Submission to NICE

HTA Bevacizumab, sorafenib, sunitinib and temsorilimus

for renal cell carcinomas

Submitted by:

[redacted] **on behalf of the NCRI Renal Clinical Studies Group/Royal College of Radiologists/Royal College of Physicians/Joint Collegiate Council for Oncology/Association of Cancer Physicians.**

Coordinated by:

[redacted]

BACKGROUND

Advanced renal cell carcinoma and efficacy of current treatments

In the UK, about 6600 patients a year develop kidney cancer, and the incidence of the disease is rising in most developed countries.[1] About half of patients either present with, or go on to develop, metastatic disease, and a third to a half of patients will die from it. Once metastatic disease has developed, median survival is only 10 months.[2]

Unlike many other types of cancer, RCC is generally unresponsive to cytotoxic, hormonal, or radiation treatments, with response rates of only 2-6%.[3] At present, standard care consists of single-agent interferon alpha or interleukin 2, both of which provide a significant benefit over placebo, but only in a few patients and at the expense of substantial side-effects.[4]

Evidence for activity of targeted agents

RCC is one of the best understood cancers in terms of its molecular mechanisms, which has led to development of several targeted agents that have shown promising results in clinical trials. About 70% of

patients with RCC have a mutation in the von Hippel-Lindau (VHL) gene, and this gene is silenced by methylation in a further 26% of patients, offering unique opportunities for targeted treatment. The VHL gene encodes a tumour suppressor gene that interacts with hypoxia-inducible factor 1 alpha (HIF-1 alpha). In hypoxic situations, VHL is not expressed, leading to an accumulation of HIF-1 alpha and the expression of several hypoxia response genes, including VEGF, PDGF, TGFß, and erythropoietin.

THE APRAISAL

Four agents that act either on or within this pathway have shown significant efficacy in multicentre randomised clinical trials.

Sunitinib

Two phase II studies of second-line sunitinib for metastatic RCC and data from a phase III study of first-line treatment, compared with interferon alpha, have been published.

Sunitinib is a tyrosine-kinase inhibitor that targets several receptors and is administered orally, once a day for 4 weeks, with 2 weeks between each cycle.

Results from both phase II studies[5,6] have been combined giving a total of 168 patients. The combined response rate was 42% with an additional 24% having stable disease for greater than 3 months. The combined median progression free survival was 8.2 months. The median progression-free survival for patients attaining a complete or partial response was 14.8 months. Median overall survival for the first

study was 16.4 months and, at the time of reporting, had not yet been reached for the second study.

Data from the phase III study of 750 patients[7,8] showed a median progression-free survival of 11 months for sunitinib vs 5 months for interferon alpha (hazard ratio 0.42 [95% CI 0.32–0.54]; p<0.001). 31% of patients in the sunitinib group showed an objective response compared with 6% in the interferon alpha arm (p<0.001). None had previously been treated with biological agents.

Sunitinib was well tolerated with patients experiencing manageable diarrhoea, high blood pressure, hand-foot syndrome and vomiting. Rates of fatigue and weakness were higher in patients who received interferon alpha. Other side-effects were similar in the two groups. Overall, quality of life was better in the sunitinib arm.

Sorafenib

Sorafenib also inhibits several kinases, mainly VEGFR2 and PDGF, and is given orally twice a day on a continuous basis.

In the phase II trial, 202 patients were initially given 400 mg sorafenib orally twice a day. After the 12-week run-in period, 73 of the 202 patients had tumour shrinkage of at least 25%. The 65 patients who showed tumour shrinkage of less than 25% during the 12-week run-in were then randomly allocated to continue sorafenib or to start placebo. At 24 weeks, 16 (50%) of the 32 patients allocated to sorafenib were progression-free versus 6 (18%) of the 33 patients allocated to placebo (p=0.0077). Median progression-free survival was significantly longer with sorafenib (24 weeks) than placebo (6 weeks; p=0.0087).[9]

Data from a randomised placebo-controlled phase III trial in the second-line treatment of 903 patients with metastatic renal cell carcinoma has been reported in a planned interim analysis after 220 patients had died. A complete response was seen in one patient in the sorafenib group, and in none in the placebo group. A partial response was seen in 10% of patients in the sorafenib group, compared with 2% in the placebo group. Disease stabilised in 74% in the sorafenib group compared with 53% in the placebo group. Median progression-free survival was 5.5 months vs 2.8 months (HR_0.44 [0.35–0.55]). The median overall survival was 14.7 months in the placebo arm and at the time of the interim analysis had not yet been reached in the sorafenib arm (HR 0.72 [0.54–0.94]; p=0.02). All subsets (age, prognostic group, sites of metastasis, previous cytokine treatment) appeared to derive equal benefit. Following the confirmation of a highly significant progression-free survival benefit, patients in the placebo arm were allowed to cross over to sorafenib. Despite the cross over of 216 of 452 patients receiving placebo, there remained an overall survival benefit from sorafenib with median overall survival of 19.3 months for patients in the sorafenib group compared to 15.9 months in the placebo group (HR 0.77 [0.63–0.95]; p=0.02).[10,11]

The most common side-effects for sorafenib are hand-foot syndrome, diarrhoea, alopecia, fatigue, nausea, and hypertension. Generally the drug is well tolerated.

Temsirolimus

This intravenously administered derivative of rapamycin targets mTOR,

a downstream component of the HIF pathway. In a randomised phase II trial, 111 patients with advanced heavily pretreated, refractory mRCC were treated at three different dose levels (25.0, 75.0 and 250mg) of temsirolimus [12]. Seven percent of patients achieved a PR or CR. No significant differences in outcome were related to the dosage. The median time-to-progression was 5.8 months, with a median overall survival for the entire population of 15.0 months. Temsirolimus was combined with IFNα in a phase I/II clinical trial of 71 patients with metastatic renal cell carcinoma. Partial responses were observed in 11% of all patients with a median time-to-progression of 9.1 months [13].

A phase III randomised trial compared temsirolimus as a single agent (25.0 mg) with temsirolimus (15.0 mg) plus interferon-α as first-line treatment in patients with poor-risk features. Six hundred and twenty-six patients were randomly assigned. The median overall survival for temsirolimus was 10.9 months compared with 7.3 months with interferon and 8.4 months with temsirolimus plus interferon. There was a significant improvement in survival for temsirolimus compared with interferon (P = 0.0069, hazard ratio = 0.73) [14].

Bevacizumab

This humanised monoclonal antibody binds and neutralises VEGF; it is given intravenously. In a randomised, double-blind phase II trial, two dose levels of the antibody were studied (3 and 10mg/kg) versus placebo, and therapy was administered every 2 weeks. Eligible patients included those who had a histologic confirmation of clear cell carcinoma and either had received previous therapy with IL-2 or for whom the use of IL-2 was contraindicated. A total of 116 patients were randomly assigned to one of three treatment groups. At the time of a

planned interim analysis, the median time-to-progression was significantly increased to 4.8 months in the patients receiving the 10-mg/kg dose of bevacizumab, compared with 2.5 months for placebo. Responses were noted only in the group treated with bevacizumab at 10mg/kg, with four patients (10%) having partial tumour regressions [15].

A randomised, controlled, double-blind phase III study of bevacizumab/interferon-α2a vs placebo/interferon-α2a as first line therapy in metastatic renal cell carcinoma has recently been reported. 649 patients were randomised and at the first preliminary analysis (111 patients were still on treatment) the addition of bevacizumab to interferon-α2a significantly increased progression free survival (10.2 vs 5.4 months) (HR = 0.63; $p<0.0001$) and objective tumour response rate (30.6% vs 12.4%; $p<0.0001$). A trend toward improved overall survival was also observed (p=0.0670). Bevacizumab related side-effects were generally mild and consistent with previous observations [16].

COMMENTS

- All four of the agents being appraised have been shown in large randomised controlled trials to improve progression free survival in metastatic renal cell carcinoma.
- In the case of sunitinib and bevacizumab/interferon treatment was first line.
- With temsorilimus there is unequivocal evidence of improved overall survival (compared with interferon-α). There are trends towards improved overall survival for sunitinib (vs interferon-α), sorafenib (vs placebo) and bevacizumab with interferon-α (vs

interferon-α). The longer-term overall survival data will be difficult to interpret because cross-over to the 'experimental' arm was allowed when studies were unblinded (the best example is in the sorafenib study).

- In three cases this is a single agent therapy; with bevacizumab this is in combination with interferon-α.
- Sunitinib and sorafenib are oral preparations; temsorilimus and bevacizumab are given intravenously.
- Sunitinib and sorafenib are licensed for use in the UK; clinicians have therefore gained experience with their use.
- In the pivotal temsorilimus trial all patients had 'poor-risk' features; with the others most patients were in 'good-risk' categories.

CONCLUSION

These agents represent a sea-change in the clinical management of metastatic renal cell carcinoma (for which, until now, there has been no effective treatment). Improved progression free survival has been demonstrated with treatments that are generally well tolerated by patients.

Temsorilimus is given intravenously and so may be less favoured by patients and clinicians; however it does have proven efficacy in the difficult-to-treat poor-risk group of patients. Bevacizumab, the other intravenous agent, is given together with interferon-α which does have recognised side-effects. This, with the inconvenience of needing injections, may make this treatment less popular with patients and clinicians. Both sunitinib and sorafenib are oral therapies with well

recognised and generally acceptable side-effects. Most renal cancer clinicians are familiar with using one or other of these agents and many PCTs are already funding treatment in eligible patients.

REFERENCES

1. Lipworth L, Tarone RE, McLaughlin JK. The epidemiology of renal cell carcinoma. *J Urol* 2006; **176:** 2353–2358.

2. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999; **17**: 2530–2540.

3. Yap TA, Eisen TG. Adjuvant therapy of renal cell carcinoma. *Clin Genitourin Cancer* 2006; **5**: 120–130.

4. Shaheen PE, Bukowski RM. Targeted therapy for renal cell carcinoma: a new therapeutic paradigm. *Cancer Invest* 2006; **24**: 640–656.

5. Motzer RJ, Michaelson MD, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24**: 16–24.

6. Motzer R J, Rini B, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; **295**: 2516–2524.

7. Motzer RJ, Hutson TE, Tomczak P, et al. Phase III randomized trial of sunitinib malate (SU11248) versus interferon-alfa (IFNa) as first-line systemic therapy for patients with metastatic renal cell

carcinoma (mRCC). *J Clin Oncol* 2006; **24**: LBA3.

8. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356**: 115–124.

9. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24**: 2505–2512.

10. Eisen T, Bukowski RM, Staehler M, et al, for the TARGET Clinical Trial Group. Randomized phase III trial of sorafenib in advanced renal cell carcinoma (RCC): Impact of crossover on survival. *J Clin Oncol* 2006; **24**: 4524.

11. Escudier B, Eisen T, Stadler WM, et al, for the TARGET Clinical Trial Group. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; **356**: 125–134.

12. Atkins MB, Hidalgo M, Stadler WM et al. Randomised phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004;22:909-918.

13. Smith JW, Ko Y-J, Dutcher J et al. Update of a phase I study of intravenous CCI-779 given in combination with interferon-alpha to patients with advanced renal cell carcinoma. *J Clin Oncol* 2004;22 (Suppl), 385S (Abstr 4513.

14. Hudes GR, Cardicco M, Tomczak P et al. A phase III, randomised 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line poor-risk patients with advanced renal cell carcinoma (adv RCC). *J Clin Oncol* 2006;24 (Suppl):930S (Abstr LBA4).

15. Yang JC, Haworth L, Sherry RM et al. A randomised trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;427-434.

16. Escudier B, Koraleuski P, Pulanska A et al. A randomised, controlled, double- blind phase III study (AVOREN) of bevacizumab/interferon-α2a vs placebo/interferon-α2a as first-line therapy in metastatic renal cell carcinoma. *J Clin Oncol* 2007;25 (suppl):2s (Abstr 3)