# National Kidney Federation

Submission to

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**Health Technology Appraisal**

**Bevacizumab, Sorafenib, Sunitinib and Temsirolimus**

**for renal cell carcinoma**

**January 2008**

# Renal Cell Carcinoma

## INTRODUCTION

The National Kidney Federation is the National Charity (No1106735) representing the interests of all renal patients including those with renal cell carcinoma. Although kidney cancer occurs in patients without Kidney disease it also occurs in;

- Renal patients with acquired cystic kidney disease which develops in association with long term kidney problems is common in dialysis patients and increases the risk of kidney cancer 3.
- End stage renal disease and dialysis duration are also positively associated with RCC 4. This increased risk is probably due to the underlying renal disease and increased duration of the uraemic state, 4 5 and is probably not a direct effect of treatment.
- Renal transplant patients are at increased risk for cancer in the non transplanted kidneys.
- Although not considered major risk factors, urinary tract infections, kidney stones, kidney infection and radiation treatment for other cancers have also been positively associated with kidney cancer.

We therefore provide assistance and support for all patients at risk from RCC.

We welcome this opportunity to make a submission but as a patient organisation we are not able to contribute to the technical aspects of the appraisal. We do however feel that our comments should be considered in your deliberations as they are based on the needs and views of the renal cancer patients we represent.

## BACKGROUND

Kidney cancer accounts for 3% of all cancers in men and fewer than 2% of all cancers in women in the UK. Even though it is a relatively rare cancer, there have been reports of increasing incidence and mortality across the world, including the UK. Much, but not all, of this apparent increase is believed to be due to the wider application of imaging techniques for any medical condition resulting in more kidney tumours being found incidentally

In the UK kidney cancer is the eighth most common cancer in men, with 4,348 new cases diagnosed in 2004. This compares to 2,696 cases in women, giving a male:female ratio of 3:2. In women it is the fourteenth most common cancer. The numbers and rates for the UK and its constituent countries are shown in **Table 1.1**

It is estimated that 3,500 patient die of Kidney Cancer each year in the UK.

Most people with RCC are older. The average age of a person at the time of diagnosis is 65 years. It is uncommon under the age of 45 and its incidence is highest between 55 and 84

The British Association of Urological Surgeons collects information on kidney cancer diagnosis in the UK. According to their figures, of all those diagnosed with kidney cancer in the UK in 2005, that could be staged

- Just over a third (38%) had stage 1
- Just under 1 in 5 (18%) had stage 2
- Just over 1 in 4 (26%) had stage 3
- Just under 1 in 5 (19%) had stage 4

Most of those with stage 4 had spread to another part of the body at the time of diagnosis (stage 4b). Around a quarter of them did not have spread to another body organ, but their cancer had grown into the tissues surrounding the kidney (stage 4a). The BAUS data for the past few years shows a small but steady trend towards finding kidney tumours at an earlier stage. This is a good thing, because they are then easier to treat.

Table 1.1: **Number of new cases and rates of kidney cancer, UK, 2004**

| | England | | Wales | | Scotland | | N.Ireland | | UK | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Cases** | | | | | | | | | | |
| **Males** | 3,567 | | 267 | | 406 | | 108 | | 4,348 | |
| **Females** | 2,178 | | 168 | | 271 | | 79 | | 2,696 | |
| **Persons** | 5,745 | | 435 | | 677 | | 187 | | 7,044 | |
| **Crude rate per 100,000 population** | | | | | | | | | | |
| **Males** | 14.5 | | 18.6 | | 16.6 | | 12.9 | | 14.9 | |
| **Females** | 8.5 | | 11.1 | | 10.3 | | 9.0 | | 8.8 | |
| **Persons** | 11.5 | | 14.7 | | 13.4 | | 10.9 | | 11.9 | |
| **Age-standardised rate (European) per 100,000 population** | | | | | | | | | | |
| **Males** | 12.5 | | 14.8 | | 14.2 | | 12.6 | | 12.8 | |
| **CI 95%** | *12.1* | *12.9* | *13.0* | *16.6* | *12.8* | *15.6* | *10.2* | *15.0* | *12.4* | *13.1* |
| **Females** | 6.3 | | 7.8 | | 7.2 | | 7.6 | | 6.5 | |
| **CI 95%** | *6.0* | *6.6* | *6.6* | *8.9* | *6.4* | *8.1* | *5.9* | *9.2* | *6.3* | *6.7* |
| **Persons** | 9.1 | | 11.0 | | 10.3 | | 9.9 | | 9.4 | |
| **CI 95%** | *8.9* | *9.4* | *10.0* | *12.0* | *9.5* | *11.1* | *8.5* | *11.3* | *9.1* | *9.6* |

A radical nephrectomy to remove the entire kidney or partial nephrectomy to remove part of the kidney is the only accepted mainstay curative treatment for patients with non metastatic RCC, the success of surgery depends on the stage of disease. The nephrectomy plus interferon alpha is also a standard practice in the UK. For some patients cancer can return after surgery requiring further surgery or alternatively immunotherapy or targeted therapies may then be recommended. This change of status with time adds complication to analysis.

With 7000 Kidney cancer patients there will be 6,300 RCC patients 2 of which 1575 will have advanced RCC.2 Using this admittedly rough calculation it can be seen the numbers of patients requiring access to the Drug therapies under discussion are therefore very small and must be seen in context.

The NHS budget impact for treating eligible patients with these new drugs will also be very small because of the very low incidence and prevalence of the disease. These new drugs given at the various stages of the disease will give help and hope to a small group of patients who will otherwise certainly die.

## THE TECHNOLOGIES

As previously discussed for people diagnosed with RCC the mains treatment is surgical removal of the tumour. However, around a 25% (of incident RCC) 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.

The four new drugs in this appraisal are capable of reversing this situation offering patients further alternative therapies and advantages in treatment.

### Sorafenib Toysalate (Nexavar)

Is an orally administered multi-targeted 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.

It is used as first line therapy to treat people with kidney cancer that has spread outside the kidney and who are no longer being helped by treatment with interferon-alpha (IFN) or interleukin-2 (IL-2), or for whom these drugs are not suitable.

### Sunitinib (Sutent)

Is a 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. It is administered orally for the treatment of advanced and/or metastatic RCC, both as a first and second line therapy.

### Bevacizumab ( Avastin)

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. The anticipated indication for Bevacizumab is first line treatment for advanced and/or metastatic RCC in conjunction with interferon-alpha.

### Temsirolimus

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. The anticipated indication is as first line therapy in patients with three or more of six indicators of poor prognosis.

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As previously mentioned in the UK the standard treatment of metastatic RCC is immunotherapy with interleukin-2 or interferon alpha which may lead to tumour shrinkage. There is however a proportion of patients who may be unsuitable for immunotherapy, primarily due to poor performance status and because of the toxicity of interferon (and even greater toxicity of IL2). This set of patients also include poor risk patients (who are estimated to comprise 28% of advanced RCC cases. The treatment needs of these patients needs to be assessed and addressed in the appraisal.

We believe the new drugs under consideration are now being used throughout most of the EU as first line therapy for advanced Renal Cell Carcinoma *** We also understand that in North America and most of Western Europe the standard is a first line tyrosine kinase inhibitor. We therefore need an urgent resolution to a problem that is denying many UK patients a more effective and appropriate treatment. *** (*Note we understand Temsirolimus will be launched in many European countries this year*).

The Department of Health has issued clear instructions to the NHS that in the absence of NICE guidance, or whilst guidance is being developed, local organisations (such as Primary Care Trusts and NHS Trusts) are expected to make their own assessment of available evidence before deciding how and if to fund the drug locally. They have also added that no patient should be denied a treatment on the basis of cost alone. Although this is the formal position our experience shows that some Primary Care Trusts appear to be using "own assessment" as a means of avoidance and are putting financial considerations before patient choice, quality of life and quality of treatment.. This situation therefore needs clear recommendations as early as possible.

## THE PATIENT PERSPECTIVE

When patients are first informed they have kidney cancer they will quickly become aware that they have a terminal condition and that without the correct treatment they will die. There is shock and a feeling of being overwhelmed by what is happening and what lies ahead. Their carer's, very often their lifetime partners, face the loss of a loved one. The patient, carers, and their family are faced with an event that will change their lives completely. Apart from the emotional and physical aspects of living with the condition, there are many practical concerns that will cause high levels of stress, including the financial implications and the complete change of lifestyle.

Patients count good days rather than bad days. Good days are when they feel on top of the problems associated with the disease, the aggressive treatment effects and severe side effects. Any treatment or combination treatment that reduces the bad days and brings the patient closer to "normality" is regarded as a plus in the patient's eyes. This may be an essential contributor to an improvement in quality of life

In a similar way progression free survival is extremely important as a measure particularly if it extends the ultimate life expectancy.

The manner in which a drug is administered is also a thing patients will consider particularly in longer term repetitive treatment. Obviously a simple oral method would be preferred by most patients but in reality most patients will readily adapt to other method of administration if the treatment offered has advantages. The administering of Iron in renal patients is just one example. Dialysis patient can also receive other drugs intravenously while on Dialysis or by injection at their GP's surgery and in the home.

Side effects are an important factor for any patient in a drug regime. Most patients will want to know what the side effects will be for any treatment. The problem is that it is difficult to determine the exact effect any drug will have on a given patient and it is common practice for a similar drug to be prescribed should a patient have a particularly bad reaction or response to a given drug. These flexible treatments variations may also need to be applied depending on the stage of the disease.

This was our experience on the NICE health technology appraisal for renal immunosuppressant drugs and we are again asking that similar consideration be given to this degree of flexibility with the RCC drugs in this appraisal.

It is essential that the Consultant and Medical Team work in partnership with the patient in determining their treatment pathway. The patients need to be advised and informed to enable them where ever possible to participate and make choices in their treatment provision.

To provide this, Consultants must have the freedom to tailor a drug regime to that which best meets the needs, response and choice of an individual patient. Patients and Consultants deserve this range of therapies in order to have the ability to make that choice. In breast cancers patients the survival rates have increased as the range of therapies increased.

The Drugs in consideration are relatively new and there is little actual data available for the long term perhaps therefore maintaining flexibility within the recommendation now will give us the further flexibility we may need in the future to demonstrate both treatment and cost effectivenss.

**National Kidney Federation**
**January 2008**



# REFERENCES


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