunitinib versus pazopanib, as pazopanib costs less and is less effective than sunitinib (for further details see Table 3 in Appendix 3).

Figure 6.5 Incremental cost-effectiveness vs sunitinib, IFN and BSC as the pazopanib PFS hazards ratio changes



The ICERs were also sensitive to changes in the PFS hazard ratios (Figure 6.5). For both IFN and BSC the ICER decreased as the hazard ratio increased. However, for sunitinib the ICER was above £100,000 when the hazard ratio was 0.3 and decreased quickly until the hazard ratio increased to 0.55, at which point pazopanib dominated sunitinib (for further details see Table 3 in Appendix 3).

6.4.4 Combining changes in costs and utilities

Further multi-way analysis was performed by combining the increases in costs with the decreases in utilities and vice versa (Table 6.3).

Table 6.3 Multi-way sensitivity analysis: combined costs and utilities

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline
Base case analysis					
BSC	4,085	0.987			
IFN	8,379	1.249	4,294	0.262	16,395
Sunitinib	36,179	1.898	27,799	0.649	Extendedly dominated
Pazopanib	36,301	1.966	122	0.068	38,925
Increase in costs and decrease in utilities					
BSC	6,127	0.773			
IFN	10,926	0.978	4,799	0.205	23,445
Sunitinib	39,840	1.477	28,913	0.499	Extendedly Dominated
Pazopanib	39,958	1.525	118	0.048	53,054
Decrease in costs and increase in utilities					
BSC	2,042	1.201			
IFN	5,833	1.520	3,790	0.319	11,874
Sunitinib	32,517	2.319	26,685	0.799	Extendedly Dominated
Pazopanib	32,644	2.407	127	0.089	30,212
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios					

Combining increases in costs along with decreases in QALYs led to sunitinib being extendedly dominated by a combination of pazopanib and IFN. However, the incremental cost per QALY of pazopanib compared with IFN increased slightly compared with the analysis conducted on utilities alone. When costs were decreased and utilities were increased sunitinib was still extendedly dominated. However, the incremental cost per QALY for pazopanib compared to IFN was still just above £30,000.

6.4.5 Time frame and discount rate

Two sets of analyses were performed: time frame was increased to 15 years and the discount rate to 6% and time frame was reduced to 5 years and discount rate to 0% (Table 6.4).

Table 6.4 Multi-way sensitivity analysis: time frame and discount rate

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline
Base case analysis					
BSC	4,085	0.987			
IFN	8,379	1.249	4,294	0.262	16,395
Sunitinib	36,179	1.898	27,799	0.649	Extendedly dominated
Pazopanib	36,301	1.966	122	0.068	38,925
Increase in time frame and discount rate					
BSC	3,935	0.953			
IFN	8,165	1.205	4,230	0.253	16,736
Sunitinib	35,040	1.859	26,876	0.654	Extendedly dominated
Pazopanib	35,225	1.930	185	0.071	37,368
Decrease in time frame decrease in discount rate					
BSC	3,957	0.962			
IFN	8,049	1.173	4,092	0.211	19,416
Pazopanib	34,999	1.680	26,950	0.507	53,173
Sunitinib	35,115	1.630	116	-0.049	Dominated
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios					

The results were not sensitive to the combined increase in both time frame and discount rates. However, the results were sensitive to the decrease of the time frame as well as the use of 0% discount rate. In this situation sunitinib was less effective and more costly than pazopanib but the incremental cost per QALY for pazopanib compared with IFN is greater than £50,000.

6.4.6 Combining time frame and changes in costs and utilities

The change in time frame was combined with the changes in costs and utilities. First the 50% decrease in costs and decrease in utility was combined with the 15 years time frame and 6% discount rate, and then with the 5 year time frame and 0% discount (Table 6.5).

Table 6.5 Multi-way sensitivity analysis: combined costs, utilities, time frame and discount rate

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline
Base case analysis					
BSC	4,085	0.987			
IFN	8,379	1.249	4,294	0.262	16,395
Sunitinib	36,179	1.898	27,799	0.649	Extendedly dominated
Pazopanib	36,301	1.966	122	0.068	38,925
Increase in cost increase in utilities, increase in time frame and increase in discount rate					
BSC	1,967	0.746			
IFN	5,710	0.944	3,742	0.198	18,941
Sunitinib	31,441	1.448	25,731	0.504	Extendedly dominated
Pazopanib	31,620	1.498	179	0.050	46,785
Decrease in cost decrease in utilities, decrease in time frame and no discount rate					
BSC	1,979	0.753			
IFN	5,690	0.917	3,711	0.164	22,677
Pazopanib	32,005	1.297	26,315	0.380	69,246
Sunitinib	32,074	1.264	69	-0.033	Dominated
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios					

The results for the increase in cost, decrease in utilities, increase in time frame and discount rate were similar to those of the base case although the ICERs were higher. Pazopanib dominated sunitinib when the costs decreased, utilities increased, time frame decreased and there was no discount rate.

6.4.7 Dosage of drug taken

In the base case analysis dose intensities were used to adjust the cost of drugs. There was some uncertainty around how these dose estimates were arrived at. Given that the use of reported dose intensity makes allowance in treatment cost (particularly given the fact that the main driver of the results is the drug cost) there is a need to further explore the uncertainty around these data. Further sensitivity analysis was performed assuming that there was no need to make adjustments for drug dose intensity (Table 6.6).

Table 6.6 One-way sensitivity analysis: dosage of drugs

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline
Base case					
BSC	4,085	0.987			
IFN	8,379	1.249	4,294	0.262	16,395
Sunitinib	36,179	1.898	27,799	0.649	Extendedly dominated
Pazopanib	36,301	1.966	122	0.068	38,925
Complete dosage of drugs					
BSC	4,085	0.987			
IFN	8,387	1.249	4,302	0.262	16,424
Sunitinib	40,876	1.898	32,489	0.649	Extendedly dominated
Pazopanib	41,020	1.966	-144	0.068	45,492
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios					

The general pattern of results was similar to the base case analysis however, the incremental cost per QALY for the comparison of pazopanib compared with IFN increased to above £45,000.

6.4.8 Combine increase in cost, decrease in utility, increase in time frame, increase in discount rate with HR OS 0.6 and then 0.7 and then 1

This analysis was conducted to explore the combined impact of the one way sensitivity analyses considered by the manufacturer along with plausible variations in pazopanib hazard ratio for overall survival being reduced to 0.6 or increased to 0.7 and 1 (Table 6.7).

Table 6.7 Multi-way sensitivity analysis: combined costs, utilities, time frame and discount rate and HR OS

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline
Base case analysis					
BSC	4,085	0.987			
IFN	8,379	1.249	4,294	0.262	16,395
Sunitinib	36,179	1.898	27,799	0.649	Extendedly dominated
Pazopanib	36,301	1.966	122	0.068	38,925
Combined costs, utilities, time frame and discount rate and HR OS(0.6)					
BSC	5,902	0.746			
IFN	10,619	0.944	4,717	0.198	23,874
Sunitinib	38,640	1.448	28,021	0.504	Extendedly dominated
Pazopanib	39,318	1.553	679	0.106	47,080
Combined costs, utilities, time frame and discount rate and HR OS(0.7)					
BSC	5,902	0.746			
IFN	10,619	0.944	4,717	0.198	23,874
Pazopanib	37,655	1.363	27,036	0.419	Extendedly dominated
Sunitinib	38,640	1.448	985	0.085	55,600
Combined costs, utilities, time frame and discount rate and HR OS(1)					
BSC	5,902	0.746			
IFN	10,619	0.944	4,717	0.198	23,874
Pazopanib	34,335	0.983	23,716	0.039	Extendedly Dominated
Sunitinib	38,640	1.448	4,305	0.465	55,600
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios					

Increasing the hazard ratio for overall survival for pazopanib to 0.7 or to 1 resulted in pazopanib being extendedly dominated by a combination of sunitinib and IFN. These hazard ratios are within the confidence intervals reported in Table 4.9, (Section 4.2.1, A3) and given the width of the confidence interval one interpretation is that it might be more appropriate to conclude that the point estimate used in the base case is not truly representative and perhaps an assumption that there is no difference in overall survival is plausible.

6.4.9 Combine decrease in cost, increase in utility, decrease in time frame, no discount rate with HR 0.4 and then 0.3

Analysis was performed by combining the changes in costs, utilities, time frame, discount rate and changes in OS hazards ratio. The ratios were reduced to 0.4 and increased to 0.3 (Table 6.8).

Table 6.8 Multi-way sensitivity analysis: combined costs, utilities, time frame and discount rate and HR OS

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline
Base case					
BSC	4,085	0.987			
IFN	8,379	1.249	4,294	0.262	16,395
Sunitinib	36,179	1.898	27,799	0.649	Extendedly dominated
Pazopanib	36,301	1.966	122	0.068	38,925
Combined costs, utilities, time frame and discount rate and HR OS (0.4)					
BSC	1,979	1.171			
IFN	5,690	1.429	3,711	0.258	14,392
Sunitinib	32,074	1.997	26,384	0.568	Extendedly dominated
Pazopanib	32,884	2.519	810	0.522	24,957
Combined costs, utilities, time frame and discount rate and HR OS(0.3)					
BSC	1,979	1.171			
IFN	5,690	1.429	3,711	0.258	14,392
Sunitinib	32,074	1.997	26,384	0.568	Extendedly dominated
Pazopanib	33,364	2.768	1,290	0.771	20,671
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios					

The results were sensitive to the increases in OS hazard ratios. As the estimates decreased to 0.4 sunitinib was more costly than pazopanib. Both sunitinib and pazopanib were dominated by IFN. As OS hazard ratios reduced to 0.3, sunitinib was extendedly dominated by pazopanib.

6.4.10 Probabilistic analysis

The manufacturer only reported pair-wise probabilistic sensitivity analysis. While useful, such analyses do not facilitate the comparison of all the interventions noted as comparators in the commissioning brief. The ERG took the base case work and, using net benefit, compared all four options. An additional net benefit approach analysis was performed excluding IFN as there may be some doubt as to the relevance of this treatment to current practice in the NHS.

Figure 6.6 shows that up to a cost per QALY threshold of approximately £15,000 best supportive care is likely to be cost-effective. Between £15,000 and £35,000 IFN is most cost-effective and beyond that threshold and at least up to £50,000 pazopanib is most likely to be considered cost-effective. However apart from best supportive care when cost per QALY threshold was less than £10,000 no treatment had much more than a 50% chance of being cost-effective. Excluding IFN resulted in pazopanib being most likely to be cost-effective once the cost per QALY threshold was above £30,000 (Figure 6.7).

It should be noted that these probabilistic sensitivity analyses have essentially taken the base case analysis at face value. The critique of the manufacturer's submission has highlighted that there is uncertainty both in terms of the methods that have been used and the point estimates that have been used in the economic model. By extension this uncertainty extends into consideration of the distributions associated with the various input parameters. It has not been possible to explore this uncertainty within additional probabilistic analyses due to the limited data available for some parameters.

Figure 6.6 Cost-effectiveness acceptability curve: comparing all interventions

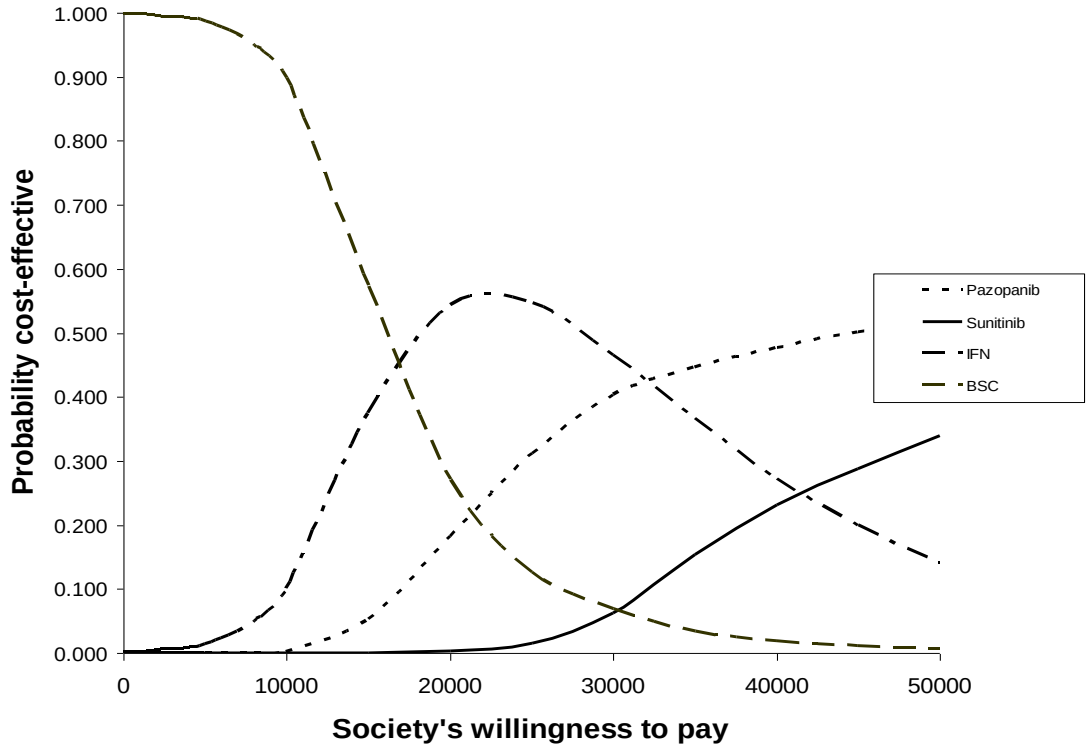
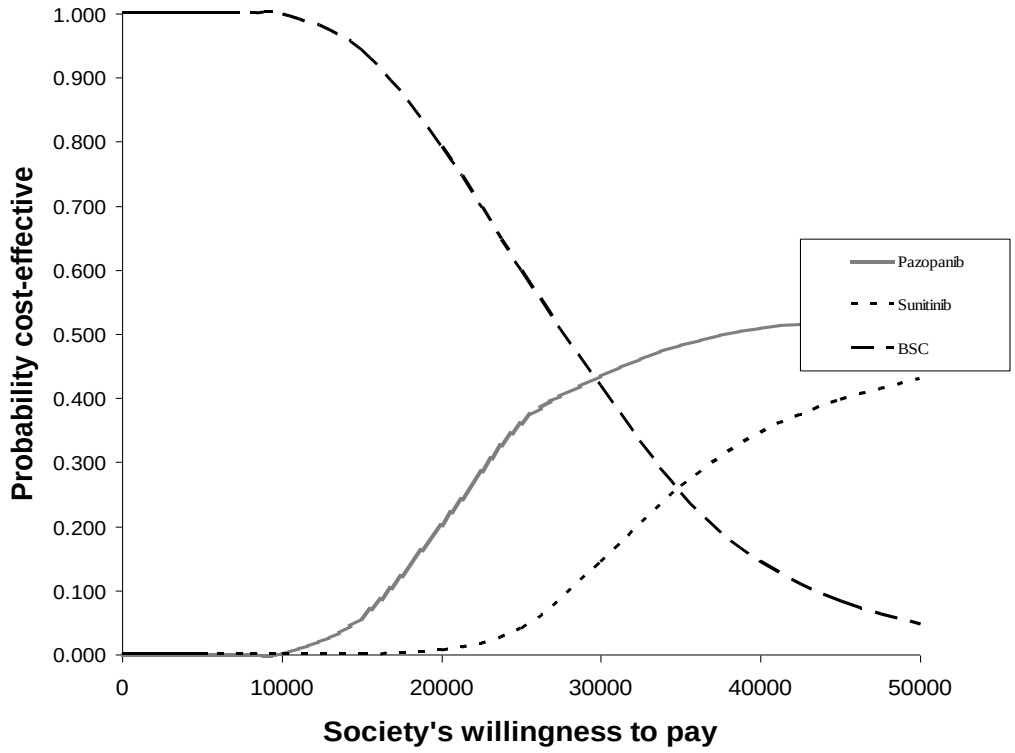


Figure 6.7 Cost-effectiveness acceptability curve: excluding IFN



Summary of results

This chapter has explored a number of uncertainties surrounding the manufacturer's submission. The additional analyses have highlighted that potentially relevant studies relating to the effectiveness of immunotherapy suggested that, in the interferon-α studies included in the indirect comparison, the effect of this treatment may have been overestimated compared with best supportive care. This has implications as IFN is treated as the baseline in the economic model. The ERG was also concerned that the manufacturer's decision to treat data where medroxyprogesterone or vinblastine has been used as being equivalent to best supportive care, may lead to an underestimate of the effect of best supportive care in the indirect comparison, and consequently the economic model, because the tolerability of these treatments may differ from best supportive care.

Consideration was also given to the estimation of hazard ratios, which along with the costs of pazopanib and sunitinib are the most important drivers of cost-effectiveness. The ERG has noted limitations in the approach used and noted that it would be difficult to estimate the impact a hypothetical (because the method does not currently exist) method of using a weighted RPSFT method of estimating hazard ratios.

Additional analysis of the economic model has concentrated on conducting multi-way sensitivity analyses as well as addressing uncertainty surrounding the estimation of hazard ratios. The manufacturer concentrated on presenting a series of one way sensitivity analyses which demonstrated that the cost-effectiveness results are not greatly altered by univariate changes. However, the results of the multi-way analyses indicate that they are sensitive to some combinations of changes and that the ICER associated with pazopanib could be increased above £50,000. The ERG also considered the impact of changes in the hazard ratios. In one respect this was to explore the impact of changes in hazard ratios and was prompted by the methodological uncertainty surrounding how they might be best estimated. Even taking the method of estimating the hazard ratio at face value the ERG notes the considerable imprecision in the estimates of the hazard ratios used, especially the hazard ratio for overall survival for pazopanib. The confidence interval surrounding this hazard ratio was very wide and hence any focus on deterministic analyses based upon the point estimate of this hazard ratio may be misleading. It is a judgement as to whether a more appropriate interpretation of the data is that the point estimate is uninformative and should really be treated as such given the relative paucity of the data. Should such a judgement be made and other things be kept equal then it is not likely that pazopanib would be cost-effective.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

7.1.1 Baseline characteristics of the participants in the included studies

The evidence that the manufacturer has relied upon for this appraisal relies on data drawn from the indirect comparison of treatments rather than on directly comparative data. Such directly comparative data do not currently exist (although some directly comparative studies are underway, e.g. VEG108844 COMPARZ) and an indirect comparison appears to be the best that can be performed. However the validity of such an approach is in part determined by the comparability of the different studies for the different treatments and whether they have considered the same outcomes in sufficiently similar populations. Overall, the baseline characteristics of the participants in the included studies were broadly similar, but some differences exist. For example, a higher percentage of participants in the sunitinib study[17] had ECOG performance status 0 while a lower proportion had ECOG status 1. However, while the pazopanib and sunitinib studies limited inclusion to participants with ECOG performance status 0 or 1, three of the IFN studies contained a percentage of participants with ECOG performance status 2 – the MRC RE01 study,[23] the study by Pyrhonen and colleagues[27] and the study by Kriegmair and colleagues.[24] If this led to the participants in the IFN studies having an overall worse prognosis than those in the pazopanib and sunitinib studies, this could introduce a potential bias into the indirect comparison which might make the relative performance of pazopanib and sunitinib against IFN appear better than it actually is.

All participants in both arms of the sunitinib study had clear cell histology, while in VEG105192 87% of pazopanib participants and 89% of placebo participants had clear cell histology, with the remainder having predominantly clear cell histology. This information was not reported for the five IFN studies.

7.1.2 Representativeness of participants in trials to UK renal cell carcinoma patients

In the international VEG105192 study, of the treatment-naïve-population (n=233), only seven patients (3%) were from the UK (five randomised to pazopanib, two to placebo). The study by Motzer and colleagues[17] reporting sunitinib versus interferon-α was a multicentre, international study (11 countries including the UK) but it was not reported how many patients were from the UK. Of the five studies reporting interferon-α that were included in the indirect comparison, only one (MRC RE-01 study) took place in the UK. With respect to the main data taken from the studies a judgement is needed as to whether information on non-UK participants is sufficiently similar to that which might be expected in the UK. This is not just

related to biological variability but perhaps more importantly unrecorded differences in care between settings which might not have the same impact across the treatments compared.

7.1.3 Estimates of relative effectiveness derived from the indirect comparison

The estimates of relative effectiveness were influenced by two areas of uncertainty:

- Which data should be used to derive the hazard ratios used to estimate relative effectiveness?
- Which method should be used to estimate the hazard ratios given the large proportion of patients who crossed over from placebo to an active treatment during trial follow-up?

Sources of data used to derive estimates of relative effectiveness

The manufacturer explored the impact of using different data in sensitivity analyses. They showed that when only the MRC RE01 study was used to represent IFN, this led to a slight reduction in the relative effectiveness of pazopanib against IFN and sunitinib for both progression-free and overall survival (for example the HR for progression-free survival for pazopanib against IFN changed from 0.512 to 0.545). The knock-on effect on the HR for pazopanib versus sunitinib was to increase the HR (for example the HR for progression-free survival changed from 0.949 to 1.012.

The data which the manufacturer relies on were also inconsistent across the documents submitted. For example in the manufacturer's systematic review, only the MRC RE01 study,[23] was used to provide data for IFN for progression-free survival but in the main submission document three IFN studies were used to provide data for this outcome.[23,25,27] The net impact of using the data relied upon in the main submission was to improve the relative effectiveness of pazopanib versus both interferon-α and sunitinib. A judgement is required as to whether the estimates obtained from combining the three studies are sufficiently robust to form the basis of the manufacturer's conclusions about relative effectiveness and cost-effectiveness.

Within the economic model interferon-α was used as the baseline comparator, and then its effectiveness was compared with best supportive care which in turn was compared with both sunitinib and pazopanib. Hence the effectiveness (and cost-effectiveness) of pazopanib and sunitinib are dependent upon the data used to derive the effectiveness of interferon-α and best supportive care. The ERG has concerns that the relative effectiveness of interferon-α compared with best supportive care might have been overestimated. This is because the manufacturer has assumed that MPA and vinblastine would have no impact on progression-

free survival and overall survival and could therefore be considered as palliative treatment equivalent to placebo with best supportive care. However, although the response rate to both MPA and vinblastine is low it is not zero, and both also have significant toxicities, therefore they cannot be regarded as being completely equivalent to placebo with best supportive care. The manufacturer undertook sensitivity analyses to assess the effect on progression-free survival and overall survival if the two studies using vinblastine were excluded from the analysis. For progression-free survival the HR for pazopanib against IFN was 0.512 (base case) and 0.495 (excluding vinblastine studies). This also had a knock-on effect on the HR for pazopanib versus sunitinib, which was 0.949 (base case) and 0.918 (excluding vinblastine studies). For overall survival, the HR for pazopanib against IFN (base case) was 0.627 and 0.580 (excluding vinblastine studies). Again this also had a knock-on effect on the HR for pazopanib versus sunitinib, which was 0.969 (base case) and 0.897 (vinblastine studies excluded). So in this sensitivity analysis excluding the vinblastine studies resulted in a slight improvement in the relative effectiveness of pazopanib against both IFN and sunitinib for progression-free and overall survival. The above sensitivity analyses demonstrate some of the uncertainties surrounding the estimates reported by the indirect comparison.

7.1.4 Using scan dates versus scheduled visit dates

In the sunitinib study the data for progression-free survival was based on actual scan dates. The pazopanib study reported data for progression-free survival for both scan dates and scheduled visit dates. For scheduled visit dates the HR for pazopanib versus placebo was 0.40 (95% CI 0.27 to 0.60), for scan dates the HR was 0.36 (95% CI0.24 to 0.55) (both as assessed by independent review committee). Therefore the relative effectiveness of pazopanib based on scan dates was slightly better than based on scheduled visits. In order to be consistent with the approach used in the sunitinib trial, in the indirect comparison the manufacturer used data for progression-free survival for pazopanib based on scan dates. However, it is unclear whether the data from the IFN studies were based on scan dates or scheduled visits – if they were based on scheduled visits this may have introduced a slight bias in favour of pazopanib and sunitinib.

7.1.5 RPSFT method used to deal with cross-over in study VEG105192

The manufacturer's conceptual approach of investigating the suitability of various options to correct for cross-over bias in estimating the effect of pazopanib on overall survival and their decision to choose an RPSFT analysis are sound. However, there are several concerns with the execution of this process, particularly in a couple of key issues. First, the timing of the final analysis meant that the data may not yet be mature enough for an effect size to be estimated with sufficient accuracy, given that the chosen statistical method is sensitive to the

maturity of the data, observed by the higher hazard ratios in the final analysis compared with the interim analysis. Second, the method advocated by the manufacturer may not be the most appropriate given the lack of an adequately developed weighted RPSFT methodology required to analyse the data robustly, forcing the adoption of a model that is acknowledged to be unsatisfactory. The current absence of an appropriate method should be a determining factor when considering the accuracy of the effect size for overall survival that the manufacturer has chosen for the economic model.

7.1.6 Adverse events and laboratory evaluations

The rates for most adverse events (all grades) were mostly higher for sunitinib compared with pazopanib, other than for hair colour change (39% versus 20%) and hypertension (39% versus 30%). For the five events grouped under the class of blood and lymphatic system disorders, the adverse event rates were consistently higher for sunitinib. For grade 3/4 adverse events, rates were higher for sunitinib for diarrhoea (9% versus 3%), fatigue (11% versus 2%), hand-foot syndrome (9% versus 0%), hypertension (12% versus 4%), leucopenia (8%, versus 0%), lymphocytopaenia (16% versus 0%), neutropenia (16% versus 1% and thrombocytopenia (8% versus 2%), while rates were higher for pazopanib for ALT increased (11% versus 2%) and AST increased (7% versus 2%).

7.1.7 Interleukin-2

Interleukin-2 was included in the final scope document as one of the comparators under immunotherapy, alongside interferon-α. However the manufacturer did not include interleukin-2 in their statement of the decision problem addressed in the submission. When the ERG queried this the manufacturer replied to say that this was because interleukin-2 did not have a licence in the UK. The manufacturer did identify one study comparing interferon-α with interleukin-2.[22] This was listed in the manufacturer's submission as one of the RCTs identified meeting the inclusion criteria for the systematic review. Results for this study were reported in the systematic review but not the manufacturer's submission, which for the comparator interventions focused on the studies included in the indirect comparison. The manufacturer did not include the Negrier[22] study in the indirect comparison on the basis that a non-immunotherapy control arm was not used.

7.2 Summary of cost-effectiveness issues

The manufacturer submitted an economic model that assessed the cost-effectiveness of pazopanib versus sunitinib, IFN and best supportive care in patients with advanced/metastatic renal cell carcinoma in the UK. The economic model was informed using different sources of data including an RCT (VEG105192) and an indirect treatment comparison analysis.

7.2.1 Model

The choice of model appeared to be appropriate given the decision problem and the data available. The rationale of using the partitioned survival analysis was that it permitted the projection of patients within states defined on the basis of progression and death. The time horizon appeared to be appropriate although there are some concerns that it may overestimate survival, as the median age of prognosis is 60-65 years and a constant all cause mortality was assumed, rather than taking data from life tables which would have the impact of mortality increasing over time.

7.2.2 Effectiveness estimates

The evidence base was not ideal for this appraisal as there are currently no data from head-to-head comparisons of pazopanib with sunitinib or interferon-α. The reliance on indirect comparison within the economic model is subject to the limitations of the effectiveness data and methods highlighted above.

The main effectiveness estimates used in the model were derived from an ongoing RCT and hence rely on immature data. The impact of that immature data can be seen from a comparison of the original submission and the revised analysis (when the 12.5% discount on price of pazopanib is excluded). In the original analysis most of the benefit from pazopanib came from additional survival in the post progression period (following progression and withdrawal from pazopanib patients in the pazopanib arm would survive almost one year longer than patients who progressed following treatment with sunitinib (Table 6.29, manufacturer's original submission)). Whether such a situation is clinically plausible is unclear. In the revised analysis presented in the addendum, which used more mature data, this finding was removed.

As noted in the clinical effectiveness section above, there were also concerns about the methods that were used to handle the cross-over from placebo to pazopanib in the trial. As mentioned the manufacturer's original submission the base case analysis was based on an adjusted weighted RPSFT analysis and this was later changed to unadjusted weighted RFPST. There is some doubt about the best method to use and the point estimates used could plausibly vary to a great extent, with a consequently large effect on the incremental cost-effectiveness of pazopanib. Furthermore, the hazard ratio estimates, especially those for overall survival, were associated with a considerable degree of imprecision (for overall survival the hazard ratio for pazopanib compared with best supportive care ranged from 0.140 to 2.350). This means that the deterministic analyses presented using such estimates should be treated very cautiously as the confidence intervals for overall survival include one. Nevertheless, the lack

of statistical significance for pazopanib in terms of overall survival is a symptom of lack of sufficient evidence rather than evidence of an absence of effect.

7.2.3 Costs

The pivotal study VEGF105192 did not collect any cost data. Therefore, costs were collected from secondary sources. The methods and assumptions applied when estimating values were not always explicit and clarification was sought from the manufacturer. As indicated in the industry submission it was assumed that once cancer progressed then treatment would cease. The model therefore did not examine the cost-effectiveness of sequential therapies. The relative cost-effectiveness was taken to be the assumed difference in incremental costs associated with disease progression. The manufacturer acknowledged that to the extent this evaluation may have over- (or for sunitinib under-) estimated these incremental costs, it may have biased their results in favour of pazopanib (and against sunitinib). Without a substantial revision to the economic model the ERG has not been able to explore the potential impact of any biases these assumptions has caused.

7.2.4 Quality of life

The values used in the estimation of quality of life were considered to be the best available. There was however a certain degree of mixing and matching valuations obtained from different sources. Furthermore, little information was provided in the submission on the utility estimates obtained from a population-based time trade-off survey. This survey was used to value the utility loss from adverse events. However, given the minimal impact adverse events had on the model (in terms of both QALYs and cost) this is not likely to be a major issue.

7.2.5 Sensitivity analysis

One of the shortcomings of the manufacturer's submission was the lack of multivariate sensitivity analysis. The results of multi-way analyses indicate that they are sensitive to some combinations of changes and that the ICER associated with pazopanib would increase to more than £50,000. Multi-way sensitivity analysis around the hazard ratio indicated that the imprecision and potential bias caused by the method of estimation could also greatly alter the cost-effectiveness. As noted above the confidence interval surrounding this hazard ratio for overall survival was very wide so any focus on the baseline deterministic analysis which used the point estimate of this value may be misleading. Furthermore, a judgement is needed, given the extent of the imprecision, as to whether an alternative point estimate and potentially distribution would better characterise the uncertainty that exists. For example should a judgement be made that the hazard ratio for overall survival for pazopanib versus best supportive care be taken as one (i.e. pazopanib cost £36,294 QALY 1.155, sunitinib cost £36,179 QALY 2.103, IFN cost £8,379 QALY 1.350, and BSC cost £4,085 QALY 1.052.) then it is unlikely that pazopanib would be cost-effective

7.3 Implications for research

It would be helpful to have an RCT directly comparing pazopanib and sunitinib, thereby avoiding the biases inherent in using an indirect comparison to generate comparative data. Such information should be provided in the near future by two RCTs (one ongoing and one planned) of pazopanib compared with sunitinib in subjects with locally advanced and/or metastatic renal cell carcinoma who have received no prior systemic therapy. VEG108844 [COMPARZ] is an ongoing phase III, randomised, open label, parallel group study whose aim is to evaluate the efficacy and safety of pazopanib compared with sunitinib. A final study report should be available in the second quarter of 2012. VEG113046 [PISCES] is a randomised, double blind, cross-over study of pazopanib versus sunitinib, whose aim is to assess how the tolerability and safety differences between pazopanib and sunitinib translate into patient preference. It is planned to start shortly.

In the absence of new trial data it would be helpful to revise the economic model with revised estimates of hazard ratios as newer methods become available. However, these methods are in development and it should be noted that they should be subject to critical assessment. This is likely to be an ongoing process so it would also be helpful if the results of such assessments were used to justify the use of any particular method in future clinical effectiveness or cost-effectiveness modelling.

Data from the existing trials are continuing to accumulate. Although there are problems with cross-over between therapies that need to be more fully explored (current analyses have excluded from consideration the use of subsequent therapies in the pazopanib arms) further data should be analysed and incorporated into the economic model.

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9 APPENDICES

Appendix 1 Independent searches undertaken by the ERG

MEDLINE (2005 – May Week 1 2010) EMBASE (2005 – 2010 Week 18) (Medline In Process 14th May 2010)

Ovid Multifile Search URL: http://ovidsp.tx.ovid.com/

Clinical Effectiveness

```
1     Carcinoma, Renal Cell/ use mesz
2     Kidney Carcinoma/ use emez
3     (renal adj2 cell adj1 (cancer or carcinoma or adenocarcinoma or
      tumo?r$)).tw.
4     (rcc or mrcc).tw
5     or/1-4
6     pazopanib.tw,rn.
7     votrient.tw,rn.
8     armala.tw,rn
9     (gw786034 or gw 786034).tw,rn.
10    pazopanib/ use emez
11    sunitinib.tw,rn.
12    sutent.tw,rn.
13    (su11248 or su 11248).tw,rn.
14    sunitinib/ use emez
15    exp Interferon-alpha/
16    Interleukin-2/
17    alpha interferon/
18    or/6-17
19    5 and 18
20    exp clinical trial/
21    randomized controlled trial.pt.  (291113)
22    controlled clinical trial.pt.  (81573)
23    randomization/ use emez (28093)
24    randomi?ed.ab.  (472485)
25    placebo.ab.  (236137)
26    drug therapy.fs.  (1378802)
27    randomly.ab.  (279418)
28    trial.ab.  (399326)
29    groups.ab.  (1849149)
30    or/20-29
31    exp animals/ not humans/ (18198313)
32    30 not 31
33    19 and 32
34    limit 33 to yr="2005 -Current"
35    limit 34 to english language
```

Economic Evaluations and Quality of Life

1 Carcinoma, Renal Cell/ use mesz
2 Kidney Carcinoma/ use emez
3 (renal adj2 cell adj1 (cancer or carcinoma or adenocarcinoma or tumo?r$)).tw.
4 (rcc or mrcc).tw
5 or/1-4
6 pazopanib.tw,rn.
7 votrient.tw,rn.
8 armala.tw,rn
9 (gw786034 or gw 786034).tw,rn.
10 pazopanib/ use emez
11 sunitinib.tw,rn.
12 sutent.tw,rn.
13 (su11248 or su 11248).tw,rn.
14 sunitinib/ use emez
15 exp Interferon-alpha/
16 Interleukin-2/
17 alpha interferon/
18 or/6-17
19 5 and 18
20 exp "costs and cost analysis"/
21 exp economic evaluation/ use emez
22 economics/
23 exp economics,hospital/
24 economics,pharmaceutical/
25 exp budgets/
26 exp models, economic/
27 exp decision theory/
28 ec.fs. use mesz
29 monte carlo method/
30 markov chains/
31 exp technology assessment, biomedical/
32 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
33 economics model$.tw.
34 (economics$ or pharmacoeconomic$ or pharmo-economic$).ti.
35 (price$ or pricing$).tw.
36 (financial or finance or finances or financed).tw.
37 (value adj2 (money or monetary)).tw. 1600
38 markov$.tw.
39 monte carlo.tw.
40 (decision$ adj2 (tree? or analy$ or model$)).tw.
41 or/20-40
42 19 and 41
43 quality of life/
44 quality adjusted life year/
45 "Value of Life"/ use mesz
46 health status indicators/ use mesz
47 health status/ use emez
48 sickness impact profile/ use mesz
49 disability evaluation/ use mesz
50 disability/ use emez
51 activities of daily living/ use mesz
52 exp daily life activity/ use emez
53 cost utility analysis/ use emez
54 rating scale/
55 questionnaires/
56 (quality adj1 life).tw.
57 quality adjusted life.tw.

```
58    disability adjusted life.tw.
59    (qaly? or qald? or qale? or qtime? or daly?).tw.
60    (euroqol or euro qol or eq5d or eq 5d).tw.
61    (hql or hqol or h qol or hrqol or hr qol).tw.
62    (hye or hyes).tw.
63    health$ year$ equivalent$.tw.
64    (hui or hui1 or hui2 or hui3).tw.
65    (health adj3 (utilit$ or disutili$)).tw.
66    (health adj3 (state or status)).tw.
67    (sf36 or sf 36 or short form 36 or shortform 36).tw.
68    (sf6 or sf 6 or short form 6 or shortform 6).tw.
69    (sf12 or sf 12 or short form 12 or shortform 12).tw.
70    (sf16 or sf 16 or short form 16 or shortform 16).tw.
71    (sf20 or sf 20 or short form 20 or shortform 20).tw.
72    willingness to pay.tw.
73    standard gamble.tw.
74    trade off.tw.
75    conjoint analys?s.tw.
76    discrete choice.tw.
77    or/43-76
78    19 and 77
78    (case report or editorial or letter).pt.
79    case report/
80    42 or 78
81    80 not (78 or 79)
82    remove duplicates from 81
83    limit 82 to yr="2005 -Current"
84    limit 83 to english language
```

Cochrane Library May 2010
(CENTRAL, CDSR, DARE, HTA. NEED)
URL: http://www.thecochranelibrary.com/view/0/index.html

```
#1    MeSH descriptor Carcinoma, Renal Cell, this term only
#2    (renal NEXT cell NEXT (cancer or carcinoma or adenocarcinoma or
      tumo?r?))
#3    (#1 OR #2)
#4    (sunitnib) or (sutent) or (su11248) or (su 11248)
#5    (pazopanib) or (votrient) or (gw786034) or (gw 786034)
#6    (#3 AND ( #4 OR #5 ))
#7    MeSH descriptor Interferon-beta explode all trees
#8    MeSH descriptor Interleukin-2, this term only
#9    (interferon):ti or (interferon):kw or (interleukin 2):ti or
      (interleukin 2):kw
#10   (#3 AND ( #7 OR #8 OR #9 ))
##11  #6 OR #10, from 2005 to 2010
```

Appendix 2 Adverse events reported by comparator studies but not data extracted by the manufacturer

Adverse event	Motzer 2009[17]	Negrier 2007[25]	MRC RE01[23]	Steineck 1990[26]	Pyrhonen 1999[27]	Kriegmair 1995[24]
Cardiac infarction/ischaemia				X		
Cardiac signs		X				X
Chills/shivering	X		X			
Confusion				X		
Constipation	X					
Cramps				X		
Cutaneous signs		X				
Cyanosis				X		
Diplopia				X		
Dry mouth	X		X			
Dry skin	X					
Dyspnea	X			X		
Erythema	X					
Flatulence	X					
Gastrointestinal signs						X
GERD	X					
Glossodynia	X					
Grand mal epilepsy/tremor				X	X	
Hearburn/acidity			X			
Haematuria				X		
Hepatic signs						X
Hypercalcemia				X		
Hypotension		X				
Increased alkaline phosphatase	X	X		X		
Increased amylase	X					
Increased creatin kinase	X					
Increased creatinine	X	X		X		
Increased lipase	X					
Increased uric acid	X					
Lack of energy			X			
Mucosal inflammation	X					

Adverse event	Motzer 2009[17]	Negrier 2007[25]	MRC RE01[23]	Steineck 1990[26]	Pyrhonen 1999[27]	Kriegmair 1995[24]
Myalgia	X					
Neurologic symptoms		X				X
Oral pain	X					
Pain behind eye				X		
Pain in extremity	X					
Performance status impairment		X				
Peripheral edema	X					
Perspiration				X		
Petechial bleedings				X		
Proteinuria				X		
Pulmonary symptoms		X				
Renal symptoms						X
Severe anxiety				X		
Thrombosis/embolism				X		
Tinnitus				X		
Vertigo				X		
Weight loss	X	X		X		

Appendix 3 Detailed cost-effectiveness results

Table 1 Comparison of manufacturer's deterministic analyses results

	Pazopanib		Difference pazopanib vs.								
			Sunitinib			IFN			BSC		
	Costs, £	**QALYs**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**
Base Case	36,301	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
HR PFS pazopanib vs. IFN=0.326	**51,928**	**2.054**	**15750**	**0.156**	**100,775**	**43,549**	**0.805**	**54,077**	**47,843**	**1.067**	**44,829**
HR PFS pazopanib vs. IFN=0.326	58,196	2.089	22,017	0.192	114,927	49,816	0.841	59,263	54,111	1.103	49,079
HR PFS pazopanib vs. IFN =0.802	**25,849**	**1.898**	**-10,329**	**0.009**	**dominant**	**17,470**	**0.658**	**26,531**	**21,764**	**0.920**	**23,646**
HR PFS pazopanib vs. IFN =0.802	23,300	1.893	-12,878	-0.005	2,625,026†	14,921	0.644	23,165	19,215	0.906	21,208
HROS pazopanib vs. IFN=0.173	**44,677**	**3.772**	**8,498**	**1.874**	**4,534**	**36,297**	**2.523**	**14,384**	**40,592**	**2.785**	**14,573**
HROS pazopanib vs. IFN=0.173	No values were identified for this SA as the results had been altered to reflect the change in values.										
HROS pazopanib vs. IFN =2.269	**18,432**	**0.576**	**-17.747**	**-1.527**	**13,220 †**	**10,052**	**-0.774**	**dominated**	**14,347**	**-0.476**	**dominated**
HROS pazopanib vs. IFN =2.269	No values were identified for this SA as the results had been altered to reflect the change in values.										
Duration of utility with Aes=0.5 x base-case	**36,301**	**1.974**	**122**	**0.061**	**1,990**	**27,921**	**0.716**	**38,988**	**32,216**	**0.983**	**32,757**
Duration of utility with Aes=0.5 x base-case	36,255	1.966	198	0.068	2,899	27,930	0.717	38,936	32,188	0.979	32,870
Duration of utility with Aes=1.5 x base-case	**36,301**	**1.958**	**122**	**0.075**	**1,626**	**27,921**	**0.718**	**38,861**	**32,216**	**0.975**	**33,041**
Duration of utility with Aes=1.5 x base-case	36,346	1.966	46	0.068	681	27,913	0.717	38,913	32,244	0.979	32,927
HR for PFS and OS for pazopanib vs. IFN calculated using only the MRC study (PFS HR=0.545, OS HR=0.460)	**36,745**	**1.898**	**566**	**0.529**	**1,070**	**28,366**	**1.178**	**24,071**	**32,660**	**1,440**	**22,675**

	Pazopanib		Difference pazopanib vs.								
			Sunitinib			IFN			BSC		
	Costs, £	**QALYs**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**
HR for PFS and OS for pazopanib vs. IFN calculated using only the MRC study (PFS HR=0.545, OS HR=0.460)	34,038	1.844	-2,141	-0.054	39,382 †	25,659	0.595	43,148	29,953	0.857	34,967
HR for PFS and OS for pazopanib vs. IFN calculated excluding the VBL studies (PFS HR=0.495, OS HR=0.400)	**40,457**	**2.656**	**4,278**	**0.758**	**5,643**	**32,077**	**1.407**	**22,795**	**36,372**	**1.669**	**21,790**
HR for PFS and OS for pazopanib vs. IFN calculated excluding the VBL studies (PFS HR=0.495, OS HR=0.400)	37,076	2.133	897	0.235	3,811	28,697	0.884	32,444	32,991	1.146	28,778
HR for PFS for pazopanib vs. IFN adjusted to reflect % w/ECOG=0/1 in sunitinib pivotal trial (HR=0.455)	**39,865**	**1.986**	**3,686**	**0.088**	**41,717**	**31,485**	**0.737**	**42,699**	**35,780**	**0.999**	**35,804**
HR for PFS for pazopanib vs. IFN adjusted to reflect % w/ECOG=0/1 in sunitinib pivotal trial (HR=0.455)	39,519	1.984	3,341	0.086	38,658	31,140	0.735	42,342	35,434	0.997	35,528

QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios †Comparator is more costly and more effective than pazopanib. Ratio is cost-effectiveness of comparator vs. Pazopanib **Bold results ERG additional work**

Table 2 Additional sensitivity analysis

	Pazopanib		Difference pazopanib vs. Sunitinib			IFN			BSC		
	Costs, £	**QALYs**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**
Base Case	36,301	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
SA1 increase in cost	39,958	1.966	118	0.068	1,727	29,031	0.717	40,472	33,830	0.979	34,547
SA2 decrease in cost	32,644	1.966	127	0.068	1,853	26,812	0.717	37,377	30,602	0.979	31,250
SA3 decrease in utility	36,301	1.525	122	0.048	2,550	27,921	0.547	51,026	32,216	0.752	42,847
SA4 increase in utility	36,301	2.407	122	0.089	1,379	27,921	0.887	31,463	32,216	1.207	26,699
SA5 combination of SA1 and SA3	39,958	1.477	118	2,460	1,727	29,031	0.547	53,054	33,830	0.752	44,994
SA6 combination of SA2 and SA4	32,644	2.407	127	0.089	1,427	26,812	0.887	30,212	30,602	1.207	25,361
SA7 Time horizon 15 years 6% discount rate	35,225	1.930	185	1.859	2,625	27,061	1.205	37,368	31,291	0.953	32,030
SA8 Time horizon 5 years 0% discount rate	34,999	1.680	-116	0.049	dominant	26,950	0.507	53,173	31,042	0.718	43,259
SA9 Decrease in cost and utilities time frame 16 year and 6% discount rate	31,620	1.498	179	0.050	3,586	25,910	0.554	46,785	29,652	0.554	39,464
SA10 Decrease in cost and utilities time frame 5 year and 0% discount rate	32,005	1.297	-69	0.033	dominant	26,315	0.380	69,246	30,026	0.544	55,228
SA12 Combine SA3 and SA7 and HR OS=0.6	39,318	1.553	679	0.106	6,426	28,699	0.610	47,080	33,416	0.807	41,400
SA13 Combine SA3 and SA7 and HR OS=0.7	37,655	1.363	-985	-0.085	11,602 †	27,036	0.419	64,510	0.617	31,753	51,490
SA14 Combine SA3 and SA7 and HR OS=1	34,335	0.983	-4,305	-0.465	9,256 †	23,716	0.039	609,471	28,433	0.236	120,228
SA11 Dosage of drug =1	41,020	1.966	144	0.068	2,102	32,633	0.717	45,492	36,935	0.979	37,717

QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios †Comparator is more costly and more effective than pazopanib. Ratio is cost-effectiveness of comparator vs. Pazopanib

Table 3 Results of sensitivity analyses on OS and PFS hazards ratio data used to generate figures 6.1 and 6.2 in chapter 6

	Pazopanib		Difference pazopanib vs.								
			Sunitinib			IFN			BSC		
	Costs, £	**QALYs**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**
Base Case	36,301	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
HR OS for pazopanib 0.300	41,442	3.075	5,264	1.177	4,472	33,063	1.826	18,107	37,357	2.088	17,892
HR OS for pazopanib 0.35	40,404	2.851	4,226	0.953	4,433	32,025	1.602	19,989	36,319	1.864	19,484
HR OS for pazopanib 0.40	39,475	2.651	3,296	0.753	4,379	31,095	1.402	22,184	35,390	1.664	21,272
HR OS for pazopanib 0.45	38,641	2.471	2,462	0.573	4,298	30,261	1.222	24,766	34,556	1.484	23,288
HR OS for pazopanib 0.5	37,891	2.309	1,712	0.411	4,165	29,512	1.060	27,835	33,806	1.322	25,569
HR OS for pazopanib 0.55	37,216	2.163	1,037	0.266	3,905	28,836	0.915	31,530	33,131	1.177	28,160
HR OS for pazopanib 0.6	36,606	2.032	427	0.134	3,186	28,226	0.783	36,047	32,521	1.045	31,121
HR OS for pazopanib 0.65	36,054	1.913	-125	0.015	dominant	27,674	0.664	41,676	31,969	0.926	34,525
HR OS for pazopanib 0.7	35,553	1.805	-625	-0.093	6,731 †	27,174	0.556	48,864	31,468	0.818	38,467
HR OS for pazopanib 0.75	35,098	1.707	-1,080	-0.191	5,656 †	26,719	0.458	58,333	31,013	0.720	43,076
HR OS for pazopanib 0.80	34,684	1.618	-1,494	-0.280	5,331 †	26,305	0.369	71,338	30,599	0.631	48,519
HR OS for pazopanib 0.85	34,306	1.536	-1,872	-0.362	5,175 †	25,927	0.287	90,266	30,221	0.549	55,032
HR OS for pazopanib 0.9	33,961	1.462	-2,218	-0.436	5,083 †	25,581	0.213	120,273	25,581	0.475	62,946
HR OS for pazopanib 0.95	33,644	1.393	-2,535	-0.505	5,023 †	25,264	0.144	174,975	29,559	0.406	72,747
HR OS for pazopanib 1	33,353	1.331	-2,826	-0.567	4,980 †	24,973	0.082	305,795	29,268	0.344	85,180

	Pazopanib		Difference pazopanib vs.								
			Sunitinib			IFN			BSC		
	Costs, £	**QALYs**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**	**Costs, £**	**QALYs**	**ΔC/ΔQ, £**
HR PFS for pazopanib 0.300	55,374	2.074	19,196	0.176	109,260	46,995	0.825	56,983	51,289	1.087	47,200
HR PFS for pazopanib 0.35	49,116	2.038	12,937	0.140	92,111	40,736	0.789	51,599	45,031	1.051	42,829
HR PFS for pazopanib 0.4	44,179	2.011	8,000	0.113	71,016	35,799	0.762	47,001	40,094	1.024	39,169
HR PFS for pazopanib 0.45	40,217	1.988	4,039	0.090	44,703	31,838	0.739	43,061	36,132	1.001	36,085
HR PFS for pazopanib 0.50	36,988	1.970	809	0.072	11,211	28,608	0.721	39,668	32,903	0.983	33,467
HR PFS for pazopanib 0.55	34,315	1.955	-1,863	0.057	dominant	25,936	0.706	36,729	30,230	0.968	31,227
HR PFS for pazopanib 0.60	32,075	1.942	-4,104	0.045	dominant	23,695	0.694	34,166	27,990	0.955	29,295
HR PFS for pazopanib 0.65	30,173	1.932	-6,005	0.034	dominant	21,794	0.683	31,918	26,088	0.945	27,614
HR PFS for pazopanib 0.7	28,542	1.923	-7,636	0.025	dominant	20,163	0.674	29,932	24,457	0.936	26,142
HR PFS for pazopanib 0.75	27,130	1.915	-9,049	0.017	dominant	18,750	0.666	28,167	23,045	0.928	24,843
HR PFS for pazopanib 0.80	25,895	1.908	-10,283	0.010	dominant	17,516	0.659	26,590	21,810	0.921	23,690
HR PFS for pazopanib 0.85	24,808	1.901	-11,370	0.004	dominant	16,429	0.653	25,174	20,723	0.915	22,660
HR PFS for pazopanib 0.90	23,845	1.896	-12,334	-0.002	dominant	15,465	0.647	23,896	19,760	0.909	21,735
HR PFS for pazopanib 0.95	22,984	1.891	-13,194	-0.007	1,974,071 †	14,605	0.642	22,737	18,899	0.904	20,900
HR PFS for pazopanib 1	22,212	1.887	-13,966	-0.011	1,266,094 †	13,833	0.638	21,682	18,127	0.900	20,143

QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios †Comparator is more costly and more effective than pazopanib. Ratio is cost-effectiveness of comparator vs. Pazopanib

Details of cells altered in analysis

For SA1 and SA2 MainInputs worksheet cells that have values Therapy initiation (one- time) (e.g. F119), Pre-progression, per month of PFS Other (e.g. F130), Post progression Other costs (e.g. F139), and in the SEInputs worksheet cells that contained values for cost per event such as F76.

For SA3 and SA4 MainInputs cells that contained values for pre-progression utility such as F149 and cell that contained values for post progression absolute decrement.

For SA7 and SA8 OtherInputs worksheet cells F22 F23 and F24

For SA11 MainInputs worksheet cells that contained values for Mg per day of use per such as F32

For SA12-SA14 in addition to the already mention cells, MainInput the cell containing hazards ratio for overall survival F22