Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Protocol

26 October 2007

PROJECT TITLE

Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma

TAR TEAM

PenTAG

PROJECT LEAD

Jo Thompson Coon
Research Fellow
PenTAG
Peninsula Medical School
Noy Scott House
Barrack Road
EXETER
EX2 5DW
Telephone: 01392 406966
Fax: 01392 406401
Email: Jo.Thompson-Coon@pms.ac.uk

TAR TEAM MEMBERS

Jo Thompson Coon, Research Fellow, Peninsula Technology Assessment Group

Colin Green, Senior Lecturer, Peninsula Technology Assessment Group

Martin Hoyle, Research Fellow, Peninsula Technology Assessment Group

Zulian Liu, Research Assistant, Peninsula Technology Assessment Group

Martin Pitt, Research Fellow, Peninsula Technology Assessment Group

Karen Welch, Information Scientist, Southampton Health Technology Assessment Group

Ken Stein, Professor of Public Health, Peninsula Technology Assessment Group

1.1 Plain English Summary

In England and Wales, around 6,000 people are diagnosed with renal cell cancer each year. In about a third of those, the disease is at an early stage and the tumour is contained entirely within the kidney. For these people the mainstay of treatment is surgical removal of the tumour. However, around a fifth of people do not find out that they have kidney cancer until the tumour is at a more advanced stage and may have spread either to other organs in the body (metastatic disease) or to other tissues surrounding the kidney (locally advanced disease). Surgical removal of these tumours may not be possible and there are currently few other treatment options. The most commonly used therapies are interferon-alpha and interleukin-2 (both are immunotherapy). There are currently no standard treatments for people with metastatic renal cell cancer who do not respond to immunotherapy. Only a small number of people (about 10%) diagnosed with late stage renal cell cancer survive for more than five years from the date of diagnosis.

This assessment will review the clinical and cost effectiveness of four new drugs for treating advanced and metastatic renal cell cancer. Bevacizumab (also known as Avastin®) used in combination with interferon-alpha, sorafenib tosylate (also known as Nexavar®), sunitinib (also known as Sutent®) and temsirolimus (also known as Torisel® or CCI-779). All four drugs, although they produce their effects in slightly different ways, aim to stop the tumour growing.

The assessment will draw together all the relevant evidence about these drugs systematically and will focus on differences in overall survival, progression-free survival, tumour response rate, health related quality of life and side effects of treatment resulting from the use of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus compared to current standard treatments for advanced and metastatic renal cell cancer. It will also assess whether the treatments are likely to be considered good value for money for the NHS.

1.2 Decision problem

1.2.1 Purpose

The purpose of this technology assessment is to appraise the clinical and cost effectiveness of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic renal cell carcinoma in line with their marketing authorisations.

1.2.2 The interventions

Bevacizumab (Avastin®; Roche Pharmaceuticals) is a recombinant human monoclonal antibody against vascular endothelial growth factor (VEGF). VEGF has an important role in angiogenesis (the formation of new blood vessels). Bevacizumab prevents VEGF from binding to its receptors, reducing

vascularisation of the tumour and leading to an inhibition of tumour growth. Bevacizumab is administered by intravenous infusion.

Sorafenib tosylate (Nexavar®; Bayer/Onyx) is an orally administered multi-kinase inhibitor which targets serine/threonine Raf-1 kinases and various receptor tyrosine kinases including those on the VEGF receptor (VEGFR), the platelet derived growth factor receptor (PDGFR) and the stem cell factor receptor (KIT). Sorafenib tosylate therefore inhibits tumour cell proliferation and tumour angiogenesis.

Sunitinib (Sutent®; Pfizer) is an orally administered multi-kinase inhibitor which targets several receptor kinase inhibitors including those on the VEGFR and the PDGFR, thereby inhibiting proliferation of tumour cells and development of tumour vasculature.

Temsirolimus (Torisel®; Wyeth) is administered by intravenous infusion and blocks the function of the mammalian target of rapamycin (mTOR) a key protein within cells that regulates cell proliferation, growth and survival.

1.2.3 The place of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus in the management of advanced renal cell carcinoma

Bevacizumab is currently being used as first-line therapy in clinical trials in combination with interferon-alpha. At the time of writing, bevacizumab has no marketing authorisation for use in the treatment of RCC in the UK. The anticipated indication for bevacizumab is first line treatment for advanced and/or metastatic RCC in conjunction with interferon-alpha.

Sorafenib tosylate has EU orphan drug designation for RCC and has received marketing authorisation for use in patients with RCC as first line therapy in those who are unsuitable for therapy with interferon-alpha or interleukin-2 and as second line therapy in those who have failed therapy with these agents.

Sunitinib has a marketing authorisation in the UK for the treatment of advanced and/or metastatic RCC, both as a first and second line therapy.

At the time of writing, Temsirolimus has no marketing authorisation for use in advanced RCC in the UK. The anticipated indication is as first line therapy in patients with three or more of six indicators of poor prognosis.

1.2.4 Population

The population will be people with advanced and/or metastatic renal cell carcinoma.

1.2.5 Comparators

Table 1 summarises the potential comparisons that may be made between interventions.[a]

First line therapy

When considered as first-line therapy, bevacizumab (in combination with interferon-alpha), sorafenib tosylate (in patients who are unsuitable for treatment with interferon-alpha or interleukin-2), sunitinib and temsirolimus will be compared with:

- Best supportive care
- Immunotherapy (interferon-alpha or interleukin-2 without the addition of bevacizumab)

Comparisons between the interventions will be made where appropriate and in line with their marketing authorisations.

Where randomised head-to-head comparison data are not available, the TAR team will investigate the validity of performing indirect comparisons between the interventions using appropriate methodology. All comparisons (direct and indirect) are contingent on the availability of good quality data.

Second line therapy

When considered as second-line therapy sorafenib tosylate and sunitinib will be compared with best supportive care.

Comparisons between the interventions will also be made in line with their marketing authorisations.

Where randomised head-to-head comparison data are not available, the TAR team will investigate the validity of performing indirect comparisons between the interventions using appropriate methodology. All comparisons (direct and indirect) are contingent on the availability of good quality data.

[a] Assumptions have been made regarding the expected marketing authorizations for bevacizumab and temsirolimus (at the time of writing, neither bevacizumab nor temsirolimus have marketing authorizations for the treatment of RCC in the UK).

Table 1: Potential comparisons between interventions

As first line therapy in those suitable for treatment with immunotherapy		
bevacizumab plus interferon-alpha	*compared with*	best supportive care
bevacizumab plus interferon-alpha	*compared with*	immunotherapy
bevacizumab plus interferon-alpha	*compared with*	sunitinib
sunitinib	*compared with*	best supportive care
sunitinib	*compared with*	immunotherapy
As first line therapy in those unsuitable for treatment with immunotherapy		
sorafenib tosylate	*compared with*	best supportive care
sunitinib	*compared with*	best supportive care
sorafenib tosylate	*compared with*	sunitinib
As first line therapy in those with ≥ three of six poor prognostic factors		
temsirolimus	*compared with*	best supportive care
temsirolimus	*compared with*	sorafenib tosylate
temsirolimus	*compared with*	immunotherapy
temsirolimus	*compared with*	sunitinib
temsirolimus	*compared with*	bevacizumab plus interferon-alpha
As second line therapy		
sorafenib tosylate	*compared with*	best supportive care
sorafenib tosylate	*compared with*	sunitinib
sunitinib	*compared with*	best supportive care

1.2.6 Outcomes to be examined

If possible, outcome measures will include:

- Overall survival
- Progression free survival
- Tumour response rate
- Adverse effects of treatment
- Health related quality of life

1.2.7 Sub-groups to be examined

Depending on the availability and quality of the data the following sub-groups may be considered:

- People who have undergone surgical resection of the primary tumour versus those who have not
- People diagnosed with clear cell carcinoma versus those diagnosed with non-clear cell carcinoma

1.3 Methods of synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus. The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination[1].

1.4 Search strategy

Refer to Appendix 1 for details of the sources to be searched and the draft search strategy for MEDLINE.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Scrutiny of bibliographies of included studies
- Contact with experts in the field
- Searching of major conference proceedings e.g. ASCO, ECCO, ESMO, EORTC, EAU, AUA, EMUC

Current research will be identified through searching the National Research Register, the Current Controlled Trials Register and the MRC Clinical Trials Register

In addition, any industry submissions to NICE as well as any relevant systematic reviews identified by the search strategy will be scrutinised in order to identify any additional studies.

1.5 Study selection criteria and procedures

Types of study to be included

Systematic reviews of RCTs and single RCTs will be included. These study design criteria may be relaxed to include other controlled and uncontrolled study designs depending on the availability of more methodologically robust evidence.

Studies will only be included if they are of bevacizumab, sorafenib tosylate, sunitinib or temsirolimus in the treatment of advanced and/or metastatic renal cell carcinoma, have used relevant comparators (see section 1.2.5) and report relevant outcomes (see section 1.2.6).

Types of study to be excluded

- Non-randomised controlled studies (unless there are insufficient RCTs or controlled studies)
- Uncontrolled studies (unless there are insufficient RCTs or controlled studies)
- Animal models
- Pre-clinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality
- Studies not available in the English language.

Study selection

The abstracts and titles of references retrieved by the electronic searches will be screened for relevance. Full paper copies of potentially relevant studies will be obtained. The retrieved articles will be assessed for inclusion by one reviewer and independently checked by a second, using the pre-specified inclusion/exclusion criteria. Discrepancies will be resolved by discussion, with involvement of a third reviewer, where necessary. All duplicate papers will be double checked and excluded.

Quality assessment strategy

The quality of individual studies will be assessed by one reviewer, and checked by a second reviewer. Any disagreement will be resolved by consensus and if necessary a third reviewer will be consulted.

The quality of the clinical effectiveness studies will be assessed according to criteria suggested by NHS CRD Report No 4, according to study type[1].

Data extraction strategy

Data will be extracted from included studies by one reviewer using a standardised data extraction form (see Appendix 2) and checked by another reviewer. Discrepancies will be resolved by discussion, with the involvement of a third reviewer if necessary.

Methods of analysis / synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate summary measures of effect on relevant outcomes, based on intention to treat analyses.

If meta-analysis is conducted it will be carried out using fixed and random effects models, using Review Manager and STATA software. Heterogeneity will be explored through consideration of the study populations, methods and

interventions by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and I^2 statistic and, where appropriate, using meta-regression.

Where randomised head-to-head comparison data are not available, the TAR team will investigate the validity of performing indirect comparisons between the interventions using appropriate methodology. All comparisons (direct and indirect) are contingent on the availability of good quality data.

All selected articles will be scanned for short and long term adverse effects of treatment. Data will be extracted from the included trials and discussed narratively.

1.6 Methods of synthesis of evidence of cost effectiveness

1.6.1 Systematic review of cost effectiveness studies

A systematic review of economic evaluations will be undertaken. Full economic evaluations[2,b] will be included where they meet the inclusion criteria set out for the review of clinical effectiveness (see section 1.5). The sources to be searched will be similar to those in the clinical effectiveness review (see Appendix 1). Searches will be limited to English Language sources.

Economic evaluations identified in the search will be critically assessed using accepted frameworks, such as the consensus-developed list of criteria developed by Evers et al[3] and Drummond and colleagues[4;5]. For included economic evaluations based on decision models, critical appraisal of these studies will make use of guidelines for good practice in decision analytic modelling in HTA[6].

Methods and findings from included economic evaluations will be summarised in a tabular format (e.g. study type, study characteristics, results) and synthesised in a narrative review. Economic evaluations carried out from the perspective of the UK NHS and Personal Social Services (PSS) perspective will be presented in greater detail.

1.6.2 Systematic literature search for other data related to cost-effectiveness

A search of the broader literature on renal cancer will be undertaken to identify the evidence base on HRQoL (i.e. health state values), resource use and costs for treatment and side-effects, and the methods available for the modelling of renal cancer to inform cost-effectiveness analyses. The search strategies employed will be reported, and findings from these explorative searches will be presented in summary format, using a tabular approach and narrative text.

---

[b] CRD NHS Economic Evaluation Handbook (2007) defines full economic evaluations as studies in which a comparison of two or more alternatives is undertaken and costs and outcomes are examined for each alternative. They are classified as cost-benefit analysis, cost-utility analysis or cost effectiveness analysis (including cost-consequences analysis).

These searches, and any additional searches to identify data to inform TAR team cost-effectiveness analyses (e.g. to populate a decision model), will be based on the methodological discussion paper '*Methods for establishing parameter values for decision analytic models'* commissioned by the UK Department of Health and produced by InterTASC (January 2005).

1.6.3 TAR Team Economic Analysis

An independent economic evaluation will be carried out from the perspective of the UK NHS and PSS, consistent with the methods recommended in the NICE reference case (NICE 2004). Any deviation from the NICE reference case will be discussed and justified as appropriate. The economic evaluation will estimate the cost effectiveness of the following technologies compared to appropriate comparator treatment strategies, in accordance with licence indications.

- Bevacizumab (in combination with interferon alpha)
- Sorafenib tosylate
- Sunitinib
- Temsirolimus

For each treatment strategy a mean incremental cost will be estimated, and combined with a mean incremental benefit. Results will be presented in the form of incremental cost-effectiveness ratios. Results will also be presented in a disaggregated format (i.e. costs and effects presented separately). Where probabilistic modelling is undertaken to inform cost effectiveness analyses, results will be presented using the cost effectiveness plane, and cost effectiveness acceptability curves (CEACs).

The estimates for resource use and associated costs will include the incremental costs associated with treatment (e.g. drug costs, related treatment costs, costs related to side effects) in a UK context (i.e. NHS and PSS perspective).

The final outcome measure(s) will depend on the available evidence, but they are likely to include:

- life years gained
- QALYs gained
- progression free life-years gained

Extensive sensitivity analyses will be undertaken to explore uncertainty. These will include one-way and multi-way sensitivity analyses, and use of probabilistic sensitivity analyses (PSA)[c] where modelling permits. The use of PSA involves sampling of parameter inputs from distributions that characterise uncertainty in the mean estimate of the parameter. PSA is used to characterise uncertainty in

[c] The principles of probabilistic sensitivity analyses (PSA) are better described as probabilistic decision analysis (PDA), as they reflect the opportunities for considering uncertainty when a decision model is structured using probabilistic inputs.

a range of parameter inputs simultaneously, to consider the combined implications of uncertainty in parameters.

1.6.4 Economic modelling

Where appropriate an economic model will be constructed by adapting an existing model or developing a new model using available evidence.[d] Where modelling is undertaken to inform cost-effectiveness analyses, we will follow guidance on good practice in decision analytic modelling for HTA.[6]

In summary, model structure will be determined on the basis of research evidence and clinical expert advice, against:

- The natural history of RCC
- The main treatment pathways in a UK NHS context (for treatment and comparator treatment pathways)
- The disease states and/or events that are most relevant in determining patients' clinical outcomes, HRQL, and resource use and costs (applying an NHS & PSS perspective.

All assumptions applied in a modelling framework will be clearly stated. All data inputs and their source will be clearly identified.

1.7 Handling the company submission (s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than January 24th 2008. Data arriving after this date will not be considered.

If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, will be assessed against NICE's guidance on the Methods of Technology Appraisal and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Where the TAR team have undertaken further analyses, using models submitted by manufacturers/sponsors or via *de novo* modelling and cost effectiveness analysis, a comparison will be made of the alternative models used for the analysis.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

[d] It is expected that the TAR team will use a decision analytic model approach to assess cost effectiveness. However, exploratory searching has not identified any published economic models for the drugs included in the scope of this appraisal.

1.8 Additional considerations

The TAR team cannot guarantee to consider any data or information relating to the technologies if received after 24th January 2008.

1.9 Competing interests of authors

None.

1.10 References

(1) NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness. 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001.

(2) Centre for Reviews and Dissemination. NHS Economic Evaluation Database Handbook. 2007. University of York.

(3) Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International Journal of Technology Assessment in Health Care 2005; 21(2):240-245.

(4) Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford University Press; 1997.

(5) Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996; 313(7052):275-283.

(6) Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 2004; 8(36).

1.11 Appendix 1

1.11.1 Sources to be searched

Medline (Ovid) – 1950-

Embase (Ovid) 1980-

Science Citation Index 1981-

Web of Science Proceedings 2000-

Biosis 2000-

Individual Conference Proceedings (e.g. ASCO, ECCO, ESMO, EORTC, EAU, AUA, EMUC 2000-

Cochrane Library including CDSR, Central, HTA and NHSEED

1.11.2 Draft search strategy for clinical effectiveness studies in Medline

1 exp Carcinoma, Renal Cell/ (13955)
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$).mp. (17055)
3 (hypernephroma$ 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$).mp. (6671)
4 exp kidney neoplasms/ (42979)
5 (cancer$ adj2 kidney$1).ti,ab. (1427)
6 (neoplasm$1 adj2 kidney$1).ti,ab. (205)
7 (neoplasm$1 adj2 renal).ti,ab. (879)
8 (cancer$ adj2 renal).ti,ab. (4024)
9 (tumo?r$1 adj2 kidney$1).ti,ab. (2162)
10 (tumo?r$1 adj2 renal).ti,ab. (5510)
11 or/1-10 (48251)
12 (bevacizumab or avastin or sorafenib or nexavar or sunitinib or sutent or torisel or temsirolimus or "CCI-779").mp. (1596)
13 11 and 12 (257)
14 limit 13 to humans (252)
15 (editorial or letter).pt. (813002)
16 14 not 15 (234)
17 from 16 keep 1-234 (234)

1.12 Appendix 2

Data extraction forms

STUDY	INTERVENTION
ID number:	**Intervention:**
Author name:	**Comparator:**
Year of Publication:	**Concurrent treatment:**
Title	**Notes:**
Country:	
Setting:	
Recruitment dates:	
Study design:	
PARTICIPANTS	
Total number:	
Inclusion criteria:	
Exclusion criteria:	
Sub-groups:	

BASELINE CHARACTERISTICS			OUTCOME MEASURES
N	**Intervention**	**Control**	**Primary outcome measure:**
			Secondary measures:
			Method of assessing outcomes:
			Length of follow-up:
			Notes:

RESULTS

Effectiveness outcomes	Intervention	Control	Effect size (95% CI or p value)
Overall survival			
Progression free survival			
Tumour response rate			
Adverse effects of treatment			
Health related quality of life			
Cost information			
Other information			

METHODOLOGICAL COMMENTS

Prospective recruitment?

Selection / randomisation:

Method of randomisation:

Block:

Stratification:

Concealment of allocation:

Groups similar at baseline?

Eligibility criteria stated?

Appropriate?

Blinding:

Outcome measures:

ITT:

If no, justified?

Protocol violations specified:

Follow up / attrition:

Data analysis:

Are they appropriate?

How were missing data accounted for?

Power calculation at design?

Does it justify any sub-group analyses carried out?

Are the conclusions supported by the results?

Was ethical approval given?

Generalisability:

Conflict of interest:

Inter centre variability:

GENERAL COMMENTS