



**Avastin<sup>®</sup> (bevacizumab)  
NICE Submission**

**ACHIEVING CLINICAL EXCELLENCE IN THE  
TREATMENT OF METASTATIC  
COLORECTAL CANCER**

**Roche Submission to the  
National Institute for Health and Clinical Excellence  
26<sup>th</sup> August 2005**

## **1. EXECUTIVE SUMMARY**

### **Background**

- Colorectal cancer is the third most common diagnosis of malignancy resulting in around 16,000 deaths every year in the UK. Death is seldom the result of disease localised to the bowel or rectum though but a consequence of metastatic spread. Having progressed to metastatic disease, the life expectancy of patients is around 6 months only if they do not undergo systemic chemotherapy treatments.
- However if patients are willing and fit to receive treatment, a programme of optimum chemotherapy can both extend median survival to around 15 - 20 months and improve quality of life but greater and more equitable access to such treatments are required across the UK. From the perspective of the patient, drug treatment has achieved much for those with this condition but also urgently needs to be further improved.
- The Government has pledged that by 2010 the cancer mortality rate in people under 75 should be cut by at least 20% from 1996 levels as set out in the NHS Cancer Plan. The National Cancer Director's progress report published in 2003 found some improvements, with under 75 year UK cancer mortality rates having fallen by 10% per cent since 1996, halfway towards the 2010 target. The then Health Secretary Dr John Reid MP stated that there was still "a long way to go" to achieve the overall objective and for the NHS to be able to offer one of the best cancer services in Europe. Five year survival for patients with colorectal cancer still remain worse in England and Wales than in Europe as a whole and more than 20% worse than in the best European countries.
- Since colorectal cancer is one of the three most common solid tumours making up more than 40% of cancer cases in the UK, improvements in outcomes for this condition can be expected to have a major impact on measures of overall UK cancer treatment success. However if UK patients do not benefit from treatment innovations now being made available elsewhere, then the Government's aspirations of closing the survival gap with Europe is unlikely to be realised.

### **Bevacizumab (Avastin®) – A New Treatment Option to Improve UK Colorectal Cancer Treatment Outcomes**

- For the last thirty years, scientists have sought to treat cancer by attacking the developing blood supply that is essential for tumour growth, a process known as angiogenesis. In 2004, a breakthrough finally occurred when it was shown that bevacizumab – an antibody against vascular endothelial growth factor (VEGF) which is a key molecule in tumour vascularisation - could dramatically extend survival in metastatic colorectal cancer.

- Bevacizumab has now been demonstrated to be effective in slowing tumour growth, producing measurable tumour shrinkage and leading to improvements in time to progression and overall survival, beyond what has been seen so far with traditional chemotherapy when the two treatment modalities are used together.
- Bevacizumab is the first and only anti-angiogenic agent to receive regulatory approval as an anticancer agent. It is a recombinant humanised monoclonal antibody of the IgG<sub>1</sub> subclass recognising all isotypes of vascular endothelial growth factor (VEGF) and is produced by recombinant DNA technology using Chinese hamster ovary cells. It was launched in the UK on 14<sup>th</sup> March 2005 and has also been successfully launched in all major European countries.

### **Demonstrating the clinical effectiveness of bevacizumab (Avastin®)**

- Bevacizumab is licensed for use throughout the EU and indicated in combination with intravenous 5-fluorouracil (5-FU) / folinic acid (FA) or intravenous 5-fluorouracil / folinic acid / irinotecan for the first-line treatment of patients with metastatic carcinoma of the colon or rectum.
- Two pivotal randomised studies (AVF2107g and AVF2192g) have demonstrated the benefits to patients of adding bevacizumab to existing chemotherapy. These include substantial prolongation of survival in both fit patients (receiving 5-FU/FA plus irinotecan) and less fit patients (receiving 5-FU/FA alone).
- In AVF2107g, the addition of bevacizumab to combination 5FU / FA treatment with irinotecan was shown to improve median overall survival from 15.61 to 20.34 months. This represented an additional 4.73 months above gold-standard combination treatment and a 30% increase in survival. In the same study, progression free survival improved from 6.24 to 10.55 months. This was an increase of 4.31 months over and above combination treatment or a 69% increase in time to progression and is the longest progression free survival ever reported in a clinical study of metastatic colorectal cancer.
- In AVF2192g, the addition of bevacizumab to combination 5FU / FA treatment was shown to improve median overall survival from 13.24 to 16.56 months. This represents an additional 3.32 months and a 25% increase in survival. Progression free survival increased from 5.52 to 9.17 months, an increase of 3.65 months or 66%.
- These remarkable increases in survival seen with the addition of bevacizumab to optimum chemotherapy were not at the expense of quality of life which was maintained when bevacizumab was added to 5-FU / FA / irinotecan and showed evidence of improvement when bevacizumab was added to 5-FU / FA in less fit patients.

- The fact that quality of life was improved or maintained was to be expected in view of the modest burdens that bevacizumab places on patients. It is administered at the same time as chemotherapy and is generally associated with only low-level toxicity. The most common side-effects associated with bevacizumab were hypertension that either required no intervention or was controlled by the administration of conventional anti-hypertensive medications, minor self-limiting nose-bleeds and asymptomatic proteinuria.
- The excellent safety and tolerability of bevacizumab is reflected in the finding that there was no significant increase in adverse-event-related deaths or study discontinuation in patients treated with bevacizumab in addition to chemotherapy, despite the longer period on which patients were on treatment.
- Other measures of antitumour activity were radically improved by the addition of bevacizumab to cytotoxic chemotherapy. For example, tumour response rates were increased by 29% and 71% respectively in studies AVF2107g and AVF2192g. Objective tumour shrinkage is likely to have important psychological value for any patient who experiences it. Additionally, for the minority of patients with isolated but inoperable liver metastases, it may render their hepatic lesions amenable to surgery - the only treatment option which can offer such patients the chance of long-term remission or cure.
- The consistency with which bevacizumab improves outcomes in colorectal cancer is striking – four separate studies have demonstrated that bevacizumab improves outcomes regardless of patient subgroup or choice of chemotherapy regimen. The extent of improvement in survival is also striking – in patients suitable for aggressive chemotherapy with irinotecan, the addition of bevacizumab increased median survival by 4.73 months. This 30% improvement on best current treatment is similar, in absolute terms, to the six month improvement in survival associated with moving from no active treatment to 5-FU based chemotherapy. Similarly, when added to 5-FU / FA alone in study AVF2192g the addition of bevacizumab more than compensates for the absence of the active, but toxic agent irinotecan.
- In summary, bevacizumab prolongs life; extends the time before a patient's cancer gets bigger; increases the chance of tumour shrinkage; and maintains or improves quality of life.

#### **Demonstrating the cost effectiveness of bevacizumab (Avastin®)**

- The results of the economic modelling which we present for bevacizumab need to be carefully considered in the context of the limitations that surround the analyses undertaken to support the broader evaluation of the clinical and cost effectiveness of this highly innovative and effective new treatment for metastatic colorectal cancer.

- One key limitation of our modelling was the availability of up-to-date UK based utility scores. For pre-progression, we have used in our base case analysis a utility score of 0.8 derived from a time trade off study conducted in 1993 but as shown in the sensitivity analyses, the results are highly sensitive to the utility scores used. For example, when using the utility scores of 0.95 used in the original ScHARR Assessment Report prepared to support the development of NICE Guidance No. 33 for oxaliplatin, irinotecan and raltitrexid, the base case incremental cost-effectiveness ratios for bevacizumab are reduced considerably.
- A further important limitation concerns the choice of distribution used to fit the progression-free survival curves which also considerably affects the results of the economic analysis. The base case economic models presented rely on extrapolations based on Weibull distributions. However, the Weibull fit appears in the case of the AVF2192g study to under-estimate the tail of the bevacizumab arm progression-free survival curve. Using an exponential curve in one-way sensitivity analysis yields an undiscounted cost per life year gained of £37,318 and a cost / QALY of £44,268.
- The incremental cost-effectiveness ratios (cost / QALYs) which we have modelled for the use of bevacizumab when compared to 5-FU / FA using study AVF2192g range from £50,300 to £59,900.
- The incremental cost-effectiveness ratios (cost / QALYs) which we have modelled for the use of bevacizumab when compared to 5-FU / FA / irinotecan using study AVF2107g ranges from £78,400 to £93,100.

### **Illustrating NHS budget impact**

- We have estimated that the total number of metastatic colorectal cancer patients in England and Wales to be 18,371, of which 6,283 will receive first-line chemotherapy treatment. Of these patients, 1,795 are assumed to receive a 5-FU / FA / irinotecan and bevacizumab containing regimen and 942 have been assumed to receive a 5-FU / FA and bevacizumab containing regimen.
- We estimate that the additional annual cost for treating patients with 5-FU / FA / irinotecan and bevacizumab will be £6.5 million in year 1 growing to 19.5 million in year 3 assuming example diffusion rates of 20%, 40% and 60% respectively.
- We estimate that the additional annual cost for treating patients with 5-FU / FA and bevacizumab will be £3.4 million in year 1 growing to £10.4 million in year 3 assuming the same example diffusion rates.
- Roche looks forward to continuing to work with the NHS to ensure that bevacizumab can be made available to UK NHS patients.