NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA169; Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma and TA178; Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma.

This guidance was issued in March 2009 (TA169) / August 2009 (TA178).

The review date for this guidance is June 2011 (deferred from February 2011 for TA169).

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

"To appraise the clinical and cost-effectiveness of bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma".

Following the original referral this appraisal was split into two separate pieces of guidance (TAs 169 and 178) in order to provide timely advice to the NHS.

3. Current guidance

TA169

1.1. Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

1.2. When using ECOG performance status score, clinicians should be mindful of the need to secure equality of access to treatments for people with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to the prognosis of renal cell carcinoma. In such cases clinicians should make appropriate judgements of performance status taking these considerations into account.

1.3. People who are currently being treated with sunitinib for advanced and/or metastatic renal cell carcinoma but who do not meet the criteria in 1.1 should

have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

TA178

1.1. Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

1.2. Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

1.3. People who are currently being treated with bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for advanced and/or metastatic renal cell carcinoma should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

4. Rationale[1]

All companies involved state that there is no significant new evidence to warrant a review at this time. Consequently, TA169 and TA178 should be transferred to the static list of technology appraisals. The appraisals can be brought back into the active list of appraisals if NICE are informed at a later date of significant new evidence that could imply re-consideration of a review is needed.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development (within other NICE work programmes) that overlaps with this review proposal.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from September 2007 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Since the publication of TA169 (March 2009) and TA178 (August 2009), the marketing authorisations for sunitinib, temsirolimus, sorafenib, and bevacizumab in renal cell carcinoma have not changed.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

Sunitinib and temsirolimus

The manufacturer of sunitinib and temsirolimus has informed NICE that they are not aware of significant new evidence for either sunitinib or temsirolimus that would be relevant to this review proposal. They confirmed that the evidence published since TA169 and TA178 are based on the phase III trials or sunitinib expanded access programme which included sub-analyses, retrospective analyses, post-hoc analyses, quality of life and patient reported outcome studies. The results of the phase III trials for sunitinib and temsirolimus and initial results of the sunitinib expanded access programme were provided in the original manufacturer's submission in 2008. All relevant data was presented for temsirolimus in the original submission in 2008.

The manufacturer is currently conducting a phase III trial (INTORSECT, NCT00474786) of temsirolimus versus sorafenib as second-line therapy in patients with advanced renal cell carcinoma who have failed first-line sunitinib. The manufacturer is also currently conducting a phase III trial (INTORACT, NCT00631371) of temsirolimus with bevacizumab versus interferon-alfa with bevacizumab as first line treatment in subjects with advanced renal cell carcinoma.

[redacted]

The manufacturer of sunitinib has no plans to change the current patient access scheme and indicates that the patient access scheme is widely used throughout the NHS. The DH are content for the scheme to continue in its current format.

Sorafenib

The manufacturer is not planning on seeking any extensions to the marketing authorisation for sorafenib in renal cell carcinoma. There is no substantial new evidence relevant to this review proposal. An open-label phase III trial (NCT00732914) is currently being conducted to compare sequential therapy of first-line sorafenib followed by sunitinib with first-line sunitinib followed by sorafenib in patients with advanced or metastatic renal cell carcinoma. The Medical Research Council's Clinical Trials Unit is currently conducting a placebo-controlled phase III trial (NCT00492258) of sorafenib therapy in patients at risk of relapse after undergoing surgery to remove kidney cancer.

Bevacizumab

The manufacturer is not planning on seeking an extension to the marketing authorisation for bevacizumab for renal cell carcinoma. There is no substantial new evidence relevant to this appraisal. For the two phase III trials considered during the original multiple technology appraisal, AVOREN and CALGB 90206, both trial results have now been published including longer follow-up for the AVOREN study.

Related guidance

In TA215, pazopanib was recommended as a first-line treatment option for people with advanced renal cell carcinoma: who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1 and if the manufacturer provides pazopanib with a 12.5% discount on the list price, and provides a possible future rebate linked to the outcome of the head-to-head COMPARZ trial. COMPARZ is a head-to-head randomised controlled trial which compares pazopanib and sunitinib in the first line treatment of advanced renal cell carcinoma. It has an estimated primary completion date of December 2011 and an estimated study completion date of May 2013. TA215 will be considered for review when the COMPARZ data will be made available and at the latest in December 2013. A review of this guidance will most likely focus on confirming the assumption of clinical trial outcome non-inferiority.

In TA219, published in April 2011, everolimus for the second-line treatment of renal cell carcinoma was not recommended. The guidance on everolimus will be considered for review in February 2013, and is not included in this review proposal.

Implementation

A submission from the NICE Implementation team is included in Appendix 3

The implementation advice suggests that sunitinib has increased in use after TA169 was published, as expected.

Equality issues

No equality issues were raised in the original guidance documents that would have a particular impact on any of the groups whose interests are protected by the equalities legislation.

GE paper sign off: Meindert Boysen, 20 February 2012

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred and added to the watchful waiting list.	NICE will defer and add to the watchful waiting list. NICE will actively consider whether a review is necessary in 3 years time.	No
A review of the TA169 and TA178 should be combined with___.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Improving outcomes in urological cancers. Cancer Service Guidance CSGUC. Published: September 2002. Review date: TBC.

Pazopanib for the first line treatment of metastatic renal cell carcinoma. Technology Appraisal TA215. Published: February 2011. Review date: December 2013.

Everolimus for the second-line treatment of advanced renal cell carcinoma. Technology Appraisal TA219. Published: April 2011. Review date: February 2013.

In topic selection[2]

[redacted]

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Sunitinib "Treatment of people with advanced and/or metastatic renal cell carcinoma".	"Treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults".
Bevacizumab "First-line treatment of people with advanced and/or metastatic renal cell carcinoma".	No change.

[2] Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

Indication considered in original appraisal	Proposed indication (for this appraisal)
Sorafenib "Treatment of people with advanced renal cell carcinoma in whom interferon-α or interleukin-2-based therapy has failed or who are considered unsuitable for such therapy".	No change.
Temsirolimus "First-line treatment of people with advanced RCC who have at least three of the six following prognostic risk factors: • less than 1 year from time of initial RCC diagnosis to randomisation or initiation of treatment • Karnofsky performance status of 60–70 • haemoglobin less than the lower limit of normal • corrected calcium greater than 10 mg/100 ml (or 2.5 mmol/litre) • serum lactate dehydrogenase more than 1.5 times the upper limit of normal • more than one metastatic organ site".	No change.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Axitinib (Pfizer)	Pre-registration filed in the EU for previously treated, advanced RCC. UK launch anticipated ~Q2 2012. Trials NCT00678392 (vs. sorafenib as second line treatment) and NCT00920816 (vs. sorafenib as first or second line treatment) are ongoing. [redacted].
Dovitinib (Novartis)	Phase III for 3rd line metastatic RCC

Drug (manufacturer)	Details (phase of development, expected launch date,)
	(trial reference NCT01223027). UK launch anticipated ~2014.
Everolimus (Novartis)	Not recommended for second-line treatment of advanced RCC in NICE TA219. Everolimus is also being investigated in the ongoing phase III EVEREST trial (NCT01120249), where it is being administered post-nephrectomy. The trial is expected to be completed in August 2013.
Girentuximab (Wilex)	Phase III as adjuvant therapy for non-metastatic RCC. The key trial ('ARISER') is expected to be completed in 2013.
IMA 901 (Immatics)	Phase III add-on to sunitinib as first-line therapy in trial NCT01265901. Expected completion date: April 2014.
Mva-5t4 (Oxford Biomedica)	Phase III in combination with standard first-line therapy for locally advanced or metastatic RCC. Results were announced in March 2009 and further analysis was published in 2011. UK launch anticipated ~2014.
Pazopanib (GlaxoSmithKline)	Launched in the UK in 2010. Received an optimised recommendation as a first-line option for metastatic RCC in NICE TA215.
Sunitinib (Pfizer)	In phase III for use as adjuvant therapy (trial NCT00326898). Expected completion date: April 2016.
Talactoferrin Alfa (Agennix)	Phase II
Temsirolimus (Pfizer)	Phase III for 2nd line treatment for metastatic RCC (following failure of first-line sunitinib). [redacted]
Tivozanib (Astellas)	Phase III trial (TIVO-1; NCT01030783) in advanced or

Drug (manufacturer)	Details (phase of development, expected launch date,)
	metastatic renal cell carcinoma due to be completed in December 2011. UK launch anticipated ~2013. [redacted]

Registered and unpublished trials

Trial name and registration number	Details
Study Comparing Bevacizumab + Temsirolimus vs. Bevacizumab + Interferon-Alfa In Advanced Renal Cell Carcinoma Subjects NCT00631371; 3066K1-3311, B1771006; INTORACT.	Phase IIIb First line therapy n = 781 Ongoing Primary completion date: March 2011 Study completion date: July 2012
Sequential Study to Treat Renal Cell Carcinoma NCT00732914; 09072008-13772; EudraCT 2008-005011-18	Phase III Sorafenib first line + sunitinib second line vs. sunitinib first line + Sorafenib second line n = 346 Primary completion date: March 2013 Study completion date: November 2013
Everolimus With or Without Bevacizumab in Treating Patients With Advanced Kidney Cancer That Progressed After First-Line Therapy NCT01198158; CDR0000684313; CALGB-90802	Phase III n = 700 Estimated primary completion date: March 2013.

Trial name and registration number	Details
Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma NCT00720941; 108844; VEG108844	Phase III First line therapy n = 876 Estimated primary completion date: December 2011 Estimated study completion date: May 2013 Pazopanib is the subject of the related TA215
Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer NCT00492258; SOURCE; CDR0000553251, MRC-RE05-SORCE, EUDRACT ID 2006-006079-19, EU-20734, ISRCTN38934710	Sorafenib vs. placebo, adjuvant setting Phase III n = 1656 Estimated completion date: August 2012
Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer NCT01064310; 113046.	Phase III First line therapy n = 161 Estimated primary completion date: October 2011 Estimated study completion date: April 2012 Pazopanib is the subject of the related TA215
Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer NCT01099423; CDR0000669243, EORTC-30073; EU-21022; PFIZER-EORTC-30073.	Phase III n = 458 Estimated completion date: October 2014.

Trial name and registration number	Details
A Study of Avastin (Bevacizumab) Added to Interferon Alfa-2a (Roferon) Therapy in Patients With Metastatic Renal Cell Cancer With Nephrectomy NCT00738530; BO17705.	Phase III First line n = 649 Estimated completion date: July 2010.
Temsirolimus Versus Sorafenib As Second-Line Therapy In Patients With Advanced RCC Who Have Failed First-Line Sunitinib NCT00474786; 3066K1-404; B1771003.	Phase III n = 508 Estimated primary completion date: March 2012 Estimated study completion date: October 2012
STAR: A Randomised Multistage Phase II/III trial of Sunitinib comparing Temporary cessation with Allowing continuation, at the time of maximal radiological response, in the first line treatment of locally advanced and/or metastatic Renal cancer ISRCTN 06473203; Eudra-CT 2011-001098-16; MReC 11/NW/0246; UKCRN 10674.	n = 210 Study closure date: March 2016
A Randomized Trial of Temsirolimus and Sorafenib as Second-Line Therapy in Patients With Advanced Renal Cell Carcinoma Who Have Failed First-Line Sunitinib Therapy 2007-000062-20; 3066K1-404-WW	Phase III n = 480 Ongoing Estimated completion date: not stated

Trial name and registration number	Details
A randomized, double-blind, placebo-controlled, multicenter phase III study to compare the safety and efficacy of RAD001 (temsirolimus) plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy 2006-002070-21; CRAD001C2240	Phase III n=362 Ongoing Estimated completion date: not stated

Appendix 3 – Submission from NICE Implementation Team

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION PROGRAMME

Guidance Executive Review

Technology appraisal TA169: Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma

1. National data

This section provides information on prescribing cost and volume for sunitinib issued in hospitals in England. The data are obtained from the IMS HEALTH Hospital Pharmacy Audit Index. All costs stated in this report are based on estimated cost.

Figure 1. Trend in volume/quantity for sunitinib in secondary care in England

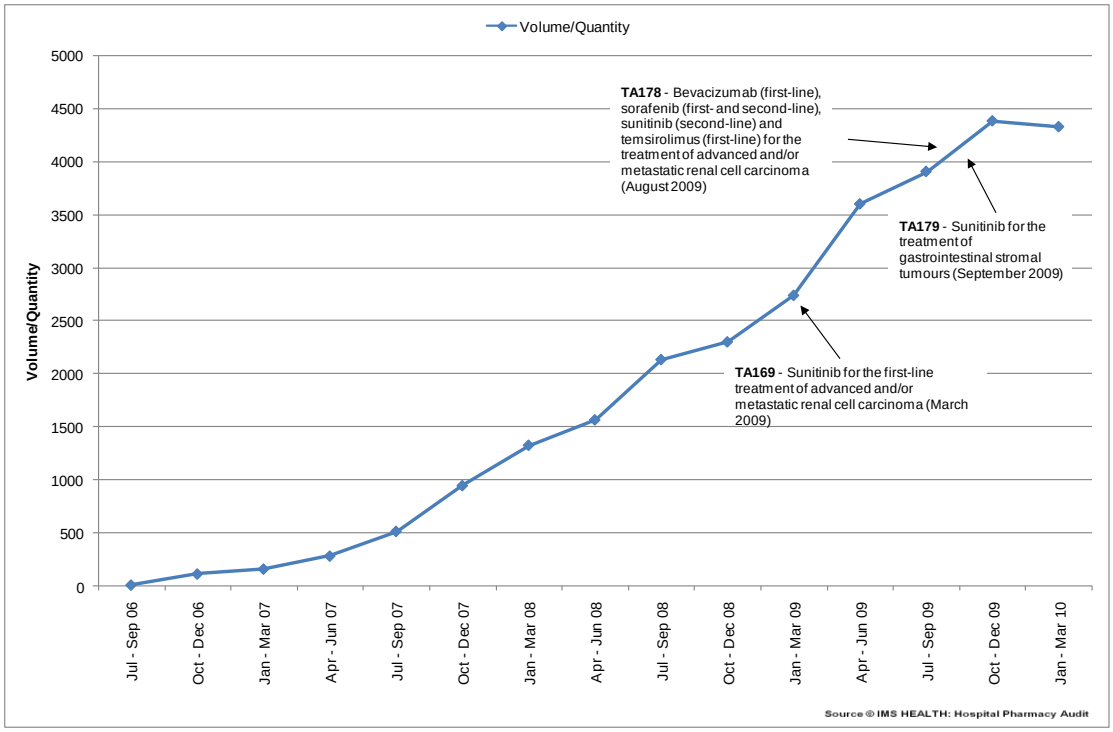
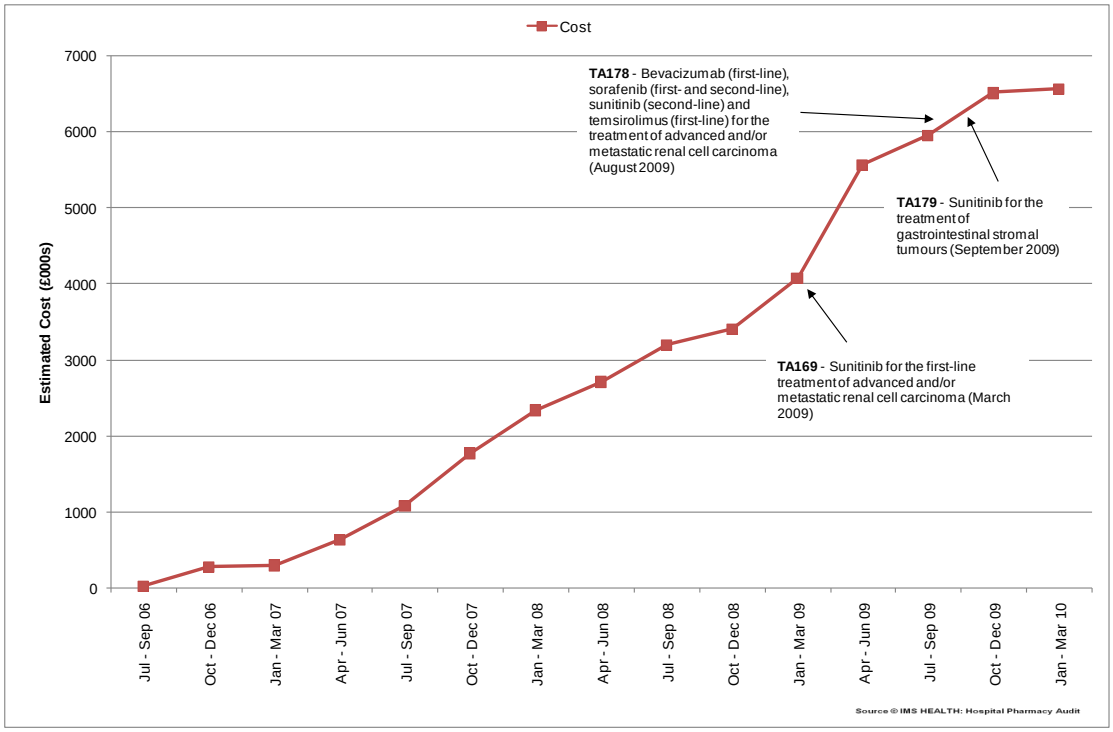


Figure 2. Trend in cost for sunitinib in secondary care in England



The estimated cost of sunitinib in hospitals in England in the 12 months to March 2010 was £24,591,846.

Notes:

- The IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI) collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

- Volume/Quantity: This is the number of packs used and should not be added together across various preparations due to differences in dosages/pack sizes

- Cost (in £s): Estimated costs are calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost. Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

- Ideally data would show the total number of patients prescribed a medicine and the volume and duration of treatment. However, the current datasets do not facilitate this type of analysis. Cost and volume therefore need to be considered together to provide the closest approximation. Cost provides a more accurate view of the total amount of a medicine dispensed. However, it does not provide an indication of the number of patients prescribed a medicine. Volume therefore provides an indication of the number of packs used for a medicine, although it does not account for patients receiving different dosages or durations.

2. External literature – Evaluation and Review of NICE Implementation Evidence (ERNIE) database

There are currently no relevant publications on the ERNIE database.