Response to the Final Appraisal Determination: 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

May 2009

Notice of Appeal

This appeal is submitted by [redacted] on behalf of:

- **The Rarer Cancers Forum**
- **Macmillan Cancer Support**

We are extremely disappointed that, despite our joint submission, the recently issued Final Appraisal Decision (FAD) on the Multiple Technology Appraisal of 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 remains negative for all of these treatments. New drugs for kidney cancer are desperately needed and the drugs NICE has rejected have been shown to be clinically effective.

Grounds for appeal:

1. **The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute's *Guide to the Technology Appraisal Process.***

2. **The Institute has prepared guidance which is perverse in the light of the evidence submitted.**

As many of the appeal points raised in this document are relevant to both appeal grounds one and two, this appeal document will be structured thematically.

We request a further oral hearing.

1. Criteria for appraising life extending, end of life treatments

1.1 In January 2009 an addition to the NICE Technology Appraisal methodology was introduced, '*Appraising life-extending, end of life treatments'*[1]*,* allowing greater flexibility in appraising medicines used to treat patients near the end of their life, such as treatments for advanced cancer. The new scheme is applicable to treatments meeting the following four criteria:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment;
- No alternative treatment with comparable benefits is available through the NHS;
- The treatment is licensed or otherwise indicated for a small patient population.

This supplementary guidance was seen as a great step forward in the appraisal of treatments for rarer cancers and gave patients renewed confidence that NICE recognises the specific problems experienced when appraising treatments at the end of life for small patient populations. However, in this appraisal we believe that the Committee has interpreted this guidance in a perverse way in relation to bevacizumab.

In point 4.3.9 of the FAD the Appraisal Committee has interpreted the 'patient population' (as described in criteria four) to mean not only the appropriate patient population for renal cell carcinoma, but also the other potential patients for which bevacizumab has licences (lung, breast, and bowel cancers). By counting all of the

[1] National Institute for Health and Clinical Excellence , *Appraising life-extending, end of life treatments,* January 2009

patients for which bevacizumab has licences this significantly increases the patient population and as such the Appraisal Committee has not allowed bevacizumab to be considered under the supplementary guidance. We consider this to be perverse and not in the spirit in which the guidance was developed.

1.2 We strongly believe that licences for other conditions should not be 'counted' in the size of the patient population. In the case of bevacizumab this is even more unreasonable as NICE has not recommended that bevacizumab should be funded by the NHS for any of these other disease areas. This therefore means that if the FAD stands the patient population for whom bevacizumab will be funded within the NHS is zero.

1.3 In the guidance '*Appraising life-extending, end of life treatments',* there is confusion about how a small patient population is defined. In point 3.2 of the guidance it states, *'second and subsequent licences for the same product will be considered on their individual merits.'* However it then goes on to say *'The Appraisal Committee will take into account the cumulative population for each product in considering the strength of any case.'*[2] Unless this apparent contradiction is resolved this could lead to inconsistent recommendations which are not based on equity, clinical efficacy or cost effectiveness.

1.4 NICE must consider the consequences of the precedent that would be set by not considering bevacizumab under the end of life scheme. There are three particular ways in which this could lead to perverse decision in the future:

- If a treatment is licensed for a particular form of cancer later than it was for others, then patients with this cancer could be unfairly denied access to the drug because NICE would define it as no longer being in a 'small' patient population. This could be particularly problematic where a treatment is licensed for a number of rare cancers and the cumulative patient population reaches the tolerability threshold.
- Some drugs could be rejected despite being more clinically and cost effective than other drugs which have been approved.

[2] National Institute for Health and Clinical Excellence , *Appraising life-extending, end of life treatments,* January 2009

- A drug which is already licensed for a number of indications could fail to qualify for the end of life scheme, even if NICE has declined to recommend the treatment for the other licence indications (as is the case in this appraisal with bevacizumab).

The precedent set by the decision about whether to consider bevacizumab under the end of life guidance could lead to those in the most need missing out due to flaws in NICE methodology.

2. Ultra-orphan treatments

2.1 The decision to reject temsirolimus is both perverse and not a fair interpretation of appraisal procedure. Temsirolimus is licensed for people with kidney cancer who have a very poor prognosis and therefore the patient population is very small. For this reason, temsirolimus is categorised as an ultra-orphan drug. The manufacturer of temsirolimus estimates that the drug would be used for a maximum of 465 patients in the UK with renal cell carcinoma.

2.2 In 2006 NICE proposed to the Department of Health that a new NICE process should be developed when considering whether ultra-orphan drugs should be made routinely available within the NHS. We are supportive of this approach as it provides a simple solution to an otherwise complex problem. To date NICE has not been asked by the Department of Health to implement this proposal, and therefore drugs with ultra-orphan status continue to be considered under NICE's existing appraisal methodology. This is in contradiction with the Department of Health's *'Selection criteria for referral of topics to NICE'*[3] published in 2006. In this document it is made clear that it is not considered appropriate for NICE to provide guidance on topics related to ultra-orphan diseases.

2.3 It is essential that the Department of Health and NICE resolve this issue as a matter of urgency, because treatments for very rare conditions, like temsirolimus, are unlikely to be approved by NICE under its current criteria. Assessing ultra-orphan treatments under the current NICE appraisal process wastes resources and falsely raises the hopes of patients. By appraising ultra-orphan treatments with the current

[3] Department of Health, *Selection Criteria for Referral of Topics to NICE,* July 2006

methodology the Department of Health and NICE are creating an unnecessary barrier to patients accessing the treatments that they need, and this will lead to patients with the rarest conditions being forced to undertake an Individual Funding Request to access treatments which should have never been referred to NICE in the first place.

2.4 We believe that the decision to reject temsirolimus is perverse and contra to NICE process. The notion of the additional benefit that this treatment would bring to this very small patient group is not readily captured in the reference case. This, coupled with the tiny budget impact that recommending this treatment would have for the NHS, makes us believe that temsirolimus should be approved for the treatment of patients with poor prognosis renal cell carcinoma.

3. Second-line treatment

3.1 There is no standard treatment for people with advanced and/or metastatic renal cell carcinoma whose condition does not respond to first-line immunotherapy, or for people who are unsuitable for immunotherapy (FAD 4.3.2). Therefore sorafenib and sunitinib for the treatment of second line renal cell carcinoma provide new options for patients who have exhausted and/or are unsuitable for immunotherapy. We believe that this should have been more fully considered in the analysis and that the notion of the additional benefits that these treatments would bring is not readily captured in the reference case.

4. Clinical trials

4.1 As the Committee is minded not to recommend either sorafenib or sunitinib for the second-line treatment of renal cell carcinoma this could have an impact on future clinical trials. Currently if a patient takes part in a clinical trial and they are enrolled on the placebo arm of the trial (and they do not have the opportunity to cross-over into the active arm of the trial) then they will automatically be excluded from receiving further treatment after the failure of the placebo treatment. This is perverse and unethical. If this continues then patients are unlikely to enrol in clinical trials and this will stifle further innovation in the treatment of renal cell carcinoma.

5. Equality

5.1 Point 4.3.28 of the FAD states that '*the guidance does not recommend the availability of the treatments to some patients and not to others. The recommendations apply to all patients with renal cell carcinomas and all such patients are affected by the guidance in the same way.'* This is only the case because sunitinib for the first line treatment of renal cell carcinoma was removed from this appraisal. If this appraisal is considered alongside the positive guidance for sunitinib then it could be considered as not in line with equalities legislation, particularly for patients who have already received and failed a first line treatment.

6. The Guidance which NICE is proposing to issue is procedurally unfair and perverse. Elements of the evaluation appear not to be consistent with NICE's own guidance on methodology and the end of life treatment guidance and therefore we believe that the FAD should be reconsidered.