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City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment – (ID-518): Pfizer responses to clarification questions

Section A: Clarification on effectiveness data

Section 2.3.3

1. ***Priority request:*** *Please clarify the discrepancy in median PFS for sunitinib from the A6181006/NCT00077974 trial reported in tables 4 and 12 of the addendum. In table 4, second column, median PFS of 8.3 (7.8-14.5) and 8.1 (5.5-10.4) are reported while table 12, last column, reports a median PFS of 8.8 (7.8-13.5).*

The objectives of A6181006/NCT00077974 trial were as follows:

- Primary objective: to determine the antitumor efficacy (response rate) of single-agent sunitinib in patients with metastatic RCC refractory to 1 prior cytokine therapy (interferon-alfa, IL-2, or the combination).
- Secondary objectives: evaluations of duration of response, progression free survival (PFS), overall survival (OS), and safety data.

Analysis of PFS were reported in two publications:

1. Motzer et al 2006b(1), which presented the results of the primary end point also included an initial assessment of PFS.
2. Motzer et al 2007(2) which presented results of a more mature data set, included an analysis of OS together with an updated analysis of PFS.

The data presented in Table 4 of the addendum for PFS are from the earlier publication presenting results from the datacut used for the analysis of the primary outcome (Motzer et al 2006b(1)).The PFS data presented in Table 12 relate to the same population, although these results are based on analyses of the more mature dataset used for the analysis of OS, published in Motzer et al 2007(2).

Section 2.4.2

2. *Please provide the baseline patient characteristics for the prior cytokine population in the VEG105192 study (the data provided in table 7 [page 10 of the addendum] is for the ITT population).*

No baseline patient characteristics of the prior cytokine population in the VEG105192 study were available when the systematic review for the indirect comparison was performed for the original NICE submission (search performed April, 2012). No additional publications that

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provided these data for the prior cytokine population were identified in the non-systematic literature search conducted by Pfizer in October 2013 prior to submission of the addendum.

Section 2.4.3

3. ***Priority request:*** *Please explain, based on the underlying assumptions of each method, which one of the two methods to assess the impact of crossover (IPCW and RPSFT) stated in table 8 (page 10 of the addendum) is Pfizer's preferred approach to estimating the hazard ratio.*

As published in Sternberg et al, (2013), both methodologies for correction of crossover resulted in the same point estimates (IPCW: 0.53 and RPSFT:0.53) and similar lower 95% confidence intervals (IPCW: 0.315 and RPSFT: 0.341) for the hazard ratio (3). We do not consider it necessary to differentiate a preferred approach in this instance, as the main difference between the results of the methodologies was the upper 95% confidence interval for the hazard ratio. More specifically, the upper 95% confidence interval for the hazard ratio after correction for cross over remained similar the ITT estimate (1.16) in the case of the IPCW (1.112), and substantially higher for the RPSFT (4.849).

4. *Please explain whether all results in Table 8 (including adverse reactions) are only for the prior cytokine population. If not, please provide data for the prior cytokine population separately.*

The data in Table 8 relate to the prior cytokine population for PFS, OS and response rate, as reported by Sternberg et al 2010 (4) and Sternberg et al 2013(3). Safety data for the pazopanib were only reported for the overall ITT population.

Section 3.1

5. *Please provide further details on the methods used in the indirect comparison in section 3 of the addendum. In particular, please highlight any differences in the methods for the analysis in the addendum compared with the methods used in the original submission.*

The methods used in the indirect comparison in section 3 of the addendum are the same as those included in the main submission, with the exception that the VEG105192 study was added to the network to enable the comparison with pazopanib. WinBUGS code for continuous outcomes, adapted from the NICE Technology support documents (5), was used for the analysis of hazard ratios (HRs) and the associated standard errors (SEs). Further details can be found in section 6.7 of the original submission.

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6. *Based on the similarities and differences between the AXIS and VEG105192 trials, please explain whether an indirect comparison of axitinib and pazopanib is considered appropriate?*

The results of the indirect comparison of PFS between axitinib and pazopanib have been previously published (6). The AXIS (7) and the VEG105192 trials (3;4) included a subgroup of 35% and approximately 47% patients who had failed prior cytokine therapy respectively. Based on available data of the ITT populations, similarities in the baseline characteristics include median age, gender and prior nephrectomy status, although differences were also noted:

- In terms of performance status, in the AXIS trial approximately 55% of patients on enrolment had an ECOG PS of 0 and approximately 45% had an ECOG of 1. In the VEG105192 trial fewer patients had an ECOG PS of 0 (approximately 42%) on enrolment and more had an ECOG of 1 (approximately 59%).
- The widely accepted MSKCC prognostic score, important in understanding prognostic differences between populations, was defined differently in the AXIS trial compared with the VEG105192 due to the predominant study population (treatment naïve vs. pre-treated). Hence, comparing these important scores, which would be crucial in interpreting comparative overall survival data in a given advanced RCC population, would be inappropriate.

7. ***Priority request:*** *Please explain whether the assessment of PFS was comparable in the AXIS and VEG105192 trials*

PFS in the VEG105192 trial was defined as the time interval between the date of random assignment and the date of progression or death. Disease assessments were performed using computed tomography or magnetic resonance imaging. All imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment. Tumor response evaluations by the investigators and the IRC were based on Response Evaluation Criteria in Solid Tumors (RECIST criteria version 1.0) (4).

In the AXIS trial, PFS was defined as the time from randomization to first documentation of objective tumour progression or to death due to any cause, whichever occurred first. Evaluations were performed using data from CT/MRI assessed by a blinded IRC. Tumour response evaluations were performed using RECIST criteria (version 1.0) (7)

The assessment of PFS was considered to be comparable between the two studies.

Section 3.2

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8. *Please clarify the following sentence on page 12 of the addendum: "The results suggest that there is a 95% probability that axitinib will always be superior to placebo, pazopanib and sorafenib."*
   - *For example, it is not clear what is meant by a 95% probability of always being superior. Please clarify whether this is a simultaneous probability, that is, does it represent the probability that axitinib will simultaneously be superior to placebo and pazopanib and sorafenib?*

This sentence is trying to convey the fact that the 95% credible intervals (CrIs) for these treatment comparisons do not cross 1.0, the point at which the treatments have equal efficacy. Since this is a Bayesian analysis, we have tried to avoid using the phrase "statistically significant result" since this would suggest there was an associated frequentist p-value. There does not seem to be a consensus in the literature on how Bayesian results should be described. Since the 95% CrI is the region where there is a 95% chance that the effect will lie, we used this description to try and highlight the fact that the 95% CrI for the comparison between axitinib and placebo, axitinib and pazopanib and axitinib and sorafenib each in turn favour axitinib and do not cross 1.0. Therefore, the 95% is not a simultaneous probability but relates back to the credible interval for each of the pairwise comparisons.

- *A similar sentence is indicated as a footnote in Table 10, referring to placebo and pazopanib. Please clarify whether this sentence also refers to sorafenib.*

The footnote under Table 10 is applicable to the comparison between axitinib and sorafenib as well. However, on the basis of the confidence interval of the direct trial data (AXIS) we could also claim that "axitinib statistically significantly prolongs PFS compared with sorafenib".

<u>Section 3.3</u>

9a. ***Priority request:*** *Please provide further explanation to support the following assumption on page 14 of the addendum. "Given that the hazard ratio 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 overall survival of 14.3 months from the TARGET trial". The ERG assumes that inferred in this sentence should be interpreted as statistically inferred.*

In the absence of a point estimate of the median OS from the BSC arm of the VEG105192, an alternative approach had to be used to provide some measure of the median OS excluding the effect of crossover. The objective of this analysis was to provide some form of

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a qualitative measure of how the cross over corrected median OS of BSC treated patients in VEG105192 would compare with those from the TARGET trial.

9b. ***Priority request:*** *If the reasoning for the above question was as follows: 22.7*0.53 = 12.03, then please explain why the two hazard ratios on page 10 of the addendum are being considered as equal, without taking into account the uncertainty around them.*

The analysis employed to explore the BSC OS estimate from the VEG105192 trial utilised the point estimate of the median OS, along with the point estimate of the crossover corrected HR. This approach was adequate for the purposes of the point being made, without the need to incorporate uncertainty into the results of the calculation.

9c. ***Priority request:*** *"Please state and justify whether the assumption of a "lower" median overall survival is clinically plausible."*

As described in our addendum and our ACD response, we consider the 17.6 months a more plausible, but potentially high, estimate for the median OS for BSC in the prior cytokine population based on the available evidence from TARGET, VEG105192 and other RCTs in the prior cytokine population.
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 (see FAD, section 4.12)..

Section 4

10. ***Priority request:*** *Please explain what is meant by a 'naive comparison' in section 4 and 5 of the addendum submission and how this was performed.*

The use of the term naïve comparison (also referred to as an unadjusted comparison in the literature) in section 4 and 5 of the addendum 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.

11. ***Priority request:*** *Please provide the confidence intervals for all the estimates presented in Table 12, or if not available, please state that this is the case*

The results of the TARGET trial were published in Escudier et al, 2007 and 2009(8;9). These publications did not provide confidence intervals for the PFS and OS estimates for the placebo treated patients. An updated table is presented below including the indication of

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whether the confidence intervals were not reported for the TARGET trial (additional text italicised).

	Indirect Comparison		AXIS	TARGET	VEG105192 (3;4)			Sunitinib	
	Axitinib	BSC	Axitinib	BSC	BSC		Pazopanib		
			AXIS: Rini et al, 2011 (7)	Censored analysis in Escudier et al, 2007 and 2009(8;9)	With crossover	Crossover adjusted		Motzer, et al, 2006a (10)	Motzer, et al. 2007 (2)
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 (*NR*)	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 (*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)

1: Sternberg et al, 2013(3) 2; Sternberg et al, 2010(4)
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.

12. ***Priority request:*** *Please clarify which median PFS and overall survival values for axitinib are considered in the conclusions from Table 12 on page 15 of the addendum.*
    - *The sentence "As presented in Table 12, based on a naïve comparison, axitinib demonstrates a PFS and overall survival benefit of more than 3 months compared to BSC, sunitinib and pazopanib" suggests that the median PFS and overall survival are those provided by AXIS. Please confirm or provide further clarification.*
    - *If the median PFS and overall survival are those from AXIS, then please explain why the simulated values are disregarded in this section.*

The median PFS and OS values being considered for axitinib are 12.1 (10.1-13.9) and 29.4 (24.5 – NE) respectively, as reported from the AXIS trial. The trial data from AXIS were used in the naïve comparison to ensure consistency of approach between the measurement of PFS and OS outcomes and also between all comparators.

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13a. ***Priority request:*** *The sentence on page 15 of the addendum "an additional 5.5 months survival vs sunitinib (using the mature results of the larger phase II study)" suggests that the overall survival median from AXIS and the study from Motzer et al 2006b are being compared. Please explain how it is established that the two populations of these two studies are similar / comparable.*

Table 3 of the addendum describes the baseline characteristics of the population in the A6181006/ NCT00077974 and the overall population in the AXIS trial. There are similarities in baseline characteristics between the populations in terms of sex, age, gender, ECOG PS and histology and differences in the populations with regards two important prognostic characteristics, prior nephrectomy status (100% v 90.6%) and MSKCC prognostic risk factors whereby the prognostic characteristics are more favourable for the population in the A6181006/ NCT00077974 study (≥ 1 MSKCC risk factor was 70% in the AXIS trial versus 42% in the A6181006/ NCT00077974 study).

13b. ***Priority request:*** *The sentence on page 15 of the addendum "an additional 6.7 months survival vs pazopanib" suggests that the overall survival median from AXIS and the VEG105192 study are being compared. Please explain how it is established that the two populations of these two studies are similar / comparable.*

As outlined in question 6 above, there are both similarities and differences between the populations. For the purposes of this comparison as requested by NICE, it is recognised that there are limitations to the naïve comparison, however this was the only option available to ensure a consistent approach could be adopted for all comparators and outcomes.

14. ***Priority request:*** *All the differences in median PFS and overall survival are measured against the medians provided by the AXIS trial. This could suggest that Pfizer believes that the results from the indirect comparison should not be used. Please clarify whether this is true or not.*

    Due to the limitations of the available evidence, the indirect comparison for axitinib could be performed only for the PFS endpoint versus BSC and pazopanib. Although, the results from the indirect comparison could be used to estimate the differences between axitinib, BSC and pazopanib for PFS, we have estimated the differences in median PFS and overall survival against the medians provided by the AXIS trial using a naive comparison to ensure consistency across the different outcomes and comparators.

Section B: Clarification on cost-effectiveness data

Section 5

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15. ***Priority request:*** *In the discussion on page 16 of the addendum, it is implied that the median overall survival estimated from the indirect comparison for best supportive care is not valid, Please explain why the results from the indirect comparison are valid for the axitinib arm and not the best supportive care arm.*
    - *If the results of the indirect comparison are valid for axitinib, then clarify whether section 4 should be adjusted to use these results rather than the medians from the AXIS trial.*
    - *Otherwise, if the AXIS trial is used as reference, then the ICER of £55K per QALY gained would not be valid since the median overall survival in AXIS is lower than 33.3 months estimated in the indirect comparison.*

We have used parametric survival models to extrapolate axitinib PFS and OS data from AXIS to a lifetime horizon for our economic modelling (see section 7.3.2.1 of evidence submission). As the Weibull parametric model was used as a base case for the prior cytokine population in our economic model, any small differences in median PFS and OS versus the Kaplan-Meier data from AXIS were only due to limitations of the parametric fit around the median time point. Therefore, we considered the median OS estimate with the Weibull model valid as it reflects the axitinib data from AXIS.

However, as explained in our evidence submission, in our ACD response and in our addendum for the prior cytokine population, the median BSC OS estimates from the indirect comparison were considered biased due to the known limitations of the evidence network and clinically implausible based on the available clinical evidence.

Although, the Weibull median OS estimate for axitinib could be used for the purposes of the naive comparison, we have estimated the differences in median OS using the medians reported in clinical trials to ensure consistency of approach across the different comparators. In addition, we believe that the ICER of £55K per QALY gained 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.

16. ***Priority request:*** *Please justify further, the assumption that the median overall survival for best supportive care in the prior cytokine population of 17.6 months is a valid.*

We consider the 17.6 months a more plausible but potentially high estimate for the median OS for BSC in the prior cytokine population 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).

17. ***Priority request:*** *In general, when multiple treatments are compared, results should be presented as a full incremental analysis, rather than pairwise comparisons. Therefore,*

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please present the results in a table like the one shown below, including the expected costs and expected QALYs for both pazopanib and sunitinib. Also include information on costs of treatment with pazopanib and sunitinib (including any associated patient access scheme), and the costs of treating adverse effects associated with all treatments.

Due to the limitations of the evidence base for the comparisons of axitinib with sunitinib and pazopanib in the prior cytokine population, we have not estimated absolute QALYs and costs for pazopanib and sunitinib.

18. ***Priority request:*** *In table 13, page 17 of the addendum, it is indicated that the ICERs of axitinib compared with sunitinib and axitinib compared with pazopanib are smaller than £55,000 per QALY gained. Please quantify how much smaller they are expected to be.*

As mentioned above, due to the limitations of the evidence base for the comparisons of axitinib with sunitinib and pazopanib in the prior cytokine population we have not estimated precise ICERs for these comparisons. In addition, we believe that BSC should be the only relevant comparator in the prior-cytokine population.

19. ***Priority request:*** *All the results presented in table 13 are based on median estimates. Please provide analyses of the associated uncertainty.*

In our evidence submission and our ACD response, we have provided extensive sensitivity analysis for the comparison with BSC in the prior cytokine population which could be assessed along with the evidence and analysis provided in the addendum.
As mentioned above, due to the limitations of the evidence base for the comparisons of axitinib with sunitinib and pazopanib in the prior cytokine population we did not consider it appropriate to perform further analyses of the associated uncertainty.

20. ***Priority request:*** *Please provide the evidence to support the following statement on page 17 of the addendum. "Advanced/mRCC patients who have received prior treatment with cytokines constitute a small patient population (less than 20 patients)".*

In responding to this question, we wish to make a clarification to the sentence referred to above, which should have read as below (additional text indicated in italics):
"Advanced/mRCC patients who have received prior treatment with cytokines, *and are eligible for second line treatment*, constitute a small patient population (less than 20 patients)".

The evidence supporting the number of mRCC patients previously treated with cytokines who would be eligible for second line treatment was previously presented in Section 8 (Table 69) of the evidence submission. On the assumption that 5% of first line patients are

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expected to receive cytokines, this concluded that 96 patients would go on to receive second line therapy after cytokine treatment.

Comments from clinicians sent to NICE during the consultation on the new draft scope in September, 2013, suggest that less than 1% of patients with advanced RCC receive cytokines as a first line treatment, compared to the 5% previously estimated (see Appendix D – NICE's response to consultee and commentator comments on the updated scope and provisional matrix).

On the basis of this information, we concluded that the number of patients eligible for second line treatment after previous cytokine therapy is likely to be less than 20.

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Section C: Additional points

Section 2.2

21. ***Priority request:*** *Please provide more details on how the non-systematic search of Medline was performed.*

A search 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 search was run on the 9th October, 2013 using OVID, and included the following databases:

- Medline
- Embase
- Medline (R) In-Process

As the searches for the systematic review of the evidence submission was run on in April 2012, the non-systematic search was restricted to the following dates: 1st January, 2012 to 9th October, 2013.

The details of the search string used are below:

1. exp Carcinoma, Renal Cell/
2. exp Kidney Neoplasms/
3. 1 or 2
4. (sunitinib or su?10398 or su ?10398 or sutent).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, tn, dm, mf, dv, kw]
5. (temsirolimus or cci 779 or cci779 or nsc 683864 or nsc683864 or torisel).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, tn, dm, mf, dv, kw]
6. (sorafenib or bay 439006 or bay439006 or nexavar).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, tn, dm, mf, dv, kw]
7. (bevacizumab or nsc 704865 or nsc704865 or avastin).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, tn, dm, mf, dv, kw]
8. (pazopanib or armala or gw 786034* or gw786034* or sb710468* or sb 710468*).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, tn, dm, mf, dv, kw]
9. (everolimus or certican or rad001* or rad 001*).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, tn, dm, mf, dv, kw]
10. (axitinib or ag13736 or ag 13736).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, tn, dm, mf, dv, kw]
11. exp Interleukin-2/
12. ((alpha adj2 interferon) or alferon or cilferon or kemron or veldona).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, tn, dm, mf, dv, kw]

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13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 3 and 13
15. limit 14 to randomized controlled trial
16. limit 15 to english language
17. limit 16 to human
18. limit 17 to yr="2012 -Current"

The search retrieved 45 hits after removal of duplicates within OVID. Evaluation of search results to assess relevance to the use of pazopanib or sunitinib after previous cytokine treatment of metastatic renal cell carcinoma was based on the title and abstract. A single publication of relevance was identified (Sternberg et al, 2013) (3).

22. ***Priority request:*** *Please provide details of any new publications on VEG105192 identified through updated searches.*

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.

23. *Please provide more information on how the two sunitinib studies were identified. Also explain the steps taken to ensure that all relevant sunitinib studies have been identified.*

The two sunitinib studies were identified from the results of the systematic review previously performed by the Assessment Group for the NICE MTA appraisal in mRCC (TA178) (11). Internal subject experts were consulted to determine the existence of other relevant Pfizer-sponsored trials, none were identified.

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Reference List

(1) 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.

(2) 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.

(3) 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.

(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) Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework For Pairwise And Network Meta-Analysis Of Randomised Controlled Trials. available from http://www nicedsu org uk 2011.

(6) 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.

(7) 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.

(8) 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.

(9) Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. Journal of Clinical Oncology 2009 Jul 10;27(20):3312-8.

(10) 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.

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(11) 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.