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Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment

Addendum to Evidence Review Group's Report following Pfizer's submission addendum post appeal dated 8 October 2013

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1. Introduction

The Evidence Review Group (ERG) was requested by NICE to provide a critique of the additional evidence submitted by the manufacturer following upheld appeal point 1.4.

Pfizer's submission addendum post appeal included data and analyses for the prior-cytokine population only. Pfizer's submission addendum post appeal is aimed to allow the comparison of axitinib with sunitinib and pazopanib in terms of clinical effectiveness and cost-effectiveness in adults with advanced renal cell carcinoma who have received prior-cytokine treatment, as specified in the updated scope.

Pfizer's submission addendum post appeal consists of two documents: "Section A – decision problem", and a main addendum report; together with an economic model in Excel. The first document, "Section A – decision problem" is more or less the same as the original submission with some parts updated to reflect the new scope. The decision problem does address the final updated scope as issued by NICE. This critique will focus on the main addendum report and the updated economic model.

2. Clinical effectiveness

The purpose of this addendum to the ERG report is to provide an assessment of the comparative clinical and cost effectiveness evidence relating to axitinib and the comparators in the updated scope (i.e. BSC, sunitinib and pazopanib) for the prior-cytokine population.

In the manufacturer's original evidence submission, an indirect comparison was conducted to compare the relative efficacy of axitinib with Best Supportive Care (BSC) in the prior-cytokine population, in line with the original final scope. The network included two studies which allowed a comparison of the relative efficacy of axitinib with BSC relevant to the prior-cytokine population:

- AXIS: a Phase III study of axitinib versus sorafenib (the pivotal trial for axitinib, reported in the original submission) and
- TARGET: a Phase III study of sorafenib versus placebo.

For the comparators in the updated final scope (pazopanib, sunitinib and BSC), the clinical evidence for the efficacy and safety of sunitinib in a prior-cytokine population consists of two, open-label, single-arm non-RCT studies (Study RTKC-0511-014 and Study A6181006/NCT00077974), both of which demonstrated response to sunitinib in patients with metastatic RCC who had failed treatment with cytokines. Furthermore, the evidence for the efficacy and safety of pazopanib consists of a single Phase III RCT conducted versus placebo (Study VEG105192), of which a proportion of enrolled patients had received prior-cytokine therapy. Pazopanib demonstrated significant improvements in progression-free survival (PFS) in a prior-cytokine population compared with placebo, however there was no significant difference in overall survival (OS) in the ITT results. As cross-over was permitted from the placebo arm to the pazopanib arm in the event of disease progression and 54% of placebo patients (ITT population) therefore received treatment with pazopanib, this introduced significant confounding of the OS results. However, results are presented based on the Inverse Probability of Censor Weighting (IPCW) and the Rank Preserving Structural Failure Time (RPSFT) methods as well the ITT-analysis.

The indirect comparison in the original evidence submission was updated in Pfizer's submission addendum post appeal to include the pazopanib study in the evidence network, in order to compare the relative efficacy of axitinib with pazopanib for PFS. According to the manufacturer, "the results of this comparison suggest that there is a 95% probability that axitinib will always be superior to placebo (BSC), pazopanib and sorafenib for the PFS endpoint". In addition the manufacturer stated that "it was not possible to include sunitinib in the evidence network, as there were no relevant RCTs available for the prior-cytokine population."

2.1 Search strategy

The manufacturer did not update the RCT and non-RCT systematic reviews. Therefore, the searches were last performed in April 2012. In addition, a non-systematic search of Medline[1] was carried out to identify further publications for sunitinib in the prior-cytokine population and any publications providing updated results for the VEG105192 study.

Based on these searches the following studies were identified in the prior-cytokine population:

- For sunitinib, two phase II, open-label, single-arm, multicentre studies (Study RTKC-0511-014 and Study A6181006/NCT00077974; N=63 and N=106, respectively) designed to assess the efficacy and safety of sunitinib in patients with metastatic clear-cell RCC after failure of prior-cytokine therapy;[2-4] and one phase II study designed to assess the efficacy and safety of sunitinib in Japanese patients with mRCC who were treatment-naïve or who had previously received cytokine therapy.[5] According to the manufacturer, this study is considered of limited relevance to the UK population and is therefore not used in Pfizer's submission addendum post appeal.
- For pazopanib, one phase III RCT designed to determine the efficacy and safety of pazopanib versus placebo in patients with advanced/mRCC who were naïve to treatment or who had previously received cytokines (VEG105192).[6, 7]

ERG Comment

Pfizer's submission addendum post appeal[8] reported that studies of sunitinib efficacy were identified from a prior NICE MTA report.[9] As the last RCT searches for this report[9] were undertaken in September/October 2007, the ERG considered this justification inadequate and the searches outdated. The ERG was unable to update these searches or screen the results for missed references; therefore the ERG was not aware of any other relevant studies.

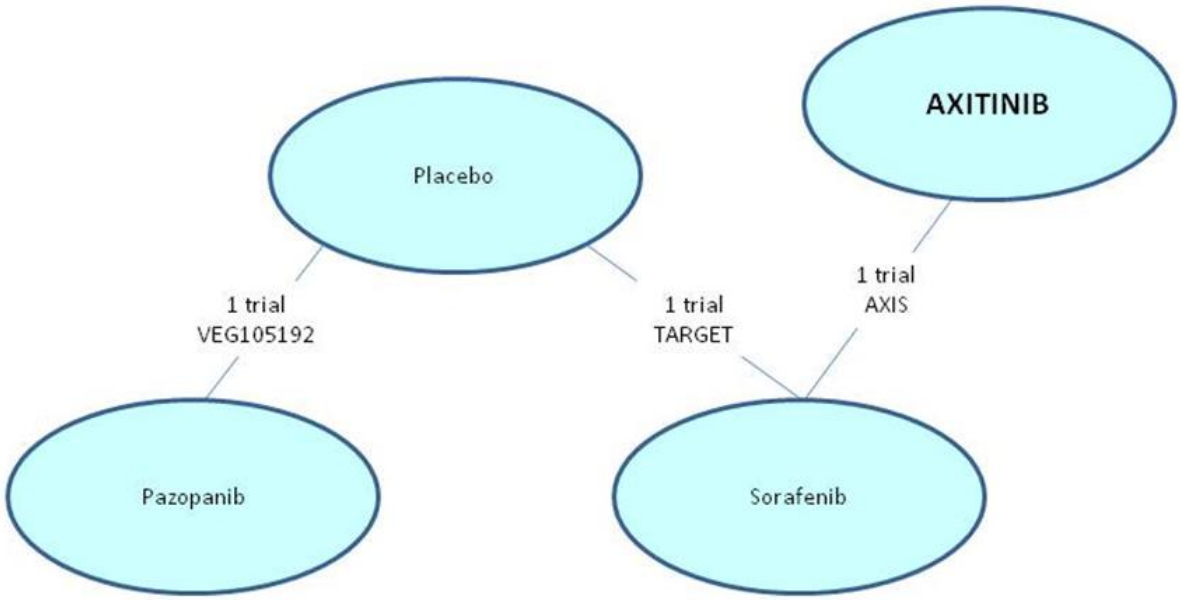
The ERG noted a paucity of free-text terminology and synonyms in the search strategy for renal cell or kidney cancer or tumours. This may have resulted in a lack of sensitivity in the Manufacturer Submission (MS) strategy[1] which might have limited recall of relevant references. There was a similar absence of Emtree indexing terms and CAS registry numbers for the intervention of interest and all comparators. The ERG noted this lack of sensitivity in the strategy, however it was not possible to replicate the search or to screen for possible missed references.

Based on the evidence presented in the Pfizer's submission addendum post appeal, the ERG agrees that the available information for sunitinib is not suitable for a comparison with axitinib, because the data for sunitinib are derived from single arm studies. Therefore, a comparison between axitinib and sunitinib is not appropriate.

To enable an indirect comparison between axitinib and pazopanib, the manufacturer identified one relevant RCT of pazopanib versus placebo (VEG105192), which was already identified in the manufacturer's original evidence submission. This study will be discussed further below.

The network diagram for the comparison of axitinib with pazopanib is provided in the figure below (see Pfizer's submission addendum post appeal, Figure 1, page 12).

Figure 1: Network diagram for the comparison of axitinib with pazopanib



2.2 Axitinib versus pazopanib in a prior-cytokine population

The manufacturer presented details of the methodology of the AXIS trial and the VEG105192 trial in Pfizer's submission addendum post appeal (see Table 5, page 8). This table is copied below. Additional information was added by the ERG when relevant and important (underlined).

Table 1: Methodology – AXIS and VEG105192 studies

Trial	AXIS[10]	VEG105192[6, 7]
Study objective	To compare the efficacy and safety of axitinib vs sorafenib in patients with advanced RCC who had disease progression after initial systemic therapy.	To determine the efficacy and safety of pazopanib in treatment-naïve or cytokine pre-treated patients with advanced RCC
Location	175 sites in 22 countries: Europe, N. America, S. America, Asia, Australia. (49 patients at 10 centres in the UK were treated)	Europe, N. America, S. America, Asia, Australasia, Africa
Design	Phase III, randomised, open-label, multicentre, international, two-arm study.	Randomised, placebo-controlled, double-blind, global, multicentre phase III study. Cross-over was permitted.
Duration of study	Treatment was to continue until disease progression, intolerable adverse drug reactions or withdrawal of consent.	Until disease progression, death, unacceptable toxicity or withdrawal of consent for any reason. <u>Patients who progressed were un-blinded and if on placebo were allowed to cross-over to receive pazopanib via an open-label study.</u>

Method of randomisation	Stratified on the basis of ECOG PS (0 or 1) and prior systemic treatment. Randomised in a 1:1 ratio.	Stratified on the basis of ECOG PS (0 or 1), prior nephrectomy (yes or no) and prior systemic treatment (naïve or cytokine pre-treated) Randomised in a 2:1 ratio.
Method of blinding	Double-blind	Double-blind
Intervention and comparator	Axitinib (N=361; Prior-cytokines: n=126, 35%), administered at a starting dose of 5 mg BD Sorafenib (N=362; Prior-cytokines: n=125, 35%), administered at a starting dose of 400 mg BD	Pazopanib 800 mg OD (n=290; Prior-cytokines: n=135, 47%) Placebo OD (n=145; Prior-cytokines: n=67, 46%)
Assessments	CT/MRI scans were required every 6 weeks for the first 12 weeks, then every 8 weeks.	Disease assessments were performed at baseline, every 6 weeks until week 24, and every 8 weeks thereafter until progression. Bone scans were performed at least every 24 weeks in all patients and on confirmation of objective response.
Primary outcomes (including scoring methods and timings of assessments)	PFS (as defined by the IRC) (the time from randomisation to tumour progression or to death)	PFS (the time interval between the date of random assignment and the date of progression or death).
Secondary outcomes (including scoring methods and timings of assessments)	• PFS (Investigator assessment) • OS • ORR • Duration of response • Safety	• OS • Response rate (CR + PR) • Safety
Duration of follow-up	Patients were followed until disease progression, intolerable adverse drug reactions or withdrawal of consent. The final assessment was performed 28 days after the last dose of study drug. All patients were followed for survival at least every 3 months after discontinuing study treatment until at least 3 years after randomisation of the last patient.	Until disease progression, death, unacceptable toxicity or withdrawal of consent. Subsequent anticancer therapy for patients with progressive disease was at the discretion of the patients and their physicians. Patients who experienced disease progression were un-blinded, and if found to be on placebo, had the option of receiving pazopanib via an open-label study.

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; OD, once daily; OR, objective response; OS, overall survival; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma.

The main difference between the two trials is that cross-over from placebo to pazopanib was allowed in the VEG105192 trial after progression of disease. A comparison of the AXIS trial with the TARGET trial was already described in the original manufacturer's submission and critiqued in the original ERG report.

Inclusion and exclusion criteria for the AXIS and VEG105192 trials are presented in Table 6 of the MS (see MS, Table 6, page 9), see also table below.

Table 2: Inclusion/exclusion criteria – AXIS and VEG105192 studies

	AXIS[10]	**VEG105192[6, 7]**
Inclusion criteria	• Histologically or cytologically confirmed mRCC with a clear cell subtype component • Progressive disease criteria per RECIST after 1 prior systemic first-line regimen for mRCC which had to have contained either sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s) • ECOG performance status of 0 or 1	• Clear cell or predominantly clear cell histology • Measurable disease as per RECIST • ≥ 18 years • ECOG PS ≤ 1 • Adequate renal, hepatic and haematological function
Exclusion criteria	• Prior treatment of mRCC with more than 1 systemic first-line regimen • Major surgery <4 weeks or radiation therapy <2 weeks before starting study treatment • Evidence of brain metastases	• CNS metastasis • Leptomeningeal lesions • Poorly controlled hypertension (systolic BP of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg, despite anti-hypertensive therapy) • QTc interval ≥ 470 ms • A history of class III/IV congestive heart failure per NYHA classification, cardiac angioplasty or stenting, myocardial infarction, unstable angina or cerebrovascular accident

Abbreviations: BP, blood pressure; ECOG PS, Eastern Cooperative Oncology Group performance status; mRCC, metastatic renal cell carcinoma; NYHA, New York Heart Association; RECIST, Response Evaluation Criteria in Solid Tumours.

Details of patient characteristics for Study VEG105192 and the axitinib study (AXIS) are presented in Table 3.

Table 3: Patient characteristics – AXIS and VEG105192 studies (ITT Population)

	AXIS[10]		**VEG105192[6]**	
	Axitinib (N=361)	**Sorafenib (N=362)**	**Pazopanib N=290**	**Placebo N=145**
Age, median (range)	61.0 (20-82)	61.0 (20-80)	59 (28-85)	60 (25-81)
Male, n (%)	265 (73.4)	258 (71.3)	198 (68)	109 (75)
ECOG performance status, n (%)				
0	195 (54.0)	200 (55.2)	123 (42)	60 (41)
1	162 (44.9)	160 (44.2)	167 (58)	85 (59)
>1	1 (0.3)	0	0	0
MSKCC risk score, n (%)				
Favourable	100 (27.7)	101 (27.9)	113 (39)	57 (39)
Intermediate	134 (37.1)	130 (35.9)	159 (55)	77 (53)
Poor	118 (32.7)	120 (33.1)	9 (3)	5 (3)
Missing data	9 (2.5)	11 (3.0)	9 (3)	6 (4)
Previous nephrectomy, n (%)	327 (90.6)	331 (91.4)	258 (89)	127 (88)

	AXIS[10]		VEG105192[6]	
	Axitinib (N=361)	**Sorafenib (N=362)**	**Pazopanib N=290**	**Placebo N=145**
Previous cytokine therapy, n (%)	126 (34.9)	125 (34.5)	135 (47)	67 (46)
Common metastatic sites				
Lung	274 (75.9)	292 (80.7)	214 (74)	106 (73)
Liver	102 (28.3)	103 (28.5)	75 (26)	32 (22)
Bone	119 (33.0)	107 (29.6)	81 (28)	38 (26)
Lymph node	209 (57.9)	202 (55.8)	157 (54)	86 (59)
Kidney	81 (22.4)	77 (21.3)	66 (23)	36 (25)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Centre; NR, not reported.

ERG Comment

The populations in the AXIS and VEG105192 trials are reasonably comparable based on a comparison of the ITT populations in both trials. Based on ECOG it looks like the VEG105192 trial has more diseased patients, as a higher percentage of patients have score 1. However, based on MSKCC it looks like AXIS patients are more diseased, as there are more patients with a poor risk score.

More importantly, no comparison was possible for the prior-cytokines populations only in both trials as data were not presented. The ERG requested this information in the clarification letter, but the manufacturer confirmed that these data are not available (See Pfizer's Response to the Clarification Letter, Question 2).[1]

Results from the indirect comparison of axitinib versus BSC in the cytokine refractory population in the original submission showed that axitinib was significantly better than BSC in terms of PFS and OS (see Table 4). However, as reported in the original ERG report, a comparison of trial populations used in the analyses was not possible, because patient characteristics were not reported for cytokine refractory patients separately in both trials. In addition, there were concerns about the results for overall survival in the TARGET trial due to treatment switching from placebo to sorafenib at the point of disease progression.

Table 4: Summary of results (Axitinib vs BSC in prior-cytokine population)

AXIS	Axitinib	Sorafenib	Difference	HR (95% CI)
Median PFS (months)	12.1 12.0	6.5 8.3	5.6 3.7	0.464 (0.318 to 0.676)[1] 0.636 (0.449 to 0.900)[2]
Median OS (months)	29.4	27.8	1.6	0.813 (0.555 to 1.191)
TARGET	**Sorafenib**	**Placebo**	**Difference**	**HR (95% CI)**
Median PFS (months)	5.5	2.8	2.7	0.54 (0.45 to 0.64)
Median OS (months)	17.8	14.3	3.5	0.78 (0.62 to 0.97)*
Indirect comparison	**Axitinib**	**BSC**	**Difference**	**HR (95% CrI)**
Median PFS (months)	11**	3.5**	7.5**	**0.251 (0.165 to 0.379)**†
Median OS (months)	33.5§	23.5§	10§	**0.63 (0.41 to 0.99)**

1 Independent Review Committee (IRC) assessment; 2 Investigator assessment
* Placebo censored at cross-over
** Approximation based on 3 extrapolated curves (Weibull, Lognormal and Gompertz) used in model
† Based on IRC assessment in the AXIS trial
§ Approximation based on 3 extrapolated curves (Weibull, Loglogistic and Gompertz) used in model

The Appraisal Committee "also noted that an assumption of proportional hazards, which assumes a constant treatment effect over a lifetime, had been used to derive the survival estimates and had not been tested. Therefore, the Committee concluded that although the indirect comparison was adequately performed, the results might not be robust." (Final Appraisal Decision (FAD), point 4.6, page 34)

In Pfizer's submission addendum post appeal, Pfizer added the results of the VEG105192 trial (pazopanib versus placebo) to the indirect comparison, allowing a comparison of axitinib versus pazopanib in the prior-cytokine population for PFS. The results of this indirect comparison are presented in Table 5. Pfizer did not perform an indirect comparison for OS due to concerns about the reliability of OS results from the VEG105192 trial where patients who progressed could cross-over from placebo to pazopanib. The ERG has calculated these results using the same analysis methods used for the PFS outcome, and the three sets of OS results from the VEG105192 trial (ITT; and the two methods adjusting for cross-over: IPCW and RPSFT). They are presented in table 5.

Table 5: Summary of results (Axitinib versus pazopanib in prior-cytokine population)

VEG105192	**Pazopanib**	**Placebo**	**Difference**	**HR (95% CI)**
Median PFS (months)	7.4	4.2	3.2	0.54 (0.35 to 0.84)
Median OS (months)	22.7	18.7	4.0	0.82 (0.57 to 1.16) ITT 0.53 (0.315 to 1.112) IPCW 0.53 (0.341 to 4.849) RPSFT
Indirect comparison	**Axitinib**	**Pazopanib**	**Difference**	**HR (95% CrI)**
Median PFS (months)	11.5*	7.4*	4.1*	**0.465 (0.255 to 0.852)**
Median OS (months)	33.3*	22.7*	10.6*	0.77 (0.27 to 2.16) ITT** 1.197 (0.37 to 3.84) IPCW** 1.198 (0.23 to 6.30) RPSFT**

HR=Hazard Ratio; ITT=Intention-to-Treat; IPCW=inverse probability of censor weighting; RPSFT=rank preserving structural failure time
* See Table 12, Pfizer's submission addendum post appeal (A copy of this table is added as Appendix 1 in this report)
** ERG calculations

Superseded - see erratum

ERG Comment

Axitinib versus sunitinib:

The manufacturer did not perform an indirect comparison of axitinib versus sunitinib in a prior-cytokine population. Instead it presented a naïve comparison of survival data for axitinib and sunitinib. The ERG asked the manufacturer to explain what was meant by a naïve comparison in the clarification letter. The manufacturer explained that "The use of the term naïve comparison (also referred to as an unadjusted comparison in the literature) in section 4 and 5 of Pfizer's submission addendum post appeal describes the approach adopted in the addendum whereby the results of individual arms from the AXIS, TARGET, VEG105192 and sunitinib trials were directly compared with each other." (See Pfizer's Response to the Clarification Letter, Question 10).[1] Based on this naïve comparison the manufacturer concludes that "axitinib may be associated with an additional 5.5 months survival versus sunitinib (using the mature results of the larger phase II study)" (MS, section 4, page 15). "In addition, axitinib may be associated with a PFS benefit of an additional 3.3 months versus sunitinib (using larger phase II study)" (MS, section 4, page 15). As these comparisons are based on evidence from single arm studies, and not a direct comparison within a study, the ERG considers these comparisons unreliable. Therefore, the ERG agrees that a reliable indirect comparison of axitinib versus sunitinib in a prior-cytokine population is not possible with the available data.

Axitinib versus pazopanib:

The manufacturer describes the challenges in performing an indirect comparison for overall survival (MS, section 3.3, page 14) and concludes that an indirect comparison was prone to considerable biases and would therefore not considered to be robust.

In a recent Health Economics and Decision Science (HEDS) discussion paper, Latimer et al discuss statistical approaches for adjusting survival estimates in the presence of treatment switching in order to determine which methods are most appropriate in a range of realistic scenarios.[11] The authors conclude that randomisation-based methods (such as RPSFT) can accurately adjust for treatment switching when the treatment effect seen in patients that switch is the same as for patients randomised to the experimental group. When this is not the case observational-based methods (such as IPCW) or simple two stage methods should be considered, although the IPCW is prone to substantial bias when the proportion of patients that switch is greater than approximately 90%. Simple methods such as censoring or excluding patients that switch should not be used.

In other words, the hazard ratio for overall survival from the TARGET trial (censoring at cross-over) has been calculated using a method which may not be reliable. Regarding the hazard ratio for overall survival for pazopanib versus placebo, we have three estimates: based on the ITT analyses, and adjusted using the RPSFT and IPCW methods. Given that treatment

switching was permitted in the VEG105192 trial after disease progression for patients on placebo the “common treatment effect” assumption of the RPSFT method may not be clinically plausible. The IPCW method is conditional on a “no unmeasured confounders” assumption. This requires that all variables which could contribute to the reasons for switching treatment are measured. This assumption is problematic with smaller data sets (the VEG105192 trial included 145 placebo patients (67 prior-cytokine patients), with 54% of placebo patients receiving pazopanib via the open-label extension study). In conclusion, all three estimates for the hazard ratio for overall survival of pazopanib versus placebo in the VEG105192 trial may be biased and unreliable. Although both adjusted methods produce the same point estimate for the HR of pazopanib versus placebo (HR = 0.53), the difference in confidence intervals is quite substantial.

We have performed an indirect comparison for OS using the same analysis methods used for the PFS outcome, and the three sets of OS results from the VEG105192 trial (ITT; IPCW and RPSFT). The results are presented in table 5 for illustration but, due to the issues stated above, none of these results can be considered reliable. Overall, both the hazard ratios for OS for axitinib versus BSC and for pazopanib versus placebo may be biased, therefore any indirect comparison results will be biased due to the high proportion of patients crossing from placebo to active treatment after disease progression.

The hazard ratio for PFS is most likely a more reliable estimate than the hazard ratio for OS: axitinib versus pazopanib HR = 0.465 (0.255 to 0.852), because it is not affected by cross-over.

As described in the original ERG report, other outcomes, such as response, quality of life and adverse events were not reported for the comparison between axitinib and BSC in cytokine refractory patients. Therefore, these outcomes are also not reported for the comparison between axitinib and pazopanib.

3. Cost-effectiveness

In this section the manufacturer performs a naïve cost-effectiveness study of axitinib compared to BSC, sunitinib and pazopanib for the prior cytokine population.

Axitinib versus BSC:

In the original submission with PAS, the base case ICER reported for the prior cytokine population of axitinib versus BSC was £55,000 per QALY gained. According to the manufacturer this ICER is overestimated. The overestimation comes basically from the bias introduced in the OS analysis in the TARGET study, where 48% of the patients crossed over to sorafenib, resulting in an underestimation of the OS gain of axitinib versus BSC. Moreover, as discussed in section 4.12 of the FAD, this idea was also supported by clinical and patient experts who considered that the base case OS for the BSC group (approximately 24 months) is not observed in clinical practice.[12]

In the manufacturer's ACD response, it was proposed to use the lower 95% CI for the OS HR. In that scenario, the median OS for BSC was estimated at 17.6 months (closer to the 14.3 months reported in TARGET), and the ICER for the prior cytokine population of axitinib versus BSC was £33,000 per QALY gained with the PAS. According to the manufacturer, it should be seen as more relevant for decision making since it is based on more clinically plausible results regarding BSC.

Axitinib versus sunitinib and axitinib versus pazopanib:

The data presented in Table 12 (a copy of this table is added as Appendix 1 in this report) in the manufacturer's addendum report[8] shows that the median OS for BSC from the indirect comparison (24 months) is higher than the median OS for pazopanib (22.7 - 95% CI: 19.3–28.3) or sunitinib (23.9 - 95% CI: 14.1-30.7). Since BSC has a lower cost than either of these treatments, it is concluded that BSC dominates both sunitinib and pazopanib (i.e. has a lower cost and higher effectiveness). Thus, in this scenario there is no rationale to compare axitinib with sunitinib or pazopanib.

Moreover, the manufacturer reasoned that, even in the situation where BSC does not dominate sunitinib or pazopanib (e.g. if a median OS for BSC is assumed to be 17.6 months), an ICER of £55,000 per QALY gained (with the PAS) can be seen as an upper bound for the ICER of axitinib versus sunitinib or pazopanib for the prior cytokine population, since these are both more expensive than BSC and they are assumed to be less effective than BSC with a median OS of 24 months (see Table 6 below).

Table 6: Cost-effectiveness results for prior cytokine population

Comparison	**ICER per QALY gained**	
	Median OS BSC = 24 months	**Median OS BSC = 17.6 months**
Axitinib vs. BSC	£55K	£33K
Axitinib vs. Sunitinib	Extended dominance (sunitinib more expensive than BSC, median OS 23.9)	< £55K
Axitinib vs. Pazopanib	Extended dominance (pazopanib more expensive than BSC, median OS 22.1)	< £55K

End of life criteria:

Based on the information previously submitted by the manufacturer, axitinib is expected to prolong survival for more than three months compared to BSC. According to the manufacturer, the data presented in Table 12 (see Appendix 1 in this report) in Pfizer's submission addendum post appeal[8] support the idea that PFS and OS benefit over sunitinib and pazopanib is greater than three months, and that life expectancy with sunitinib and pazopanib will likely be around 24 months.

Conclusion:

According to the manufacturer, only BSC should be considered as comparator for the prior-cytokine population. Thus, they conclude that, compared to BSC, axitinib is cost-effective for the prior cytokine population since it is expected to fulfil end of life criteria and the relevant ICERs for decision making are lower than the accepted thresholds for other end of life treatments.

ERG Comment

First it should be noted that, as mentioned in the introduction, an updated electronic model was provided. However, the only change between this model and the previous version was the addition of a worksheet containing Table 12 (see Appendix 1) from Pfizer's submission addendum post appeal.[8] So we will here only discuss the so-called 'naïve economic analysis' that was reported in the addendum.

Most of the discussion in this section is focused on the validity of the median OS estimated from the indirect comparison for BSC (24 months) which is seen as too high by the manufacturer (due to the limitations of the evidence network and clinical implausibility of this estimate). On the other hand, the manufacturer considered the median OS estimate from the indirect comparison for axitinib (estimated median 33 months) to be valid "*as it reflects the axitinib data from AXIS*" (observed median 29 months). Nevertheless, for the purposes of the naïve comparison, the manufacturer considered the median OS reported in clinical trials (in particular the OS of 29 months for axitinib) "*to ensure consistency of approach across the different comparators*".

However, it is important to realise that the ICER of £55,000 per QALY gained, which results from the manufacturer analyses, and therefore from the indirect comparison, is used as reference ICER for the naïve analyses and "*would be valid since the differences between the estimates of median OS with the Kaplan-Meier method in AXIS and the Weibull parametric model only reflect the limitation of the parametric model fit around the median time point but are ultimately based on the same RCT data for axitinib*".

The ERG does not fully agree with this. Following the same reasoning as the manufacturer's, a naïve comparison based on AXIS data could be performed and it could be concluded that if the OS for axitinib is smaller than 33 months (e.g. 29 months reported in AXIS) then the ICER would be larger than £55,000.

The manufacturer further assumed (as an alternative) a 17.6 months median OS for BSC in the prior cytokine population which resulted in £33,000 per QALY gained with the PAS. The manufacturer considers this median value "*more plausible but potentially high based on the available evidence from TARGET, VEG105192 and the totality of evidence in the prior cytokine population (see section 6 of the Addendum and section 2.3 of the response to the ACD)*". Therefore, it could be further argued that if the real median OS for BSC in the prior cytokine population is lower than 17.6 months, as the manufacturer suggested, then the corresponding ICER should be lower than £33,000. However, also in this case discussion about the OS for axitinib is missing.

The above way of reasoning relies not only on the median OS, but also on the costs of treatment with sunitinib and pazopanib. While the ERG agrees that it seems likely that these treatment costs are higher, because of drug costs and possible side effects, than the costs of BSC, no attempt has been made by the manufacturer to estimate these treatment costs.

In general, when multiple treatments are compared, results should be presented as a full incremental analysis, rather than pairwise comparisons. This analysis should include the expected costs and expected QALYs for all the treatments being compared, thus also pazopanib and sunitinib. However, due to the limitations of the evidence base for the comparisons of axitinib with sunitinib and pazopanib in the prior cytokine population, the manufacturer was not able to estimate expected costs and expected QALYs for pazopanib and sunitinib. Therefore, it is not possible to quantify to what extent the ICERs of axitinib compared with sunitinib and axitinib compared with pazopanib are smaller than £55,000 per QALY gained.

All the results presented in this naïve analysis are based on median estimates only, with no analyses of uncertainty. For the valid estimation of ICERs however, means should always be used rather than medians. The manufacturer provided sensitivity analyses for the comparison of axitinib with BSC in the prior cytokine population in their evidence submission and ACD response, but these were not performed for the comparisons of axitinib with sunitinib and pazopanib "*due to the limitations of the evidence base*".

4. Conclusions

Based on the evidence presented in the manufacturer's addendum, the ERG agrees that the available information for sunitinib is not suitable for an indirect comparison with axitinib. Therefore, a comparison between axitinib and sunitinib is not appropriate.

For the comparison between axitinib and pazopanib, both the hazard ratios for OS for axitinib versus BSC and for pazopanib versus placebo may be biased. Therefore, the hazard ratio for OS for axitinib versus pazopanib may also be biased. The hazard ratio for PFS is most likely a more reliable estimate than the hazard ratio for OS: axitinib versus pazopanib HR = 0.465 (0.255 to 0.852) as it is not affected by cross-over.

Other outcomes, such as response, quality of life and adverse events were not reported for the comparison between axitinib and BSC in cytokine refractory patients. Therefore, these outcomes are also not reported for the comparison between axitinib and pazopanib.

Regarding the health economic analysis, we agree with the qualification of 'naïve' that the manufacturer used in their addendum, as the whole approach is based on a comparison of observed OS medians. Thus, the analysis can only be seen as indicative and does not provide an estimate of the cost-effectiveness of axitinib compared to sunitinib or pazopanib, respectively, but only a possible upperbound. However, given the evidence base, no good options are available to robustly estimate an ICER for axitinib compared to sunitinib or pazopanib.

5. References

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Appendix 1: Table 12 in Pfizer's submission addendum post appeal

Table 12: Naïve presentation of results for therapies for the second-line treatment of advanced RCC (prior-cytokine) – As presented in Pfizer's response to the Clarification letter.[1]

	Indirect Comparison		**AXIS**	**TARGET**	**VEG105192[6, 7]**			**Sunitinib**	
	Axitinib	**BSC**	**Axitinib**	**BSC**	**BSC**		**Pazopanib**		
			AXIS: Rini et al, 2011[10]	**Censored analysis in Escudier et al, 2007[13] and 2009[14]**	**With crossover**	**Crossover adjusted**		**Motzer, et al, 2006a[2]**	**Motzer, et al. 2007[3]**
Patients, N	-	-	126	452	67[b]		135[b]	63	106
PFS, months (95% CI)	11.5 (Weibull)	3.7 (Weibull)	12.1 (10.1-13.9)	2.8 (*NR*)	4.2(NR)[b]		7.4 (NR)[b]	8.7 (5.5-10.7)	8.8 (7.8-13.5)
OS, months (95% CI)	33.3 (Weibull)	24 (Weibull)	29.4 (24.5 – NE)	14.3 (*NR*)	18.7(14.2–26.3)	NR	22.7 (19.3–28.3)	16.4 (10.8-NA)	23.9 (14.1-30.7)

a: Sternberg et al, 2013[7]; b: Sternberg et al, 2010[6]

Abbreviations: CI, confidence interval; IPCW, inverse probability of censor weighting; NA, not attained; NE, not estimable;NR, not reported; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural failure time.