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

ADDENDUM to GSK'S SUBMISSION TO NICE 20 JULY 2010

EXECUTIVE SUMMARY

The VEG105192 study provides the primary evidence for the efficacy and safety of pazopanib, the intervention under consideration, in the first-line treatment of renal cell carcinoma (RCC). At the time of GSK's submission to NICE for pazopanib in this setting (16 April 2010), overall survival (OS) data from this study were immature and the results of a final analysis were awaited. This addendum presents the final OS data conducted with a clinical cut-off of 15 March 2010, together with associated analyses to adjust for the effects of post-study therapy. Updated results for an indirect comparison of OS for pazopanib versus sunitinib and versus interferon (IFN), the comparators in this appraisal, and updated cost-effectiveness estimates are also presented. Details of the proposed patient access scheme (PAS) are provided in the NICE PAS template.

Clinical evidence:

The hazard ratio (HR) for the final OS data for the treatment-naive sub-population in VEG1015192 was 1.01 in the pre-specified intent-to-treat (ITT) analysis (based on a Pike estimator) (95% CI: 0.72-1.42, p=0.525). As noted in GSK's original submission, following disease progression subjects could receive further anti-cancer therapy at the discretion of the attending physician according to the standard of care in the region. Patients progressing on the placebo arm of the study had the opportunity to cross over to pazopanib via the VEG107769 extension study. At the time of the clinical cut-off, 64% of patients in the placebo arm (N=78) and 34% of those in the pazopanib arm (N=155) had received further anti-cancer therapies. Of note, 40 (51%) of patients in the placebo arm crossed over to receive pazopanib, some as early as 2 months post-randomisation. This imbalance in post-disease progression therapy has therefore confounded the ITT OS analysis, attenuating the true effect of pazopanib treatment by improving survival times for the group randomised to placebo. This is evident in the fact that placebo subjects who crossed over to pazopanib received a similar benefit from treatment as those subjects who were randomised to pazopanib at the start of VEG105192 (median OS 22.7 vs. 22.9 months, Table 1.8).

Since there is no universally accepted way to adjust for cross-over/post-study therapy in survival analysis in RCTs, and all methods have their strengths and limitations, a number of approaches were utilised to comprehensively evaluate this effect in VEG105192: i) censoring at the point of cross-over or receipt of other anti-cancer therapy; ii) inverse probability of censoring weighted (IPCW) analysis; iii) rank preserving structural failure time (RPSFT) analysis; and (vi) no post-study therapy analyses. In particular, significant effort has gone into the application of the IPCW and RPSFT methods, complex statistical techniques which have been conducted in collaboration with and under the direction of leading international experts in this field.

Taken as a whole, the results of these analyses indicate that treatment with pazopanib is consistently associated with a clinically relevant survival benefit compared with placebo across the various methodologies (HRs adjusted for cross-over/receipt of further anti-cancer therapies ranging from 0.300 to 0.797, depending on the methodology and whether or not adjusted for baseline patient characteristics, see Table 1.17).

The HR of 0.501 (95% CI 0.136 to 2.348 by bootstrap, and a 95% CI which is statistically significant on test inversion[1]) obtained using the weighted, unadjusted RPSFT method has been used in the base case in the indirect comparison and in the economic evaluation. The RPSFT method was selected over the IPCW method for the base case because it is deemed to be the more robust from a statistical perspective since randomisation is preserved and an assumption of no unmeasured confounders is not required. Indeed, a recent NICE appraisal acknowledged RPSFT as being more methodologically robust for the same reasons (Everolimus FAD, June 2010).

In the absence of a single agreed and established methodology for evaluating the impact of cross-over/post-study therapy, we believe that the estimate of 0.501 provides a reasonable representation of the likely benefit of pazopanib on survival. It lies within the range of estimates generated from our extensive analyses to adjust for cross-over/receipt of further anti-cancer therapies (0.300 to 0.797). If anything it could be considered to be conservative: the HR of 0.380 obtained from an analysis in patients with no post-study therapy (excluding patients still on study) was not adopted for the base case, even though sunitinib was recommended for use by NICE (TA 169) on the basis of survival estimates derived from a similar analysis in patients with no post-study therapy.

Comparative clinical effectiveness:

Since there are no data directly comparing pazopanib with IFN or sunitinib, a clinical comparison was only possible using an indirect comparison. Full details of the methodology employed and the data sources can be found in GSK's original submission to NICE (section 5.7).

Results of the base case indirect comparison using the final OS data (adjusted using the weighted RPSFT HR estimate) suggest that pazopanib has similar efficacy to sunitinib in terms of a survival benefit (HR: 0.969 [95% CI: 0.359-2.608]). The projected median OS estimates for pazopanib and sunitinib are similar with respect to the point estimates (27.8 and 26.8 months, respectively) and this is supported by the fact that the 95% CIs overlap. The 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 RCC. A pooled analysis of these data is required by the European Medicines Agency (EMA) as part of the conditional marketing authorisation for pazopanib. This is intended to detect non-inferiority of pazopanib to sunitinib where the non-inferiority margin is 1.22 with respect to the primary endpoint of PFS (i.e. the upper limit of the CI for the PFS HR between pazopanib and sunitinib must be ≤ 1.22 to declare non-inferiority). Using the sample size and the margin, it is possible to back-calculate that the required point estimate of the HR for PFS will need to be approximately 1.06 or less in order to declare non-inferiority[2]. This strict non-inferiority margin seeks to ensure that should pazopanib be found to be non-inferior to sunitinib, clinicians and their patients can be confident that the two drugs have very similar efficacy. As such, patients and physicians will have access to an alternative, clinically effective medicine with a different tolerability profile that is considered to offer a major advantage in the context of the currently available therapies for this disease.

The indirect comparison also demonstrates that pazopanib is associated with a reduced risk of death compared with IFN (HR: 0.627 [95% CI: 0.173-2.269]). As discussed in our original submission, we believe that pazopanib should be afforded the same consideration under

[1] The upper 95%CI limit for the HR based on upper 95%CI limit for ψ^* based on inversion of the test statistic was less than 1.0 (0.991).

[2] Note these calculations are based on an unadjusted HR, even though the final analysis will be stratified because this is a best estimate given it is not possible to entirely predict how the stratification will impact the results.

NICE's Supplementary Advice on appraising End of Life (EoL) medicines as sunitinib in relation to IFN. Median OS was estimated to be 15.8 months (95% CI: 15.8-15.8) for IFN and 27.8 months (95% CI: 5.7-137.9 based on percentiles) for pazopanib based on the final OS data. This equates to a survival gain of 12.0 months for patients receiving pazopanib, exceeding the ≥3-month extension-to-life criterion set out in NICE's guidance, as well as being a treatment for a small patient population with a limited life expectancy of less than 24 months.

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Economic evaluation:

As discussed above, several approaches were utilised to adjust for the high rate of crossover/post-study therapy, including the IPCW and RPSFT methods, since there is currently no consensus on which is the most appropriate. For reasons described above, the weighted RPSFT estimate of the HR for OS (0.501) was used for the economic base case. This is a reasonable, if not conservative, approach since the estimate (0.501) lies within the range of estimates generated by our analyses to adjust for cross-over/post-study therapy (0.300 to 0.797). Secondly, the no post-study therapy analysis which yielded an HR of 0.380 was not adopted for the base case, even though sunitinib was recommended on the basis of survival estimates derived from a similar no post-study therapy analysis.

GSK has submitted a patient access scheme for pazopanib for which PASLU has issued draft positive advice to the Department of Health on 6th July 2010. In consequence, results from the updated economic evaluation need to be assessed in conjunction with the completed NICE PAS template provided with this submission.

Briefly, the proposed patient access scheme for pazopanib linked to this submission is a financially-based scheme which has two parts: part A is a straight discount given at the point of invoice, and [redacted] proposed patient access scheme attempts to address

a) The current difference between the list price of pazopanib and the effective price of sunitinib to the NHS under the sunitinib patient access scheme (part A of the scheme; 12.5% discount from list price).

[redacted]

As a result, the patient access scheme seeks to enable patients and physicians to have access to pazopanib, a clinically effective, alternative treatment option with a different tolerability profile, pending receipt of definitive comparative data.

Results of economic evaluation

Table 1: Base-case cost-effectiveness results incorporating a 12.5% straight discount

	Pazopanib	Sunitinib	IFN	BSC
Technology acquisition cost, disc.	28,987*	28,856**	40	0
Other costs, disc.	7,314	7,371	5,649	4,094

Total costs, disc.	36,301	36,179	8,379	4,085
Difference in total costs		122	27,922	32,216
LYG, disc	3.097	3.018	2.020	1.598
LYG difference		0.079	1.077	1.499
QALYs, disc.	1.966	1.898	1.249	0.990
QALY difference		0.68	0.717	0.976
ICER		1,790	38,925	32,898

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

* Includes 12.5% discount from list price

** Includes patient access programme of one cycle free

Table 2: Incremental cost-effectiveness results incorporating a 12.5% discount for pazopanib

Technology	Total Cost	Total QALY	Incremental cost	Incremental QALY	ICERs vs. baseline	Incremental analysis
BSC/placebo (baseline)	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

Relative to sunitinib, pazopanib (with 12.5% discount) appears to be a cost-effective first-line treatment for patients with advanced RCC. The baseline estimate of the incremental cost per QALY gained versus sunitinib was £1,790. Probabilistic sensitivity analysis for the base case estimate of pazopanib versus sunitinib demonstrated that at cost-effectiveness thresholds of £30,000/QALY pazopanib would be cost effective relative to sunitinib in approximately 55% of cases.

A range of deterministic sensitivity analyses suggests that in the majority of cases pazopanib is cost effective vs. sunitinib in the base case at a threshold of £20,000-£30,000/QALY (with 12.5% discount) appears The main driver of uncertainty is the estimate of the relative efficacy of pazopanib versus IFN, which in turn impacts on the relative efficacy of pazopanib and sunitinib, mainly due to the method used to account for cross-over/post-study therapy in the VEG105192 trial. Results of sensitivity analyses in which the method for accounting for cross-over/switch in VEG105192 was varied are displayed below.

Table 3. Summary of cost-effectiveness estimates for all final OS analyses incorporating a 12.5% discount from list price for pazopanib

Final OS analysis	HR vs. IFN	Pazopanib			ICER 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	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	0.627	£36,301	3.097	1.966	£1,790	£38,925	£32,898

unadjusted (base case)							
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
†Comparator is more costly and more effective than pazopanib. Ratio is cost-effectiveness of comparator vs. pazopanib							

In the present evaluation, the ICER for pazopanib versus IFN is £38,925/QALY in the base case analysis but the method of accounting for cross-over/post-study therapy has a significant impact on the estimate. Every effort was made to fully explore the impact of cross-over/post-study therapy on OS in VEG105192 and the most up-to-date methodologies were employed. Experts in the application of these methods were consulted in the conduct of these analyses. The limitations of these methods are fully described in section 1.4 and Appendix 1. Nevertheless, using the weighted unadjusted RPSFT method for the base case analysis constitutes a conservative estimate of comparative efficacy for the reasons described earlier.

It should be noted that sunitinib was approved by NICE under the Supplementary Advice on appraising end-of-life medicines based on an ICER of £54,366/QALY versus IFN (TA 169). The corresponding estimates for sunitinib and pazopanib versus IFN in the current evaluation of £42,832/QALY, and £38,925/QALY, respectively, suggest that given the same consideration, pazopanib should be considered as a cost-effective option for this patient population. Similarly the ICER for pazopanib versus BSC is £32,898/QALY. Pazopanib is therefore likely to be a cost-effective option for patients for whom sunitinib or IFN is not appropriate.

Conclusion:

In conclusion, studies involving over 350 treatment-naive patients with advanced RCC demonstrate that pazopanib significantly improves PFS (11.1 vs. 2.8 months, $p<0.0001$) and response rates (32 vs. 4%, $p<0.001$) in this population compared with BSC (Sternberg 2010; Hawkins 2009b; Hutson 2010). Comprehensive analyses adjusting for the impact of cross-over/post-study therapy in the VEG105192 trial demonstrate that pazopanib offers a meaningful survival benefit over BSC (base case estimate HR 0.501, 95% CI statistically significant on test inversion). As discussed in our original submission, pazopanib is a more selective tyrosine kinase inhibitor than sunitinib and this may partially explain the favourable tolerability profile observed (low incidence of grade 3/4 fatigue [2%], hand-foot syndrome (<1%), mucositis/stomatis [<1%] and haematological toxicities [<5%]). Of particular importance, was that pazopanib did not negatively impact on quality of life when compared with placebo as measured by validated tools (Hawkins 2009a).

The indirect comparison undertaken as part of this submission confirms that pazopanib has comparable efficacy in terms of a survival benefit to sunitinib, the current UK standard of care. The CHMP opinion was that the benefit/risk profile of pazopanib was favourable despite the lack of comparative data and recommended that the drug be made available as the tolerability profile was seen to offer an improvement over the currently available agents.

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

GSK is also currently preparing to initiate a trial of pazopanib in adjuvant RCC in October 2010.

GSK acknowledges there is uncertainty in the current cost-effectiveness estimates and the proposed patient access scheme attempts to reduce the uncertainty in the comparative effectiveness of pazopanib versus sunitinib, until the head-to-head data are available. Therefore, alongside the straight discount, [redacted] In conclusion, this will enable patients and physicians to have access to pazopanib; an alternative, clinically effective, oral option with a different and manageable tolerability profile considered to offer major advantage in the context of the therapies for this disease.

INTRODUCTION

The purpose of this document is to provide final overall survival (OS) data and associated analyses for the first-line population from the pivotal registrational trial of pazopanib versus placebo in patients with advanced/metastatic renal cell carcinoma (RCC), the VEG105192 trial.

At the time of GSK's submission to NICE for pazopanib in the first-line treatment of advanced RCC (submitted 16 April 2010), only interim overall survival (OS) data from this study were available (61% of the required death events; 23 May 2008 cut-off). The final OS analysis was scheduled to be carried out after 287 deaths, based on 90% power to detect a 50% improvement in median OS with pazopanib compared with placebo in the overall study population. The clinical cut-off date for the final OS analysis was 15 March 2010, at which point 290 (67%) patients in the overall study population had died (148 [64%] in the treatment-naive group).

Since subsequent anti-cancer therapy for patients with progressive disease could be provided at the discretion of patients and their physician following discontinuation of study medication, with patients in the placebo arm having the option to cross-over to receive pazopanib (via the open-label VEG107769 study), the utility of the intent-to-treat (ITT) OS analysis is limited. Various statistical methodologies to adjust for the effects of cross-over were conducted on the interim OS data (presented in GSK's original submission) and these have now been applied, with some adjustments as detailed below, to the final OS data from VEG105192.

An updated indirect comparison of OS for pazopanib versus sunitinib, the main comparator in this appraisal, and versus interferon-α (IFN), utilising these final OS data has also been conducted. Updated cost-effectiveness analyses conducted using the hazard ratios (HRs) generated by the updated indirect comparison are also presented.

Section 1: CLINICAL EVIDENCE

1.1 Subject disposition

VEG105192 enrolled a total of 435 subjects with advanced/metastatic RCC (233 treatment-naive and 202 cytokine pre-treated subjects); 290 patients were randomly assigned to pazopanib and 145 to placebo. The treatment-naive sub-population, which forms the focus of this submission, comprised 155 patients in the pazopanib arm and 78 in the placebo arm.

Subject disposition for the treatment-naive sub-population (i.e. the patient group relevant to the current decision problem) as of the 15 March 2010 cut-off date for the final OS analysis is summarised in Table 1.1. Deaths were reported for 99 (64%) patients in the pazopanib arm and 49 (63%) patients in the placebo arm in the treatment-naive sub-population (Table 1.1). All patients in the placebo arm and 91% of those in the pazopanib arm had discontinued study treatment at the time of clinical cut-off. The main reason for discontinuation was disease progression (pazopanib: 59% and placebo: 79%), with 13% discontinued due to AEs and 19% for other reasons in the pazopanib arm compared with 6% and 14%, respectively, for the placebo arm. Comparison of reasons for discontinuation of study medication should be interpreted with caution due to competing risks. The longer a subject receives study medication, the more likely it is that they may discontinue treatment for a reason other than disease progression or death.

Table 1.1: Summary of subject disposition (VEG105192, ITT treatment-naive population, 15 March 2010 cut-off)

	Pazopanib N=155 n (%)	Placebo N=78 n (%)
Subjects		
Died	99 (64)	49 (63)
Status		
Ongoing (still on study treatment)	14 (9)	078 (100)
Discontinued study treatment	141 (91)	
Reasons for discontinuation		
Disease progression	92 (59)	62 (79)
Adverse event	20 (13)	5 (6)
Subject decided to withdraw from study	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

1.2 Exposure to study drug

The median duration of exposure to study medication was longer in the pazopanib arm than the placebo arm (7.4 vs. 4.2 months in the treatment-naive sub-population). Just under half (45%) of the subjects in the placebo arm discontinued study medication within 3 months compared with a quarter (25%) of those in the pazopanib arm. In the pazopanib arm, 38% of treatment-naive subjects remained on pazopanib for more than 12 months, compared with 19% of those randomised to placebo.

Table 1.2: Summary of exposure to investigational product (VEG105192 Treatment-naive Safety population, 15 March 2010 cut-off)

	Treatment-naive population	
	Pazopanib N=155	Placebo N=78
Duration of treatment (dose interruptions included)		
Median (range), months	7.4 (0-41)	4.2 (0-24)
< 3months	38 (25%)	35 (45%)
3-6	34 (22%)	15 (19%)
6-12 months	39 (25%)	13 (17%)
>12+ months	44 (38%)	15 (19%)
Duration of treatment (dose interruptions excluded)		
Median (range), months	7.1 (0-41)	4.2 (0-24)
< 3months	36 (23%)	35 (45%)
3-6	34 (22%)	15 (19%)
6-12 months	39 (25%)	13 (17%)
>12+ months	46 (30%)	15 (19%)
Daily dose (dose interruptions included)		
Mean (SD), mg	800.0 (219.22)	800..0 (102.95)
Daily dose treatment (dose interruptions excluded)		
Mean (SD), mg	800.0 (182.03)	800.0 (76.07)

1.3 Summary of post disease progression anti-cancer treatment

Subsequent anti-cancer therapy for patients with progressive disease could be provided at the discretion of patients and their physician following discontinuation of study medication at any point according to the standard of care in the region. Subjects who progressed on placebo were eligible to receive pazopanib through the open-label extension study (VEG107769), provided they met the eligibility criteria.

A summary of systemic anti-cancer therapies during the follow-up period is presented in Table 1.3. Use of anti-cancer therapies of any kind, including pazopanib treatment via VEG107769, was more common in the placebo than pazopanib group during the follow-up period (64% versus 34% of patients). There was limited access to targeted therapies for advanced RCC in many of the countries participating in the VEG105192 study. The open-

label extension study VEG107769 allowed access to pazopanib treatment only to the placebo subjects. This difference in access to follow-up therapies has created an imbalance in patients receiving post-progression therapy between the placebo and pazopanib treatment arms.

Table 1.3: Summary of all systemic anti-cancer therapy post discontinuation of investigational product (VEG105192, Treatment-naive ITT population, 15 March 2010 cut-off)

	Treatment-naive population	
	Pazopanib N=155	**Placebo N=78**
Any anti-cancer therapy	52 (34%)	50 (64%)
Anti anti-VEGF therapy	24 (15%)	47 (60%)
Pazopanib	1 (<1%)	40 (51%)
Sunitinib	16 (10%)	8 (10%)
Sorafenib	8 (5%)	3 (4%)
Bevacizumab	1 (<1%)	0
Any mTOR inhibitor	2 (1%)	5 (6%)
Everolimus	1 (<1%)	2 (3%)
Temsirolimus	1 (<1%)	3 (4%)
Any cytokine	14 (9%)	4 (5%)
Other	4 (3%)	0
No. of post progressive disease systemic anti-cancer therapies		
0	117 (75%)	29 (37%)
1	30 (19%)	38 (49%)
2	8 (5%)	11 (14%)
Time to start of anti-cancer therapy (days)* Median (range)	317 (45-1037)	231 (51-750)

*Time to start of anti-cancer therapy is number of days from the start of study medication until the date of the subject's first anti-cancer therapy.

As shown in Table 1.4, as early as only 5 or 10 months post-randomisation many of the placebo subjects in follow-up had crossed over to receive pazopanib therapy and a smaller but still sizeable number began treatment with another anti-cancer therapy. This indicates that the area on the right of the survival curves corresponding to follow-up of one year or more is strongly influenced by pazopanib cross-over treatment within the placebo arm. The table also shows that most of the subjects with long survival times on the placebo arm received some form of post-study therapy. This is in contrast to the pazopanib arm where most of the subjects with long survival times did not receive additional therapy. This indicates that the long survival on the pazopanib arm is mainly representative of pazopanib treatment alone, whereas long survival on the placebo arm is confounded by the impact of additional therapies (primarily treatment with pazopanib).

Table 1.4: Summary of new anti-cancer treatment by time of new treatment (Treatment-naive population, 15 March 2010 cut-off)

Placebo subjects N=78					
Duration of survival follow-up	**5 months**	**10 months**	**20 months**	**30 months**	**40 months**
Number of subjects at risk for death	**n=58**	**n=47**	**n=40**	**n=32**	**n=5**
Post disease progression systemic therapy initiated					
Any, n (%)	13 (22)	28 (60)	31 (78)	29 (91)	5 (100)
Pazopanib	9 (16)	23 (49)	26 (65)	23 (72)	3 (60)
Other anti-VEGF/mTOR inhibitor	3 (5)	3 (6)	4 (10)	5 (16)	2 (40)
Other systemic	1 (2)	2 (4)	2 (3)	1 (3)	0
Pazopanib subjects N=155					
Duration of survival follow-up	**5 months**	**10 months**	**20 months**	**30 months**	**40 months**
Number of subjects at risk for death	**n=136**	**n=110**	**n=74**	**n=48**	**n=7**
Post disease progression systemic therapy initiated					
Any, n (%)	6 (4)	14 (13)	16 (22)	11 (23)	2 (29)
Pazopanib	0	0	1 (1)	0	0
Other anti-VEGF/mTOR inhibitor	3 (2)	8 (7)	13 (18)	8 (17)	0
Other systemic	3 (2)	6 (5)	2 93)	3 (6)	2 (29)

1.3.1 Summary of placebo subject cross-over to VEG107769

At the time of the cut-off (23 May 2008) for final PFS analysis / interim OS analysis, 31 (40%) of treatment-naive subjects from the placebo arm in VEG105192 had crossed over to receive pazopanib via the VEG107769 extension study. Subsequently, 9 additional treatment-naive subjects from the placebo arm were enrolled in VEG107769. Thus, a total of 40 (51%) of treatment-naive subjects in the placebo arm of VEG105192 had crossed over to receive pazopanib at the 15 March 2010 cut-off (Table 1.3).

Enrolment in VEG107769 was almost entirely concurrent with enrolment in the VEG105192 parent study, allowing placebo subjects the opportunity to cross-over to pazopanib immediately upon disease progression. Median time from date of randomisation into VEG105192 to the first dose of pazopanib (in VEG107769) was 8.1 months; the minimum time was 2 months (Table 1.5). Subjects with such early cross-over should not be expected to have a clinically meaningful difference in OS than if they had been randomised to pazopanib treatment originally.

Table 1.5: Summary of time to cross-over (VEG105192, Treatment-naive population, 15 March 2010 cut-off)

	Placebo N=78
n	40
Min (months)	2
Median (months)	8.1
Max (months)	25

Median time on pazopanib treatment in VEG107769 (i.e. once patients had crossed-over) for patients who were treatment-naive at entry to the VEG105192 parent study was 11.2 months (range: 1 to 39 months) (Table 1.6). Thus, placebo subjects who crossed-over had a median duration of pazopanib treatment almost 4 months longer than subjects who received blinded randomised pazopanib treatment in VEG105192 (median 11.2 versus 7.4 months).

Longer duration of treatment might be expected if the subjects enrolled in VEG107769 had a better prognosis at the start of pazopanib dosing than subjects in VEG105192. However, subjects in VEG107769 had a worse overall worse ECOG performance status (the inclusion of subjects with PS 2 was permitted), where ECOG PS is a strong predictor for survival (Bukowski 2009). This difference in average duration of treatment may be partially explained by a proportion of subjects in the extension study being treated with pazopanib beyond disease progression, despite there being no definitive data to support a clinical benefit of continued treatment with anti-angiogenic agents beyond RECIST-defined disease progression and the VEG107769 protocol stipulating that treatment should be discontinued at progression.

Table 1.6: Summary of exposure to investigational product (VEG107769 Treatment-naive Safety population, 15 March 2010 cut-off)

	Treatment-naive at entry to parent study N=41*
Duration of treatment (dose interruptions included)	
Median (range), months	11.2 (1-39)
< 3months	9 (22%)
3-6	4 (10%)
6-12 months	8 (20%)
>12+ months	20 (49%)
Duration of treatment (dose interruptions excluded)	
Median (range), months	10.9 (1-39)
< 3months	10 (24%)
3-6	3 (7%)
6-12 months	8 (20%)
>12+ months	20 (49%)

* 40 treatment-naive subjects at entry to VEG105192 crossed over to receive pazopanib in VEG107769. An additional subject who was randomised to pazopanib in VEG105192 was enrolled in VEG107769 as an exemption at the investigator's request due to improvement in clinical signs and symptoms despite progression

1.4 Adjusting for impact of cross-over / receipt of other anti-cancer therapies

More patients in the placebo arm of VEG105192 received subsequent anti-cancer therapy following disease progression than in the pazopanib arm (64% versus 34%), largely as a consequence of the cross-over to pazopanib via the VEG107769 study (51% of patients randomised to placebo crossed over). Consequently, the utility of the intent-to-treat (ITT) OS analysis is limited by these imbalances between the treatment groups.

The likely effect of the cross-over is to have attenuated the true effect of pazopanib treatment by improving survival times for the group randomised to placebo relative to what would have been observed had placebo subjects not crossed over. In addition to the high percentage of post-study treatment in the placebo arm and the early timing of the initiation of post-study treatment relative to randomisation in VEG105192, the longer median exposure to pazopanib in the placebo 'cross-over' subjects compared with subjects in the pazopanib arm (11.2 vs. 7.4 months) is likely to have further impacted the treatment comparison.

An estimate of the treatment effect with pazopanib on OS in a counterfactual setting where there is no access to subsequent anti-cancer therapies following disease progression is therefore required. Survival for subjects receiving pazopanib would be identical to that of subjects randomised to the pazopanib arm in VEG105192 but who received no subsequent anti-cancer therapy; survival for subjects receiving placebo would be identical to a hypothetical cohort of subjects who received placebo in VEG105192, but who were not allowed to cross-over to receive pazopanib or to receive other anti-cancer therapies upon disease progression.

Several methods have been used to analyse OS in randomised controlled trials (RCTs) in which OS might be confounded by cross-over or receipt of further active treatment. These include censoring patients at the point of cross-over or receipt of post-study therapies or excluding such patients from the analyses. More recently, Inverse Probability of Censoring Weighted (IPCW) and Rank Preserving Structural Failure Time (RPSFT) methods have been employed to address this issue. Both methods are more sophisticated than simply censoring on cross-over and have been used to estimate the effects of everolimus on OS among metastatic RCC patients who had failed anti-VEGF TKI therapy (Wiederkehr 2009; Korhonen 2009; Korhonen 2010). The RPSFT method was used recently to analyse OS in a sunitinib trial in gastrointestinal stromal tumours (GIST) in which a high proportion of patients (>80%) crossed over from placebo to active treatment (NICE TA 179).

Since the optimal method to control for cross-over/switch in survival analysis remains an area of academic debate and all the available approaches have their strengths and limitations, a range of methodologies were utilised to comprehensively evaluate this effect on the final OS data in VEG105192 as listed below. Specifically, RPSFT and IPCW were employed due to the level of crossover in VEG105192. The RPSFT and IPCW analyses were conducted in consultation with leading experts in the conduct of these methods including Dr. James Robins, Department of Epidemiology and Department of Biostatistics, Harvard School of Public Health. The application of the methodologies was also reviewed by Dr. Lee-Jen Wei, Department of Biostatistics, Harvard School of Public Health. The results using these methods for the interim overall survival data were also reviewed by Ian White, an in dependent statistician from the MRC Biostatistics Unit, University of Cambridge. Mr. White was also involved at the early stages of methodology discussions for adjustment for cross-over analyses for the final OS.

(i) Censoring cross-over patients at time of cross-over or receipt of other anti-cancer therapies

This is an analysis where any subject who crossed over or received other anti-cancer therapies is censored at the date of cross-over/switch. For all other subjects, OS is measured from time of randomisation to death or last contact. This analysis is limited by the

fact that subjects could have died soon after cross-over or receipt of further active treatment. Also, since only those patients who progressed crossed over or switched, their health status is likely to be worse than subjects at a comparable level of follow-up who did not progress. Additionally, it does not account for the time that those patients who crossed over or received other treatments spent on subsequent therapy. It has previously been acknowledged that censoring subjects at cross-over/switch can be an unreliable method for controlling for cross-over (NICE TA 179).

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

The IPCW method aims to adjust for cross-over/switch by recreating the population that would have been evaluated if cross-over or switch to other therapies had not occurred. Subjects are analysed in a Cox model with censoring at the start of subsequent anti-cancer therapy, but unlike a standard Cox model, subjects are weighted equal to the inverse probability of not receiving an additional treatment. The weighting of the data attempts to balance out the selection bias of additional treatments and obtain a pure measure of the treatment effect between placebo and pazopanib in the absence of additional therapies.

Our application of the IPCW method to the interim OS data from VEG105192 as presented in our original submission considered only the 'cross-over' patients. Our IPCW analysis on the final OS data has been refined to adjust not only for patients in the placebo arm crossing over to pazopanib treatment, but also for patients in both arms switching to other anti-cancer therapies following discontinuation of study medication at disease progression. The analysis consisted of the following steps:

1. *Create Panel Data*: For all patients, follow-up time from randomisation until cross-over to pazopanib or switch to other anti-cancer therapies ("cross-over/switch") or end of follow-up (defined as death, withdrawal of consent, or end of study, whichever occurred first) was partitioned into intervals based on visits dates.[3] For each of these intervals, time-dependent variables that might be predictive of cross-over/switch and mortality were calculated. These variables included ECOG performance status, occurrence of grade 3/4/5 adverse events (AEs), a binary indicator of progression,[4] time since disease progression, and the number of anti-cancer treatments available (licensed and/or reimbursed) in a patient's country at each visit.

2. *Calculate Stabilised Weights*: Using the panel data created in Step 1, for each patient (*i)* and interval *(j)*, stabilised weights, $SW_i(j)$, were calculated. The numerator of the weights was the probability of remaining uncensored (i.e. not crossing over or switching) from the moment of eligibility to cross-over/switch defined in Step 1 to the end of interval *(j)* given only baseline confounders. The denominator of the weights was the probability of remaining uncensored (i.e. not crossing over or switching) to the end of interval *(j)* given baseline and time-dependent confounders. Estimates were obtained by fitting pooled logistic models with censoring (cross-over/switch) as the dependent variable separately for placebo and pazopanib patients, respectively.

3. *Estimate HR and 95% CIs:* A HR for OS was estimated using a weighted Cox proportional hazard regression model, where patient-intervals were weighted by the stabilised weights calculated in Step 2. Patients who crossed over or switched were censored (i.e. received a weight of zero during the intervals after cross-over/switch and, therefore, dropped from the model). Because the unadjusted 95% CIs for the

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

[4] Progression status was included in the model only for placebo subjects since the remaining 14 placebo patients all became eligible for cross-over after 12 November 2008, when the double-blind phase was stopped early for placebo subjects based on the efficacy of pazopanib demonstrated by the interim analysis.

HRs are biased due to the variability introduced by the stabilised weights, exact 95% CIs were obtained by a bootstrap procedure.

Each of these steps is described in greater detail in Appendix 1. It has previously been acknowledged that IPCW can be a valid option to correct for cross-over bias (NICE Pre-briefing meeting for everolimus, Dec 2009). However, it is subject to the assumption of no unmeasured confounders and randomisation is not preserved. In addition, the results of our IPCW analysis are limited by a lack of post disease progression data that might have impacted whether a patient received subsequent anti-cancer therapy and which might have influenced survival (see Section 1.5.2 for further discussion on this).

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

The RPSFT method estimates the difference in OS between treatment groups as if placebo patients had not crossed-over to pazopanib treatment (i.e. had remained on placebo for the duration of the trial). It proportionally 'shrinks' the estimated amount of additional survival conferred to subjects who crossed over.

The method is based on an accelerated failure time (AFT) model for a time-varying treatment which uses a structural assumption relating each patient's observed failure time and treatment history to the failure time that would have been observed if they had never been treated. A simple version of an RPSFT model specifies that U_i, the lifetime of the i^{th} individual, had that individual, possibly contrary to fact, never received treatment, can be described by the following relationship:

$$U_i = \int_0^{T_i} \exp\left\{\psi^* D_i(x)\right\} dx$$

where

ψ^* is an unknown parameter representing the causal effect of treatment on survival time
$D_i(t)$ is an indicator for whether patient i received treatment at time t
T_i is the observed failure time for patient i

Note that $\psi^* = 0$ implies no effect of treatment on survival whereas $\psi^* < 1$ implies that continuous treatment would increase life by a factor of $\exp(-\psi^*)$, and $\psi^* > 1$ implies that continuous treatment would decrease life by a factor of $\exp(-\psi^*)$.

Since the RPSFT method is based on an intention-to-treat population, it avoids the potential pitfalls and biases that may be introduced by methods that adjust for post-randomisation time-dependent covariates. The method maintains the original randomised group definitions and thus preserves the validity of between-group comparisons and therefore is said to produce "randomisation-based effect estimators" (Branson 2002). The methodological robustness of the RPSFT method was acknowledged by the Evidence Review Groups (ERGs) involved in the recent everolimus RCC and sunitinib GIST appraisals (NICE TA 179; Everolimus FAD, June 2010).

Examining at the survival curves and the number of patients crossing over from placebo to pazopanib, it was felt most appropriate to estimate the optimal weights for detecting a treatment effect i.e. to utilise a weighted RPSFT approach. Due to treatment cross-over in the placebo arm (after progression), the power of the usual (unweighted) log rank test or its adjusted version (based on fitting a Cox model that included pre-randomisation covariates) would be poor. Indeed, in the treatment-naïve population, patients in the placebo arm were

more likely to be taking study drug than those in the pazopanib group by 400 days (as the latter stopped taking pazopanib at progression). To explore the effect of this reversal in the fraction of each arm on the study drug, a weighted log rank test was calculated in the treatment-naïve population with the weights at each time (*t)* equal to the difference in the percentage of patients receiving pazopanib in the treatment arm vs. the placebo arm. Note that this test preserves the α-level in large samples, and appropriately results in negative weights after approximately 400 days. Using this weighted log-rank test, the unadjusted p-value was 0.005 (compared with a p-value of 0.881 for a similar unweighted log-rank test).[5,6] These results provide strong evidence that treatment with pazopanib has a beneficial effect on mortality. However, because this test was not naturally associated with an estimate of the HR for pazopanib vs. placebo under the counterfactual that patients in the placebo arm did not receive active treatment, it was appropriate to estimate the RPSFT model (which can be used to obtain such an estimate) using estimated optimal weights consistent with the RPSFT model in order to try to increase the power to detect an effect of active treatment.

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

1. *Estimate* ψ^*: An estimate of the effect of exposure to the active treatment on survival time, ψ^*, was obtained using a G-estimation procedure. This requires estimated p-values for the comparison of active treatment versus control under various assumptions regarding the value of ψ^*. In our RPSFT analysis using the interim OS data, these p-values were obtained using an unweighted log rank test statistic from a Cox proportional hazard regression analysis comparing pazopanib versus placebo. For the updated analyses using the final OS data, this was supplemented with an analysis wherein the p-values were calculated using a weighted log rank test statistic, with weights derived to obtain near maximal power under the null hypothesis ($\psi^* = 0$) against alternatives generated under the RPSFT model. For the weighted approach a weighted log rank test in the treatment-naïve population was calculated with the weights at each time, *t*, equal to the difference in the percent of patients receiving pazopanib in the treatment arm vs. the placebo arm.

2. *Estimate HR*: The HR for OS for randomisation to pazopanib vs. randomisation to placebo with no cross-over to pazopanib was estimated by fitting a Cox proportional hazards regression model to the pazopanib failure times as observed in the VEG105192 trial and re-censored adjusted failure times for placebo patients based on the estimate of $\exp(\psi^*)$. Further methodological details regarding these steps can be found in Appendix 1.

Due to time constraints, our updated RPSFT analysis only controlled for cross-over of placebo patients to pazopanib treatment but did not control for receipt of other post-study anti-cancer therapy in either the placebo or pazopanib groups. In addition, our results are limited by the high degree of re-censoring in the placebo group, resulting in the analysis being heavily weighted toward the early follow-up period which may not be representative of treatment effects over the entire uncensored follow-up period (see Section 1.5.2(ii) and Appendix 1 for further discussion).

[5] This p-value differs from that reported in the Background section as the latter was stratified based on ECOG performance status.
[6] In a similar analysis conducted for the cytokine-pre-treated group, the p-value based on the weighted log rank test was 0.009 (compared with a p-value of 0.490 for a similar unweighted log-rank test).

Both our IPCW and RPSFT analyses were conducted using SAS Statistical Analysis Software and double-coded by independent analysts at different institutions to ensure the validity of the results. Full technical details regarding the application of these methods to the final OS data from the treatment-naive sub-population in the VEG105192 trial can be found in Appendix 1 and are summarised below.

(iv) Analysis in subjects with no post-study therapy

As discussed earlier, a considerable proportion of patients in both treatment arms received subsequent anti-cancer therapy (most notably cross-over to pazopanib) following discontinuation of study medication at disease progression. Additional analyses were therefore performed in the sub-set of patients who did not receive any post-study cancer treatment.

It should be acknowledged that this approach is biased since patients were not randomised to receive or not to receive additional therapy, leading to imbalances in baseline prognostic factors between the two arms. Related issues include the handling of subjects who are still on study therapy, those who have died on study therapy or those who withdrew from the study shortly after stopping study therapy, since bias can be introduced by including or excluding these subjects. The data were therefore examined in 3 ways:

(i) All subjects with no post-study therapy (irrespective of progression status)
(ii) All subjects with no post-study therapy, but excluding subjects still on study therapy (i.e. regardless of progression status)
(iii) Only subjects who were eligible for post-study therapy but chose not to receive (excluding subjects who were still on pazopanib, died on study medication, or withdrew from the study).

It is worth highlighting that an analysis in subjects with no post-study cancer therapy was performed on the final OS data from the pivotal trial of sunitinib versus IFN (Motzer 2009) and provided by the manufacturer of sunitinib in their submission to NICE (NICE TA 169). Whilst the analysis was criticised by the ERG/Decision Support Unit (DSU) in representing only about half the trial population and the fact that the characteristics of the patients included may not have been representative of the original trial population, it nevertheless formed the basis for the cost-effectiveness estimates on which sunitinib was recommended for use by NICE (NICE TA 169). It should be noted, however, that cross-over from control to active treatment was handled differently in the sunitinib study (patients in the IFN arm were eligible for cross-over to sunitinib following the interim analysis rather than at disease progression as in VEG105192). In addition, the clinical landscape in terms of the availability of alternative cancer therapies for advanced RCC was different in the participating countries of that study at the time.

Adjusting for baseline patient/disease characteristics

Certain baseline patient characteristics and clinical features can influence survival outcomes in RCC. The Memorial Sloan Kettering Cancer Center (MSKCC) scoring system is a widely accepted and validated predictive tool for survival in RCC (Motzer 1999). This categorises patients into 3 risk groups (favourable, intermediate and poor) based on five factors, including performance status and presence/absence of prior nephrectomy. Disease stage at diagnosis and time from initial diagnosis are also strong independent predictors of outcome in RCC (Furniss 2008; Elson 1988). As well as the presence of advanced/metastatic disease, the number and site of metastases have also been shown to have some prognostic significance (Furniss 2008; Elson 1988). In particular, the presence of liver metastases has been identified as being a predictor of rapid disease progression (Negrier 2005).

In order to control for such factors and isolate the pure treatment effect on OS, some of the cross-over analyses described above were conducted as multivariate analyses adjusting for

the following factors, selected on the basis of clinical opinion and the availability of data in VEG105192:

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

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

1.5 Final overall survival results

1.5.1 Unadjusted analysis

a) Kaplan-Meier analysis / Pike estimator

Final OS results for the pre-specified intent-to-treat analysis based on a Pike estimator for the treatment-naive sub-population in VEG105192 are shown in Table 1.7. At the time of the cut-off (15 March 2010), 64% of subjects in the pazopanib arm and 63% of those in the placebo arm had died. Subjects without death reports were censored at date of last contact.

The median OS has increased in both arms compared with the results from the interim OS analysis. Compared with the interim data, OS has increased from 19.8 to 22.9 months in the pazopanib arm and from 20.0 to 23.5 months in the placebo arm. The final OS result is not different in terms of statistical significance between the two treatment arms (HR 1.01, stratified log rank p-value 0.525). However, the study was not powered to detect differences in OS between treatments in the sub-populations. Secondly as previously discussed, the ITT analysis does not represent a robust comparison of OS following solely placebo or pazopanib treatment. Subjects in both arms were treated with additional anti-cancer therapies following discontinuation of study medication which is likely to have confounded the OS results. Specifically, 51% of treatment-naive subjects in the placebo arm crossed over to receive pazopanib, some starting as early as 2 months after initial randomisation to placebo.

Table 1.7: OS in VEG105192 – unadjusted for cross-over (Treatment-naive ITT population, 15 March 2010 cut-off)

	Treatment-naive population	
	Pazopanib N=155	**Placebo N=78**
Subjects died, n (%)	99 (64)	49 (63)
Censored, follow-up ended	56 (36)	29 (37)
Kaplan-Meier estimates for OS, median (months)	22.9	23.5
95% CI	17.6-25.4	12.0-34.3
Hazard ratio* (95% CI)	1.01 (0.72-1.42)	
Stratified log-rank p-value†	p=0.525	

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

The Kaplan Meier curves for final OS in the treatment-naive population are shown in Figure 1.1. There is a distinct separation of the curves early on representing the true treatment

effect of pazopanib versus placebo. The curves subsequently cross at 20 months reflecting the effect of cross-over of placebo patients to pazopanib.

Figure 1.1: Kaplan Meier curve of overall survival in VEG105192 (Treatment-naive population, 15 March 2010 cut-off)

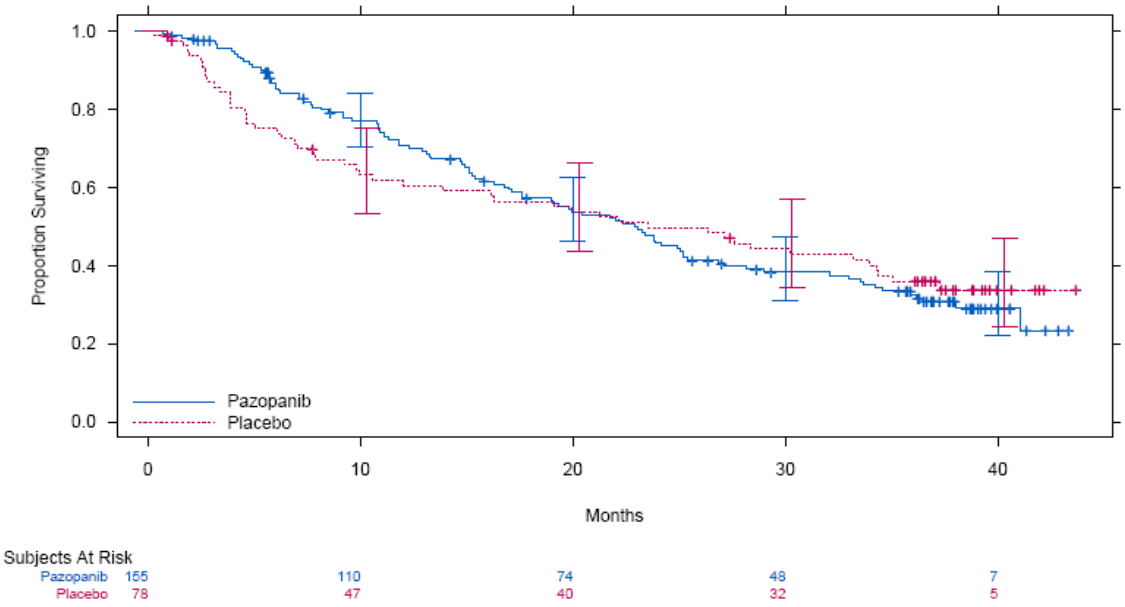


Table 1.8 summarises the median OS from start of pazopanib treatment in VEG107769 and the median OS from randomisation to the pazopanib arm in VEG105192. The results indicate that placebo subjects who crossed over to pazopanib received a similar benefit from treatment as those subjects who were randomised to pazopanib in the parent study.

Table 1.8: Median overall survival from start of pazopanib treatment (Treatment-naive subjects, 15 March 2010 cut-off)

	VEG105192 Treatment-naive N=155	VEG107769 Treatment-naive at entry to parent study N=41*
Median (range), months	22.9 (17.6-25.4)	22.7 (13.9-34.0)

* 40 treatment-naive subjects at entry to VEG105192 crossed over to receive pazopanib in VEG107769. An additional subject who was randomised to pazopanib in VEG105192 was enrolled in VEG107769 as an exemption at the investigator's request due to improvement in clinical signs and symptoms despite progression

b) Cox proportional hazards model

In a univariate analysis of OS in the ITT treatment-naive population using a Cox proportional hazards model, the HR for pazopanib versus placebo was 1.027 (95% CI: 0.728-1.447; p=0.8812). A Cox regression analysis controlling for the baseline patient characteristics discussed earlier (age, gender, MSKCC risk score, years since diagnosis of RCC, stage of disease at diagnosis, presence of liver metastases, number of metastatic sites) resulted in a HR for the treatment effect of 0.859 indicating a 14% reduction in risk of death for patients treated with pazopanib compared with placebo (Table 1.9). A similar result for pazopanib versus placebo was achieved without imputation for missing data (HR 0.846 [95% CI: 0.583-1.228], p=0.3793).

Table 1.9: OS in VEG105192 – Unadjusted for cross-over but adjusted for baseline characteristics (Treatment-naive ITT population, 15 March 2010 cut-off)

Variable	Treatment-naive population N=233	
	HR (95% CI)	p-value
Univariate analysis		

Pazopanib	1.027 (0.728-1.447)	p=0.8812
Mutivariate analysis		
Pazopanib	0.859 (0.602-1.223)	p=0.3985
Age (Continuous variable)	0.991 (0.975-1.007)	p=0.2663
Gender (Female / Male)	1.204 (0.832-1.743)	p=0.3238
MSKCC risk score (Intermediate-poor / Favourable)	1.744 (1.199-2.538)	p=0.0036
Years since diagnosis (<1 year / ≥1 year)	1.688 (1.144-2.490)	p=0.0083
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.200 (0.775-1.859)	p=0.4147
Presence of liver metastases (Yes / No)	1.237 (0.814-1.880)	p=0.3186
No. of metastatic sites (Continuous)	1.318 (1.151-1.509)	p<0.0001

For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested.
Patients with missing values for the covariates were assigned the mean value for the trial population. [7]

1.5.2 Analyses of OS conducted to adjust for impact of cross-over or receipt of further anti-cancer therapies

(i) Censoring patients at time of cross-over or receipt of other therapies

Censoring those patients who crossed over or received other anti-cancer therapies at the point of cross-over/switch resulted in a HR for pazopanib versus placebo of 0.640 (p=0.0769) estimated using a Cox model and adjusting for baseline characteristics, indicating a 36% reduction in risk of death for patients treated with pazopanib compared with placebo (Table 1.10). The results without imputation for missing data were similar (HR 0.626 [95% CI: 0.376-1.043], p=0.0723).

Table 1.10: OS in VEG105192 – Subjects censored at cross-over or receipt of other therapies (Treatment-naive population, 15 March 2010 cut-off)

Variable	**Treatment-naive population N=233**	
	HR (95% CI)	**p-value**
Univariate analysis		
Pazopanib	0.797 (0.493-1.289)	p=0.3553
Mutivariate analysis		
Pazopanib	0.640 (0.390-1.049)	p=0.0769
Age (Continuous variable)	0.996 (0.976-1.018)	p=0.7391
Gender (Female / Male)	1.565 (0.996-2.457)	p=0.0520
MSKCC risk score (Intermediate-poor / Favourable)	2.140 (1.309-3.498)	p=0.0024
Years since diagnosis (<1 year / ≥1 year)	1.930 (1.160-3.211)	p=0.0114
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.218 (0.650-2.282)	p=0.5381
Presence of liver metastases (Yes / No)	1.756 (1.050-2.937)	p=0.0318
No. of metastatic sites (Continuous)	1.247 (1.054-1.476)	p=0.0101

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

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

Results of the IPCW Cox proportional hazards model to adjust for post-disease progression treatment in both arms are shown in Table 1.11. The HR of 0.642 indicates a 36% reduction in risk of mortality associated with pazopanib compared to placebo (bootstrap p=0.1600) when adjusting for cross-over or receipt of other anti-cancer therapy as well as baseline covariates. The results of all the intermediate stages of this analysis can be found in Appendix 1. A similar result was achieved without imputation of missing data (HR 0.637 [95% CI: 0.389-1.045]).

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

Table 1.11: Summary of IPCW adjusted Cox proportional hazards model for OS in VEG105192: Informative censoring defined as cross-over from placebo to pazopanib or receipt of other cancer therapy (Treatment-naive population, 15 March 2010 cut-off)

Variable	Treatment-naive population N=233				
	HR	95% CI	p-value	Bootstrap	
				95% CI	p-value
Pazopanib	0.642	0.400-1.028	p=0.0649	0.266-1.248	p=0.1600
Age (Continuous variable)	0.999	0.979-1.020	p=0.9575	0.973-1.023	p=0.8980
Gender (Female / Male)	1.577	1.022-2.432	p=0.0394	0.949-2.659	p=0.0860
MSKCC risk score (Intermediate-poor / Favourable)	1.845	1.166-2.921	p=0.0090	1.221-3.540	p=0.0020
Years since diagnosis (<1 year / ≥1 year)	1.815	1.125-2.929	p=0.0146	1.156-3.448	p=0.0140
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.266	0.692-2.314	p=0.4439	0.641-2.590	p=0.4060
Presence of liver metastases (Yes / No)	1.696	1.041-2.762	p=0.0340	0.930-2.930	p=0.0900
No. of metastatic sites (Continuous)	1.281	1.091-1.503	p=0.0025	1.084-1.663	p=0.0120

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

Results of the IPCW Cox proportional hazards model to adjust for the effect of cross-over from placebo to pazopanib only (as applied to the interim OS data) can be found in Appendix 1. These indicate that treatment with pazopanib was associated with a 22% reduction in the risk of mortality (HR=0.781; bootstrap p=0.370) compared with placebo when adjusting for cross-over of 51% of placebo patients.

As discussed earlier, the IPCW method does not maintain the α-level associated with randomisation. Furthermore, IPCW estimates are unbiased only to the extent that the model includes all relevant confounders and is correctly specified. In the VEG105192 trial, there was relatively little information on time-varying clinical and other factors that might be predictive of cross-over or receipt of other anti-cancer therapies on the one hand and OS on the other. In particular, ECOG performance status, history of grade 3/4/5 AEs, ongoing grade 3/4/5 AE up to time of progression, time since progression, and the availability and reimbursement status of other anti-cancer therapies were the only characteristics available as time-dependent covariates. Furthermore, ECOG status was largely unavailable after disease progression. Data on MSKCC risk score, presence of liver metastasis, and number of metastatic disease sites were not available after baseline and therefore could not be used in the estimation of the denominator for the stabilised weights. The extent to which this may have biased our findings is unknown. However, because the results of the IPCW analysis were very similar to that of the analysis in which patients who crossed over were censored, suggesting that the impact of IPCW weights was small, and that to the extent that patients who crossed over were dissimilar from those who did not, this was not captured by the IPCW weights.

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

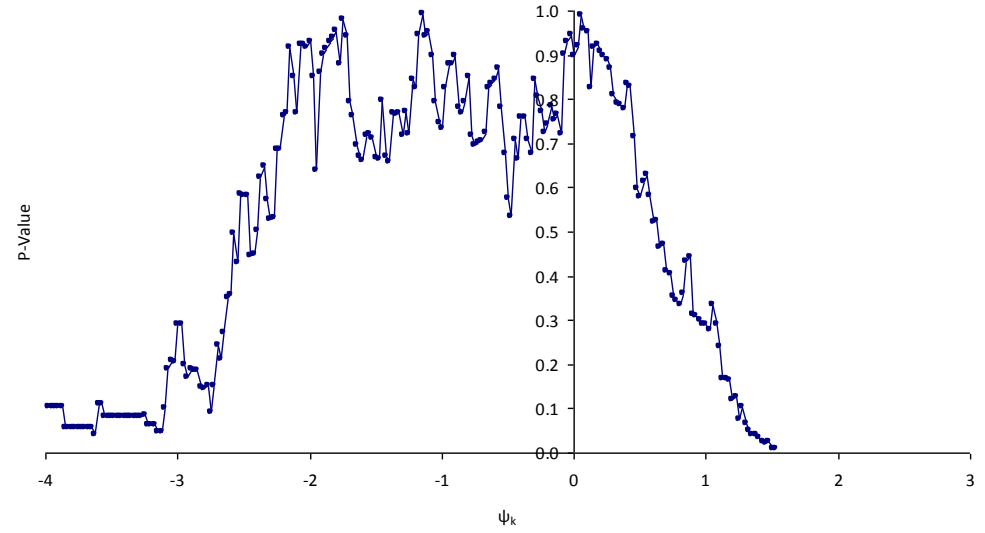
Results of the RPSFT analyses are shown in Figure 1.2 A-C and Tables 1.12 and 1.13 for the unweighted, unadjusted analysis (A), unweighted, adjusted analysis (B) and weighted, unadjusted analysis (C), respectively. It should be noted that analyses A and B were applied to the interim VEG105192 OS data as presented in our original submission; the weighted analysis, C, represents an additional analysis applied to the final OS data due to the fact that the power of the unweighted approach would be compromised as a result of the high degree of cross-over of placebo patients to receive pazopanib.

Figures 1.2A-C report the plots of p-values by ψ_k for each analysis. There is a clear peak in the p-value at ψ_k = -2.225 for the unweighted, adjusted analysis (B) and at ψ_k = -2.000 for the weighted, unadjusted analysis (C). In contrast, in the unweighted, unadjusted analysis (A), there are several peaks in the p-values at ψ_k = -1.75, ψ_k = -1.150 and ψ_k =.050. Thus, there is insufficient information to obtain a unique estimate of ψ^* with this analysis and no

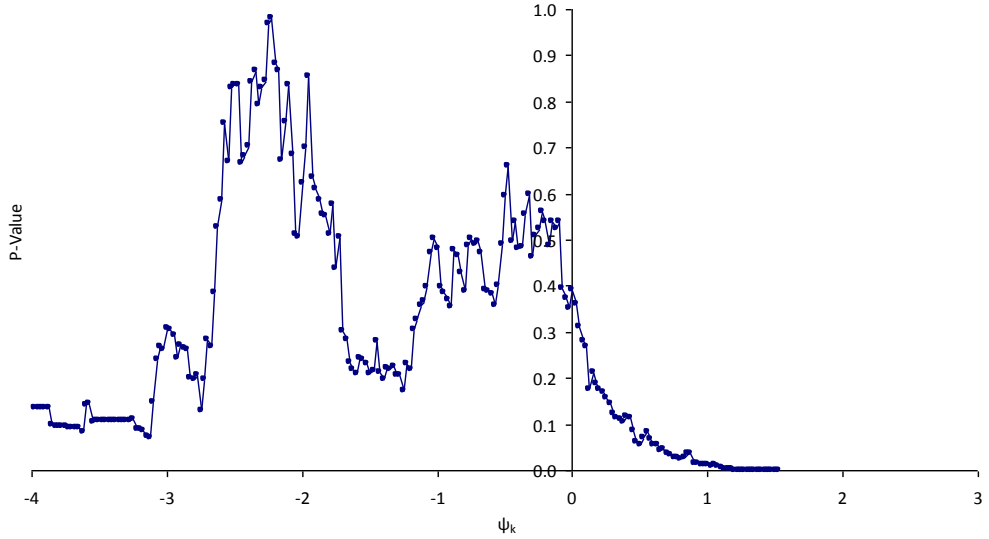
further calculations were conducted accordingly. Interestingly, this problem was largely attenuated in the unweighted, adjusted analysis (B), and even more so in the weighted analysis (C) suggesting the true value of ψ^* in this analysis.

Figure 1.2. Plots of ψ^* vs. p-value for unweighted, unadjusted analysis (A); unweighted, adjusted analysis (B); and weighted (unadjusted) analysis (C)

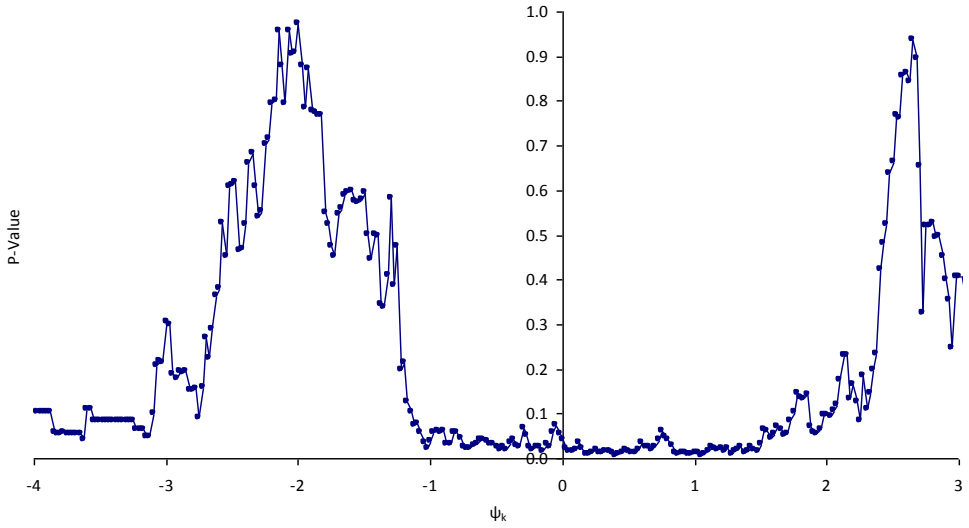
A. Unweighted and Unadjusted for Baseline Covariates



B. Unweighted and Adjusted for Baseline Covariates



C. Weighted and Not Adjusted for Baseline Covariates



Estimates of ψ^* along with corresponding confidence intervals and p-values are reported in Table 1.12 for the three analyses.

Table 1.12: Estimated causal rate ratio (ψ*) for OS for pazopanib in VEG105192 (Treatment-naïve population, 15 March 2010 cut-off)

Parameter	Unweighted		C. Weighted
	A. Not Adjusted for Patient Characteristics	B. Adjusted for Patient Characteristics	
$\hat{\psi}^*$	na	-2.225	-2.000
Inversion of test statistic			
95% upper confidence limit	na	0.575	-0.050
p-value	na	0.3912	0.0434
Bootstrap			
SE	na	1.330	1.795
95% CI	na	<-3.975 to 0.300	-3.00 to 2.775
p-value	na	0.118	0.538
$\exp(\hat{\psi}^*)$	na	0.108	0.135
95% upper confidence limit from inversion of test statistic	na	1.777	0.607
Bootstrap 95%CI	na	<0.019 to 1.350	0.050 to 16.039

For the unweighted, adjusted analysis (B), the upper 95% CI for ψ^* based on inversion of the test statistic (define as the largest value of ψ^* = for which the corresponding p-value is greater than 0.05, disregarding p-values greater than .05 associated with distinct peaks far from the point estimate) is 0.575 (includes 0.0 and thus not significant). The treatment effect of pazopanib based on the unweighted, adjusted analysis also is not significant by inverting the test statistic based on the p-values, as the p-value at ψ^*=0 is 0.379 and thus not less than 0.05. The 95%CI for ψ^* based on bootstrapping was <-3.975 to 0.300. The bootstrap p-value was 0.118.

For the weighted, unadjusted analysis (C), the upper 95% CI for ψ^* based on inversion of the test statistic is -0.050 (does not include 0.0 and thus statistically significant). The

treatment effect of pazopanib based on the unweighted, adjusted analysis also is significant by inverting the test statistic based on the p-values, as the p-value at ψ^*=0 is 0.0434 and thus less than 0.05. However, based on the bootstrap 95%CI for ψ^* (-3.000 to 2.775) the treatment effect was not significant. The bootstrap p-value was 0.538.

The Cox model estimates and bootstrap 95% CIs for the HR for OS for pazopanib vs. placebo for the unweighted, adjusted analysis and the weighted, unadjusted analysis are reported in Table 1.13. In analysis B, adjustments were made for the same baseline characteristics as in the IPCW analysis as well as the patient theoretical maximum follow-up time (C_i), as defined by time from patient's randomisation date to the cut-off date (15 March 2010).

Table 1.13: Cox proportional hazards regression analysis for OS in VEG105192 using RPSFT adjusted and re-censored failure times for placebo patients (Treatment-naive population, 15 March 2010 cut-off)

Variable	Treatment-naive population N=233
	HR (95% Bootstrap CI)
Unweighted	
A. Not adjusted for patient characteristics	
Pazopanib	NA (NA-NA)
B. Adjusted for patient characteristics*	
Pazopanib	0.310 (0.073-1.715)
Ci	1.032 (0.919-1.153)
Age (Continuous variable)	0.990 (0.966-1.010)
Gender (Female / Male)	1.311 (0.762-2.165)
MSKCC risk score (Intermediate-poor / Favourable)	1.449 (0.931-2.446)
Years since diagnosis (<1 year / ≥1 year)	1.922 (1.102-3.180)
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.130 (0.643-2.135)
Presence of liver metastases (Yes / No)	1.078 (0.674-1.951)
No. of metastatic sites (Continuous)	1.479 (1.218-1.786)
C. Weighted	0.501 (0.136-2.348)

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

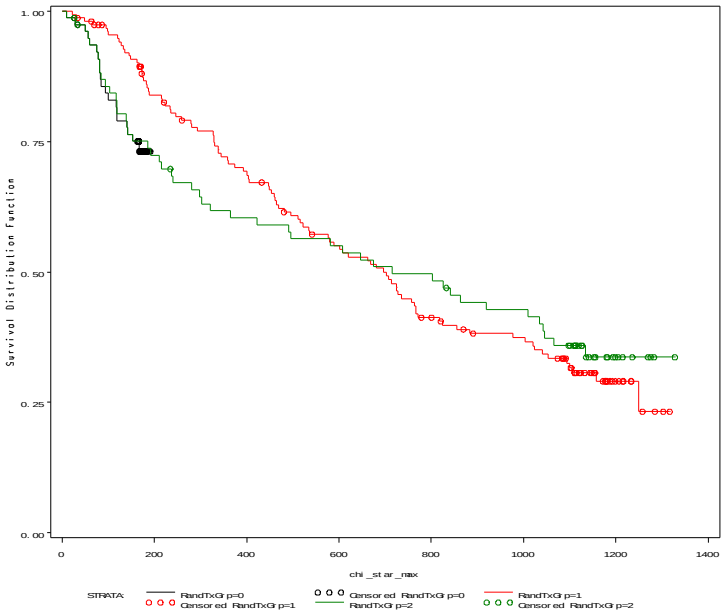
The unweighted, adjusted analysis indicates that a treatment strategy of pazopanib and no other anti-cancer therapy after progression reduces the risk of death by 69% (HR 0.310) compared with a treatment strategy of placebo and no other anti-cancer therapy after progression. However, this effect was not statistically significant (95% CI: 0.073 to 1.715 by bootstrap and an upper 95% CI limit of 1.045 based on the upper 95% CI limit for ψ^* based on inversion of the test statistic). The bootstrap p-value for the HR was 0.194.

Results for the RPSFT analysis using the nearly optimal weights suggest pazopanib reduces the risk of death by 50% (HR=0.501) compared with placebo. The upper 95% confidence limit on the HR based on the inversion of the test statistic is less than 1.0 (0.991) and therefore statistically significant. However, the bootstrap 95% CI on the HR is 0.136 to 2.348 (spanning 1.0) and thus not statistically significant. The bootstrap p-value for the HR was 0.548. See Appendix 1 for further discussion regarding the different approaches to calculating these confidence intervals.

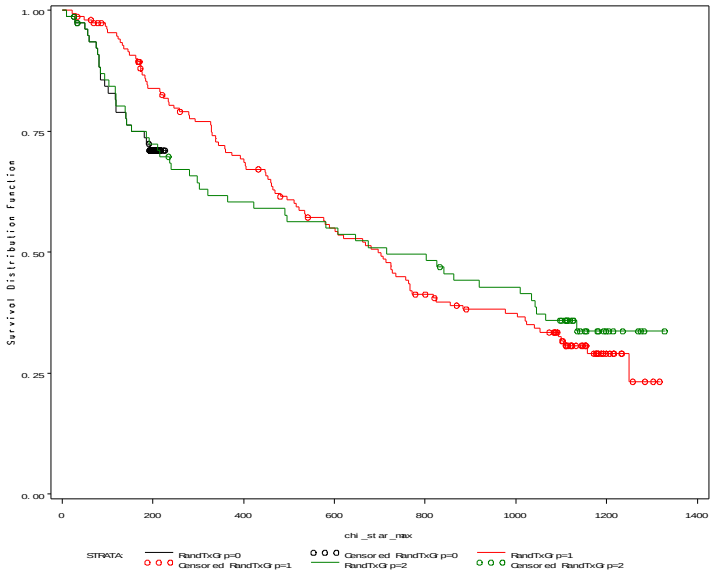
Kaplan-Meier plots of observed failure times for pazopanib patients and RPSFT adjusted re-censored failure times for placebo patients are reported in Figure 1.3 for the unweighted, adjusted analysis (B) and the weighted, unadjusted analysis (C), respectively. The Kaplan-Meier curves are virtually identical up to approximately 200 days, suggesting that the principal driver of the RPSFT adjustment is the re-censoring of placebo patients.

Figure 1.3. Kaplan-Meier plot of observed survival times (months) for pazopanib patients and observed and RPSFT adjusted and re-censored survival times for placebo patients (VEG105192 Treatment-naïve patients, 15 March 2010 cut-off)

B. Unweighted and Adjusted for Baseline Covariates



C. Weighted and Not Adjusted for Baseline Covariates



As mentioned earlier, other than cross-over of placebo patients to pazopanib, our RPSFT analyses did not control for receipt of other post-study anti-cancer therapies in the placebo or pazopanib groups which may have biased our results in favour of pazopanib. This is not likely, however, as results from IPCW analyses were more favourable when receipt of other anti-cancer therapies were considered informative censoring events. Also, for the weighted RPSFT analysis using the estimated optimal weights, only an unadjusted analysis was conducted due to the lack of a robust algorithm for calculating an adjusted p-value based on the weighted log-rank statistic.

The results of the RPSFT are limited by the high degree of re-censoring in the placebo group, which was required to ensure an unbiased estimate of ψ^*. This has two effects. Firstly, the analysis is heavily weighted toward the early follow-up period which may not be representative of the treatment effect over the entire un-recensored follow-up period Secondly, it prevents a lower confidence limit for ψ^* being obtained when intervals are formed by test inversion, a well known consequence of re-censoring, which also results in our inability to set lower limits for the HR. Additional research is being considered in an attempt to address some the limitations of this methodology.

(iv) Analysis in subjects with no post-study therapy

Results of the sub-set analyses in patients who did not receive post-study cancer treatment are shown in Tables 1.14 to 1.16. In all three analyses, pazopanib appeared to be associated with a statistically significant reduction in risk of death (62-70%) compared with placebo (p<0.001). However, it should be acknowledged that the patient numbers in the placebo arm are small due to the high level of post-study therapy in this group. Also, as mentioned earlier, the treatment groups are no longer balanced with respect to baseline prognostic factors. In all three analyses, there are more subjects in the pazopanib arm than the placebo arm with an ECOG PS of 0, a low number of metastatic sites and MSKCC favourable risk scores – all of which are important prognostic factors for survival (Elson 1988; Furniss 2008; Motzer 1999; Negrier 2005).

Table 1.14: OS in VEG105192 – Subjects with no post-study therapy regardless (Treatment-naive population, 15 March 2010 cut-off)

	Treatment-naive population	
	Pazopanib N=117	**Placebo N=29**
Subjects died, n (%)	71 (69)	23 (79)
Censored, follow-up ended	46 (39)	6 (21)
Kaplan-Meier estimates for OS, median (months)	21.7	3.9
95% CI	(15.4-26.9)	2.7-6.3
Hazard ratio* (95% CI)	0.300 (0.150-0.620)	
Stratified log-rank p-value	p<0.001	

* Hazard ratios estimated with a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the log-rank test are not adjusted for stratification factors.

Table 1.15: OS in VEG105192 – Subjects with no post-study therapy, excluding subjects still on study therapy (Treatment-naive population, 15 March 2010 cut-off)

	Treatment-naive population	
	Pazopanib N=103	**Placebo N=29**
Subjects died, n (%)	71 (69)	23 (79)
Censored, follow-up ended	32 (31)	6 (21)
Kaplan-Meier estimates for OS, median (months)	17.0	3.9
95% CI	(12.3-22.9)	2.7-6.3
Hazard ratio* (95% CI)	0.380 (0.200-0.720)	
Stratified log-rank p-value	p<0.001	

* Hazard ratios estimated with a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the log-rank test are not adjusted for stratification factors.

Table 1.16: OS in VEG105192 – Subjects eligible for post-study therapy but chose not to receive (excluding subjects still on pazopanib, died on study medication or withdrew from study (Treatment-naive population, 15 March 2010 cut-off)

	Treatment-naive population	
	Pazopanib N=117	**Placebo N=19**
Subjects died, n (%)	56 (72)	16 (84)
Censored, follow-up ended	22 (28)	3 (16)
Kaplan-Meier estimates for OS, median (months)	20.4	5.0
95% CI	(15.8-24.9)	3.8-7.1
Hazard ratio* (95% CI)	0.380 (0.170-0.820)	
Stratified log-rank p-value	P<0.001	

* Hazard ratios estimated with a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the log-rank test are not adjusted for stratification factors.

1.5.3 Summary of final OS analyses

A summary of the HR estimates for OS for pazopanib versus placebo in treatment-naive patients in VEG105192 is provided in Table 1.17.

As discussed earlier, the ITT analysis does not represent a meaningful comparison of pazopanib treatment effect on OS, due to the cross-over/switch to subsequent anti-cancer therapies in both arms post-discontinuation of study medication upon disease progression. This is evident in the fact that placebo subjects who crossed over to pazopanib received a similar benefit from treatment as those subjects who were randomised to pazopanib at the start of VEG105192 (median OS 22.7 vs. 22.9 months, Table 1.8). There is no universally accepted statistical methodology to adjust for the confounding effects of cross-over/switch in survival analysis in RCTs and this is an area of continued academic debate. Several methods were therefore applied to the final OS data from VEG105192 in order to provide a comprehensive and balanced approach.

The results of these analyses consistently demonstrate that the cross-over/receipt of further therapies does attenuate the OS benefit attributable to pazopanib in the ITT analysis as evidenced by the downward shift in HRs (i.e. they are numerically lower than the unadjusted HR). In all of the analyses undertaken, pazopanib was associated with a clinically relevant reduction in risk of death compared with placebo (HRs for OS for pazopanib vs. placebo ranging from 0.300 to 0.797, depending on methodology employed and whether or not adjusted for baseline patient characteristics, Table 1.17).

The HR estimate of 0.501 for OS for pazopanib versus placebo obtained using the weighted RPSFT analysis has been used for the base case in the indirect comparison and in the economic evaluation. As discussed earlier, the RPSFT method is considered to be a robust approach to control for cross-over/post study therapy because randomisation is preserved and it does not make the assumption of no unmeasured confounders (Everolimus FAD, June 2010).

The HR obtained with an unweighted, unadjusted RPSFT analysis was used for the base case in our original submission based on the interim OS data. However, this particular analysis was not feasible with the final OS data as it did not yield a unique estimate of the ψ^* parameter. In contrast, in the weighted, unadjusted analysis, there is a clear peak for ψ^* with a significant p-value (p=0.0434) at ψ_k equal to 0 (Figure 1.2C). While the 95% CI of the HR 0.501 by bootstrap is not significant (0.136 to 2.348), the upper 95% confidence limit on the HR based on the inversion of the test statistic is less than 1.0 (0.991) and therefore statistically significant.

We believe that the weighted RPSFT estimate of 0.501, as chosen for our base case, is a reasonable representation of the likely benefit of pazopanib on survival. It lies within the range of estimates generated from our comprehensive analyses to adjust for cross-over/post-study therapy. It should be noted that the HR of 0.380 from an analysis in patients with no post-study therapy (excluding patients still on study) was not adopted for the base case, despite the fact that this is very favourable for pazopanib, and even though sunitinib was recommended for use by NICE (TA 169) on the basis of survival estimates derived from a similar analysis in patients with no post-study therapy. It should be acknowledged, however, that there is a level of uncertainty associated with the weighted RPSFT estimate, reflected in part in its wide confidence interval (by bootstrap), and because of the lack of validation in small samples.

Table 1.17: Summary of final OS results for treatment-naive population in VEG105192 (15 March 2010 cut-off)

Population / Method of estimation	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)	0.797	0.493-1.289	p=0.3553
- Unadjusted for baseline characteristics	0.640	0.390-1.049	p=0.0769
- Adjusted for baseline characteristics			
IPCW (informative censoring defined as cross-over to pazopanib or receipt of other anti-cancer therapy)			
- Adjusted for baseline characteristics	0.642	0.266-1.248	0.160*
RPSFT Unweighted			
- Unadjusted for baseline characteristics	NA	NA	NA
- 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 choose not to	0.380	0.170-0.820	p<0.001
Method used for base case analysis			

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

1.6 Updated indirect comparison using final OS results

Full details of the methodology and data sources employed in the indirect comparison are available in GSK's original submission to NICE (section 5.7).

1.6.1 Base case results

Updated results for the base case indirect analysis of OS are presented in Table 1.18. In this analysis, the HR for IFN versus placebo/BSC was estimated by pooling data from five IFN trials (MRC RE-01 [Hancock 2000]; Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999). The HR for sunitinib versus IFN is taken from an analysis conducted in patients who did not receive any post-study cancer therapy (Motzer 2009). The HR for pazopanib versus. placebo/BSC in VEG105192 is from the weighted, unadjusted RPSFT method to adjust for cross-over with imputation for missing data (i.e. patients with missing values for the covariates were assigned the mean for the trial population).

Table 1.18: Indirect comparison of OS (base case results)

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

† HR adjusted for cross-over using weighted unadjusted RPSFT method with imputation for missing data
‡ Includes all 5 IFN trials: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999
$ Patients with no post-study cancer therapy (Motzer 2009)

The results indicate that pazopanib is associated with a decreased risk of death (37% reduction) compared with IFN. Pazopanib appears to have comparable efficacy in terms of

OS to sunitinib. It should be noted that the 95% CIs around the HRs are wide indicating a level of uncertainty with these estimates. This is largely driven by the uncertainty in the RPSFT-derived OS HR for VEG105192.

1.6.2 Results of Sensitivity Analyses

Results of the sensitivity analyses conducted using the final OS data from VEG105192 are shown below.

1. *Using HR for OS in VEG105192 adjusted using weighted RPSFT method but varying inclusion of IFN trials:* Like the base case analysis, sensitivity analyses 1A and 1B use the weighted RPSFT-adjusted HR for OS in VEG105192. Rather than using pooled data from the five IFN trials for the OS HR for IFN vs. placebo/BSC, sensitivity analysis 1A uses only the MRC RE-01 trial and sensitivity analysis 1B excludes the IFN trials using vinblastine (VBL) such that only the three trials of IFN versus medroxyprogesterone acetate (MPA) are included.

Table 1.19: Indirect comparison: Sensitivity analysis 1A (Weighted RPSFT-adjusted HR for OS in VEG105192 / MRC RE-01 trial only)

Sensitivity analysis 1A	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.501†	0.140-2.350
IFN vs. placebo/BSC‡	0.75	0.66-0.94
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.668	0.183-2.437
Pazopanib vs. sunitinib	1.032	0.379-2.801

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

Table 1.20: Indirect comparison: Sensitivity analysis 1B (Weighted RPSFT-adjusted HR for OS in VEG105192 / IFN vs. MPA trials only)

Sensitivity analysis 1B	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.501†	0.140-2.350
IFN vs. placebo/BSC‡	0.863	0.706-1.056
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.580	0.160-2.110
Pazopanib vs. sunitinib	0.897	0.330-2.425

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

2. *Using HR for OS for VEG105192 adjusted for cross-over using IPCW method:* These sensitivity analyses were conducted using the IPCW-adjusted HR for OS in VEG105192 (with cross-over to pazopanib or receipt of other anti-cancer therapy considered informative censoring), and using the pooled IFN trials (2A), using the MRC RE-01 trial only (2B), and excluding the VBL studies (2C), respectively.

Table 1.21: Indirect comparison: Sensitivity analysis 2A (IPCW-adjusted HR for OS for VEG105192 / Pooled IFN trials)

Sensitivity analysis 2A	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.642†	0.266-1.248
IFN vs. placebo/BSC‡	0.799	0.674-0.948
Sunitinib vs. IFN	0.647$	0.483-0.870

Results of indirect comparison		
Pazopanib vs. IFN	0.803	0.327-1.971
Pazopanib vs. sunitinib	1.242	0.678-2.266

† HR adjusted for cross-over using IPCW multivariate analysis with imputation for missing data
‡ Includes all 5 IFN trials: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999
$ Patients with no post-study cancer therapy (Motzer 2009)

Table 1.22: Indirect comparison: Sensitivity analysis 2B (IPCW-adjusted HR for OS for VEG105192 / MRC RE-01 trial only)

Sensitivity analysis 2B	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.642†	0.266-1.248
IFN vs. placebo/BSC‡	0.75	0.66-0.94
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.856	0.345-2.124
Pazopanib vs. sunitinib	1.323	0.714-2.442

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

Table 1.23: Indirect comparison: Sensitivity analysis 2C (IPCW-adjusted HR for OS for VEG105192 / IFN vs. MPA trials only)

Sensitivity analysis 2C	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.642†	0.266-1.248
IFN vs. placebo/BSC‡	0.863	0.706-1.056
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.744	0.301-1.836
Pazopanib vs. sunitinib	1.149	0.624-2.110

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

3. *Using HR for OS for VEG105192 in subjects with no post-study therapy:* Since the OS HR for sunitinib versus IFN utilised in the indirect comparison is taken from an analysis in patients with no post-study therapy, it is reasonable to conduct additional sensitivity analyses in which the OS HR for pazopanib versus placebo in VEG105192 is adjusted in a similar way. Again, this sensitivity analysis was conducted using the pooled IFN trials (3A), using the MRC RE-01 trial only (3B), and excluding the VBL studies (3C).

Table 1.24: Indirect comparison: Sensitivity analysis 3A (Subjects with no post-study therapy / Pooled IFN trials)

Sensitivity analysis 3A	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.380†	0.200-0.720
IFN vs. placebo/BSC‡	0.799	0.674-0.948
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.476	0.245-0.924
Pazopanib vs. sunitinib	0.735	0.507-1.062

† HR from analysis in patients with no post-study therapy excluding subjects still on study therapy
‡ Includes all 5 IFN trials: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999
$ Patients with no post-study cancer therapy (Motzer 2009)

Table 1.25: Indirect comparison: Sensitivity analysis 3B (Subjects with no post-study therapy / MRC RE-01 trial only)

Sensitivity analysis 3B	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.380†	0.200-0.720
IFN vs. placebo/BSC‡	0.75	0.66-0.94
Sunitinib vs. IFN	0.647$	0.483-0.870

Results of indirect comparison		
Pazopanib vs. IFN	0.507	0.257-1.000
Pazopanib vs. sunitinib	0.783	0.532-1.149

† HR from analysis in patients with no post-study therapy excluding subjects still on study therapy
‡ Includes MRC RE-01 trial as the only IFN vs. placebo/BSC trial (Hancock 2000 data)
$ Patients with no post-study cancer therapy (Motzer 2009)

Table 1.26: Indirect comparison: Sensitivity analysis 3C (Subjects with no post-study therapy / IFN vs. MPA trials only)

Sensitivity analysis 3C	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.380†	0.200-0.720
IFN vs. placebo/BSC‡	0.863	0.706-1.056
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.440	0.225-0.863
Pazopanib vs. sunitinib	0.683	0.465-0.991

† HR from analysis in patients with no post-study therapy excluding subjects still on study therapy
‡ Includes IFN vs. MPA trials only: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990
$ Patients with no post-study cancer therapy (Motzer 2009)

4. *Using HR for OS for VEG105192 censored on cross-over:* These sensitivity analyses were conducted using the HR for OS in VEG105192 generated by censoring on cross-over, again conducted using the pooled IFN trials (4A), using the MRC RE-01 trial only (4B), and excluding the VBL studies (4C).

Table 1.27: Indirect comparison: Sensitivity analysis 4A (HR for OS in VEG105192 censored on cross-over / Pooled IFN trials)

Sensitivity analysis 4A	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.640†	0.390-1.049
IFN vs. placebo/BSC‡	0.799	0.674-0.948
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.801	0.475-1.352
Pazopanib vs. sunitinib	1.238	0.983-1.553

† HR generated by censoring patients on cross-over (Cox model)
‡ Includes all 5 IFN trials: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999
$ Patients with no post-study cancer therapy (Motzer 2009)

Table 1.28: Indirect comparison: Sensitivity analysis 4B (HR for OS in VEG105192 censored on cross-over / MRC RE-01 trial only)

Sensitivity analysis 4B	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.640†	0.390-1.049
IFN vs. placebo/BSC‡	0.75	0.66-0.94
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.854	0.496-1.468
Pazopanib vs. sunitinib	1.319	1.027-1.687

† HR generated by censoring patients on cross-over (Cox model)
‡ Includes MRC RE-01 trial as the only IFN vs. placebo/BSC trial (Hancock 2000 data)
$ Patients with no post-study cancer therapy (Motzer 2009)

Table 1.29: Indirect comparison: Sensitivity analysis 4C (HR for OS in VEG105192 censored on cross-over / IFN vs. MPA trials only)

Sensitivity analysis 4C	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.640†	0.390-1.049
IFN vs. placebo/BSC‡	0.863	0.706-1.056
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	0.741	0.435-1.265
Pazopanib vs. sunitinib	1.145	0.900-1.453

† HR generated by censoring patients on cross-over (Cox model)
‡ Includes IFN vs. MPA trials only: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990
$ Patients with no post-study cancer therapy (Motzer 2009)

5. *Using HR for OS for VEG105192 from ITT analysis:* For completeness sensitivity analyses were conducted using the HR for OS in VEG105192 from the ITT analysis (Log rank test), conducted using the pooled IFN trials (5A), using the MRC RE-01 trial only (5B), and excluding the VBL studies (5C).

Table 1.30: Indirect comparison: Sensitivity analysis 5A (ITT analysis HR for OS in VEG105192 / Pooled IFN trials)

Sensitivity analysis 5A	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	1.010†	0.720-1.420
IFN vs. placebo/BSC‡	0.799	0.674-0.948
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	1.264	0.865-1.847
Pazopanib vs. sunitinib	1.953	1.791-2.123

† HR from ITT analysis (Log rank)
‡ Includes all 5 IFN trials: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999
$ Patients with no post-study cancer therapy (Motzer 2009)

Table 1.31: Indirect comparison: Sensitivity analysis 5B (ITT analysis HR for OS in VEG105192 / MRC RE-01 trial only)

Sensitivity analysis 5B	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	1.010†	0.720-1.420
IFN vs. placebo/BSC‡	0.75	0.66-0.94
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	1.347	0.898-2.020
Pazopanib vs. sunitinib	2.081	1.859-2.322

† HR from ITT analysis (Log rank)
‡ Includes MRC RE-01 trial as the only IFN vs. placebo/BSC trial (Hancock 2000 data)
$ Patients with no post-study cancer therapy (Motzer 2009)

Table 1.32: Indirect comparison: Sensitivity analysis 5C (ITT analysis HR for OS in VEG105192 / IFN vs. MPA trials only)

Sensitivity analysis 5C	OS	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	1.010†	0.720-1.420
IFN vs. placebo/BSC‡	0.863	0.706-1.056
Sunitinib vs. IFN	0.647$	0.483-0.870
Results of indirect comparison		
Pazopanib vs. IFN	1.170	0.789-1.735
Pazopanib vs. sunitinib	2.081	1.859-2.322

† HR from ITT analysis (Log rank)
‡ Includes IFN vs. MPA trials only: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990
$ Patients with no post-study cancer therapy (Motzer 2009)

The results of these sensitivity analyses of the indirect comparison were similar to those of the base case analysis. In all of the analyses, pazopanib was associated with a reduced risk of death compared with IFN and appeared to have comparable efficacy in terms of OS to sunitinib. Again, however, the 95% CIs around the HR estimates are wide.

When using the weighted RPSFT-derived HR of 0.501 for OS for pazopanib vs. placebo/BSC, the resulting HRs for pazopanib vs. IFN and for pazopanib vs. sunitinib improved slightly on excluding the VBL studies (i.e. were numerically lower) and were marginally less favourable (i.e. were slightly numerically higher) when using only the MRC RE-01 trial, compared with the base case results.

This pattern was repeated when the analyses were conducted using the HRs from the ITT, censored, IPCW and no post-study therapy analyses, but as expected the resulting HRs for pazopanib vs. IFN and for pazopanib vs. sunitinib were slightly higher than in the base case results with the ITT, censored and IPCW-derived HRs and lower with the HR obtained from the analysis in patients with no post study therapy.

1.6.3 Model projections of median OS for pazopanib and comparators

Median OS for the interventions included in the indirect comparison were estimated using the Weibull survival model used in the economic evaluation. The confidence intervals were calculated by simulation based on percentiles and normal approximation (Table 1.33).

Table 1.33: Model projections of median OS for comparators

Outcome	Comparator	HR vs IFN	Median (months)	95% CI	
				Percentiles	Normal approximation
OS	Pazopanib – weighted RPSFT	0.627	27.8	5.7-137.9	-43.6-99.2
	Pazopanib – IPCW	0.803	20.6	7.0-60.9	-7.7-48.9
	Pazopanib - ITT	1.264	11.9	7.6-18.8	6.3-17.6
	Pazopanib – No post study therapy	0.476	38.7	17.0-81.9	4.5-72.9
	Sunitinib	0.647	26.8	18.9-37.9	17.0-36.5
	IFN	1.000	15.8	15.8-15.8	NA-NA
	Placebo/BSC	1.251	12.1	9.9-14.9	9.6-14.6

Medians calculated using formula t=[-ln(.5)/(HR x Lambda)]^(1/gamma). Confidence intervals were calculated by simulation based on percentiles and normal approximation[8]

When using the base case HR for OS (derived using the RPSFT weighted method) for pazopanib vs. placebo/BSC, the median OS estimates for pazopanib and sunitinib are similar (27.8 and 26.8 months, respectively) with respect to the point estimates and this is supported by the fact that the 95% CIs overlap.

In the base case scenario, median OS for pazopanib appears to be considerably longer than for IFN, with estimates of 15.8 months for IFN and 27.8 months (95% CI: 5.7-137.9 based on percentiles) for pazopanib. As discussed in our original submission (section 5.10.3), we believe that pazopanib should be afforded the same consideration under NICE's Supplementary Advice on appraising End of Life (EoL) medicines as sunitinib in relation to IFN. Based on the OS medians above, pazopanib offers a survival gain of 12.0 months compared with IFN, exceeding the 3-month extension to life criterion set out in NICE's guidance, as well as being a treatment for a small patient population with a limited life expectancy of less than 24 months.

[8] The 'percentile ' estimates are based on 0-25 and 97.5% tiles of the simulated values. The 'normal approximation' estimates were obtained by calculating the SD of the simulated values and calculating the SD of the simulated values and calculating the 95% CIs as Estimate +/- 1.96 x SD. The negative lower bound on the CI is based on normal approximation suggesting that the normality assumption may not be appropriate and that the CIs based on percentiles of the simulation should be used. The CI on the median for IFN is exact because it is based on the fitted lambdas and gammas. These were obtained by OLS regression on the reported S[t] from the sunitinib trial report. This approach does not yield SE for these parameters. The values are therefore constant in the simulation.

Section 2: COST-EFFECTIVENESS – ADDENDUM

[redacted]

2.1 Introduction

The present economic evaluation provides an updated assessment of the lifetime cost-effectiveness of pazopanib versus sunitinib, interferon-α (IFN) and best supportive care (BSC) in patients with advanced RCC in the UK taking into account final overall survival data from the VEG105192 trial[9]. It is important to note that GSK has submitted a patient access scheme for pazopanib for which PASLU has issued draft positive advice to the Department of Health on 6th July 2010. Consequently, results from the updated economic evaluation need to be assessed in conjunction with the completed NICE PAS template provided with this submission.

Briefly, the proposed patient access scheme for pazopanib is a financially based scheme which has two parts: part A is a straight discount given at the point of invoice, [redacted]

The proposed patient access scheme attempts to address:

a) The current difference between the list price of pazopanib and the effective price of sunitinib to the NHS under the sunitinib patient access scheme (part A of the scheme).

[redacted]

As a result, the patient access scheme seeks to enable patients and physicians to have access to an alternative, effective treatment option with a different tolerability profile in this patient group.

The following information will be provided as part of the updated economic evaluation:

- Summary of changes to the economic model
- Clinical parameters used in the economic model
- Cost-effectiveness results *
- Interpretation of results

* Further detail regarding CE estimates with and without the patient access scheme can be found in the NICE PAS template submitted alongside this addendum.

2.2 Updated clinical parameters used in economic model

2.2.1 Updated overall survival data

As mentioned previously, at the time of GSK's submission to NICE for pazopanib in the first-line treatment of advanced RCC (submitted 16 April 2010), only interim overall survival (OS)

[9] As stated previously, the clinical cut-off date for the final OS analysis was 15 March 2010, at which point 148 [64%] patients in the in the treatment-naive group had died.

data from this study were available (61% of the required death events; 23 May 2008 cut-off). The final OS analysis was scheduled to be carried out after 287 deaths, based on 90% power to detect a 50% improvement in median OS with pazopanib compared with placebo. The clinical cut-off date for the final OS analysis was 15 March 2010, at which point 290 (67%) patients in the overall study population had died (148 [64%] in the treatment-naive group). These data are included in the clinical section of this addendum (Section 1.5), and have been incorporated into the economic model.

2.2.2 Analyses to adjust for cross-over/receipt of further anti-cancer therapy
There is consensus among academics about the challenges in obtaining adequate effectiveness and hence cost effectiveness estimates when evaluating new cancer treatments, as treatment cross-over following disease progression is very common in oncology trials. Thus the overall survival advantage associated with the experimental treatment cannot be estimated with confidence based on the intent-to-treat (ITT) data, because a proportion of the patients randomised to the control treatment will have received the experimental treatment following disease progression. While estimates of the progression free survival advantage are likely to be robust (because patients typically cross over following disease progression), the overall survival estimates will not.

In the UK, treatment cross-over has been an important issue in a number of NICE appraisals of cancer treatments, but the methods used to account for the impact of the cross-over on the treatment effect have been limited. Most regularly censoring approaches have been used, but in other appraisals the cross-over has been ignored and standard ITT analysis has been conducted. In a number of appraisals the cross-over that occurred in pivotal trials has not even been acknowledged as a factor in the economic evaluation, despite the potentially important difference this could make to incremental cost effectiveness ratios (ICERs). Consequently, new methods to account for the impact of cross-over/post-study therapy have emerged during the last few years seeking to obtain more reliable estimates of survival benefits for oncology therapies which then can be used in cost-effectiveness calculations.

The VEG105192 protocol stated that subsequent anti-cancer therapy for patients with progressive disease could be provided at the discretion of patients and their physician following discontinuation of study medication, with patients in the placebo arm having the option to cross over to receive pazopanib (via the open-label VEG107769 study). This could occur at any point upon disease progression. As a result, the utility of the (ITT) OS analysis is limited as discussed above. In addition to a high rate of post-study treatment in the placebo arm and early timing of the initiation of post-study treatment relative to randomisation in VEG105192, the longer median exposure to pazopanib in the placebo 'crossover' subjects compared with subjects in the pazopanib arm (11.2 vs. 7.4 months) is likely to have further impacted the treatment comparison. These factors are described in Sections 1.3.1 and 1.4 of the clinical discussion.

Since the optimal method to control for cross-over/switch in survival analysis remains an area of academic debate and all the available approaches have their strengths and limitations, a range of methodologies was utilised to comprehensively evaluate this effect on the final OS data in VEG105192[10].

[10] Various statistical methodologies to adjust for the effects of crossover were conducted on the interim OS data (presented in GSK's original submission) and these have now been applied, with some adjustments as detailed in the clinical sections, to the final OS data from VEG105192.

Specifically, RPSFT and IPCW were employed due to the level of crossover in VEG105192. The RPSFT and IPCW analyses were conducted in consultation with leading experts in the conduct of these methods including Dr. James Robins, Department of Epidemiology and Department of Biostatistics, Harvard School of Public Health. The application of the methodologies were also reviewed by Dr. Lee-Jen Wei, Department of Biostatistics, Harvard School of Public Health. The results using these methods for the interim overall survival data were also reviewed by Ian White, an in dependent statistician from the MRC Biostatistics Unit, University of Cambridge. Mr. White was also involved at the early stages of methodology discussions for adjustment for cross-over analyses for the final OS. A table listing the adjustment for cross-over analyses that were undertaken alongside derived results has been presented in the clinical section (table 1.17) and is replicated in Table 2.1 below:

Table 2.1: Summary of final OS results for treatment-naive population in VEG105192 (pazopanib versus best supportive care (i.e. placebo); 15 March 2010 cut-off)

Population / Method of estimation	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)	0.797	0.493-1.289	p=0.3553
- Unadjusted for baseline characteristics	0.640	0.390-1.049	p=0.0769
- Adjusted for baseline characteristics			
IPCW (informative censoring defined as cross-over to pazopanib or receipt of other anti-cancer therapy)			
- Adjusted for baseline characteristics	0.642	0.266-1.248	0.160*
RPSFT Unweighted			
- Unadjusted for baseline characteristics	NA	NA	NA
- 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 choose not to	0.380	0.170-0.820	p<0.001
Method used for base case analysis			

Patients with missing values for the covariates were assigned the mean for the trial population.
* Not adjusted for baseline characteristics except stratification on baseline ECOG PS
† Not adjusted for stratification factors
NA = Bootstrap 95% CI, p-value not applicable.

Because of the uncertainty associated with the weighted RPSFT estimate, reflected in part by its wide confidence interval, as well as because of a lack of validation of the weighting methodology in small samples, a number of secondary analyses were conducted in which alternative estimates of the HR for OS for pazopanib vs. placebo were employed. First, analyses based on the unweighted, adjusted RSPFT estimate (HR=0.310, 95% CI: 0.073 to 1.715) and the IPCW estimate (HR=0.642., 95%CI 0.266 to 1.248) were conducted. In addition, estimates from analyses obtained from a multivariate Cox regression model with censoring on cross-over or receipt of other anticancer therap**y** (HR=0.640, 95%CI: 0.390 to 1.049) based on an analysis in which patients who received any study therapy or were remaining on study therapy as of the data cut-off were excluded (HR=0.38, 95%CI: 0.20 to 0.72) were also conducted. Finally, an analysis in which the estimated HR for pazopanib vs. placebo was based on the intent-to-treat (ITT) analysis (i.e. without any adjustment for cross-over) (HR=1.01, 95%CI: 0.72 to 1.42) was conducted.

2.3.3 Selection of cross-over/switch analysis for cost-effectiveness base case

While the above results, taken as a whole, provide convincing evidence of the benefits of pazopanib on mortality in treatment-naïve advanced RCC patients, there remains uncertainty regarding the precise magnitude of such benefit (versus placebo). However, for the purposes of this submission, the HR of 0.501 (95% CI: 0.14 to 2.35 by bootstrap) for OS for pazopanib versus placebo obtained using the weighted unadjusted RPSFT method has been used in the base case analysis (in the indirect comparison and in the economic evaluation).

It was considered that for technology assessments that require a point estimate of the OS HR for a strategy of treatment with pazopanib or treatment with BSC (i.e. placebo) without further anti-cancer therapy, it would not be unreasonable to use the weighted RPSFT estimate (0.501), because it lies within the range of estimates generated by our different analyses to adjust for the impact of cross-over/post-study therapies (HRs 0.300 to 0.797). Furthermore, selection of RPSFT seems to be in line with recent NICE appraisals in which it was acknowledged as being more methodologically robust since randomisation is preserved and it does not make the assumption of no unmeasured confounders.

2.2.4 No post study therapy analyses

As noted above, a *post hoc* data analysis pertaining to sub-groups of participants who did not receive any systemic post-study treatments was also conducted. Three sub-groups were identified and the resultant HRs are shown in Table 2.1 above. These *post hoc* analyses are similar to the one conducted by Pfizer for sunitinib in advanced RCC upon which NICE based their positive recommendation. The HR for overall survival from the no post-study treatment analysis for sunitinib vs. IFN was 0.647 (Motzer 2009). This analysis was selected by the Appraisal Committee as part of its preferred assumptions to be used in the CE base case[11]. Consequently, 0.647 is the OS HR used in the current cost-effectiveness analysis to assess the survival gain of sunitinib vs. IFN. It should also be noted that for the purpose of the sensitivity analyses we have chosen the sub-group analysis which excludes patients receiving systemic post-study therapy, but not patients randomised to BSC who despite not having progressed, crossed over to the pazopanib arm. This analysis yields a HR of 0.380 compared with the 0.300 obtained by the more crude approach of excluding all patients who crossed over to pazopanib regardless of progression status.

In conclusion, it is not unreasonable to suggest that the use of the weighted, unadjusted RPSFT method as our base case constitutes a conservative approach. Nonetheless, using the alternative no post-study treatment analysis (HR 0.38) might also be justifiable, as it is aligned with the approach adopted by NICE when assessing the cost-effectiveness of sunitinib.

2.2.5 Clinical effectiveness data used in the economic model

Clinical effectiveness data (PFS and OS) used in the economic model for the base case analysis is outlined in table 2.2 below (updated values are in bold). The resultant survival curves are shown in Figures 2.1-2.3. Survival curves were obtained by applying estimated HRs to parametric survival curves for IFN that had been fitted to Kaplan-meier data from published clinical trials, as reported in GSK's previous submission.

A comparison of model results and clinical trial results is provided in Table 2.2.

[11] Please refer to PenTAG report and NICE TA 169 guidance for a discussion on the robustness of the sunitinib no post study treatment analysis:
http://www.nice.org.uk/nicemedia/live/11817/43144/43144.pdf (sections 2.2. and 2.3)
https://www.htainsite.com/Search/TA/TA_169.pdf (section 4.2.11)

Table 2.2. Effectiveness estimates used in the economic model (updated values in bold)

		PFS			OS			sources
		Est.	95%CI		Est.	95%CI		
IFN	λ	0.154			0.070			PFS: Motzer 2007 ASCO
Weibull distribution	γ	0.895			0.830			OS: TA169/ Figlin 2008
HR vs. BSC	Pazopanib	0.360	0.240	0.550	**0.501**	**0.140**	**2.350**	PFS: VEGF105192 IRC Scan dates
								OS: VEGF105192 RPSFT weighted unadjusted model
	IFN	0.704	0.580	0.854	0.799	0.674	0.948	Pooled analysis
								PFS: Negrier (2007), Hancock/MRC (2000) and Pyrhonen (1999)
								OS: Negrier (2007) , Hancock/MRC (2000), Pyrhonen (1999), Kriegmair (1995), Steineck (1990)
HR vs. IFN	Pazopanib	0.512	0.326	0.802	**0.627**	**0.173**	**2.269**	**Indirect comparison**
								HR Paz vs. BSC ÷ HR IFN vs BSC
	Sunitinib	0.539	0.431	0.643	0.647	0.483	0.870	PFS: Motzer JCO 2009 (Final analysis)
								OS: Motzer JCO 2009 (Final analysis- Pts w/PS tx excl.)

Figure 2.1. Predicted PFS survival curves utilised in the economic model

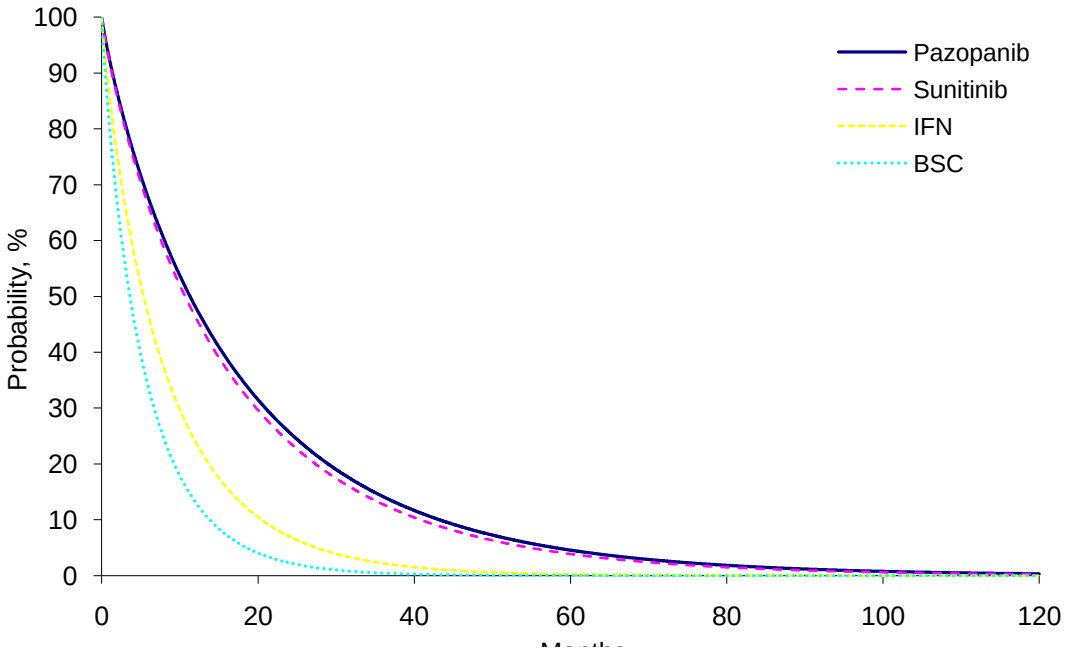


Figure 2.2. Predicted OS survival curves utilised in the economic model

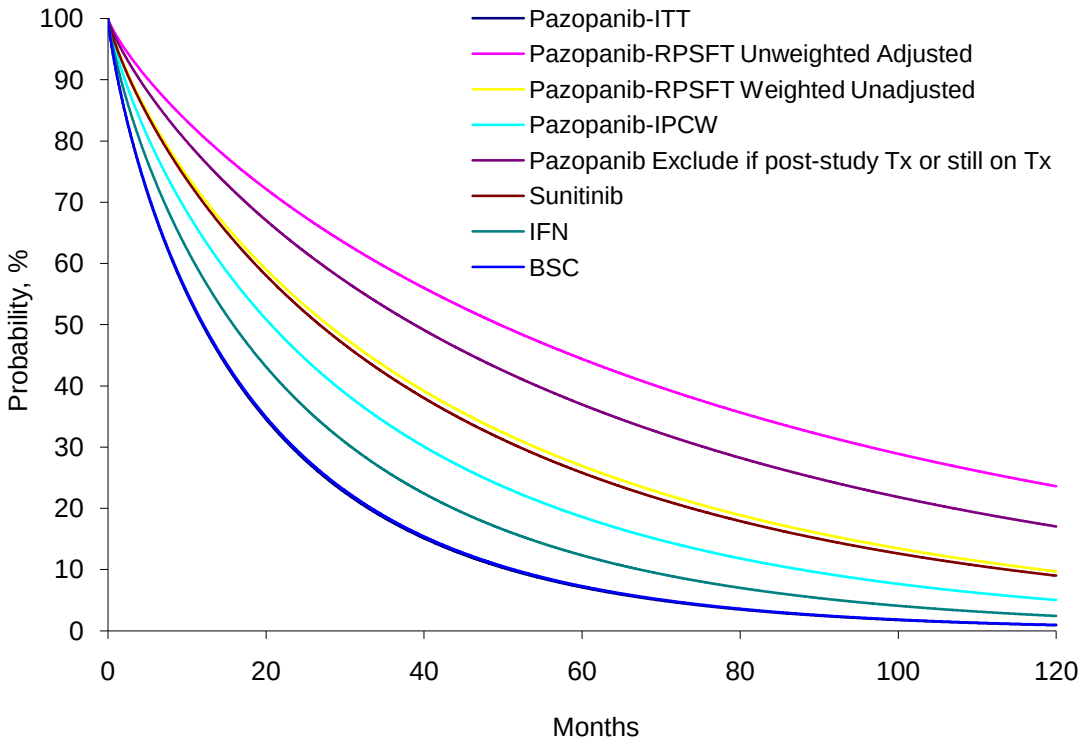


Figure 2.3. Predicted PPS survival curves utilised in the economic model

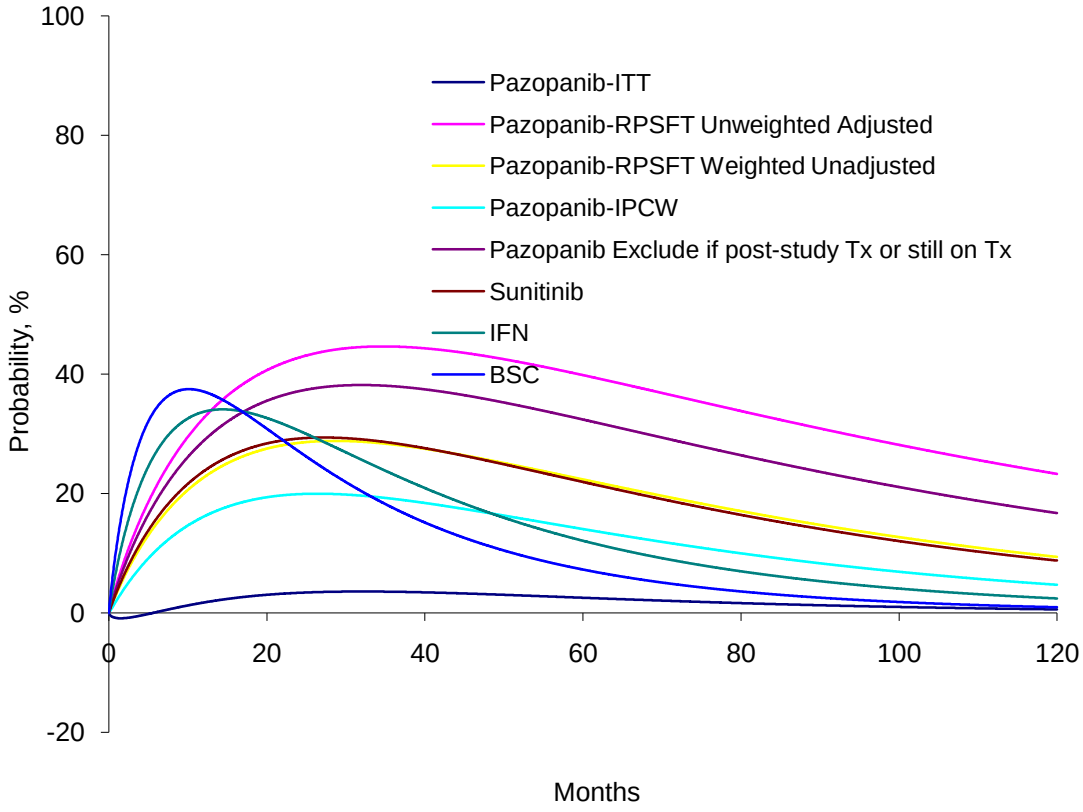


Table 2.3: Summary of economic model base case results compared with clinical data

	Pazopanib		Sunitinib		IFN		BSC	
Outcome Months (median)	**Clinical trial result**	**Model result ¥**	**Clinical trial result**	**Model result**	**Clinical trial result***	**Model result**	**Clinical trial result****	**Model result**
PFS	11.1	11.3	11.0	10.7	4.0	5.4	2.8	5.6
PPS	11.8	16.5	15.4	16.1	5.0	10.4	20.7	6.5
OS	22.9	27.8	26.4	26.8	9.0	15.8	23.5†	12.1

¥ RPSFT weighted unadjusted (base case)
*from Hancock 2000. **from placebo arm of VEG105192.†not adjusted for cross over (ITT)

2.3 Results

Results of the updated economic evaluation are first presented using the list price for pazopanib as per our previous submission. Results are then presented incorporating a 12.5% discount. Please note that this discount forms part of a proposed patient access scheme and that these results are also presented within the patient access scheme template submitted alongside this addendum.

2.3.1 Cost effectiveness results (no discount)

As discussed above the weighted unadjusted RPSFT estimate was used for the economic base case (i.e. HR 0.627 pazopanib vs. IFN). Disaggregated incremental QALYs and costs by health state, and resource use predicted by the model by category of cost, are shown below (Tables 2.4-2.6). This is followed by base case cost-effectiveness results and incremental results (Tables 2.7-2.8).

Table 2.4. Summary of QALY gain by health state

A. Pazopanib vs. Sunitinib

Health state	Pazopanib QALY	Sunitinib QALY	Increment	% Increment
PFS	0.972	0.907	0.065	95.59
PPS	0.994	0.991	0.003	4.41
Total	1.966	1.898	0.068	100.00
QALY, quality adjusted life year				

B. Pazopanib vs. IFN

Health state	Pazopanib QALY	IFN QALY	Increment	% Increment
PFS	0.972	0.465	0.507	70.71
PPS	0.994	0.784	0.21	29.29
Total	1.966	1.249	0.717	100.00
QALY, quality adjusted life year				

C. Pazopanib vs. BSC

Health state	Pazopanib QALY	BSC QALY	Increment	% Increment
PFS	0.972	0.325	0.647	66.29
PPS	0.994	0.665	0.329	33.71
Total	1.966	0.990	0.976	100.00
QALY, quality adjusted life year				

Table 2.5. Summary of costs by health state

A. Pazopanib vs. Sunitinib

Health state	Pazopanib Costs (£)	Sunitinib Costs (£)	Increment (£)	% Increment
PFS	35,832	31,583	4,249	99.7
PPS	4,610	4,596	14	0.3
Total	40,442	36,179	4,263	100.0

B. Pazopanib vs. IFN

Health state	Pazopanib Costs (£)	IFN Costs (£)	Increment (£)	% Increment
PFS	35,832	4,745	31,087	97.0
PPS	4,610	3,635	975	3.0
Total	40,442	8,380	32,062	100.0

C. Pazopanib vs. BSC

Health state	Pazopanib Costs (£)	BSC Costs (£)	Increment (£)	% Increment
PFS	35,832	1,001	34,831	95.8
PPS	4,610	3,084	1,526	4.2
Total	40,442	4,085	36,357	100.0

Table 2.6. Summary of predicted resource use by category of cost

A. Pazopanib vs. Sunitinib

Item	Pazopanib (£)	Sunitinib (£)	Increment (£)	% Increment
Acquisition cost	33,128	28,856	4,271	100.2
Administration costs	0	0	0	0.0
Adverse event costs	91	243	-152	-3.6
Other pre progression costs	2,613	2,484	129	3.0
Other post progression costs	4,610	4,596	15	0.3
Total	40,441	36,179	4,263	100.0

B. Pazopanib vs. IFN

Item	Pazopanib (£)	IFN (£)	Increment (£)	% Increment
Acquisition cost	33,128	2,754	30,374	94.7
Administration costs	0	532	-532	-1.7
Adverse event costs	91	108	-17	-0.1
Other pre progression costs	2,613	1,351	1,262	3.9
Other post progression costs	4,610	3,635	975	3.0
Total	40,441	8,380	32,062	100.0

C. Pazopanib vs. BSC

Item	Pazopanib (£)	BSC (£)	Increment (£)	% Increment
Acquisition cost	33,128	0	33,128	91.1
Administration costs	0	0	0	0.0
Adverse event costs	91	35	56	0.2
Other pre progression costs	2,613	967	1,646	4.5
Other post progression costs	4,610	3,084	1,526	4.2
Total	40,441	4,085	36,356	100.0

Table 2.7. Base case results

				vs. BSC			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987				
IFN	8,379	2.020	1.249	4,294	0.421	0.262	16,395
Sunitinib	36,179	3.018	1.898	32,094	1.420	0.911	35,231
Pazopanib	40,441	3.097	1.966	36,356	1.499	0.979	37,126

				vs. IFN			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987	-4,294	-0.421	-0.262	16,395†
IFN	8,379	2.020	1.249				
Sunitinib	36,179	3.018	1.898	27,799	0.999	0.649	42,832
Pazopanib	40,441	3.097	1.966	32,062	1.077	0.717	44,697

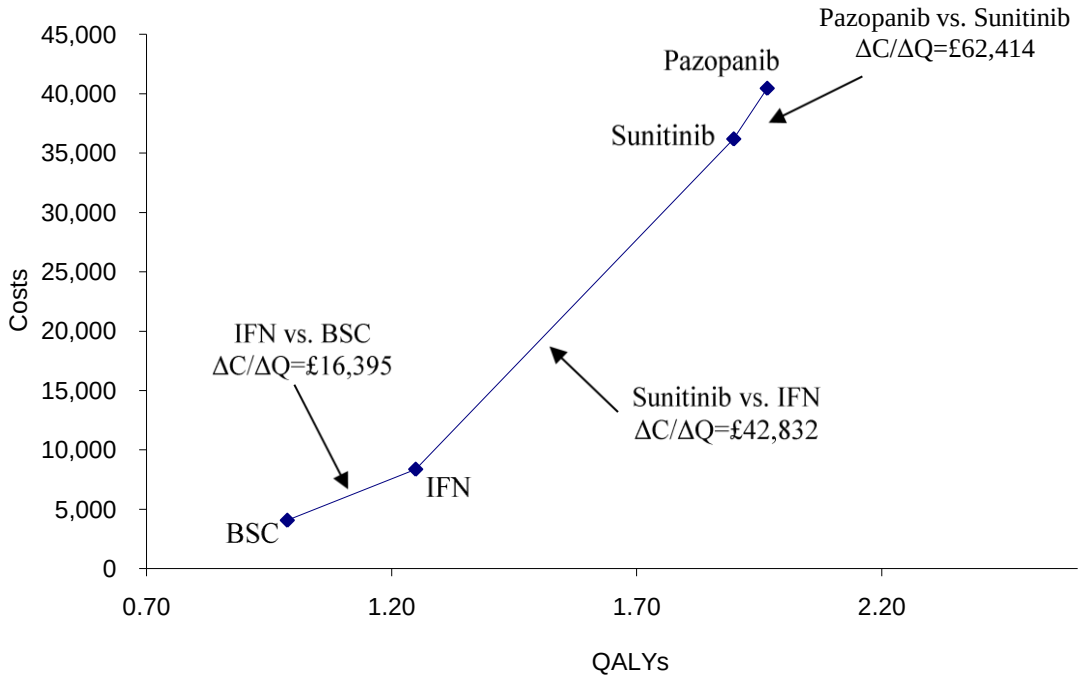
				vs. sunitinib			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987	-32,094	-1.420	-0.991	35,231†
IFN	8,379	2.020	1.249	-27,799	-0.999	-0.649	42,832†
Sunitinib	36,179	3.018	1.898				
Pazopanib	40,441	3.097	1.966	4,263	0.079	0.068	62,414

† Intervention is less costly but less effective than comparator

Table 2.8. Incremental base case results

Technology (and comparators)	Total Cost	Total QALY	Incremental cost	Incremental QALY	ICERs vs. baseline	Incremental analysis
BSC (baseline)	4,085	0.987				
IFN	8,379	1.249	4,249	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

Figure 2.4. Incremental cost effectiveness



2.3.3. Cost-effectiveness results incorporating a 12.5% discount

Part A of the proposed patient access scheme constitutes a 12.5% discount from the pazopanib 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 12.5% discount[12]. Tables 2.9 and 2.10 display base case cost-effectiveness results including this discount. Since this is the effective price to the NHS further sensitivity and analyses are presented only for this pricing scenario.

Table 2.9. Base case results (incorporating 12.5% discount)

				vs. BSC			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987				
IFN	8,379	2.020	1.249	4,294	0.421	0.262	16,395
Sunitinib	36,179	3.018	1.898	32,094	1.420	0.911	35,231
Pazopanib	36,301	3.097	1.966	32,216	1.499	0.979	32,898

[12] Further details of the calculation of this price were provided as part of our submission to PASLU (May 2010).

Technologies				vs. IFN			
	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	4,085	1.598	0.987	-4,294	-0.421	-0.262	16,395†
IFN	8,379	2.020	1.249				
Sunitinib	36,179	3.018	1.898	27,799	0.999	0.649	42,832
Pazopanib	36,301	3.097	1.966	27,921	1.077	0.717	38,925

Technologies				vs. sunitinib			
	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	4,085	1.598	0.987	-32,094	-1.420	-0.991	35,231†
IFN	8,379	2.020	1.249	-27,799	-0.999	-0.649	42,832†
Sunitinib	36,179	3.018	1.898				
Pazopanib	36,301	3.097	1.966	122	0.079	0.068	1,790

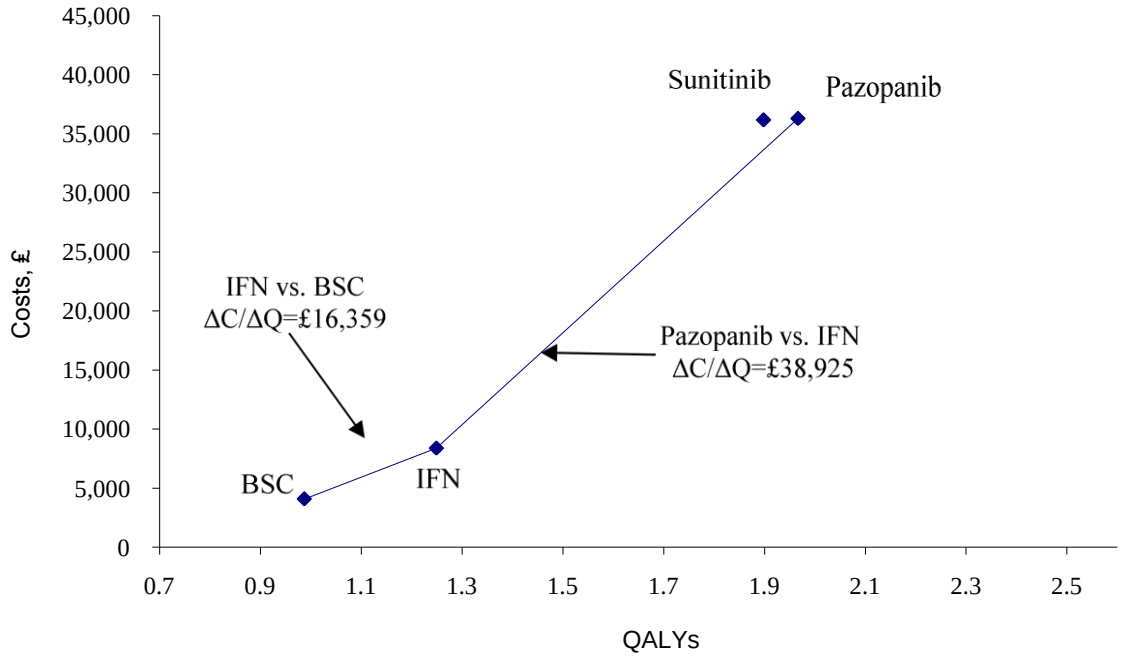
† Intervention is less costly but less effective than comparator

Table 2.10. Incremental base case results (incorporating 12.5% discount)

Technology	Total Cost	Total QALY	Incremental cost	Incremental QALY	ICERs vs. baseline	Incremental analysis
BSC (baseline)	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						

Results of incremental cost-effectiveness analysis of pazopanib, sunitinib IFN, and BSC are shown in Figure 2.5. In terms of cost-effectiveness, sunitinib is dominated by pazopanib by extended dominance (i.e. it has a higher cost-effectiveness ratio vs. IFN [£42,832] than pazopanib [£38,925]). The cost per QALY gained with IFN vs. BSC is £16,395 (see Table 2.10).

Figure 2.5. Incremental cost-effectiveness results (incorporating 12.5% discount)



2.3.4. Sensitivity Analyses

Deterministic sensitivity analyses
Deterministic sensitivity analyses (as per original submission) for the base case incorporating a 12.5% discount are shown in Table 2.11 overleaf. In addition cost-effectiveness results using alternative methods of adjusting for cross over in VEG105192 are displayed in Table 2.12.

Table 2.11. Deterministic sensitivity analysis for base case

	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	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	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=0.106	40,826	2.942	4,647	1.044	4,451	32,447	1.693	19,164	36,741	1.955	18,793
HROS pazopanib vs. IFN =1.750	32,264	1.101	-3,915	-0.797	4,911 †	23,885	-0.148	dominated	28,179	0.114	247,380
Cost IFN admin=0.5 x base-case	36,301	1.966	122	0.068	1,790	28,187	0.717	39,295	32,216	0.979	32,898
Cost IFN admin=1.5 x base-case	36,301	1.966	122	0.068	1,790	27,656	0.717	38,554	32,216	0.979	32,898
Cost therapy initiation=0.5 x base-case	36,230	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
Cost therapy initiation=1.5 x base-case	36,372	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
Other Cost PFS=0.5 x base-case	35,065	1.966	58	0.068	847	27,290	0.717	38,045	31,393	0.979	32,058
Other Cost PFS=1.5 x base-case	37,536	1.966	187	0.068	2,733	28,552	0.717	39,804	33,039	0.979	33,739
Other Cost PPS=0.5 x base-case	33,996	1.966	115	0.068	1,687	27,434	0.717	38,245	31,453	0.979	32,119
Other Cost PPS=1.5 x base-case	38,606	1.966	129	0.068	1,893	28,409	0.717	39,604	32,979	0.979	33,677
Cost of 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
Cost of 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
Incidence of AEs=lower 95% confidence interval	36,231	1.975	153	0.071	2,145	27,884	0.724	38,536	32,162	0.986	32,622
Incidence of AEs=upper 95% confidence interval	36,518	1.949	192	0.058	3,309	28,095	0.703	39,982	32,403	0.965	33,595
Utility PFS=0.75 x base-case	36,301	1.424	122	0.055	2,242	27,921	0.529	52,803	32,216	0.717	44,932
Utility PFS=1.75 x base-case	36,301	2.508	122	0.082	1,489	27,921	0.906	30,823	32,216	1.242	25,949
Utility PFS=0.65	36,301	1.811	122	0.064	1,899	27,921	0.663	42,085	32,216	0.904	35,624

	Pazopanib		Difference Pazopanib vs.								
			Sunitinib			IFN			BSC		
	Costs, £	QALYs	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £
Utility PFS=0.75	36,301	2.121	122	0.072	1,692	27,921	0.771	36,206	32,216	1.054	30,560
Utility PFS and PPS that of healthy person (0.78), no decrement for Aes	36,301	1.983	122	0.055	2,240	27,921	0.715	39,052	32,216	0.988	32,617
Decrement utility w/Progression 0.5 x base-case	36,301	2.059	122	0.069	1,782	27,921	0.737	37,890	32,216	1.010	31,899
Decrement utility w/Progression 1.5 x base-case	36,301	1.874	122	0.068	1,797	27,921	0.698	40,018	32,216	0.949	33,962
Decrement in 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
Decrement in 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=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	36,346	1.966	46	0.068	681	27,913	0.717	38,913	32,244	0.979	32,927
Decrement in utility with AEs from Oxford Outcomes	36,312	1.940	84	0.067	1,240	27,908	0.699	39,932	32,165	0.982	32,756
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)	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)	39,519	1.984	3,341	0.086	38,658	31,140	0.735	42,342	35,434	0.997	35,528

	Pazopanib		Difference Pazopanib vs.								
			Sunitinib			IFN			BSC		
	Costs, £	QALYs	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £
HRs for OS for pazopanib vs. IFN using HR for pazopanib vs. placebo in VEG105192 without censoring on crossover or adjustment for baseline covariates (HR=0.930)	33,767	1.420	-2,411	-0.478	5,044 †	25,388	0.171	148,462	29,682	0.433	68,560
HR for OS for sunitinib vs. IFN based on final analysis (HR=0.820)	36,301	1.966	1,679	0.404	4,156	27,921	0.717	38,925	32,216	0.979	32,898
HRs for PFS and OS for pazopanib vs. IFN = HRs for sunitinib vs. IFN (PFS HR=0.539, OS HR=0.647)	34,647	1.912	-1,532	0.014	dominant	26,267	0.663	39,634	30,562	0.925	33,051
HR for OS for pazopanib vs. IFN = HR for sunitinib vs. IFN (HR=0.647)	36,085	1.920	-93	0.022	dominant	27,706	0.671	41,300	32,000	0.933	34,306
HR for OS for pazopanib vs. IFN to make PPS equal to that of sunitinib (HR=0.629)	36,279	1.961	100	0.064	1,578	27,899	0.713	39,152	32,194	0.975	33,035
Pazopanib arm VEG105192 as reference	24,647	1.424	737	0.050	14,733	17,569	0.459	38,303	21,274	0.616	34,538
Time Frame=5 years	33,283	1.573	-51	0.046	dominant	25,549	0.464	55,067	29,529	0.658	44,907
Time Frame=15 years	36,942	2.089	183	0.079	2,333	28,450	0.815	34,897	32,818	1.093	30,020
Annual discount rate=0%	38,816	2.181	105	0.078	1,346	29,950	0.831	36,043	34,442	1.129	30,518
Annual discount rate=6%	35,345	1.887	132	0.065	2,035	27,150	0.676	40,156	31,370	0.925	33,917

† Pazopanib is less costly and less effective than comparator; value represents CE of comparator vs Pazopanib

Table 2.12. Summary of cost-effectiveness estimates for all final OS analyses incorporating a 12.5% discount from list price for pazopanib

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
¥ A full PSA (and related CEAC) for the no post-study therapy subgroup is provide in appendix 2

Probabilistic sensitivity analyses

Results of probabilistic sensitivity analyses incorporating a 12.5% discount are summarised in Table 2.13 and displayed on the cost-effectiveness plane in Figure 2.6. Acceptability curves for pair-wise comparisons of pazopanib vs. sunitinib, pazopanib vs. IFN, and pazopanib vs. BSC are shown in Figure 2.7. Acceptability curves for an incremental (i.e., multi-way) comparison of pazopanib, sunitinib, IFN, and BSC are shown in Figure 2.8.

Results of these analyses suggest that there is a high degree of uncertainty regarding the incremental costs and benefits of pazopanib vs. sunitinib. There is relatively less uncertainty regarding the incremental costs and benefits of pazopanib vs. IFN or BSC.
In 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.

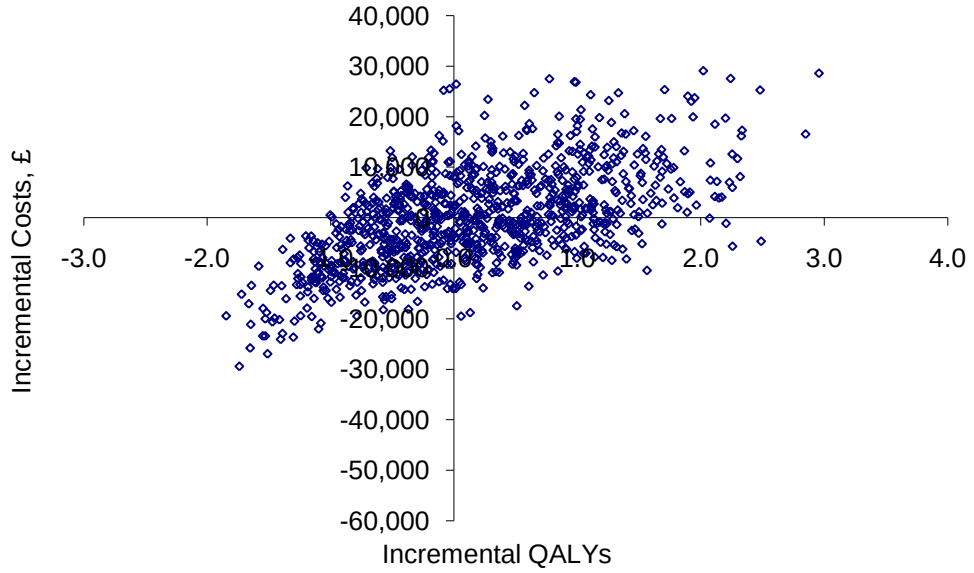
Table 2.13 Summary of probabilistic sensitivity analysis

	Pazopanib	Sunitinib	IFN	BSC
Number of Simulations	1000	1000	1000	1000
Costs, £				
Mean	36,286	36,457	8,358	4,107
SD	8,530	3,996	980	922
Median	35,941	36,272	8,243	4,014
Low	9,074	25,374	6,215	2,018
High	65,695	49,197	12,695	9,999
95% CI-Lower	19,531	28,973	6,710	2,680
95% CI-Upper	53,360	44,641	10,538	6,085
QALYs				

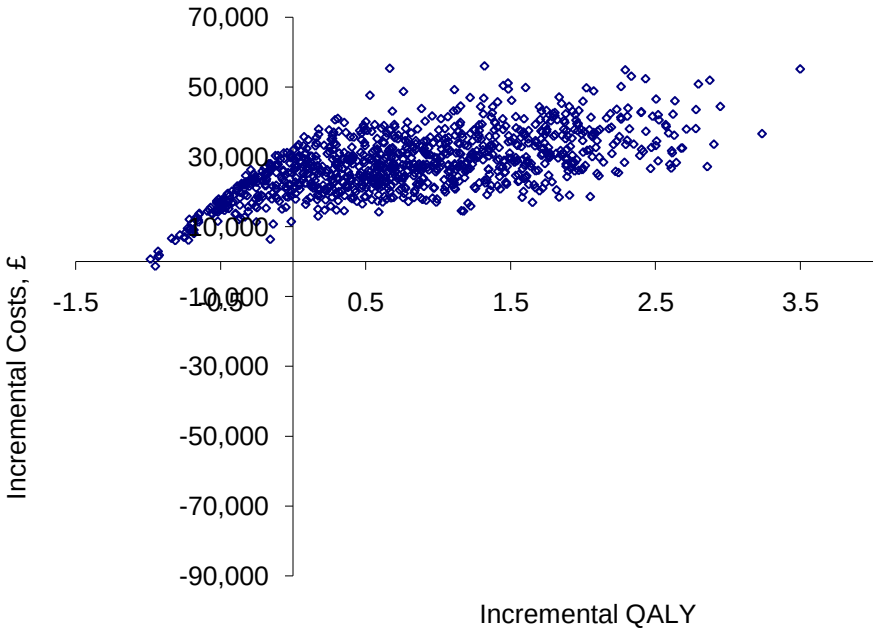
Mean	2.058	1.906	1.249	0.985
SD	0.840	0.219	0.020	0.087
Median	1.975	1.900	1.250	0.982
Low	0.263	1.354	1.191	0.712
High	4.746	2.533	1.312	1.255
95% CI-Lower	0.636	1.504	1.211	0.823
95% CI-Upper	3.774	2.346	1.289	1.168
Difference in Costs, Pazopanib vs. Comparator, £				
Mean		-170	27,928	32,179
SD		9,469	8,585	8,591
Median		-552	27,620	31,738
Low		-29,460	-1,266	4,476
High		29,051	55,983	63,039
95% CI-Lower		-18,004	11,915	15,836
95% CI-Upper		19,843	45,816	49,951
Difference in QALYs, Pazopanib vs. Comparator				
Mean		0.152	0.808	1.073
SD		0.870	0.840	0.845
Median		0.097	0.729	0.997
Low		-1.848	-0.985	-0.788
High		2.956	3.499	3.696
95% CI-Lower		-1.327	-0.647	-0.367
95% CI-Upper		1.949	2.518	2.797

Figure 2.6. Scatterplot of PSA (1,000 runs) – Weighted unadjusted RPSFT (+12.5% discount). A vs. sunitinib; B vs. IFN; C vs. BSC

A. Pazopanib vs. sunitinib



B. Pazopanib vs. IFN



C. Pazopanib vs. BSC

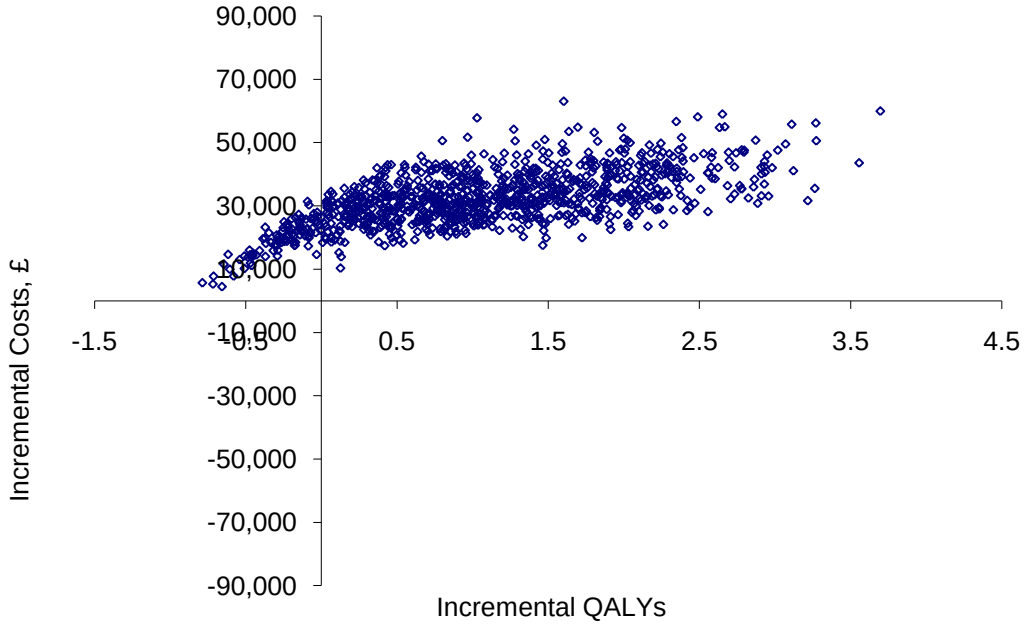
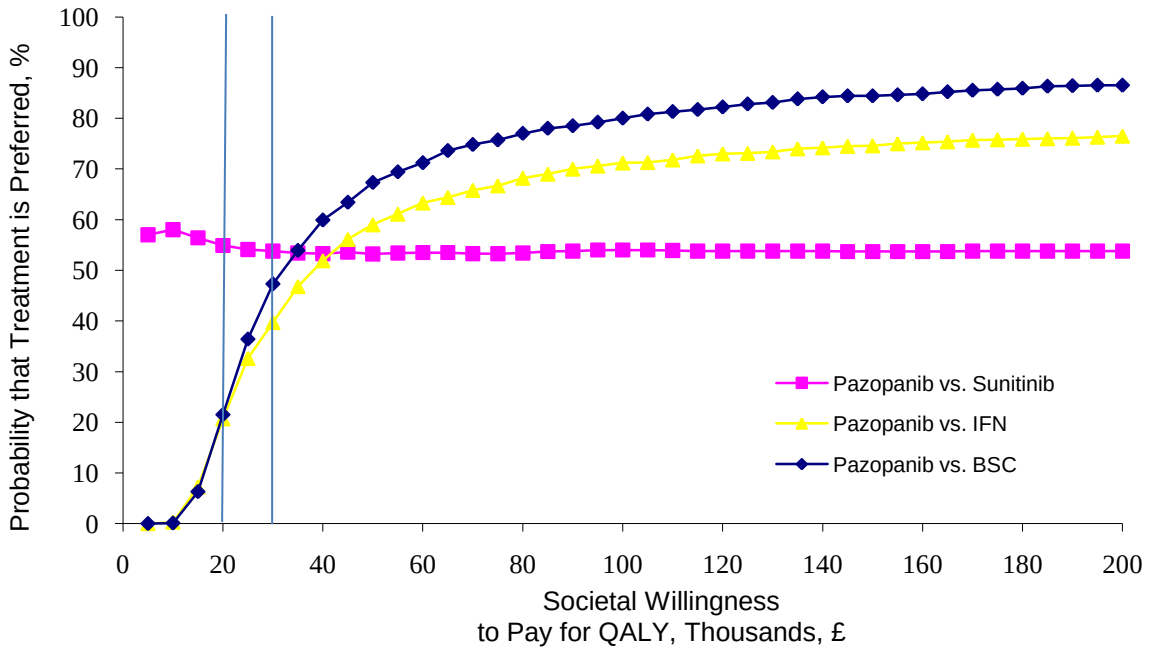


Figure 2.7. Cost-effectiveness acceptability curve – weighted RPSFT (+12.5% discount): pair-wise comparisons of pazopanib vs. sunitinib, pazopanib vs. IFN, and pazopanib vs. BSC



2.4 Interpretation

This study was an evaluation of the cost-effectiveness of pazopanib in treatment naive – advanced RCC patients using a partitioned survival analysis model, and data from the VEG105192 pivotal trial of pazopanib and a variety of primary and secondary data sources. In our primary base-case analysis (table 2.15), the HR for OS for pazopanib vs. IFN was based on an analysis of OS data from VEG105129 using weighted RPSFT methods to control for cross-over from placebo to pazopanib. Consistent with the proposed patient access scheme (part A) the daily cost of pazopanib was assumed to be 12.5% less than that of sunitinib (based on the sunitinib list price). Based on these assumptions, in pair-wise analyses, the cost effectiveness of pazopanib is £1,790 per QALY gained vs. sunitinib, £38,925 per QALY gained vs. IFN, and £32,898 per QALY gained vs. BSC. In an incremental cost-effectiveness analysis, sunitinib is dominated by pazopanib (by extended dominance). Results are highly sensitive to the assumed HR for OS for pazopanib vs. IFN which depends on both the estimated HR for pazopanib vs. placebo and the HR for IFN vs. placebo. There is uncertainty associated with the former because of inherent limitations in analyses conducted to control for the confounding effects of cross-over in the VEG105192 trial. There is also uncertainty in the latter because of limitations inherent in the conduct of adjusted indirect comparisons.

Table 2.15. Base-case results

					Difference Pazopanib vs.		
	Pazopanib	**Sunitinib**	**IFN**	**BSC**	**Sunitinib**	**IFN**	**BSC**
Effectiveness, not discounted							
PFLY	1.492	1.410	0.710	0.480	0.082	0.782	1.012
PPLY	1.685	1.680	1.328	1.127	0.005	0.356	0.558
LY	3.445	3.352	2.187	1.707	0.093	1.259	1.738
QALYs	2.181	2.103	1.350	1.052	0.078	0.831	1.129
Effectiveness, discounted							
PFLY	1.412	1.339	0.691	0.471	0.074	0.721	0.941
PPLY	1.954	1.942	1.477	1.227	0.012	0.477	0.727
LY	3.097	3.018	2.020	1.598	0.079	1.077	1.499
QALYs	1.966	1.898	1.249	0.987	0.068	0.717	0.979
Costs, £							
Study medications							
Acquisition	28,987	28,856	2,754	0	131	26,233	28,987
Administration	0	0	532	0	0	-532	0
Treatment of AEs	91	243	108	35	-151	-17	56
Other pre-progression	2,613	2,484	1,351	966	129	1,262	1,646
Post-progression	4,610	4,596	3,635	3,084	14	975	1,526
Total	36,301	36,179	8,379	4,085	122	27,921	32,216
Incremental Cost/LY, £					1,552	25,916	21,497
Incremental Cost/PFLY, £					1,660	38,718	34,236
Incremental Cost/QALY, £					1,790	38,925	32,898

2.4.1 Key drivers of cost-effectiveness

The key drivers of cost-effectiveness were the efficacy estimates for pazopanib versus IFN which subsequently contribute to the relative efficacy of pazopanib and sunitinib. Specifically the model is sensitive to the method used for adjusting for cross over for OS data from VEG105192. Cost effectiveness results using different methods for adjusting for cross over are summarised in table 2.12.

2.4.1 Strengths of the updated economic evaluation over and above those highlighted in original submission

- Every effort was made to fully explore the impact of cross over on OS in VEG105192 and the most up to date methodologies were employed. Experts in the application of these methods were consulted in the conduct of the analyses. The limitations of these methods are fully described. It should be recognized that there are limitations associated with all methods to account for crossover. Therefore the decision on which methodology should be used for the base case analysis was not straightforward. Nevertheless, using the weighted unadjusted RPSFT method for the base case analysis constitutes a conservative approach for two main reasons: a) the weighted RPSFT estimate (0.501) was employed because it lies within the range of estimates generated by our different analyses to adjust for cross-over/post study therapy (HRs 0.300 to 0.797), and b) the no post-study analysis (HR 0.38) has not been adopted for the base case, even if sunitinib was recommended on the basis of survival estimates derived from a similar (arguably a less robust) analysis.[13]

2.4.3 Limitations of the economic evaluation over and above those highlighted in original submission

- The HR for OS in VEG105192 was adjusted for crossover using the weighted unadjusted RPSFT method. As with all methods for adjusting for crossover the weighted unadjusted RPSFT approach is associated with limitations. Appendix 1 provides further details around the limitations of methodologies used in this analysis.

- Although crossover occurred in the sunitinib trial we were unable to apply IPCW and RPSFT methodology to sunitinib data due to a lack of patient level data. However, the sunitinib analysis used in the present economic evaluation uses an OS HR derived from a no post-study therapy subgroup conducted by Pfizer. To provide a more comparable estimate a no post-study subgroup analysis for pazopanib final OS has also been provided in this submission.

[13] A full PSA (and related CEAC) for the no post-study therapy subgroup is provide in appendix 2

3. DISCUSSION

The strengths and limitations of the VEG105192 study have been discussed in detail in GSK's original submission to NICE (section 5.10.2). Overall survival was the main secondary endpoint in the study. The sample size allowed 90% power to detect a 50% improvement in median OS with pazopanib compared with placebo in the overall study population, but the study was not powered to detect differences in OS within the treatment-naive sub-population.

The main issue limiting the utility of the OS data from the VEG105192 trial, however, is that subsequent active anti-cancer therapy was permitted immediately following disease progression. Patients in the placebo arm were given access to pazopanib via the VEG107769 study, whereas there was otherwise limited access to effective alternative therapies. This has resulted in an imbalance in post-disease progression treatment such that almost twice as many patients in the placebo arm received follow-on medication than in the pazopanib arm (64% vs. 34%), largely as a consequence of cross-over to pazopanib (51% of placebo patients crossed over to receive pazopanib). In some placebo patients, this occurred as early as 2 months post-randomisation to the parent study, due to overlap in the enrolment times for the VEG107769 and VEG105192 and the short PFS for patients receiving placebo treatment.

Thus, the high degree of post-study treatment in the placebo arm, the early initiation of such treatment relative to randomisation in VEG105192, and the longer median exposure to pazopanib in the placebo cross-over subjects compared with subjects in the pazopanib arm (11.2 vs. 7.4 months) are together likely to have confounded the OS endpoint when analysed on an intent-to-treat basis to the point of being rendered ineffectual. This is evident in the fact that placebo subjects who crossed over to pazopanib received a similar benefit from treatment as those subjects who were randomised to pazopanib at the start of VEG105192 (median OS 22.7 vs. 22.9 months).

OS endpoints in oncology trials, particularly when effective treatments are trialled against placebo, are notoriously difficult to interpret due to patients being allowed, for ethical reasons, to receive active treatment upon disease progression. The VEG105192 trial is a case in point and although exposure to placebo was minimised by a 2:1 randomisation, the number of patients in the placebo arm crossing over to receive pazopanib (and other active anti-cancer therapy) has clearly diluted the true treatment effect.

It should be noted that this situation was expected and that the main efficacy data for pazopanib in advanced RCC lie in the primary endpoint of progression-free survival (PFS). PFS remains an appropriate and well accepted surrogate for survival in RCC trials (EMA 2005; George 2009; Bracarda 2009) and is not impacted by cross-over/post-study therapy. In the VEG105192 trial, large treatment effects by pazopanib were observed in PFS in the treatment-naive population (11.1 vs. 2.8 months; HR 0.40 [95% CI: 0.27-0.60]; $p<0.0001$), clearly delineating the true treatment effect of pazopanib compared with placebo.

In order to estimate the true treatment effect on OS, methodologies are required to adjust for the cross-over/receipt of other anti-cancer therapies post-disease progression. Significant effort has therefore been made to control for this effect in VEG105192 through the application of complex statistical techniques, including the RPFST and IPCW methods, with the help of leaders in this field (discussed in section 1.4).

Regardless of the analysis undertaken to adjust for cross-over/post-study therapy, our results consistently indicate that treatment with pazopanib is associated with a clinically meaningful survival benefit compared with placebo/BSC in treatment-naive patients with advanced RCC.

The HR estimate of 0.501 for OS for pazopanib versus placebo/BSC obtained using the weighted, unadjusted RPSFT method has been used for the base case in the indirect comparison and in the economic evaluation. Selection of the RPSFT over the IPCW method is line with previous NICE appraisals in which RPSFT was acknowledged as being the more methodologically robust since randomisation is preserved and an assumption of no unmeasured confounders is not required (Everolimus FAD, June 2010).

We believe that the HR=0.501 estimate provides a reasonable representation of the likely benefit of pazopanib on survival. The upper 95% confidence limit on the HR based on inversion of the test statistic is less than 1.0 and is therefore statistically significant. The estimate lies within the range of HRs generated by our comprehensive analyses (0.300 to 0.797, Table 1.17). If anything it could be considered to be a conservative estimate. An analysis conducted in patients with no post-study therapy yielded an OS HR for pazopanib versus placebo of 0.380. A similar OS analysis in patients with no post-study therapy was conducted on the sunitinib pivotal study (Motzer 2009). Whilst this analysis was criticised by the ERG/DSU involved in the sunitinib appraisal, it nevertheless formed the basis for the cost-effectiveness estimates on which sunitinib was recommended for use by NICE (NICE TA 169). Our analysis may be more robust in excluding patients still on study therapy (i.e. those who have not progressed) and thus it would not have been unreasonable for use in our base case. A full PSA (and related CEAC) for the no post-study therapy sub-group is provided in Appendix 2.

A limitation of the evidence base is the lack of head-to-head data for pazopanib versus sunitinib or IFN, the comparators of interest in this appraisal, and consequently, a clinical comparison was only possible using indirect comparison methodology (Bucher 1997). As discussed in section 5.7 of our original submission, the 7 studies utilised in the indirect comparison (VEG105192; the sunitinib pivotal trial [Motzer 2009]; and 5 IFN studies) were of similar design and involved subjects with broadly similar baseline characteristics.

Results of the base case indirect comparison using the final OS data (adjusted using the weighted RPSFT HR estimate) demonstrate that pazopanib has a similar survival benefit to sunitinib (HR: 0.969 [95% CI: 0.359-2.608]). This HR, when applied to the economic model, leads to a projected median OS of 27.8 months for pazopanib and 26.8 months for sunitinib (with 95% CIs that overlap). The projected median OS for sunitinb of 26.8 months is very close to the median reported in the pivotal study (26.4 months; Motzer 2009), confirming the validity of the weighted RPSFT approach. The ongoing head-to-head study of pazopanib versus sunitinib (VEG108884 [COMPARZ]) should address the uncertainty in the comparative efficacy of the two agents in the first-line treatment of advanced RCC. This trial, which is due to report by Q2 2012, constitutes the first head-to-head trial ever to be conducted comparing two targeted agents in the advanced RCC setting.

Results from the updated economic evaluation suggest that pazopanib, in context of part A of the patient access scheme, constitutes a cost-effective treatment option for the first-line treatment of advanced/metastatic RCC. The ICER for pazopanib versus sunitinib is £1,790/QALY in the present evaluation and pazopanib was found to be cost-effective versus sunitinib in the majority of deterministic sensitivity analyses. Furthermore, sunitinib was approved by NICE under the Supplementary Advice on appraising End of Life (EoL) medicines based on an ICER versus IFN of £54,366/QALY. In the present evaluation, the ICERs for sunitinib and pazopanib versus IFN are £42,832/QALY and £38,925/QALY, respectively. If afforded the same consideration relative to IFN, pazopanib meets the three EoL criteria in being a treatment for a small population with a life expectancy of less than 24 months and offering an extension to life of at least 3 months (median OS 27.8 months [95% CI: 5.7-137.9] for pazopanib versus 15.8 months [95% CI: 15.8-15.8] for IFN). In this particular scenario, pazopanib should be considered a cost-effective treatment option.

Similarly, the base case ICER versus BSC is £32,898/QALY; therefore, pazopanib is likely to be a cost-effective option for patients for whom sunitinib or IFN are unsuitable.

It is acknowledged that there is uncertainty surrounding the comparative clinical effectiveness of pazopanib due to the indirect comparison required and the necessity to make adjustments for cross-over/post-study therapy to ascertain its true survival benefit. This is illustrated by probabilistic sensitivity analyses, where for the base case analysis there is a 54% chance of pazopanib being cost-effective versus sunitinib at a threshold of £30,000/QALY.

The favourable risk/benefit profile of pazopanib led to the CHMP adopting a positive opinion recommending a conditional licence as the benefits were seen to outweigh any risks inherent in a lack of head-to-head data. The commitment to the European Medicines Agency (EMA) in relation to the conditional licence is a non-inferiority analysis of pazopanib compared to sunitinib using data integrated from the COMPARZ study and a sub-study [VEG113078] in Asian subjects. The integrated analysis will be performed when 794 PFS events have been observed. The non-inferiority margin is 1.22 (i.e. the upper bound of the confidence interval must be at or below 1.22 in order to declare non-inferiority). Using the sample size and the inferiority margin, it is possible to back-calculate that the required point estimate of the hazard ratio for PFS will need to be approximately 1.06 or less in order to declare non-inferiority[14]. This strict non-inferiority margin seeks to ensure that should pazopanib be found to be non-inferior to sunitinib, clinicians and their patients can be confident that the two drugs have very similar efficacy.

In conclusion, the analyses conducted to adjust for the confounding effects of cross-over/post-study therapy in VEG105192 clearly demonstrate that pazopanib has a meaningful survival benefit compared with placebo/BSC. It also offers a similar survival benefit to sunitinib, currently the only recommended treatment for patients with advanced RCC, when assessed via an indirect comparison. The proposed patient access scheme attempts to reduce current uncertainty in the comparative effectiveness of pazopanib versus sunitinib until the results of the head-to-head study are available [redacted] This can be achieved with minimal additional administrative burden to the NHS. Taken in this context, GSK believes that pazopanib represents a cost-effective therapy and should be recommended as a first-line treatment option by NICE for patients with advanced RCC. As such, patients and physicians will have access to an alternative, clinically effective medicine with a different tolerability profile that is considered to offer a major advantage in the context of the currently available therapies for this disease.

14 Note these calculations are based on an unadjusted HR, even though the final analysis will be stratified because this is a best estimate given it is not possible to entirely predict how the stratification will impact the results.

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