NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment [ID518]

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)[1]

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the company or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical experts and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include companies manufacturing comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

[1]Response to ACD consultation post appeal

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Pfizer Ltd	Thank you for giving us the opportunity to comment on the second Appraisal Consultation Document (ACD) for the above appraisal. We welcome the review of the evidence by the Appraisal Committee and the preliminary positive recommendation for axitinib use in the NHS and the conclusion that axitinib is a cost effective use of NHS resources. As part of our response we have provided clarification around the additional post appeal evidence provided by Pfizer. This is particularly in relation to the analysis by Grünwald et al., and the end of life criteria considerations in the prior cytokine population.	Comment noted. No action required.
Pfizer Ltd	**Pfizer response to ACD2 on Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment (ID 518)** **Executive Summary** Pfizer welcome the review of the evidence by the Appraisal Committee and the preliminary finding of the Committee that axitinib is a cost effective use of NHS resources. This preliminary decision means that metastatic renal cell carcinoma (mRCC) patients in England and Wales could have access to a NHS funded second line treatment for the first time. Pfizer agree with the conclusions of the Appraisal Committee that axitinib is a cost effective end of life treatment and that the results of Grünwald et al. support the simulated treatment comparison (STC) with respect to the post-progression survival benefits of axitinib over best supportive care. Further to these conclusions, we provide clarifications to reassure the Committee with regards to the additional evidence accepted post-appeal and the end of life	Comment noted. No action required. Comment noted. No action required.

Consultee	Comment	Response
	considerations. Finally, we note the preliminary recommendation is wider than the licensed indication for axitinib. Medicines regulation has been developed in Europe to assess how medicines should be authorised for use and there is clearly a need to ensure that the special position of the regulatory bodies is recognised. We fully recognise that in making this preliminary recommendation NICE has taken into consideration the views expressed by clinical experts, but we are also concerned to ensure that NICE guidance that is inconsistent with the marketing authorisation cannot be seen to undermine the regulatory framework by inappropriately influencing clinicians' professional obligation to act in the best interests of their patients.	Comment noted. The Committee concluded that axitinib was shown to be a life-extending, end-of-life treatment for the prior-sunitinib population. It also agreed that it was not reasonable to limit this conclusion to people whose prior-tyrosine kinase inhibitor was sunitinib, given the growing, if not majority use, of pazopanib as a first-line treatment. This would leave an unmet need and would not reflect clinical practice. Therefore the Committee concluded that its recommendations should apply to the whole prior-tyrosine kinase inhibitor population. See FAD section 4.21. The Committee noted that the marketing authorisation of axitinib is for treating adults with advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine and does not include previous treatment with pazopanib. However it reiterated that it was not reasonable to limit its

Consultee	Comment	Response
		recommendation to people whose prior-tyrosine kinase inhibitor was sunitinib, given the growing, if not majority use, of pazopanib as a first-line treatment. This would leave an unmet need and would not reflect clinical practice. The Committee recognised that the requirement to provide funding by the relevant health bodies (clinical commissioning groups, NHS England and local authorities) within 3 months of its date of final guidance publication applies only within the marketing authorisation. See FAD section 4.25. The recommendations for the prior pazopanib group have been amended to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.
Pfizer Ltd	***Further comments on the additional evidence submitted*** In the majority of phase II and III clinical trials evaluating targeted treatments in mRCC, tumour response is measured in solid tumours using the internationally recognised Response Evaluation Criteria In Solid Tumours (RECIST). These criteria provide guidance on how to quantify the change in a patient's tumour burden from baseline, and how to categorise the quantified response. Specifically, the dimensions of select tumours, referred to as target lesions, are used to calculate the change in tumour burden	Comment noted. No action required.

Consultee	Comment	Response
	between images from different time points. The calculated response is then categorised as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR is complete disappearance of tumour (- 100%), PR is a change/shrinkage between -100% and -30%, SD is a change/shrinkage between -30% and +20%, and PD is an increase of 20% or greater. Of note, when scans show the appearance of new lesions/tumours the change in tumour burden cannot be quantified numerically, but the response is categorized as PD.	
Pfizer Ltd	In the age of targeted therapies, there is increased interest in the extent to which tumour response can be used as a prognostic tool. The rationale for the analysis performed by Grünwald et al. was to examine in greater detail the relationship between the extent of tumour response and overall survival. To quantify the strength and significance of this association between tumour response and overall survival, Grünwald et al. incorporated data from eight Pfizer sponsored trials of first and second line treatments for mRCC. The analysis utilised results from a uniform method of assessing response to treatment across the trials (RECIST as determined by the clinical trial investigators). Tumour response was incorporated into a multivariate Cox-proportional hazard analysis as a categorical variable, with the following categories (the -30% to 0% category was used as the control): 1) Shrinkage of ≤ 100% to < 60%; 2) Shrinkage of ≤ 60% to < 30%; 3) Shrinkage of ≤ 30% to < 0%; 4) Growth of between ≥ 0% to < 20%; 5) Growth of ≥ 20%; 6) Missing data. The multivariate model showed that in addition to tumour shrinkage, the factors below were also significantly associated with prognosis (all P<0.0001) (Grünwald et al. (slide 9). • time from diagnosis to treatment, ≥1 vs. <1 yr • Baseline LDH, >1.5 vs. ≤1.5 ULN • Baseline corrected calcium, >10 vs. ≤10 mg/dl	Comments noted. The Committee noted the evidence from Grunwald et al. suggesting that there is plausible post-progression benefit because of tumour shrinkage and agreed that the evidence from Grunwald et al. gave some support to the company's simulated treatment comparison results on the post-progression survival benefits of axitinib over best supportive care. See FAD section 4.10.

Consultee	Comment	Response
	• Baseline hemoglobin, >LLN vs. ≤LLN • Baseline ECOG performance status, 0 vs. 1–2 In addition to the multivariate Cox proportional hazards analysis, a six month landmark analysis was performed to minimise the potential bias associated with the inclusion of maximum tumour shrinkage as a factor in the model. Furthermore, Grünwald et al. also performed Kaplan-Meier analysis of OS for the different categories of response. This approach demonstrated across a variety of subgroup analyses according to type of intervention and line of therapy, that patients with a worse tumour response have a shorter median OS. In addition, the 95% CIs for OS corresponding to each of the response categories tend to form mutually exclusive, non-overlapping ranges (see Table 1 of previously submitted summary of Grünwald et al. for the 95% CI's of the overall analysis); a finding consistent with the prognostic importance of tumour response. The analyses by Grünwald et al. were performed on all patients who received study treatment. To this point, it should be noted that the abstract by Grünwald et al. mistakenly refers to the number of sorafenib-treated patients included from the AXIS trial as 335, whereas the actual number of sorafenib-treated patients included in this analysis (355) is correctly stated on slide 11 of the oral presentation.	
Pfizer Ltd	As all trials included in the analysis were either single arm studies or comparative trials versus an active treatment, no placebo-treated patients were present in the dataset. However, as poorly responding patients have a short median OS independent of therapy received or line of treatment, we would also expect these results to apply to patients receiving a placebo, who also typically have a poor response to therapy. Therefore, the absence of placebo treated patients in the dataset used by Grünwald et al. does not impact the validity of weighting the results of this analysis using the distribution of tumour responses for placebo treated patients from the RECORD-1 trial. This point was further supported by the clinical expert at the Appraisal Committee meeting on the 4th of February. In summary, the results of the analysis by Grünwald et al. demonstrate that patients with a good tumour response had a significantly longer overall	Comments noted. The Committee considered the evidence from Grunwald et al, including the information that no patients receiving best supportive care were included in the analysis, and agreed that the evidence from Grunwald et al. gave some support to the company's simulated treatment comparison results on the post-progression survival benefits of axitinib over best supportive

Consultee	Comment	Response
	survival than those with a poor tumour response, implying a post-progression survival benefit associated with therapy. As accepted by the Appraisal Committee (Section 4.10 of the ACD), the results of this analysis further supports the results of the STC analysis previously submitted by Pfizer.	care. See FAD section 4.10.
Pfizer Ltd	***Axitinib and end of life criteria in the post-cytokine population*** Section 4.22 of the ACD states that for the prior cytokine population, the end of life criteria could only be considered met if best supportive care were the only comparator. This conclusion was reached based on the Committee's view that there was substantial uncertainty that remained around the naive comparisons between axitinib vs. sunitinib and pazopanib. Pfizer believe that the indirect comparison comparing PFS between axitinib and pazopanib (HR = 0.465, 95% CrI 0.255-0.852)[1] provides robust evidence of at least three months PFS benefit of axitinib over pazopanib, an extent of benefit that would support axitinib meeting the end of life criteria, as per section 6.2.10 of the Guide to the methods of technology appraisal. The extent of PFS benefit associated with the hazard ratio can be estimated using the economic model to predict the median PFS for pazopanib, and comparing it to that of axitinib. More specifically, applying this hazard ratio to axitinib PFS data results in a predicted median PFS for pazopanib of 6.1 months vs. 11.5 months for axitinib (Weibull extrapolation). These additional data support a PFS benefit of 5.4 months for axitinib compared with pazopanib. When these results are considered in the context of the comparison between axitinib and sunitinib, and in addition to the results of the naïve comparison and evidence previously submitted compared with BSC, Pfizer believe that there is evidence to demonstrate that axitinib meets the end of life criteria against all comparators in the post-cytokine population.	Comments noted. The Committee agreed that although evidence in favour of a relative advantage for axitinib was available from the progression-free survival comparison, the ERG's indirect comparisons for overall survival data were more appropriate than the company's naive comparison, and these did not favour axitinib. The Committee concluded that the results generated from the naive and indirect comparisons for overall survival and progression free survival were all subject to substantial uncertainty. See FAD section 4.7. The clinical specialist supported this uncertainty and did not consider axitinib to be very different to sunitinib or pazopanib in effectiveness after prior cytokine treatment. The Committee concluded that

Consultee	Comment	Response
		axitinib was likely to have comparable clinical effectiveness to pazopanib and sunitinib. See FAD section 4.8. There was indirect comparison evidence only for axitinib compared with pazopanib and not with sunitinib. Therefore, the Committee agreed that in the prior-cytokine population, substantial uncertainty remained around the naive comparisons between axitinib, sunitinib and pazopanib, and the end-of-life criteria could only be considered met if best supportive care were the only comparator. See FAD section 4.22.
Pfizer Ltd	**ICER for axitinib compared with BSC in the post-cytokine population** During the consultation on the ACD, Pfizer became aware of a discrepancy between our first ACD response and the addendum on the post-cytokine population with respect to the results of a scenario analysis in the comparison between axitinib and BSC in the post-cytokine population. This scenario analysis provided an example of what the ICER would be if the OS of post-cytokine patients receiving BSC was less than the 24 months in the base case. The 24 months was an over-estimate derived from the network meta-analysis, which was biased due to cross-over from the TARGET trial. The lower 95% confidence interval of the 24 month was used as an illustration of a lower OS in BSC, but it should be noted that this still results in a high estimate of median OS for post-cytokine patients (17.6	Comment noted. Comments noted. The final appraisal document has been amended accordingly. See FAD section 3.42. The ERG also noted the

Consultee	Comment	Response
	months). As a result the associated ICER is also likely to be overestimated. The ICER originally submitted using the 17.6 months BSC OS estimate for this comparison was as part of the first ACD response and was £36,493 per QALY. The addendum on the post-cytokine population quoted an ICER of £33,000 per QALY for this population, a difference due to typographical error.	typographical error and stated that using the lower 95% CI for the overall survival hazard ratio of 0.41 for axitinib compared with best supportive care resulted in an overall survival of 17.46 months for best supportive care, rather than 17.6 months as stated in the company's submission addendum after appeal. See FAD section 3.57.
	Given the relatively high estimate of OS in the patients receiving BSC (17.6 months), Pfizer feel strongly that the actual ICER for this population will be considerably less than £36,493 per QALY.	Comment noted. The Committee noted that the company's base-case ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) generated for the prior-cytokine group compared with best supportive care was based on the overall survival for best supportive care of 24 months, but fell to £36,500 per QALY gained if 17.46 months for overall survival for best supportive care was used (see section 4.14). The Committee noted there were uncertainties that might increase or decrease this ICER, and concluded that the most

Consultee	Comment	Response
		plausible ICER is above the range usually considered to be a cost-effective use of NHS resources in NICE technology appraisals (between £20,000 and £30,000 per QALY gained). Based on the comparable clinical effectiveness evidence in the prior-cytokine group and the differences in NHS costs, the Committee concluded that axitinib, sunitinib and pazopanib could have comparable cost effectiveness. See FAD section 4.18.
Pfizer Ltd	**Factual inaccuracies** • Section 1.1 of the ACD states that: *"Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line kinase inhibitor or a cytokine, only if the manufacturer provides axitinib with the discount agreed in the patient access scheme."* Pfizer suggest that the word "tyrosine" is included in description of the population as "first-line *tyrosine* kinase inhibitor"	Comment noted. The recommendation has been amended to: Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme. See FAD section 1.1. The recommendations for the prior pazopanib group have

Consultee	Comment	Response
		been amended further to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.
	• Section 3.43 of the ACD states: *"Grünwald et al. was a retrospective cohort study correlating tumour shrinkage with progression-free survival and overall survival in patients with metastatic renal cell carcinoma treated with systemic therapy (tyrosine kinase inhibitors, mTOR inhibitors and/or interferon)."* PFS was not included in the analysis presented by Grünwald et al. at ECCO/ESMO 2013.	Comment noted. FAD section 3.44 has been amended accordingly.
Pfizer Ltd	**References** 1. Larkin J, Paine A, Tumur I, Cappelleri JC, Healey PJ Sr, Foley G, Mitchell S, Kroes M, Chen C. 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	Comment noted. No action required.
Kidney Cancer UK	**The Recommendations** KCUK most warmly welcomes the recommendations reached by the Appraisal Committee. If adopted as final recommendations, these will ensure that patients suffering from this deadly disease will have access to second-line treatment with all the benefits that flow from it. KCUK thoroughly approves of the condition that the recommendation is only to apply if the manufacturer provides the drug with the discount agreed in the patient access scheme. It is also pleased to see that the Committee couches its decision in terms of the broader 'a first-line kinase inhibitor' rather than specifying just sunitinib. This removes the possibility of some patients whose	Comment noted. The recommendations for the prior pazopanib group have been amended to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.

Consultee	Comment	Response
	first-line treatment indicates the taking of pazopanib being unfairly discriminated against. **Our Gratitude** We would like to express our heart-felt thanks to the Appraisal Committee for arriving at this determination. It's going to mean a lot to patients suffering from advanced renal cell carcinoma	Comment noted. No action required.
Royal College of Physicians (on behalf of NCRI/RCP/RCR/ACP/JCCO)	I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who work together to submit joint responses to NICE oncological appraisals. We are very grateful for the opportunity to comments and would like to make the following joint submission with relation to the specific questions: 1. Has all of the relevant evidence been taken into account? Yes. 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes. 3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes. 4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No.	Comments noted. The recommendations for the prior pazopanib group have been amended to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.
Royal College of Nursing	Please note that there are no comments to submit on behalf of the Royal	Comment noted. The

Consultee	Comment	Response
	College of Nursing for this consultation.	recommendations for the prior pazopanib group have been amended to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.
Royal College of Pathologists	I am just writing to inform you that the Royal College of Pathologists has no comments to make at this stage of the appraisal.	Comment noted. The recommendations for the prior pazopanib group have been amended to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comments noted. The recommendations for the prior pazopanib group have been amended to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal College of Physicians – clinical specialist	That is good news. Thank you. I am happy with the outcome and have no comments on the report	Comments noted. The recommendations for the prior pazopanib group have been amended to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.

Comments received from commentators

Commentator	Comment	Response
GSK	GSK thank NICE for the opportunity to comment on the ACD for Axitinib for the treatment of advanced renal cell carcinoma, and can confirm that we have no additional comments to make.	Comment noted. The recommendations for the prior pazopanib group have been amended to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.

Comments received from members of the public

Role*	Section	Comment	Response
Pharmaceutical industry	**Section 1** (Appraisal Committee's preliminary recommendations)	We welcome the opportunity to comment on the draft guidance for axitinib. The draft guidance recommends axitinib as follows: Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line kinase inhibitor or a cytokine, only if the manufacturer provides axitinib with the discount agreed in the patient access scheme. The licence for axitinib is as follows: Axitinib is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine. We do not agree with the draft recommendation for two main reasons: • The draft recommendation is not in line with the axitinib licence from the European Medicines Agency (EMA) • It is beyond the remit of NICE to recommend a medicine outside of its marketing authorisation The draft recommendation by NICE clearly covers a broader population than the licensed population for axitinib and therefore not in line with the licence axitinib received from the EMA. Although the AXIS trial included patients that had received prior targeted therapies such as bevacizumab and temsirolimus, the efficacy of axitinib in this patient group was not proven. The EMA EPAR states that there is not adequate information on the use of axitinib after first line bevacizumab or temsirolimus treatment. The group of patients previously treated with temsirolimus and bevacizumab+IFN; are very small (n=25 and n=59, respectively),	Comments noted. The Committee concluded that axitinib was shown to be a life-extending, end-of-life treatment for the prior-sunitinib population. It also agreed that it was not reasonable to limit this conclusion to people whose prior-tyrosine kinase inhibitor was sunitinib, given the growing, if not majority use, of pazopanib as a first-line treatment. This would leave an unmet need and would not reflect clinical practice. Therefore the Committee concluded that its recommendations should apply to the whole prior-tyrosine kinase inhibitor population. See FAD section 4.21. The Committee noted that the marketing authorisation of axitinib is for treating adults with advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine and does not include previous treatment with pazopanib. However it reiterated that it was not reasonable to limit its recommendation to people whose prior-tyrosine kinase inhibitor was sunitinib, given the growing, if not majority use, of pazopanib as a first-line treatment. This would leave an unmet need and would not reflect clinical practice. The Committee recognised that the requirement to provide funding by the relevant

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		and this resulted in inconsistencies in the efficacy results of axitinib across the subpopulations based on prior therapy. Therefore no firm conclusions can be made regarding the efficacy of axitinib in these subgroups. Due to these concerns, the licence for axitinib was limited to patients who had failed prior sunitinib or cytokine therapy. NICE's remit requires that the Institute recommends medicines within their licensed indications. The draft recommendation is at odds with this remit. The updated scope released by NICE following the appeal clearly states that the remit or appraisal objective was to appraise the clinical and cost effectiveness of axitinib within its licensed indication for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment. This remit has not been followed in this draft guidance. In addition, section 6.1.12 of the NICE Methods Guide 2013 states that: The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation. Exceptionally, the Department of Health (DOH) may direct the Appraisal Committee to make recommendations about a technology outside of the terms of its marketing authorisation or instructions for use. As far as we are aware, there is no exceptionality that applies to this indication nor has NICE shared with stakeholders any communication from the DOH directing the Appraisal Committee to make a recommendation for axitinib outside of its licence. We therefore strongly believe that NICE has exceeded its powers by recommending axitinib outside of its licence. Everolimus is the only second line therapy that can be used in patients whose disease has progressed on or after treatment with VEGF-targeted therapy, in line with its licence that was supported by a robust phase 3 trial (RECORD1). We therefore urge NICE to	health bodies (clinical commissioning groups, NHS England and local authorities) within 3 months of its date of final guidance publication applies only within the marketing authorisation. See FAD section 4.25. The recommendations for the prior pazopanib group have been amended further to provide clarity regarding the prescribing and funding requirements for axitinib in this group. See FAD sections 1.2 and 1.3.

Role*	Section	Comment	Response
		issue a recommendation for axitinib that is within its licensed indication in line with NICE's remit. References 1. Final NICE scope for axitinib: this can be accessed on: http://www.nice.org.uk/nicemedia/live/13688/65408/65408.pdf 2. Guide to the methods of technology appraisal 2013 http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf 3. Axitinib European Public Assessment Report (EPAR). This can be accessed on: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002406/WC500132190.pdf 4. Everolimus summary of product characteristics (smPC) accessed on: http://www.medicines.org.uk/emc/medicine/22281/SPC/Afinitor+Tablets/ 5. Axitinib summary of product characteristics (smPC) accessed on: http://www.medicines.org.uk/emc/medicine/27051/SPC/Inlyta+1+mg+3mg%2c+5+mg+%26+7mg+film-coated+tablets/	