Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

**final protocol**

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# Title of the project

Axitinib, everolimus, sorafenib and sunitinib for treated advanced or metastatic renal cell carcinoma.

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# Plain English Summary

In 2012 kidney cancer was the eighth most common cancer in the UK, accounting for 3% of all new cases.(1) Around 75% of people diagnosed with kidney cancer are over 60 years old, while this condition is rare in people under 50.(2) Renal cell carcinoma (RCC) is the most common type of kidney cancer, with over 80% of kidney cancer cases diagnosed as RCC in the UK.(3) Around 40% of people diagnosed with RCC are stage 1. This means that the tumour is contained entirely within the kidney and the prognosis is generally good with 80% of stage 1 RCC patients surviving for 5 years or more after diagnosis.(1) Most patients have more advanced RCC at diagnosis, with 25% of patients being diagnosed stage 3 and 20% of patients having stage 4 disease.(1) In stage 3 and stage 4 of RCC the cancer cells have spread to a lymph node (advanced disease) or to the tissues around the kidney and may have spread to other organs in the body (metastatic disease).(1) If the cancer has spread out of the kidney a complete cure may not be possible, and the goal of treatment regimens is to slow the cancer’s progression and treat symptoms.(4) Approximately 60% of patients with stage 3 RCC will survive for 5 years or more after diagnosis, while only around 5% of patients with stage 4 disease will survive for 5 years or more after diagnosis.(1)

The main treatments for RCC include nephrectomy, embolisation, radiotherapy, targeted therapies and (less frequently) immunotherapy. Immunotherapy treatments are now rarely used to treat advanced kidney cancer because targeted therapies tend to be more effective in controlling the condition, and immunotherapy can sometimes cause serious side effects. Targeted therapies are designed to target and interrupt the functions needed by cancer to grow and spread. At present, targeted therapies recommended by the National Institute for Health and Care Excellence (NICE) for people with advanced or metastatic RCC are sunitinib(5) and pazopanib(6) for first line treatment and axitinib(7) for second-line treatment. They're available on the NHS for people who are still relatively healthy and have advanced kidney cancer, or kidney cancer that's spread to other parts of their body.

The aim of this project is to review the clinical and cost-effectiveness of axitinib, everolimus, sorafenib and sunitinib for treated advanced or metastatic RCC, in a multiple technology appraisal (MTA). This will include a review of TA333 (Axitinib for treating advanced RCC after failure of prior systemic treatment), TA219 (Everolimus for the second-line treatment of advanced RCC), and a part-review of TA178 (Sorafenib and sunitinib for second-line treatment of advanced and/or metastatic RCC). The medical benefit and risks associated with these treatments will be assessed and compared across the treatments and against best supportive care for advanced or metastatic RCC. This project will also include an assessment of whether these drugs are likely to be considered good value for money for the National Health Service (NHS). A review of NICE guidance for untreated advanced or metastatic RCC is outside the scope of this MTA.

# Decision problem

4.***1 Purpose***

The purpose of this technology assessment will be to appraise the clinical and cost-effectiveness of axitinib, everolimus, sorafenib and sunitinib for treated advanced or metastatic RCC in line with their respective marketing authorisations.

***4.2 Interventions***

Axitinib (Inlyta®, Pfizer) is an inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases. It has a marketing authorisation in the UK for the treatment of adults with advanced RCC after failure of previous treatment with sunitinib or a cytokine.

Everolimus (Afinitor®, Novartis) is an inhibitor of mammalian target of rapamycin (mTOR). It has a marketing authorisation in the UK for the treatment of people with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Sorafenib (Nexavar®, Bayer/Onyx) is a multikinase inhibitor. It has a marketing authorisation in the UK for the treatment of people with advanced RCC whose disease has failed previous interferon-alpha or interleukin-2 based (cytokine agents) therapy, or who are considered unsuitable for such therapy.

Sunitinib (Sutent®, Pfizer) is an inhibitor of several receptor tyrosine kinases. It has a marketing authorisation in the UK for the treatment of advanced/metastatic RCC in adults.

All the technologies are given orally.

***4.3 Place of the interventions in the treatment pathway***

Currently only axitinib is recommended for second-line treatment of advanced or metastatic RCC in patients who have received previous cytokine or VEGF-targeted therapy. Sorafenib and sunitinib both have a market authorisation for second-line treatment of advanced of metastatic RCC, however, neither drug are currently recommended by NICE for this indication.

Everolimus is also not recommended by NICE but was available in England through the Cancer Drugs Fund (CDF), however the drug was removed from the CDF on 4th November 2015, with the exception of patients contraindicated to second-line axitinib or patients with excessive toxicity to axitinib necessitating discontinuation of axitinib within 3 months of starting therapy if there is no evidence of disease progression by then).

This MTA will consider the clinical and cost-effectiveness evidence for axitinib, sorafenib and sunitinib for advanced or metastatic RCC patients who have received previous cytokine therapy (aldesleukin or interferon alfa) and also the evidence available for axitinib, sunitinib and everolimus for advanced or metastatic RCC patients who have received previous VEGF-targeted therapy (which may include pazopanib, bevacizumab, sorafenib, sunitinib or axitinib).

***4.4 Relevant comparators***

For patients who have received previous cytokine therapy (aldesleukin or interferon alfa) the relevant comparators are:

* Axitinib;
* Sorafenib;
* Sunitinib;
* Best supportive care.

For patients who have received previous VEGF-targeted therapy the relevant comparators are:

* Axitinib;
* Everolimus;
* Sunitinib;
* Best supportive care.

To note is that any cost-effectiveness analysis undertaken will only consider interventions and comparators within their marketing authorisation, including axitinib which has been recommended by NICE outside its marketing authorisation.

***4.5 Population and relevant subgroups***

The population of interest to the current appraisal is people with previously treated, advanced or metastatic RCC. If the evidence allows the following subgroups will be considered:

* Previous treatment;
* Patients’ prognostic scores (for example ECOG or Motzer).

***4.6 Outcomes to be addressed***

If data allow, outcome measures will include:

* Overall survival;
* Progression-free survival;
* Response rates (objective response rate, clinical benefit rate, disease control rate);
* Adverse effects of treatment;
* Health-related quality of life (HRQoL).

# Report methods for synthesis of evidence of clinical effectiveness

This MTA will include a review of axitinib, sorafenib, and sunitinib for people who have received previous cytokine therapy (aldesleukin or interferon alfa), and axitinib, everolimus and sunitinib for people who have received previous vascular endothelial growth (VEGF)-targeted therapy for the treatment of advanced and/or metastatic RCC. This will include a review of TA333 (Axitinib for treating advanced RCC after failure of prior systemic treatment), TA219 (Everolimus for the second-line treatment of advanced RCC) and a part-review of TA178, (sorafenib and sunitinib) for the second-line treatment of advanced and/or metastatic RCC). The systematic review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.(8)

***5.1 Search strategy***

This MTA will include a review of axitinib, sorafenib and sunitinib for patients who have received previous cytokine therapy (e.g. aldesleukin or interferon alfa), and axitinib, everolimus and sunitinib for people who have received vascular endothelial growth factor-targeted (VEGF) therapy.

Should the randomised evidence base be insufficient to inform the decision problem that is the focus of this MTA, a search for comparative non-randomised trials will be conducted. Any non-RCT evidence identified will be considered for suitability and recommended methods used to minimise the introduction of bias.(9)

To identify relevant RCTs, a comprehensive search strategy will be designed and used to search multiple electronic databases including MEDLINE, EMBASE, Cochrane Library (CENTRAL), and DARE. Bibliographies of retrieved studies (RCTs and systematic reviews) identified as relevant will be manually reviewed for potentially eligible studies. Ongoing clinical trials will be identified by searching clinical trial registries, including ClinicalTrials.gov and the EU Clinical Trials Register. The Index to Scientific and Technical Proceedings will be searched to identify relevant conference proceedings. Appropriate organisational websites, databases, and registers will also be searched. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, submissions provided by companies will be assessed for unpublished data.

The search strategy will combine terms for the interventions or comparators of interest with terms for the target condition (RCC). Additional search terms of interventions outside the scope of this MTA that may be relevant for creating a connective network diagram will be used. However, trials of interventions not listed in the scope will only be included if they are needed to create a network linking the interventions and comparators listed in the scope.

No date or language restrictions will be applied to the search strategy. Full details of the terms used in the scoping search are presented in Appendix 9.1. All searches will be updated when the draft report is under peer review, prior to submission of the final report.

***5.2 Study selection criteria and procedures***

Two reviewers will independently screen all titles and abstracts according to the inclusion criteria (see Table 1). It is anticipated that relevant companies will provide submissions that may include unpublished data that will be considered. Full paper manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each study assessed. Discrepancies will be resolved by consensus, with involvement of a third reviewer when necessary.

Table 1. Inclusion criteria

| Inclusion criteria |
| --- |
| Study design | RCTs (comparative non-RCTs will be considered when RCT evidence is insufficient to inform decision problem) |
| Population | Patients with previously treated, advanced or metastatic RCC |
| Interventions | For people who have received previous cytokine therapy (aldesleukin or interferon alfa):* Axitinib
* Sorafenib
* Sunitinib

For people who have received previous VEGF-targeted therapy:* Axitinib
* Everolimus
* Sunitinib
 |
| Comparators | * The interventions listed above compared with each other
* Best supportive care
 |
| Outcome | * Overall survival
* Progression free survival
* Response rates
* Adverse effects of treatment
* HRQoL
 |
| Abbreviations used in table: HRQoL, health-related quality of life; RCC, renal cell carcinoma; RCT, randomised controlled trial; VEGF, vascular endothelial growth factor |

***5.3 Subgroups***

If the evidence allows, data will be analysed according to the following subgroups:

* Previous treatment;
* Patients’ prognostic scores (for example ECOG or Motzer).

***5.4 Outcomes***

Data on the following outcome measures will be assessed:

* Overall survival;
* Progression-free survival;
* Response rates;
* Adverse effects of treatment;
* HRQoL.

***5.5 Data extraction strategy***

Full paper manuscripts of any included reference will be obtained where possible. Data will be extracted independently by two reviewers using a standardised data extraction form (see Appendix 9.2). Information extracted will include details of the study’s design and methodology, baseline characteristics of participants and results including any adverse events reported. Where there is incomplete information the study authors will be contacted to gain further details, allowing about two weeks timeframe. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

***5.6 Quality assessment strategy***

The quality of the clinical effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The study quality will be assessed according to recommendations by the NHS Centre for Reviews and Dissemination(8) and *Cochrane Handbook for Systematic Reviews of Interventions*.(10) This will include assessing the following factors:

* Random sequence generation;
* Allocation concealment;
* Blinding of participants, personnel and outcome assessment;
* Incomplete outcome data;
* Selective outcome reporting;
* Other bias.

***5.7 Methods of analysis/synthesis***

Extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Should sufficient comparable data be identified, standard pair-wise comparisons and/or mixed-treatment comparisons (MTC) will be performed to evaluate the clinical effectiveness.

Treatment effects will be presented as odds ratios for dichotomous data, (weighted) mean differences for continuous data or as hazard ratios where appropriate. Mixed-treatment comparisons will be performed using a Bayesian (Markov Chain Monte Carlo (MCMC) simulation.(11) Pair-wise meta-analysis will be carried out using Comprehensive Meta Analysis software, with the use of fixed- and/or random-effects model appropriate to the assembled datasets. Clinical and methodological heterogeneity of potentially included studies will be assessed prior to data analysis. Statistical heterogeneity will be investigates to identify plausible potential causes based on the studies analysed.

# Report methods for synthesising evidence of cost-effectiveness

The purpose of this MTA will be to assess the cost-effectiveness of axitinib, everolimus, sorafenib and sunitinib within their marketing authorisations for the treatment of advanced or metastatic RCC in the UK. These interventions will be compared with each other and with best supportive care used in the NHS. This overarching objective will be met through identification and appraisal of:

* Published economic evaluations from the literature or submitted economic evaluations from companies’ submissions;
* HRQoL studies of advanced or metastatic RCC including safety data;
* UK specific resource use data. Non-UK sources will be considered if there is insufficient UK specific information.

Should the published or submitted economic evaluations prove insufficient to answer the review question; an independent *de novo* economic model will be developed.

**6.1 Search strategy**

This MTA is an update of TA333 (search for cost-effectiveness evidence on axitinib carried in June 2012), TA219 (search for cost-effectiveness evidence on everolimus carried in June 2009) and a part-update of TA178 (search for cost-effectiveness evidence on sorafenib and sunitinib carried in February 2008). The cost-effectiveness search will aim to identify full economic evaluations, costing studies and HRQoL studies. The following electronic databases will be searched in order to identify economic evaluations and quality of life studies for the interventions considered:

* MEDLINE (Ovid);
* EMBASE (Ovid);
* Database of Reviews of Effects (DARE);
* NHS Economic Evaluations Database (NHS EED).

Databases will be searched from inception for evidence on all the relevant interventions.

As an example, the details of the MEDLINE search strategy are presented in full in Appendix 9.1. The search strategy will combine terms capturing the interventions or comparators of interest and the target condition (RCC). Health economic and quality of life search terms will be applied to capture the study designs of interest (cost-effectiveness, cost and quality of life, health state utility values [HSUVs]). No language (to assess volume of foreign language studies available), setting or country restrictions will be applied to the search strategy. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and companies’ submissions will be searched for additional references. All searches will be updated when the draft report is under peer review by the Assessment Group’s clinical and health economist experts, prior to submission of the final report.

***6.2 Inclusion and exclusion criteria***

The titles and abstracts of papers identified through the searches outlined above will be independently assessed for inclusion by two reviewers using the following criteria:

*Inclusion criteria:*

* All economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequence or cost-minimisation);
* Any setting (to be as inclusive as possible);
* Intervention or comparators as per the final scope:
	+ Axitinib
	+ Everolimus
	+ Sorafenib
	+ Sunitinib
* Study outcomes reported in terms of life-years gained (LYG) or quality adjusted life years (QALYs);
* Full publications in English (numbers of relevant non-English studies will be reported);
* Quality of life studies in RCC;
* Costing/resource use studies in RCC (for resource use review).

*Exclusion criteria:*

* Abstracts with insufficient methodological details;
* Systematic reviews;
* Studies not available in the English language.

Sources of evidence reporting data for additional interventions considered relevant in advanced and metastatic RCC treatment will be identified in the systematic search. These sources however will not be data-extracted and included in the literature review unless:

* They report data of special interest or relevance, or;
* The evidence already collected is not considered sufficient.

The additional interventions considered are: bevacizumab, interferon-$α$, nivolumab, pazopanib, temsirolimus and tivozanib.

***6.3 Data extraction strategy***

Data will be extracted by one reviewer using a standardised data extraction table and checked by a second reviewer for accuracy. Disagreement will be resolved by discussion, however, if no consensus is reached, a third reviewer will be consulted. In cases where there are missing data or unclear reporting in the published or submitted economic evidence or quality of life studies, attempts will be made to contact authors. Studies published in the UK will be reported in greater detail than non-UK studies as they are more likely to be relevant to the NHS. Tables 2 and 3 exemplify the health economic evaluation and quality of life data that will be sought from each study. In addition, the reason for exclusion of each excluded study will be documented (Table 4).Table 2. Health economic evaluation data extraction table

| Author, year, country | Perspective, discounting & cost year | Model type | Patient population | Intervention/comparator | Outcomes | Results ICER (per QALY gained) incl. uncertainty |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| Reviewer’s comments: |
| Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year |

Table 3. Quality of life data extraction table

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author, year,country | Sample size | Patient population | Instrument (Valuation) | Utility results |
|  |  |  |  |  |
| Reviewer’s comments: |

Table 4. Data exclusion table

|  |  |
| --- | --- |
| Bibliographic reference | Reasons for exclusion |
|  |  |
| Reviewer’s comments: |

***6.4 Quality assessment strategy***

All published economic evaluations identified within the review and any economic evaluations submitted by companies to NICE will be subject to critical appraisal. The methodological quality of each economic evaluation will be assessed against the NICE reference checklist for economic evaluations(9) together with the Philips checklist(12) on mathematical models used in technology assessments (see Appendix 9.3). Each economic evaluation will be assessed by one health economist and the details of the assessment checked by a second health economist.

***6.5 Methods of analysis***

*Published and submitted economic evaluations*

A narrative summary and accompanying data extraction table will be presented to summarise evidence from published or submitted economic evaluations.

*Economic modelling*

Should the economic evidence identified prove insufficient to answer the research question; a *de novo* economic model will be developed in Microsoft Excel®. The structure of the *de novo* model will be informed by economic evaluations identified in the published literature, clinical expert opinion and company submissions.(13, 14) All structural assumptions will be documented and accompanying rationales provided. It is anticipated that the model used in the previous RCC MTA will be the most informative in the development of any *de novo* economic evaluation.(15) However, the previous MTA considered first-line treatment regimens in RCC, while the present MTA will only consider further treatment lines for advanced or metastatic RCC. The clinical effectiveness parameters required for the economic model will be informed by the review of clinical effectiveness discussed in Section 5. Parameters such as estimates of quality of life (utility data) will be informed by the published literature, identified in the review. In cases where parameters required to populate the model are not available from published studies or company submissions, expert clinical opinion will be considered.

The cost-effectiveness of the interventions will be estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per LYG. As appropriate, cost data will be obtained from NHS reference costs(16), British National Formulary(17), Unit Costs of Health and Social Care(18) or company submissions. Costs will consist of direct medical costs (e.g. drug costs and cost of adverse events, monitoring and administering costs) and direct non-medical costs (e.g. costs of healthcare professional). Resource use and costs will be valued from the NHS and Personal Social Services (PSS) perspective. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with NICE methods guidance.(9) The time horizon for the economic analysis will be long enough to reflect any differences in costs or outcomes between the technologies under comparison.

***6.6 Methods for estimating quality of life***

Ideally, evidence of the impact of axitinib, everolimus, sorafenib and sunitinib on patients’ quality of life will be available directly from identified trials. In the absence of such evidence, any *de novo* economic model may use indirect evidence on quality of life from alternative literature sources, such as related technology appraisals or clinical guidelines. In accordance with NICE methods guidance, utility values will be taken from studies that have been based on “public” preferences elicited using a choice-based method.(9)

***6.7 Analysis of uncertainty***

Extensive sensitivity analysis will be undertaken to explore uncertainty. Probabilistic sensitivity analysis (PSA) will be undertaken, by which all relevant input parameters will be entered as probability distributions and Monte Carlo simulations will be run to reflect uncertainty in the model’s results. In addition, uncertainty will also be explored through one-way sensitivity analysis. The outputs of the PSA will be presented in the cost-effectiveness plane and through the use of cost-effectiveness acceptability curves. One way sensitivity analysis outputs will be presented in tables and tornado diagrams. Where possible, uncertainty pertaining to the structural assumptions used will be assessed in scenario analyses using alternative structural assumptions. If data permits, the impact of patient heterogeneity (e.g. previous RCC treatments received) on cost-effectiveness results will be explored in subgroup analyses.

# Handling the company submission(s)

All data submitted by the drug companies/sponsors will be considered if received by the TAR group on or before 05/05/2016. Data arriving after this date will not be considered. Data meeting the inclusion criteria for the review will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the companies’ submissions, provided it complies with NICE’s advice on presentation, will be assessed for clinical validity and appropriateness of the data and assumptions used in the economic model.

Any ‘commercial in confidence’ data taken from a company’s submission, and specified as confidential in the supplied check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company’s name, for example, in brackets). Any ‘academic in confidence’ data taken from a company’s submission, and specified as confidential in the supplied check list, will be highlighted in yellow and underlined in the assessment report.

# Competing interests of authors

None.

# Appendices

**Appendix 9.1. Draft search strategy**

***Clinical draft search strategy***

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; search run on 08/12/15

Limits:

* Animal-only studies excluded
* No limits applied for study design, date or language

1 Carcinoma, Renal Cell/ 2 (renal cell carcinoma$ or cell renal carcinoma$ or renal carcinoma$ or kidney carcinoma$ or kidney cell carcinoma$ or renal adenocarcinoma$ or kidney adenocarcinoma$ or adenocarcinoma$renal or adenocarcinoma$kidney$).mp 3 (hypernephroma$ or nephroid carcinoma$ or hypernephroid carcinoma$ or kidney hypernephroma$ or kidney pelvic carcinoma$ or kidney pyelocarcinoma$ or renal hypernephroma$ or grawitz tumo?r$ or renal cell neoplasm$ or renal cell cancer$ or renal tumo?r$ or carcinoma chromophobe cell kidney$ or chromophobe cell kidney carcinoma$).mp 4 kidney neoplasms/ 5 (cancer$ adj2 kidney$1).ti,ab 6 (neoplasm$1 adj2 kidney$1).ti,ab 7 (neoplasm$1 adj2 renal).ti,ab 8 (cancer$ adj2 renal).ti,ab 9 (tumo?r$1 adj2 kidney$1).ti,ab 10 (tumo?r$1 adj2 renal).ti,ab 11 or/1-10 12 (axitinib or inlyta or AG013736 or "AG 013736").mp 13 (sorafenib or nexavar or bay 43-9006 or bay 439006 or bay43-9006 or bay439006).mp 14 (sunitinib or sutent or pha 2909040ad or pha2909040ad or "su 010398" or "su 011248" or su 10398 or su10398 or su 11248 or su010398 or su011248 or su11248).mp 15 (everolimus or afinitor or certican or zortress or nvp-rad-001 or rad-001 or rad 001a or rad001 or rad001a or sdz rad).mp 16 (nivolumab or opdivo or ONO4538 or ONO 4538 or BMS936558 or BMS 936558 or MDX1106 or MDX 1106).mp 17 (temsirolimus or cci-779 or cell-cycle-inhibitor-779 or nsc 683864 or nsc683864 or torisel).mp 18 (bevacizumab or avastin or nsc 704865 or nsc704865 or anti-vegf or rhumab-vegf).mp 19 (alpha-interferon or alfaferone or alferon or alpha ferone or cilferon or ginterferon or interferon-alpha or introma or kemron or leukinferon or leukinferron or leukocyte interferon or refecon a or referon a3 or sumiferon or sumipheron or veldona).mp 20 (armala or pazopanib or gw786034 or gw 786034 or sb 710468 or sb710468 or votrient).mp 21 (biotest or bioleukin or interleukin-ii or 'interleukin-2 or il-2 or il2 or ro-236019 or tcgf or tsf).mp 22 or/12-21 23 11 and 22 24 Animals/ not Humans/ 25 23 not 24 26 (editorial or letter).pt 27 25 not 26

***Health economics draft search strategy***

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; search run: 8/12/2015

1 Carcinoma, Renal Cell/

2 (renal cell carcinoma$ or cell renal carcinoma$ or renal carcinoma$ or kidney carcinoma$ or kidney cell carcinoma$ or renal adenocarcinoma$ or kidney adenocarcinoma$ or adenocarcinoma$renal or adenocarcinoma$kidney$).tw. (30852)

3 (hypernephroma$ or nephroid carcinoma$ or hypernephroid carcinoma$ or kidney hypernephroma$ or kidney pelvic carcinoma$ or kidney pyelocarcinoma$ or renal hypernephroma$ or grawitz tumo?r$ or renal cell neoplasm$ or renal cell cancer$ or renal tumo?r$ or carcinoma chromophobe cell kidney$ or chromophobe cell kidney carcinoma$).tw.

4 kidney neoplasms/

5 (cancer$ adj2 kidney$1).ti,ab.

6 (neoplasm$1 adj2 kidney$1).ti,ab.

7 (neoplasm$1 adj2 renal).ti,ab.

8 (cancer$ adj2 renal).ti,ab.

9 (tumo?r$1 adj2 kidney$1).ti,ab.

10 (tumo?r$1 adj2 renal).ti,ab.

11 or/1-10

12 (axitinib or ag013736 or inlyta).tw.

13 (tivozanib or av-951).tw.

14 (pazopanib or armala or gw786034 or sb710468).tw.

15 (alpha-interferon or alfaferone or alferon or alpha ferone or cilferon or ginterferon or interferon-alpha or introma or kemron or leukinferon or leukinferron or leukocyte interferon or refecon a or referon a3 or sumiferon or sumipheron or veldona).tw.

16 (biotest or bioleukin or interleukin-ii or interleukin-2 or il-2 or il2 or ro-236019 or tcgf or tsf).tw.

17 interleukin$.tw.

18 (sunitinib or sutent or pha 2909040ad or pha2909040ad or "su 010398" or "su 011248" or su 10398 or su10398 or su 11248 or su010398 or su011248 or su11248).tw.

19 (sorafenib bay 43-9006 or bay 439006 or bay43-9006 or bay439006 or nexavar).tw.

20 (everolimus or afinitor or nvp-rad-001 or rad-001 or rad 001a or rad001 or rad001a or sdz rad).tw.

21 (temsirolimus or cci-779 or cell-cycle-inhibitor-779 or nsc 683864 or nsc683864 or torisel).tw.

22 (bevacizumab or avastin or nsc 704865 or nsc704865 or anti-vegf or rhumab-vegf).tw.

23 (nivolumab or opdivo or ONO4538 or ONO 4538 or BMS936558 or BMS 936558 or MDX1106 or MDX 1106).tw.

24 or/12-23

25 11 and 24

26 Animals/ not Humans/

27 25 not 26

28 economics/

29 exp "costs and cost analysis"/

30 exp economics, hospital/

31 economics, medical/

32 economics, pharmaceutical/

33 (economic$ or pharmaeconomic$ or pharmacoeconomic$ or pharmaco-economic$).tw.

34 (cost or costs or costly or costing or costed).tw.

35 value for money.tw.

36 (Quality-adjusted life year$ or QALY$).tw.

37 or/28-36

38 limit 37 to yr=2006-2015

39 27 and 38

40 27 and 37

**Appendix 9.2. Data extraction form clinical effectiveness studies**

| **STUDY:**  |
| --- |
| Full reference: |
| **DESIGN** |
| Study design |  |
| Number of centres & Country/countries |  |
| Recruitment dates |  |
| Length of follow-up |  |
| Source of funding |  |
| **PARTICIPANTS & TREATMENT ARMS** | Arm 1 | Arm 2 | Arm 3 |
| Intervention, dose and frequency |  |
| Method of delivery, number of cycles, dose reductions |  |
| Concomitant medication(s) |  |
| Number randomised |  |
| Number withdrawn |  |
| Advanced and/or metastatic disease |  |
| Previous treatments |  |
| Age, years: mean±SD (range) |  |
| Ethnicity, n (%) |  |
| Inclusion criteria |  |
| Exclusion criteria |  |
| Subgroups |  |
| **ANALYSIS** |
| Primary outcome |  |
| Secondary outcomes |  |
| **BINARY OUTCOMES** | **Arm 1 (n=)** | **Arm 2 (n=)** | **Arm 3 (n=)** |
| Overall survival, n (%) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Complete response, n (%) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Partial response, n (%) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Overall response, n (%) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Stable disease, n (%) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Withdrawals |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Any other outcome |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Adverse events of treatment, n (%) | i. |  |  |
| ii. |  |  |
| ii. |  |  |
| iv. |  |  |
| v. |  |  |
| vi. |  |  |
| Notes: p-value, 95% CI and subgroups |
| **CONTINUOUS OUTCOMES** | **Arm 1 (n=)** | **Arm 2 (n=)** | **Arm 3 (n=)** |
| Progression free survival, monthsmean ± SD (median [range]) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Time to response, months mean ± SD (median [range]) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Duration of response, monthsmean ± SD (median [range]) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| Health-related quality of lifemean ± SD (median [range]) |  |  |  |
| Notes: p-value, 95% CI and subgroups |
| **RISK OF BIAS OF RCTs** |
|  | **Risk assessment** (low risk, high risk, unclear risk) | **Comments** |
| **Random sequence generation** |  |  |
| Allocation concealment |  |  |
| Selective reporting |  |  |
| Blinding (who [participants, personnel], and method) |  |  |
| Blinding of outcome assessment |  |  |
| Incomplete outcome data: |  |  |
| *-Overall survival* |  |  |
| *-Progression free survival* |  |  |
| *-Complete response* |  |  |
| *-Partial response* |  |  |
| *-Overall response* |  |  |
| *-Stable disease* |  |  |
| *-Time to response* |  |  |
| *-Duration of response* |  |  |
| *-Other outcomes (name)* |  |  |
| *-Adverse events* |  |  |
| Selective reporting: |  |  |
| *-Overall survival* |  |  |
| *-Progression free survival* |  |  |
| *-Complete response* |  |  |
| *-Partial response* |  |  |
| *-Overall response* |  |  |
| *-Stable disease* |  |  |
| *-Time to response* |  |  |
| *-Duration of response* |  |  |
| *-Other outcomes (name)* |  |  |
| *-Adverse events* |  |  |
| Other biases: |  |  |
| *-Overall survival* |  |  |
| *-Progression free survival* |  |  |
| *-Complete response* |  |  |
| *-Partial response* |  |  |
| *-Overall response* |  |  |
| *-Stable disease* |  |  |
| *-Time to response* |  |  |
| *-Duration of response* |  |  |
| *-Other outcomes (name)* |  |  |
| *-Adverse events* |  |  |
| Abbreviations used in table: CI, confidence interval; n, number of patients; RCT, randomised controlled trial; SD, standard deviation; |

**Appendix 9.3. Health economic evaluation study quality assessment**

***NICE reference case(11)***

| **Attribute** | Reference case | Reviewer’s comments |
| --- | --- | --- |
| Decision problem | The scope developed by NICE |  |
| Comparator(s) | Alternative therapies routinely used in the NHS |  |
| Perspective costs | NHS and Personal Social Services  |  |
| Perspective benefits | All health effects on individuals |  |
| Form of economic evaluation | Cost-utility analysis |  |
| Time horizon | Sufficient to capture differences in costs and outcomes |  |
| Synthesis of evidence on outcomes | Systematic review |  |
| Outcome measure | QALYs  |  |
| Health states for QALY | Described using a standardised and validated instrument |  |
| Benefit valuation | Time-trade off or standard gamble |  |
| Source of preference data for valuation of changes in HRQoL  | Representative sample of the public |  |
| Discount rate | An annual rate of 3.5% on both costs and health effects  |  |
| Equity  | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit  |  |
| Sensitivity analysis | Probabilistic sensitivity analysis  |  |
| Abbreviations used in table: NICE, National Institute for Health and Clinical Excellence; NHS, National Health Service; QALY, quality adjusted life year. |

***Philips checklist(14)***

| **Dimension of quality** | **Reviewers comments** |
| --- | --- |
| **Structure**  |
| S1 Statement of decision problem/objective |   |
| S2 Statement of scope/perspective |   |
| S3 Rationale for structure |   |
| S4 Structural assumptions |   |
| S5 Strategies/comparators  |   |
| S6 Model type |   |
| S7 Time horizon |   |
| S8 Disease states/pathways |   |
| S9 Cycle length |   |
| **Data**  |
| D1 Data identification |   |
| D2 Premodel data analysis  |   |
| D2a Baseline data |   |
| D2b Treatment effects |   |
| D2d Quality of life weights (utilities) |   |
| D3 Data incorporation |   |
| D4 Assessment of uncertainty |   |
| D4a Methodological |   |
| D4b Structural  |   |
| D4c Heterogeneity |   |
| D4d Parameter  |   |
| **Consistency** |
| C1 Internal consistency |   |
| C2 External consistency |   |

Please send all correspondences to the project lead, Steve Edwards, and the main reviewer, Mariana Bacelar.

A Progress Report (to NETSCC, HTA who forward it to NICE within 24h) will be submitted on 19 May 2016;

A draft Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted “date to be confirmed”.

The Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted on 8th August 2016.

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