Avastin (bevacizumab) renal cell carcinoma
NICE Submission

ACHIEVING CLINICAL EXCELLENCE IN RENAL CELL CARCINOMA

Roche Submission to the
National Institute for Health and Clinical Excellence
16 January 2008

EXECUTIVE SUMMARY

Executive summary bevacizumab + interferon-alfa-2a for the treatment of advanced renal cell carcinoma (RCC)

RCC: the Disease

- Renal cell carcinoma (RCC) accounts for approximately 2% of cancers worldwide
- In 2004, kidney cancer accounted for 5,745 new cancer cases in England
- Deaths from kidney cancer in England in 2005 totalled 2,943
- Survival varies significantly according to the stage and spread of disease at first presentation
- Although 40% of kidney cancers are diagnosed in the earlier disease stages when disease is localised, a significant proportion of patients (~25-30%) present with metastatic RCC (mRCC)

RCC in the UK: clinical management

- Clinical management guidelines relevant to RCC treatment in the UK include the NICE Guideline on Cancer Services (September 2002) and the Guidelines on Renal Cell Carcinoma (European Association of Urology 2007)
- Introduction of medical therapies generally follows nephrectomy, since studies have shown that nephrectomy followed by immunotherapy improves patient survival
- Immunotherapies have become standard of care therapy in the UK since their introduction twenty years ago
- The most widely used immunotherapy for RCC is interferon-α–2a (IFN α-2a)
- However, IFN α-2a offers limited clinical efficacy in mRCC and associated side-effects make it an unsuitable treatment option for certain patients
- Given the limitations of standard therapies, in recent years a greater emphasis has been placed upon potential molecular targets as new treatment options for RCC patients
- For example, an improved understanding of the biology of clear-cell RCC identified VEGF as a critical factor in the growth and metastases of this tumour type
- Bevacizumab which is the subject of this MTA review provides a new hope of improved clinical outcomes for RCC patients.

Clinical effectiveness of bevacizumab

- Bevacizumab is a humanised monoclonal antibody (93% human and 7% murine). When administered systemically, it produces inhibition of angiogenic processes which are reliant upon VEGF signalling
- The efficacy and safety of bevacizumab for the treatment of patients with mRCC was established in a clinical programme consisting of

    - A randomised, double-blind, placebo-controlled pivotal phase III trial (BO17705 'AVOREN' study; Escudier et al., 2007a, 2007b; Bracarda et al., 2007; Melichar et al., 2007) of bevacizumab in combination with IFN α-2a as first line treatment in patients with advanced and/or mRCC; and

    - Two controlled Phase II studies, which provided information on the appropriate dose and safety of bevacizumab.

- The AVOREN study demonstrated that the addition of bevacizumab to IFN α-2a as first-line therapy substantially improved efficacy over IFN α-2a alone in patients with advanced and/or mRCC. This was shown by statistically significant and clinically relevant increases in progression-free survival (10.2 months versus 5.4), time to treatment failure, time to disease progression and objective response rate
- Although the overall survival (OS) data is still immature, according to an interim analysis, there is a trend towards increased OS in patients treated with bevacizumab and IFN α-2a (hazard ratio 0.79 for bevacizumab plus IFN α-2a in the interim analysis of the AVOREN study)
- Overall incidence of adverse events experienced in bevacizumab+ IFN α-2a patients was higher than in the placebo+ IFN α-2a arm. This may in part result from the fact that the median duration of treatment was significantly longer in the bevacizumab + IFN α-2a arm, resulting in more accumulation of adverse event data. This would also apply to the increased incidence of grade 3-4 adverse events, serious adverse events and withdrawals observed in the bevacizumab + IFN α-2a arm.
- The adverse events reported most often in the bevacizumab+ IFN α-2a group were expected toxicities known to be caused by IFN treatment or bevacizumab-related events. Most of the bevacizumab-related events were of low-grade severity.
- A retrospective analysis showed that the ability to reduce the IFN α-2a dose used in combination with bevacizumab allows IFN α-2a related toxicity to be managed, enabling patients to remain on therapy, without compromising on efficacy of the bevacizumab and IFN α-2a combination.
- Based on an indirect comparison, we conclude that the efficacy of bevacizumab in combination with IFN α-2a appeared to be comparable to the efficacy of sunitinib as monotherapy in first-line patients.
- In an indirect comparison of safety profiles, sunitinib monotherapy appeared to be associated with more treatment-related adverse events. Overall, the combination of bevacizumab and IFN α-2a appeared to be better tolerated with fewer and less severe adverse events.

Cost effectiveness of bevacizumab

- A 3 stage markov model was developed to estimate the lifetime NHS direct costs and clinical outcomes of α-2a, Bevacizumab+I IFN α-2a and sunitinib treatment. The baseline risk of disease progression and overall survival was estimated by extrapolating the IFN α-2a arm of the Avoren trial. For PFS, the treatment effect of Bevacizumab+ IFN α-2a was estimated by extrapolating the data from the Bev+ IFN α-2a arm of Avoren and for OS the hazard ratio from Avoren was used.
- When including a treatment capping programme which is described further in our submission and is an approach which limits the treatment cost of bevacizumab to an annual capped level, compared to IFN α-2a monotherapy, bevacizumab plus IFN α-2a has an ICER of approximately £75,000. At an incremental cost effectiveness threshold of £75,000 there is a probability of approximately 47% that bevacizumab plus IFN α-2a will be cost effective compared to IFN α-2a alone.

- We therefore conclude that bevacizumab plus IFN α-2a is unlikely to be cost effective compared to IFN monotherapy given an ICER threshold of £30,000.

Budget impact

- We anticipate that if bevacizumab received fully positive guidance, the total budget impact would be approximately £7million pounds in the first year of NICE guidance reaching around £18 million in the third year when the combination reaches 40% market share.