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BY EMAIL

8th November 2013

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment (ID 518) - Addendum

Dear Frances,

In response to the invitation to submit evidence on the 27th September 2013 and further e-mail correspondence, we have included data and analyses for the prior cytokine population only as part of the addendum below in line with your request. We hope that the information provided within this addendum will be pertinent to the Appraisal Committee's consideration of the comparison of axitinib with sunitinib and pazopanib, introduced as a result of the updated scope, following upheld appeal point 1.4. These data will allow an assessment of the comparative clinical and health economic evidence relating to axitinib and the new comparators.

We are disappointed that despite our formal request on the 29th October 2013 we are not allowed to submit additional analyses or new data to respond to information for the prior sunitinib population that only became apparent during the appeal and is pertinent to the Appraisal Committee steps to address appeal point 1.7. We maintain our view that such an approach is unfair and unreasonable and does not properly reflect either NICE's procedures or the appeal decision.

As explained in our letter on the 29th October, Pfizer did not intend to provide a full resubmission of data in relation to the prior-sunitinib population. During the course of the appeal, further information was provided by the Chair of the Appraisal Committee in relation to the reasons for refusing to recommend axitinib in these patients, despite an ICER which fell within the range normally viewed as cost-effective by NICE (upheld appeal point 1.7) which we have not previously been able to comment upon. We maintain our view that in the interests of fairness, Pfizer should be given the opportunity to comment on this information.

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More specifically, our intention was to respond to the Appraisal Committee's concerns with the level of uncertainty as clarified in the appeal. We are able to provide the results of further analyses demonstrating that the level of uncertainty in the ICER is considerably reduced when based upon estimates of BSC overall survival that the Appraisal Committee have already stated as being most clinically plausible. Furthermore, new analyses and data recently presented at the European Cancer Congress in September, 2013 are now available that provide further evidence to support the validity of axitinib's clinical- and cost-effectiveness versus BSC presented in our evidence submission. These analyses and data demonstrate that any remaining uncertainty does not preclude axitinib from being a cost-effective treatment option for a small group of patients with a very high unmet need for whom there are no NICE recommended second-line treatments.

We strongly believe that these data along with the evidence provided in the addendum below would allow NICE to recommend axitinib as a second-line treatment for patients with advanced/metastatic renal cell carcinoma (mRCC) after failure of prior treatment with sunitinib or a cytokine. Furthermore, Pfizer request that subsequent to the meeting in February, the Appraisal Committee issues an ACD that allows Pfizer to provide further information on the prior-sunitinib population. We believe such an action would be a reasonable approach that would enable Pfizer to consult further on this population, whilst remaining within the NICE appraisal process.

Yours sincerely,

Ben Osborn

Head of Oncology Business Unit UK

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

An addendum to the Single Technology Appraisal submitted on 13th August 2012

Submitted by Pfizer Ltd.

8th November 2013

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Abbreviations

AC	Appraisal Committee
ACD	Appraisal Consultation Document
AE	Adverse event
BD	Twice daily
BP	Blood pressure
BSC	Best supportive care
CI	Confidence interval
CR	Complete response
CrI	Credible interval
CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
EoL	End of life
ECOG PS	Eastern Cooperative Oncology Group performance status
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFN-α	Interferon alpha
IL-2	Interleukin-2
IPCW	Inverse probability of censoring weighted
IRC	Independent review committee
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
NA	Not yet attained
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NYHA	New York Heart Association
OD	Once daily
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PFS	Progression-free survival
PR	Partial response
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank preserving structural failure time

STA	Single Technology Appraisal
TTP	Time to progression

Executive summary

In August 2012, Pfizer Ltd developed a Single Technology Appraisal (STA) evidence submission for the appraisal of axitinib 'for the treatment of adults with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine'. Following the Appraisal Committee's decision not to recommend axitinib and the subsequent appeal decision, a new scope was issued in October 2013. In addition to the comparator of best supportive care (BSC) from the original scope, the updated scope also contains sunitinib and pazopanib as comparators for patients who have failed prior cytokine therapy (the prior-cytokine population).

Pfizer Ltd maintains the view that BSC should be the only relevant comparator in the prior-cytokine population. The rationale for this position, previously expressed during the consultation of the draft scope, is that neither sunitinib nor pazopanib have been recommended by NICE for the second-line treatment of patients with advanced/mRCC. Sunitinib was found not to be cost-effective as a second line treatment for mRCC (TA178), while pazopanib was removed from the NICE work program following consideration by Ministers of the small number of patients who may be eligible to receive pazopanib.

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

In the original evidence submission, an indirect comparison was conducted to compare the relative efficacy of axitinib with 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 vs sorafenib (the pivotal trial for axitinib, reported in the original submission) and TARGET: a Phase III study of sorafenib vs placebo.

For the new comparators in the updated scope, 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 high levels of 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 vs 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 therefore received treatment with pazopanib, this introduced significant confounding of the OS results.

The indirect comparison in the original evidence submission was updated to include the pazopanib pivotal study in the evidence network, in order to compare the relative efficacy of axitinib with pazopanib for PFS. 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. It was not possible to include sunitinib in the evidence network, as there were no relevant RCTs available for the prior-cytokine population.

The limitations of performing an indirect comparison for OS have been extensively discussed in the original evidence submission, Appraisal Consultation Document (ACD) and Final Appraisal Determination (FAD), with consensus that confounding due to unadjusted cross-over in TARGET study (48% patients in the placebo arm crossed over to sorafenib) substantially overestimates OS for BSC in the evidence network and therefore produces clinically implausible results.

As an indirect comparison for OS was not considered to be a robust approach due to biased evidence from TARGET, extension of the evidence network to include the pazopanib study would further confound the results, a naïve comparison was performed. By comparing the median PFS and OS of each of the comparator therapies with axitinib, a naïve comparison demonstrates that axitinib would offer at least 3 months additional overall survival vs. sunitinib and pazopanib. More specifically, the results suggest that axitinib treatment for prior cytokine patients could be associated with an additional 3.3 months PFS (12.1 months vs. 8.8 months) and 5.5 months OS (29.4 months vs. 23.9 months) vs. sunitinib and an additional 4.7 months PFS (12.1 months vs. 7.4 months) and 6.7 months OS (29.4 months vs. 22.7 months) vs. pazopanib based on this naive comparison.

In our ACD response (1), the base case ICER with the revised Patient Access Scheme (PAS) in the prior cytokine population of axitinib versus BSC was £55K per QALY gained, assuming a median OS of 24 months for patients receiving BSC. As mentioned previously, the ICER is an over-estimation in this population due to the limitations of the evidence network, in particular the bias introduced in the OS analysis by the unadjusted cross-over in the TARGET study. As discussed in section 4.12 of the FAD the Appraisal Committee, clinical specialists and patient experts considered that the overall survival of approximately 24 months for BSC of the prior-cytokine group is not seen clinically. As described in our ACD response, when the lower 95% CI for OS HR was used, the median OS for BSC in the prior cytokine population was 17.6 months which is close to the 14.3 months reported in TARGET. The ICER of axitinib versus BSC for this scenario was £33K per QALY with the revised PAS, which is close to the base case ICER in the prior sunitinib population and should be considered more relevant for decision making.

However, in contrast to the evidence provided in the ACD, the Appraisal Committee has selected the median 24 months OS for BSC as the basis for the decision. Based on this assumption and the naive comparison results, it seems that BSC from the indirect comparison has a numerically higher median OS (24 months) than median OS data for pazopanib (22.1 - 95% CI: 19.3–28.3) from the pivotal trial or sunitinib (23.9 - 95% CI: 14.1-30.7) from the large Phase II trial. Further to that, BSC has a lower cost than either of these active treatments. Therefore in this naïve comparison, BSC dominates both sunitinib and pazopanib (i.e. has a lower cost and greater effectiveness) and as a result, there is no economic rationale in this scenario to compare axitinib with sunitinib or pazopanib (i.e. sunitinib and pazopanib are extendedly dominated by axitinib). In this situation given the high median OS assumed for BSC, it can be deduced that if the ICER of axitinib compared with BSC is £55, 000 per QALY with the revised PAS, the ICER of axitinib compared with a treatment (sunitinib or pazopanib) which is both more expensive and less effective than BSC will be substantially lower than £55,000 per QALY.

In conclusion, axitinib is a cost-effective treatment option for the prior-cytokine population as it is expected to fulfil end of life criteria vs. BSC and the relevant ICERs for decision making are lower than the accepted thresholds.

Pfizer point out that on the 11th November, the Scottish Medicines Consortium (SMC) published advice that axitinib has been recommended for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine. The recommendation from the SMC for axitinib in both patient populations demonstrates that other health technology appraisal bodies in the UK have considered the same clinical evidence and results of the health economic analyses to be sufficiently robust for the basis of decision making in light of the benefit expected for patients when treated with axitinib.

1 Introduction

In February 2012, the appraisal of axitinib 'for the treatment of adults with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine' was referred by the Department of Health to NICE. A manufacturer's submission was subsequently developed by Pfizer Ltd and was submitted to NICE in August 2012.

Following the publication of the Final Appraisal Determination (FAD) on 23rd March 2013, Pfizer Ltd submitted an appeal against the decision to not recommend axitinib for the above indication. The appeal was upheld on two, ground 1 points:

- Point 1.4 (The Appraisal Committee's refusal to find that use of axitinib in post-cytokine patients satisfied the "end of life" criteria on the basis that no comparison with sunitinib or pazopanib had been provided was inconsistent with the Scope for this appraisal) was upheld because the Appraisal Committee did not act in accordance with the scope for this appraisal, resulting in unfairness to Pfizer Ltd.
- Point 1.7 (The Appraisal Committee's final conclusions in relation to the cost-effectiveness of axitinib are not stated and its reasons for failing to recommend second-line treatment in patients with advanced or metastatic RCC are therefore unclear, in circumstances where the incremental cost-effectiveness ratio (ICER) values appear to fall within the range generally regarded as acceptable in other appraisals) was upheld because the Appraisal Committee did not provide sufficiently clear reasons for not recommending axitinib for use in the NHS under the end-of-life (EoL) criteria.

Subsequently, an updated scope was issued for the appraisal of the clinical and cost effectiveness of axitinib for the treatment of adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine (4th October 2013).

The comparators for the updated scope have been specified as follows:

- For people who received previous cytokine therapy (that is, people who have not received any targeted therapy for advanced disease)
  - Sunitinib
  - Pazopanib
  - Best supportive care (BSC)
- For people who received previous sunitinib therapy
  - BSC

Pfizer Ltd maintains the view that BSC is the only relevant comparator in the prior-cytokine population. The rationale for this position, previously expressed during the consultation of the draft scope, is that neither sunitinib nor pazopanib have been recommended by NICE for the second-line treatment of patients with advanced/mRCC. Sunitinib was found not to be cost-effective as a second line treatment for mRCC (TA178) (2), while pazopanib was removed from the NICE work program following consideration by Ministers of the small number of patients who may be eligible to receive pazopanib.

However, to support the Appraisal Committee in the decision problem posed by the new scope, we present data on the additional comparators included in the updated scope of 4th October 2013, providing a summary of the comparative evidence for pazopanib and sunitinib in patients who have received previous cytokine therapy (from here on referred to as the prior-cytokine population). This document is intended to serve as an addendum to the original evidence submission (August 2012) and the Appraisal Consultation Document (ACD) response sent to NICE on 11th January 2013. The additional economic analyses presented in this submission have been conducted on the basis of the revised patient access scheme (PAS) that was approved by the Department of Health in January 2013.

2 Summary of the clinical evidence for pazopanib and sunitinib in a prior-cytokine population

2.1 *Summary of the original clinical evidence*

The evidence submission (dated August 2012) included a systematic literature review conducted to identify randomised controlled trial (RCT) evidence on the efficacy and safety of axitinib and relevant comparators for the management of advanced/metastatic RCC (mRCC) in the second-line setting. The systematic review was conducted on 1st July 2010 and updated on 27th April 2012. In total, 25 RCTs were identified. Of these, in the second-line setting, one reported data on axitinib, one on pazopanib and one on sunitinib:

- AXIS: a Phase III study of axitinib vs sorafenib (the pivotal trial for axitinib, reported in the original submission) (3)
- VEG105192: a Phase III study of pazopanib vs placebo (4)
- Open-label Phase II study of sunitinib (am) vs sunitinib (pm) (5)

The phase II study comparing the use of sunitinib in the morning vs in the evening was not utilised in the original submission as it did not include different interventions, and therefore could not contribute information to comparative effectiveness

In addition, a systematic review was conducted on 24th April 2012 to identify non-RCTs reporting on the efficacy and safety of axitinib only, in the second-line setting.

2.2 *Summary of additional clinical evidence*

Due to the time restrictions for submission of this addendum, it was not possible to update the RCT and non-RCT systematic reviews. In order to satisfy the requirements of the new scope, studies reporting efficacy data for sunitinib in patients who had received previous cytokine therapy were identified from the systematic review of a previous NICE Multi-Technology Appraisal for first and second-line treatments (6). A non-systematic search of Medline was also carried out to identify further publications for sunitinib in the prior cytokine population and any publications providing updated results for the VEG105192 study.

The following studies of relevance were identified in prior-cytokine populations and are described further in Sections 2.3 and 2.4:

Sunitinib:

- RTKC-0511-014: A Phase II, open-label, single-arm, multicentre study designed to assess the efficacy and safety of sunitinib in patients (N=63) with metastatic clear-cell RCC after failure of prior cytokine therapy (described in Section 2.3)

  Relevant publications:

  Motzer et al, J Clin Onc 2006; 24:16–24 (7)

- A6181006/NCT00077974: A Phase II, open-label, single-arm, multicentre study with independent central review, designed to confirm the anti-tumour efficacy of sunitinib monotherapy in patients (N=106) with metastatic clear-cell RCC after failure of prior cytokine therapy (described in Section 2.3)

  Relevant publications:

  Motzer et al, JAMA 2006; 295(21):2516-2524 (8)

  Motzer et al, J Urol 2007; 178:1883–1887 (9)

- Japanese study: A 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. This study is considered of limited relevance to the UK population and is therefore not reported here (10).

Pazopanib:

- VEG105192: A Phase III RCT designed to determine the efficacy and safety of pazopanib vs placebo in patients with advanced/mRCC who were naïve to treatment or who had previously received cytokines (described in Section 2.4)

  Relevant publications:

  Sternberg et al, J Clin Oncol 2010; 28(6):1061-1068 (4)

  Sternberg et al, Eur J Cancer 2013; 49, 1287-1296 (11)

2.3 *Sunitinib in a prior-cytokine population*

Relevant publications were identified that reported details on the efficacy and safety of two single-arm, non-RCTs (RTKC-0511-014 and A6181006/NCT00077974). Details of the methodology and results are presented in Sections 2.3.1-2.3.4.

2.3.1 *Methods*

Details of the methodology for the studies of sunitinib in the prior-cytokine population are reported in Table 1. Details of the methodology for the pivotal Phase III axitinib study (AXIS) are also provided for comparison.

Table 1: Methodology – studies of sunitinib in the prior-cytokine population

Study	AXIS (3)	RTKC-0511-014 (7)	A6181006/NCT00077974 (8;9)
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 assess the efficacy and safety of sunitinib in patients with cytokine-refractory metastatic RCC	To confirm the efficacy of sunitinib as a second-line treatment in patients with metastatic clear-cell RCC
Location	175 sites in 22 countries	USA	USA
Design	Phase III, randomised, open-label, multicentre, international, two-arm study	Multicentre, phase II, single-arm study	Open-label, single-arm, multicentre study
Duration of study	Treatment was to continue until disease progression, intolerable adverse drug reactions or withdrawal of consent	Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent	Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent
Intervention and comparator	Axitinib (N=361), administered at a starting dose of 5 mg BD Sorafenib (N=362), administered at a starting dose of 400 mg BD	Patients (N=63) received oral sunitinib at a starting dose of 50 mg/day in 6 week cycles (4 weeks on-treatment, 2 weeks off-treatment).	Patients (N=106) received oral sunitinib at a starting dose of 50 mg/day in 6 week cycles (4 weeks on-treatment, 2 weeks off-treatment).
Assessments	CT/MRI scans were required every 6 weeks for the first 12 weeks, then every 8 weeks.	Objective clinical response was assessed by RECIST after cycles 1, 2, and 4, and every two cycles thereafter until the end of treatment	Clinical response was assessed according to RECIST after each cycle for the first 4 cycles and every other cycle thereafter until the end of treatment
Primary outcomes	PFS (as defined by the IRC)	Overall ORR (defined as the proportion of patients with confirmed CR or PR)	Overall ORR (defined as the proportion of patients with confirmed CR or PR)
Secondary outcomes	• PFS (Investigator assessment) • OS • ORR • Duration of response • Safety • HRQoL	• Time to progression • Median survival • Safety	• Duration of response • Progression-free survival • Overall survival • Safety

Abbreviations: BD, twice daily; CR, complete response; CT, computed tomography; IRC, independent review committee; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours.

2.3.2 *Participants*

Key inclusion/exclusion criteria for the studies of sunitinib in the prior-cytokine population and the pivotal axitinib study (AXIS) are reported in Table 2.

Table 2: Key inclusion and exclusion criteria – studies of sunitinib in the prior-cytokine population

Study	AXIS (3)	RTKC-0511-014 (7)	A6181006/NCT00077974 (8;9)
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	• Histologic confirmation of RCC • Measurable disease with evidence of metastasis • Failure of 1 cytokine-based therapy (IFN-α, IL-2) because of disease progression or unacceptable toxicity • ECOG performance status of 0 or 1	• Patients aged ≥ 18 years with histological confirmation of clear-cell RCC with metastases • Prior nephrectomy • Measurable disease • Failure of 1 cytokine therapy (IFN-α, IL-2 or combination) due to disease progression • ECOG performance status of 0 or 1
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	• Presence of brain metastases • Ongoing cardiac dysrhythmia • Prolongation of QTc interval or any significant cardiac event ≤ 12 months	• Presence of brain metastases • Significant cardiac events ≤ 12 months prior to study drug administration

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IFN-α, interferon alpha; IL-2, interleukin-2; RCC, renal cell carcinoma; RECIST, Response evaluation criteria in solid tumours .

Patient baseline characteristics for the sunitinib prior-cytokine studies and the pivotal axitinib study (AXIS) are reported in Table 3.

Table 3: Baseline characteristics – studies of sunitinib in the prior-cytokine population

Baseline characteristics	AXIS (3)		RTKC-0511-014 (7)	A6181006/ NCT00077974 (8;9)
	Axitinib (N=361)	Sorafenib (N=362)	Sunitinib (N=63)	Sunitinib (N=106)
Sex, n (%)				
Male	265 (73.4)	258 (71.3)	43 (68)	67 (63)
Female	96 (26.6)	104 (28.7)	20 (32)	39 (37)
Age (years), median (range)	61.0 (20-82)	61.0 (20-80)	60 (24-87)	56 (32-79)
ECOG performance status				
0	195 (54.0)	200 (55.2)	34 (54)	58 (55)
1	162 (44.9)	160 (44.2)	29 (46)	48 (45)
>1	1 (0.3)	0	0	0
Histology				
Clear cell	355 (98.3)	359 (99.2)	55 (87)	106(100)[1]
Papillary	0	0	4 (6)	0
Sarcomatoid variant	0	0	1 (2)	0
Unspecified	1 (0.3)	0	3 (5)	0
NR	5 (1.4)	3 (0.8)	0	0
Previous nephrectomy				
Yes	327 (90.6)	331 (91.4)	58(92)	106(100)
No	34 (9.4)	31 (8.6)	5(8)	0
Prior systemic treatment				
Cytokines	126 (34.9)	125 (34.5)	63 (100)	106 (100)
IFN-α	NR	NR	35 (56)	47 (44)
IL-2	NR	NR	19 (30)	50 (47)
IFN-α and IL-2	NR	NR	9 (14)	9 (9)
Prior radiation therapy	NR	NR	25 (40)	20 (19)
Main sites of metastasis				
Lung	274 (75.9)	292 (80.7)	52 (81)	86 (81)
Liver	102 (28.3)	103 (28.5)	10 (16)	29 (27)
Bone	119 (33.0)	107 (29.6)	32 (51)	27 (26)
Lymph nodes	209 (57.9)	202 (55.8)	-	62 (59)
No disease sites				
1	NR	NR	8 (13)	13 (12)
≥ 2	NR	NR	55 (87)	93 (88)
MSKCC risk factors				
0	100 (28)	101 (28)	34 (54)	61 (58)
≥ 1	252 (70)	250 (69)	29 (46)	45 (42)
Not applicable	9 (2)	11 (3.0)	0	0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; NR, not reported.
1 Available from the sunitinib EPAR (12)

2.3.3 *Results*

Results of the studies of sunitinib in the prior-cytokine population are reported in Table 4.

Table 4: Results – studies of sunitinib in the prior-cytokine population

RTKC-0511-014 (7)	A6181006/NCT00077974 (8;9)
Objective clinical response: In total, 25 (40%; 95% CI 28-53%) patients achieved a partial response. A total of 17 (27%) patients experienced stable disease. ***Time to progression:*** Median TTP was 8.7 months (95% CI, 5.5–10.7 months). ***Median survival:*** Median survival was 16.4 months (95% CI, 10.8 to NA). ***AEs:*** The most common treatment-related adverse events were fatigue (38% of patients), diarrhoea (24% of patients) and nausea (19% of patients).	***Objective clinical response:*** In total, 36 (34%; 95% CI 25-44%) patients experienced a partial response and 30 (29%) patients had stable disease according to independent third-party assessment. According to investigator assessment, 45 (43%) patients experienced a partial response, 1 (1%) patient experienced a complete response and 23 (22%) patients had stable disease. ***Duration of response:*** For the 46 patients that experienced a response according to investigator assessment, the median duration of response was 10 months (95% CI 8 months-not calculable). ***Progression-free survival:*** Median PFS based on independent assessment was 8.3 months (95% CI 7.8-14.5 months). Median PFS based on investigator assessment was 8.1 months (95% CI 5.5-10.4 months). ***Overall survival:*** Median overall survival was 23.9 months (95% CI 14.1–30.7). A total of 43/105 patients had survived at a median follow-up of 29.7 months ***AEs:*** The most common treatment-related AEs were fatigue (28% of patients), diarrhoea (20% of patients), dyspepsia and hypertension (18% of patients each).

Abbreviations: AE, adverse event; CI, confidence interval; NA, not yet attained; OS, overall survival; PFS, progression-free survival; TTP, time-to-progression.

2.3.4 *Conclusions*

Study RTKC-0511-014 and Study A6181006/NCT00077974 demonstrated high levels of response to sunitinib in patients with metastatic RCC who had failed treatment with cytokines (40% and 34% of patients, respectively responded to treatment). In addition, overall survival in Study RTKC-0511-014 and Study A6181006/NCT00077974 was 16.4 months and 23.9 months, respectively (7-9).

2.4 *Pazopanib in a prior-cytokine population*

The evidence for the efficacy and safety of pazopanib in a prior-cytokine population is taken from a single RCT; VEG105192. Results from this study were initially published in 2010 (Sternberg et al, 2010 (4)), and results of the mature OS analysis were published in 2013 (Sternberg et al, 2013 (11)).

2.4.1 *Methods*

Details of the methodology for Study VEG105192 are provided in Table 5. Details of the methodology for the pivotal Phase III axitinib study (AXIS) are also provided for comparison.

Table 5: Methodology – Study VEG105192

Trial	AXIS(3)	VEG105192 (4;11)
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, 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. Patients who progressed were un-blinded and if on placebo were allowed to cross-over to receive pazopanib via an open-label study.
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), administered at a starting dose of 5 mg BD Sorafenib (N=362), administered at a starting dose of 400 mg BD	Pazopanib 800 mg OD (n=290) Placebo OD (n=145)
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)	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

Trial	AXIS(3)	VEG105192 (4;11)
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.

2.4.2 *Participants*

Inclusion and exclusion criteria for Study VEG105192 and the pivotal axitinib study (AXIS) are presented in Table 6.

Table 6: Inclusion/exclusion criteria – Study VEG105192

	AXIS (3)	VEG105192 (4;11)
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 pivotal axitinib study (AXIS) are presented in Table 7.

Table 7: Patient characteristics – Study VEG105192

	AXIS (3)		VEG105192 (4)	
	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)
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.

2.4.3 *Results*

Results for Study VEG105192 are presented in Table 8.

Table 8: Results – Study VEG105192 (11)

VEG105192 (2, 7)
Progression-free survival (PFS): Pazopanib significantly prolonged PFS compared with placebo in the prior-cytokine population (7.4 months vs 4.2 months, respectively; [HR 0.54; 95% CI 0.35-0.84] p<0.001).
Overall survival (OS): At the time of the final PFS analysis, the OS data for VEG105192 were not mature (2). Final OS data were subsequently published (7). The difference in OS was not statistically significant between pazopanib and placebo (22.7 months vs 18.7 months, respectively; (HR 0.82; [95% CI 0.57–1.16]). Post-hoc analyses to assess the impact of crossover using IPCW and RPSFT models resulted in a reduction in the HR from 0.82 to 0.53 (CI 0.315–1.112) and 0.53 (0.341–4.849), respectively, although the additional uncertainty inherent in the crossover corrected HR meant that no statistically significant difference in survival was shown between pazopanib and placebo.
Response rate: For prior-cytokine patients, the response rate was 29% in the pazopanib group (95% CI 21.2 - 36.5) vs 4% in the placebo group (95% CI 0.0-7.1).
AEs: The most common AEs in the pazopanib group were diarrhoea (52%), hypertension (40%), hair colour changes (38%), nausea (26%), anorexia (22%) and vomiting (21%); most were mild or moderate.

Abbreviations: AE, Adverse Event; CI, confidence interval; HR, Hazard Ratio; IPCW, inverse probability of censor weighting; PFS, Progression Free Survival; RPSFT, rank preserving structural failure time.

2.4.4 *Conclusion*

Pazopanib demonstrated significant improvements in PFS in a prior-cytokine population compared with placebo, however there was no significant difference in OS.

3 Summary of the indirect evidence for pazopanib and sunitinib in a prior-cytokine population

3.1 *Summary of the indirect comparison for the PFS endpoint*

In the evidence submission, an indirect comparison was conducted to compare the relative efficacy of axitinib with BSC, in line with the original NICE scope. Evidence from other RCTs of second-line treatments of mRCC was used to link the AXIS trial (3) to BSC in the evidence network.

PFS and OS were chosen as the endpoints for the indirect comparison in line with the requirements of the economic model and the key outcome measures in the axitinib clinical trial programme. The analysis utilised hazard ratio (HR) data and therefore studies identified from the systematic review were considered for inclusion if they contained HR data (or data from which a HR could be estimated).

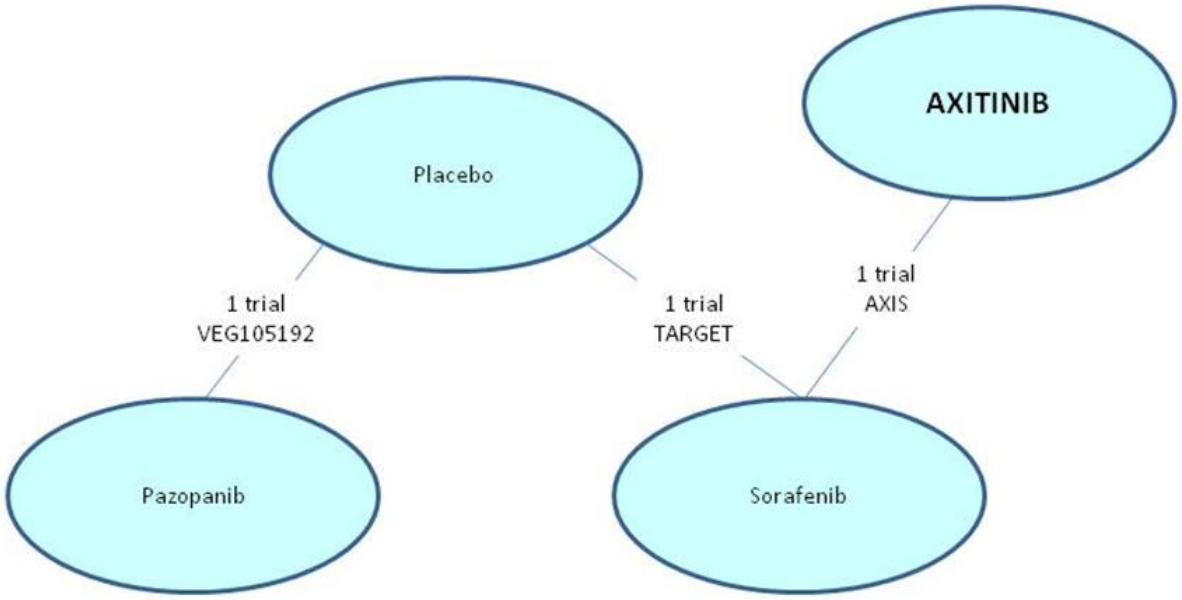
In the original evidence submission, two studies were identified that were relevant to the prior-cytokine population and allowed a comparison of the relative efficacy of axitinib with BSC:

- AXIS: a Phase III study of axitinib vs sorafenib (the pivotal trial for axitinib, reported in the original submission) (3)
- TARGET: a Phase III study of sorafenib vs placebo (13)

A study, reporting on the efficacy and safety of pazopanib, identified as part of the systematic literature review conducted in 2012, has now been included to reflect the new scope issued by NICE: VEG105192: a Phase III study of pazopanib vs placebo (4). This study is included in the publication of the indirect comparison of second line treatments in the management of advanced RCC using a fixed effects Bayesian model to assess the relative effectiveness of treatment and reported as hazard ratio (HR) and 95% credible intervals (Crl) (14).

A summary of the network diagram for the PFS endpoint is provided in Figure 1.

Figure 1: Network diagram for the PFS endpoint



The HR values for PFS for those patients who have received prior treatment with a cytokine regimen from the relevant studies are detailed in Table 9.

Table 9: Indirect comparison input data (14)

	AXIS (axitinib vs sorafenib)	**TARGET (sorafenib vs placebo)**	**VEG105192 (pazopanib vs placebo)**
	HR (95% CI)		
PFS (IRC)	***Cytokine refractory population:*** 0.464 (0.318-0.676)	***Cytokine refractory population:*** 0.54 (0.45-0.64)	***Cytokine refractory population:*** 0.54 (0.35-0.84)

Abbreviations: CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

Due to the fact that the existing sunitinib studies were either single-arm or compared sunitinib with itself (administered at different times of the day(3) it was not possible to incorporate sunitinib into the network of evidence.

3.2 *Indirect comparison results for the PFS endpoint*

Results from the Bayesian fixed-effects model for the PFS endpoint are presented in Table 10. The results suggest that there is a 95% probability that axitinib will always be superior to placebo, pazopanib and sorafenib.

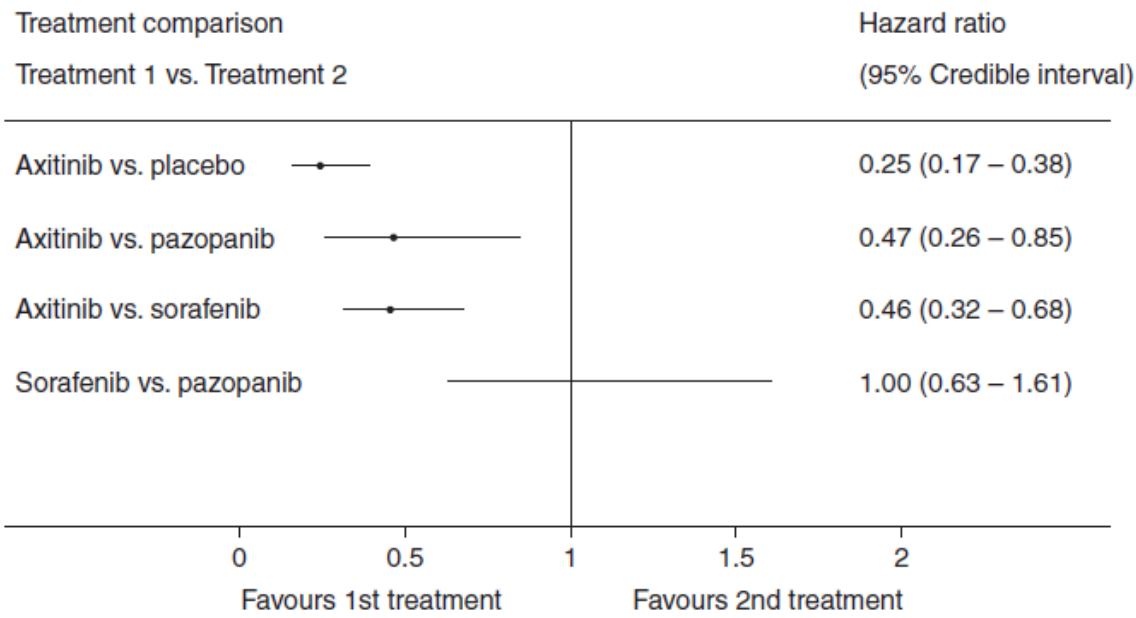
Table 10: PFS – prior-cytokine patients (14)

Treatment comparison	Median HR	95% CrI
Axitinib vs placebo	0.251*	0.165-0.379
Axitinib vs pazopanib	0.465*	0.255-0.852
Sorafenib vs pazopanib	1.002	0.626-1.608
Axitinib vs sorafenib	0.464†	0.318-0.676

* Axitinib has a 95% chance that it will always be superior in these pairwise comparisons; †Consistent with results from the AXIS trial as would be expected as the model only had one set of direct trial data for the treatment comparison.
Abbreviations: CrI, credible interval; HR, hazard ratio; PFS, progression-free survival.

Figure 2 shows the results of the Bayesian analysis reported in a forest plot.

Figure 2: Forest plot of PFS in the prior-cytokine subgroup



Based on the data produced by the Baysesian model, axitinib was ranked as the most likely intervention (99% chance) of being the best treatment, followed by pazopanib, sorafenib and placebo (Table 11).

Table 11: Probability of best treatment for pre-treated cytokine-regimen PFS

Therapy	Bayesian model
Axitinib	99%
Pazopanib	1%
Sorafenib	0%
Placebo	0%

3.3 *Challenges in performing an indirect comparison for OS*

The inevitable limitations of performing indirect comparison for OS for the prior cytokine population have been extensively discussed in our evidence submission and ACD response. In addition, the Appraisal Committee, clinical specialists and patient experts all expressed the view that the median OS of approximately 24 months (in the base case) for the BSC group of the prior-cytokine group with the indirect comparison is not seen clinically. It was noted in the ACD and FAD the manufacturer's comment that the implausibility observed may have resulted from the median OS of 14.3 months in the placebo arm of TARGET which was not properly adjusted for crossover. The Appraisal Committee considered that this possible over-estimation of the OS of BSC in TARGET was carried over into the OS results in the indirect comparison and ultimately affected the model results for the best supportive care group.(15).

The final ITT analysis in the prior-cytokine population of the VEG105192 study reported a median OS of 18.7 months for the BSC arm. This analysis was, however, confounded by an early and high rate of patient cross-over (54% from as early as six weeks) from the BSC arm to the pazopanib arm. Although HRs adjusted for cross-over by IPCW and RPSFT were reported, estimates of median OS were not available. Therefore, given that the HR for pazopanib in each of the crossover adjusted analyses, was 0.53, it could be inferred that the adjusted median overall survival for the BSC arm of the VEG105192 study could be lower than unadjusted median OS of 14.3 months from the TARGET trial (7). A comparison of the median OS for BSC from the indirect comparison (i.e. 24 months) with the BSC estimate from the pazopanib trial (i.e. 18.7 with cross-over and potentially less than 14 months), is suggestive of significant heterogeneity that would be introduced if the evidence network was extended to the VEG105192 study.

Performing an indirect comparison on the basis of the above limitations was therefore not considered to be robust was therefore prone to considerable biases (and there was consensus that it was generating clinically implausible results for BSC (15). As a result, extending the evidence network for OS to include the pazopanib study (VEG105192), which also allowed patients to cross-over to active therapy if they progressed on placebo, would add significant additional biases to the approach and the results would inevitable lack clinical plausibility.

4 Naïve comparison of survival data for axitinib, sunitinib and pazopanib

A naïve comparison of survival data for axitinib, sunitinib and pazopanib was performed. Table 12 presents a summary of median PFS and median OS results for axitinib and other comparators from the updated scope for the prior-cytokine population (i.e. BSC, sunitinib and pazopanib).

Table 12: Naïve presentation of results for therapies for the second-line treatment of advanced RCC (prior-cytokine)

	Indirect Comparison		**AXIS**	**TARGET**	**VEG105192(4;11)**			**Sunitinib**	
	Axitinib	**BSC**	**Axitinib**	**BSC**	**BSC**		**Pazopanib**		
			AXIS: Rini et al, 2011 (3)	**Censored analysis in Escudier et al, 2009(13)**	**With cross-over**	**Cross-over adjusted**		**Motzer, et al, 2006a (7)**	**Motzer, et al. 2006b(9)**
Patients, N	-	-	126	452	67[2]		135[2]	63	106
PFS, months (95% CI)	11.5 (Weibull)	3.7 (Weibull)	12.1 (10.1-13.9)	2.8	4.2(NR)[2]		7.4 (NR)[2]	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	18.7(14.2–26.3)	NR	22.7 (19.3–28.3)	16.4(10.8-NA)	23.9 (14.1-30.7)

1: Sternberg et al, 2013 2; Sternberg et al, 2010
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.

As presented in Table 12, based on a naïve comparison axitinib demonstrates a PFS and OS benefit of more than 3 months compared to BSC, sunitinib and pazopanib.

With respect to OS, the naïve comparison demonstrates that axitinib may be associated with:

- an additional 5.5 months survival vs sunitinib (using the mature results of the larger phase II study)
- an additional 6.7 months survival vs pazopanib.

In addition, axitinib may be associated with a PFS benefit of:

- an additional 3.3 months vs sunitinib (using larger phase II study)
- an additional 4.7 months vs pazopanib

Together with the evidence previously submitted by Pfizer demonstrating that axitinib provides at least 3 months OS when compared to BSC in the prior-cytokine population,

these data support the view that axitinib provides at least 3 months OS or PFS benefit in the prior-cytokine population compared with all comparators in the updated scope.

It is important to note that there were key differences between the two phase II studies for sunitinib in terms of eligibility criteria. Specifically, Study RTKC-0511-014 differed in that prior nephrectomy was not required and any RCC tumour histology was allowed, Absence of nephrectomy is a poor prognostic indicator, and patients with non-clear cell tumour histologies are expected to have a lower treatment response.

It would be preferable to use the median OS of 23.9 months as this is from a larger study, in a full clear cell population, a more mature dataset, and was considered the pivotal study in the original regulatory submission in the absence of the availability of the phase III data for sunitinib.

5 Naïve economic analysis of axitinib, best supportive care, sunitinib and pazopanib

In our evidence submission, the base case ICER in the prior cytokine population of axitinib versus BSC was £55K per QALY gained, assuming a median OS of 24 months for patients receiving BSC. As mentioned previously, the ICER is an over-estimation in this population due to the limitations of the evidence network such as the bias introduced in the OS analysis by the cross-over in the TARGET study. As discussed in section 4.12 of the FAD the Appraisal Committee, clinical specialists and patient experts considered that the overall survival of approximately 24 months (in the base case of our evidence submission) for the BSC group of the prior-cytokine group is not seen clinically(15).

Therefore, the overestimation of the OS in the BSC arm of TARGET in the base case, which was due to 48% of patients crossing over to sorafenib, resulted in an underestimation of the OS gain of axitinib versus BSC in the base case.

As described in our ACD response, when the lower 95% CI for OS HR was used, the median OS for BSC in the prior cytokine population was 17.6 months which is close to the 14.3 months reported in TARGET. The ICER of axitinib versus BSC for this scenario was £33K per QALY with the revised PAS, which is close to the base case ICER in the prior sunitinib population and should be considered more relevant for decision making as it is based on more clinically plausible results for BSC.

However, in contrast to the evidence provided in the ACD, the Appraisal Committee has selected the 24 months median OS for BSC as the basis for the decision. Based on this assumption, and the results presented in Table 12**Error! Reference source not found.**, it seems that BSC from the indirect comparison has a numerically higher median OS (24 months) than the trial data for pazopanib (22.1 - 95% CI: 19.3–28.3) or sunitinib (23.9 - 95% CI: 14.1-30.7). Further to that, BSC has a lower cost than either of these active treatments. Therefore in this naïve comparison, BSC dominates both sunitinib and pazopanib (i.e. has a lower cost and great effectiveness) (see Table 13) and as a result in this scenario there is no economic rationale to compare axitinib with sunitinib or pazopanib (i.e. sunitinib and pazopanib are extendedly dominated by axitinib). In this situation given the high median OS assumed for BSC, it can be deduced that if the ICER of axitinib compared with BSC is £55, 000 per QALY

with the revised PAS, the ICER of axitinib compared with a treatment (sunitinib or pazopanib) which is both more expensive and less effective than BSC will be substantially lower than £55,000 per QALY. (see Table 13).

Table 13: 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	< £55K
Axitinib vs. Pazopanib	Extended dominance	< £55K

As previously mentioned, we believe that BSC should be the only relevant comparator in the prior-cytokine population. Therefore, in conclusion, axitinib is a cost-effective treatment option in the prior cytokine population as it is expected to fulfil end of life criteria vs. BSC and the relevant ICERs for decision making are lower than the accepted thresholds for other end of life treatments.

In relation to the end of life criteria:

- Axitinib is expected to offer more than 3 months additional survival over BSC based on the information previously submitted by Pfizer. The naïve comparison presented in this addendum shows a greater than three month PFS and OS benefit over sunitinib and pazopanib (see Table 12).
- Patients with advanced/mRCC have a very poor prognosis if untreated after progression on first line therapy, and are expected to survive less than 24 months in the prior cytokine population (as shown in Table 12). For prior cytokine patients who are treated with sunitinib and pazopanib, the trial data presented in Table 12 indicate an expected overall survival of around 24 months.
- Advanced/mRCC patients who have received prior treatment with cytokines constitute a small patient population (less than 20 patients).

6 Interpretation of the evidence

In determining its final conclusions for cost-effectiveness in the FAD, the Appraisal Committee assumed that a PFS:OS gain relationship of 1:1 for axitinib compared with BSC was clinically plausible for the prior-cytokine population and applied the same underlying assumption in the prior sunitinib population results. This was based on the inevitable biases around the median OS estimate from the indirect comparison for BSC previously presented

by Pfizer, which as discussed above, has been recognised as a clear overestimation which markedly weakens the PFS:OS gain relationship as emphasised in our ACD response and clinical expert opinion during the appraisal process.

Furthermore, the lack of clinical plausibility of this BSC median OS estimate is further highlighted when compared with the median OS data presented in Table 12 from patients treated with sunitinib (23.9 - 95% CI: 14.1-30.7), pazopanib (22.7 - 95% CI:19.3–28.3) or placebo (14.3 to 18.7 months) in the prior cytokine population. As discussed above, we believe a more realistic estimate of median OS for BSC patients is 17.6 months, a value which corresponds to a PFS:OS gain of 1:1.8 compared with axitinib, and results in an ICER of £33K per QALY gained. Such a relationship is reflective of what would be expected when comparing an active therapy with a placebo/BSC.

In the 2009 abstract publication, the meta-analysis by Delea *et al*, included a total of 21 studies representing 6,182 patients, 52 treatment groups, and 35 comparisons(16). In addition, a subgroup analysis was conducted including studies with patients treated with prior therapies. In this subgroup the reported relationship estimated a 1 month gain in PFS with an associated 1.4 month gain in OS (1:1.4).

The meta-analysis by Delea *et al* was updated in 2012 and included 31 studies representing 10,943 patients, 75 treatment groups, and 41 comparisons and in the prior treatment subgroup, the reported relationship estimated that a 1 month gain in PFS was associated with a 1.04 month gain in OS (17). The addition of 10 new studies in the analysis of the absolute differences between the treatment groups in median PFS/TTP (in months) vs. the absolute differences between groups in median OS (in months) included key studies such as Sternberg et al (4) and Motzer et al (18), specifically in the updated subgroup analysis of prior treatments, data from the above key studies were included. Of note, in these studies comparing targeted therapy with placebo/BSC cross-over occurred in 54% (11) and 80% (19) respectively. The authors have highlighted that it is well established that crossover from control to active treatment may attenuate observed treatment effects on OS relative to what would have been observed in the absence of such crossover and to include results of studies with extensive crossover without controlling for it would add no useful information to the analyses.

A serious limitation in this analysis is that median OS estimates unadjusted for cross-over from the Sternberg *et al* study were used in the updated subgroup analysis as adjusted median OS estimates were not available as previously described (see table 1 note k) (17). More specifically, the input values from Sternberg *et al*, 2009/2010 (4;20) were 5.0 months absolute difference between the treatment groups in median PFS and 2.4 months of absolute difference between groups in median OS resulting in a 1:0.48 median PFS:OS gain relationship for this study. The inclusion of the median OS estimates unadjusted for cross-over from this study introduces bias in the updated analysis results and inevitably weakens the PFS:OS gain relationship which decreased to 1:1.04 compared from 1:1.4 from the original analysis (21). The relatively large size of the study compared to other new studies in the updated analysis, means that this study makes a large contribution to the results of the meta-analysis. Excluding this study from the updated meta-analysis or including the median OS estimates adjusted for cross-over would result in a similar or even stronger PFS:OS gain relationship respectively, compared to the 1:1.4 in the original analysis (21).

Recognising the limitations of analyses including cross-over, the investigators explored the relationship in those studies where cross-over was not permitted. In the original analysis, the reported PFS:OS gain relationship was 1:1.61 for this subgroup of studies (21) with an updated analysis in 2012 reporting a PFS:OS gain relationship of 1:1.29 (17).

In the updated analysis for studies where cross-over was not permitted, one of the new studies included was Rini *et al,* 2010 (22). In this study, patients with previously untreated, metastatic clear cell RCC were randomly assigned to receive either bevacizumab plus IFN-alpha or the same dose and schedule of IFN-alpha monotherapy in a multicenter phase III trial. Based on the updated Delea analysis, the input values used from Rini *et al*, 2010 (CALGB 90206) were 3.3 months absolute median PFS difference and 0.9 absolute median OS difference (PFS:OS gain relationship 1:0.27), which clearly demonstrates that this large study (N for comparison = 732) substantially contributed to a weakened PFS:OS gain relationship of 1:1.29 vs. 1.61 in the original analysis.

In addition, although cross-over was not pre-planned in Rini et al, 2010 study, the authors suggested that there were confounding effects of the emergence of multiple active therapeutic options during the conduct of this trial. The majority of patients on this trial received one or more active therapies on disease progression before death. Therefore, they concluded that it was possible that the initial impact of more favourable disease control with bevacizumab plus IFN-alpha (as reflected by the PFS advantage) did not translate into a statistically significant OS advantage for this reason.

Importantly this trial compares two active treatments, albeit interferon is not considered as active as targeted therapy, however it is nonetheless anticipated that the survival gain relationship will differ when comparing two active treatments versus comparing an active treatment versus placebo. This was conveyed to the Appraisal Committee in response to their reliance on the observed PFS:OS gain relationship of two targeted therapies axitinib versus sorafenib in the AXIS trial to support their rationale for supporting a 1:1 gain relationship in both populations. As outlined in the ACD response and also asserted by clinical expert opinion throughout the appraisal process a strong PFS:OS gain relationship (i.e. substantially greater than 1:1) is particularly evident when comparing an active treatment with placebo/BSC whereby a survival benefit in the post progression survival period is certainly anticipated over no active treatment.

The evidence above suggest that the updated Delea meta-analysis provides less reliable results in the comparison of absolute differences in the relationship between the median PFS and OS compared to the original analysis. This is due to a number of biases described above that have been introduced with the addition of new studies since the original analysis. Most importantly, we believe that the PFS:OS gain relationship of 1:1.04 from the updated analysis in the prior therapy subgroup is substantially confounded by the use of median OS estimates from the Sternberg et al, 2009/2010 study which were unadjusted for cross-over..

The Appraisal Committee relied upon this flawed relationship of 1:1 which underpins the ICER of around £50K per QALY for both the prior cytokine and prior sunitinib populations. This was predominantly justified by the PFS:OS gain relationship observed by the confounded results generated in the indirect comparison for the prior cytokine analysis and the gain relationship of 1:1.04 in the updated Delea analysis. In this addendum we provided evidence which suggests that both of those justifications were inappropriate and should not

be relied upon in determining the final conclusions about cost effectiveness for both populations. We strongly believe that the subgroup analysis PFS:OS gain relationship from the Delea meta-analysis that included trials with no cross-over should be relied upon (1.61 in the original analysis and 1.29 in the updated analysis) or the prior treatment subgroup analysis from the original Delea meta-analysis (i.e.1:1.42 .. Relying upon these results which are also in-line with clinical opinion will result in plausible ICERs with the revised PAS close to the £30K per QALY threshold and ultimately remove most of the uncertainty around axitinib cost-effectiveness in the prior cytokine population and also in the prior sunitinib population.

7 References

(1) National Institute for Health and Clinical Excellence. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. Apraisal Consultation Document . 2012.

(2) National Institute for Health and Clinical Excellence. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. Technology Appraisal Guidance 178 (TA178) 2009.

(3) Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011 Dec 3;378(9807):1931-9.

(4) Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010 Feb 20;28(6):1061-8.

(5) Srinivas S, Roigas J, Gillessen S, Harmenberg U, De Mulder PH, Fountizilas G, et al. Continuous daily administration of sunitinib in patients (pts) with cytokine-refractory metastatic renal cell carcinoma (mRCC): updated results. J Clin Oncol 2007;25(18s):Abstract 5040.

(6) Thompson Coon J., Hoyle M, Green C, Liu Z, Welch K, Moxham T, et al. Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation. Health Technol Assess 2010 Jan;14(2):1-iv.

(7) Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 2006 Jan 1;24(1):16-24.

(8) Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006 Jun 7;295(21):2516-24.

(9) Motzer RJ, Michaelson MD, Rosenberg J, Bukowski RM, Curti BD, George DJ, et al. Sunitinib efficacy against advanced renal cell carcinoma. J Urol 2007 Nov;178(5):1883-7.

(10) Uemura H, Shinohara N, Yuasa T, Tomita Y, Fujimoto H, Niwakawa M, et al. A phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma: insights into the treatment, efficacy and safety. Jpn J Clin Oncol 2010 Mar;40(3):194-202.

(11) Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013 Apr;49(6):1287-96.

(12) - Summary of Malignancy and Prior Treatment (Intent-to-Treat Population). sunitinib European public assessment report , 34. 2013.

(13) Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007 Jan 11;356(2):125-34.

(14) Larkin J, Paine A, Tumur I, Cappelleri JC, Healey PJ, Sr., Foley G, et al. Second-line treatments for the management of advanced renal cell carcinoma: systematic review and meta-analysis. Expert Opin Pharmacother 2013 Jan;14(1):27-39.

(15) National Institute for Health and Clinical Excellence. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. Final Appraisal Determination 2013 May.

(16) Delea T, Khuu A, Kay A, Zheng J, Baladi J. Association between treatment effects on disease progression (DP) endpoints and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC). J Clin Oncol 27[15s], abstr 5105. 2009.

(17) Delea TE, Khuu A, Heng DY, Haas T, Soulieres D. Association between treatment effects on disease progression end points and overall survival in clinical studies of patients with metastatic renal cell carcinoma. British Journal of Cancer 2012 Sep 25;107(7):1059-68.

(18) Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008 Aug 9;372(9637):449-56.

(19) Korhonen P, Zuber E, Branson M, Hollaender N, Yateman N, Katiskalahti T, et al. Correcting overall survival for the impact of crossover via a rank-preserving structural failure time (RPSFT) model in the RECORD-1 trial of everolimus in metastatic renal-cell carcinoma. Journal of Biopharmaceutical Statistics 2012;22(6):1258-71.

(20) Sternberg C, Szczylik C, Lee E, Salman P, Mardiak J, Davis I, et al. A randomized, double-blind phase III study of pazopanib in treatment-naive and cytokine-pretreated patients with advanced renal cell carcinoma (RCC). J Clin Oncol 27[15S], abstract 5021. 2009.

(21) National Institute for Health and Clinical Excellence. Everolimus for the second-line treatment of advanced renal cell carcinoma. Technology Appraisal Guidance 219 (TA219) . 2011.

(22) Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. Journal of Clinical Oncology 2010 May 1;28(13):2137-43.