NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment [ID518]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Robert Hawkins[1], Professor of Medical Oncology.
Janet Brown[2], Senior Clinical Lecturer in Medical Oncology

Name of your organisation [1]The Christie Hospital and University of Manchester
[2]University of Leeds and St James's Hospital, Leeds

Are you (tick all that apply):

- *a specialist in the treatment of people with the condition for which NICE is considering this technology*?
-

YES – specialist medical oncologist specialising in the management of renal cancer.

- *a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?*

YES – I am familiar with the data.

- *an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?*

NO

- *other? (please specify)*

Nothing to declare

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There is data supporting the use of Axitinib after failure of prior VEGF targeted therapy after Temsirolimus and after cytokines. These situations will be considered separately.

After Failure of Cytokines.
This is a small group of patients now being either patients who have had interferon or interleukin-2. Very few patients are currently commencing interferon and only a few receive high-dose interleukin-2 as first line therapy. After failure of cytokines most patients would be offered Sunitinib or Pazopanib based on good activity of both drugs in these patients in Phase II studies and on the fact that cytokine-failure patients were included in the pivotal phase III study of Pazopanib. The balance of use between the drugs varies by clinician and there is no clear data on the best drug. Sorafenib is licensed but generally not funded by the NHS and is generally thought not to have advantages over the funded drugs. With the licensing of Axitinib the choice for cytokine failure patients would now be of Sunitinib/Pazopanib or Axitinib. Certainly Axitinib would appear to be a reasonable choice for this group given the excellent PFS compared to Sorafenib, however, it has not been compared directly with the other used agents. Given the very small number of patients this affects it is unlikely that these trials will be done in the future. Benefit of Axitinib over the other drugs is unclear but it is certainly a reasonable option based on indirect comparisons.

After failure of prior VEGF-targeted therapy
This represents the majority of the potential use of Axitinib - > 95%. The only current licensed treatment is Everolimus and although not NICE approved it is widely used and generally funded by the Cancer Drugs Fund (in England). The benefits of Axitinib have not been directly compared with Everolimus but appear comparable. There are complexities that clinicians will consider – these include 1) The Everolimus pivotal study included patients who had failed multiple VEGF-targeted agents but the Axitinib trial only included patients with one prior therapy. Therefore a reasonable sequence clinically would be Sunitinib-Axitinib-Everolimus. Clinicians may wish to maximise “lines of therapy” and thus favour this route over Sunitinib/Pazopanib-Everolimus where there is then no licensed third-line therapy. 2) In general in cancer medicine if there is rapid progression on a treatment, a drug with a completely different mechanism of action may be preferred as cross-resistance may be less likely than with a drug with a similar mechanism of action. If that is the “ best approach” is not certain but that may mean some patients have Sunitinib/Pazopanib, followed byEverolimus (an mTOR inhibitor, not a tyrosine kinase inhibitor) anyway even if Axitinib is available. Making the most appropriate choice for individual patients in these different groups is likely to be the subject of on-going research/audit as at present there is little data and there is NO definitive data.

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There are small groups of patients for whom the choice may be guided in part by toxicity profile. These might include patients with lung disease / difficult to control diabetes where Axitinib may be preferred or cardiac disease/hard to control hypertension where Everolimus may be preferred.

For the group of patients who receive Pazopanib as first-line TKI the benefit of Axitinib is speculative (not based on trial data), but given the general similarity of efficacy of Sunitinib and Pazopanib it seems reasonable to consider the benefits may be similar.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There are different prognostic groups, based on MSKCC score (favourable, intermediate and poor). All three prognostic groups were included in this trial and all appeared to benefit to a similar extent (overlapping hazard ratios). The majority of the patients in the trial had received Sunitinib or Cytokines. However, some patients had received Bevacizumab and some Temsirolimus. There was no evidence of benefit in patients who had received Bevacizumab but there was for those who received Temsirolimus. Although the numbers of patients who receive Temsirolimus as first line therapy are small it is perhaps important to recognise the Temsirolimus group as this is licenced for poor prognosis patients. In those rare patients who do well on treatment with Temsirolimus, there is no licensed second-line therapy so this is a potentially important for this small group of patients.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Treatment should be given by experienced oncologists with a team of specialist nurses to support the patients. There is a gradual increase in the need for such professionals and other supporting groups as the prognosis and survival and number of lines of therapy improves. All of these points indicate more specialist input and yet it has not been fully recognised by the NHS. The availability of Axitinib will lead to a further, although limited increase in that trend for more professional and supporting technologies (eg scanning, blood tests) – whilst not significant alone it should be noted that it may add to pressures. However, as noted above, many patients already receive Everolimus as second line therapy through the Cancer Drug Fund in England In cases where Axitinib is used instead of Everolimus, this may not significantly increase resource need.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

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N/A It is understood that marketing approval was announced in Europe on 4th September 2012.

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

NCCN guidelines.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Axitinib is generally relatively easy to use. Clinical requirements, practical implications and patient acceptability/ease of use are probably very much the same as in the use of other tyrosine kinase inhibitors and with Everolimus. The toxicities are very similar to other drugs in the class although the exact frequency varies from drug to drug. There should be no difficulty in these being managed by appropriate specialists.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Patients would only start Axitinib if they had failed first-line therapy, either clinically or radiologically. Scans to monitor response to first-line therapy are already carried out in standard practice. Patientson Axitinib therapy will normally have regular scans. If patients show evidence of clinical or scan progression consideration is given to stopping treatment. The actual decision will be a clinical judgement and will depend if the patient is judged to be clinically benefiting overall or not – it is not based solely on the scan result. Stopping may be required when patients are not fit to continue due to toxicity or disease progression.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The trial appears to broadly reflect the experience of the drug.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

It is generally a reasonably well tolerated drug. The side effects are similar to those of others in the class. Hypertension may be slightly more of an issue with this drug than with others but it is common with all TKIs used to treat renal cancer.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- *Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
- *Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*
- *Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities*

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Not applicable

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None?

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Delivery of this technology falls within the specialist training of medical and nursing staff in oncology units. Although limited specific training for this technology would be needed, no specific extra resources are needed although it does continue the trend for increased resources needed for the management of patients with renal cancer. These have not universally kept up with demand and it should be mentioned. For example, in the Christie Hospital in Manchester, whilst medical input has increased (largely as a result of increased specialisation) the specialist nursing input is the same now as 10 years ago whilst the overall patient activity has increased about 8 fold. This is due to more patients being referred (about 3 fold increase), median duration of treatment increasing about 3-4 fold and median survival increasing 2-3 fold.

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