



Submission from CancerBACUP to NICE Appraisal Committee on the use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

CancerBACUP welcomes the opportunity to contribute to the appraisal of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. As the leading specialist provider of independent information on all types of cancer, CancerBACUP has regular contact with people living with colorectal cancer and those caring for them.

CancerBACUP received over 5,000 enquiries last year from people affected by colorectal cancer.

CancerBACUP believes that everyone with cancer should be offered the most effective and appropriate treatment, based on the available evidence and the patient's own wishes and preferences. We believe that:

- Patients should have access to the most effective treatments appropriate to them as individuals;
- Patients should be able to choose – in partnership with their oncologist – the treatment that is likely to suit them best in terms of relative benefits and side-effects;
- The impact of treatments on patient's quality of life, as well as length of life, should be given full consideration by the Appraisal Committee.

Bevacizumab and cetuximab offer additional tools to extend the survival of patients with metastatic colorectal cancer. We urge the Appraisal Committee to recommend that bevacizumab and cetuximab should be available for the treatment of metastatic colorectal cancer, in accordance with their licences; and thus increase the options available to patients and clinicians.

Living with metastatic colorectal cancer

An estimated 30,909¹ new cases of colorectal cancer are diagnosed each year in England and Wales. In most people the cause of cancer of the large bowel is still unknown, but research is going on all the time to try to find the cause. Research

¹ CancerStats Monograph 2004, Cancer Research UK

suggests that diet, inherited faulty genes and bowel diseases can all be risk factors for colorectal cancer.

Like most types of cancer, colorectal cancer is more common in older people and it is unusual for bowel cancer to be diagnosed in people under 50.

Common symptoms include blood in, or on, the stools (bowel motion), a change in normal bowel habit, unexplained weight loss and pain in the abdomen or back passage. Less common symptoms include sickness, constipation, griping pain and a bloated feeling in the abdomen.

Colorectal cancer is commonly staged using the Dukes staging system. This ranges from Dukes A where the cancer is contained in the bowel wall to Dukes D where the cancer has metastasised or spread to another part of the body such as the liver or the lungs.

Approximately 55 percent of patients diagnosed with colorectal cancer present with advanced colorectal cancer, but about half of those who did not have advanced disease at presentation will later progress to this stage.² Colorectal cancer is difficult to treat once it has advanced and the symptoms of metastatic disease – including pain, weight loss and lack of energy – are distressing and debilitating. Median survival from diagnosis of advanced colorectal cancer is 6-9 months. During this time patients may experience a wide range of physical and psychological symptoms resulting in decreased quality of life.³

Current treatment options for metastatic colorectal cancer

Table 1 outlines the main advantages and disadvantages in chemotherapy treatments currently licensed in metastatic colorectal cancer.

Table 1

Chemotherapy	Advantages	Disadvantages
5FU/FA	Established evidence base. Lots of clinical experience, predictable survival outcomes and side effects.	Side effects include mucositis, hand-foot syndrome, rash, nausea, vomiting.
Capecitabine	Oral fluoropyrimidine with equivalent survival and side effects as 5FU. Can be taken at home. Therefore a reduced need for hospital visits.	GI disorders, mucositis, hand-foot syndrome, rash, nausea, vomiting.

² NICE guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

³ *ibid*

Uftoral and FA	Oral fluoropyrimidine with equivalent survival and side effects as 5FU. Can be taken at home. Therefore a reduced need for hospital visits.	Diarrhoea, nausea, vomiting, abdominal pain, weight loss, fatigue.
Irinotecan	Improved survival when added to 5FU/FA (17 months vs. 14 months). Irinotecan monotherapy vs. best supportive care (BSC) - prolonged survival with irinotecan Improved quality of life with Irinotecan (Irinotecan vs. BSC or 5FU/FA) – reduced cancer pain, appetite improvement, less fatigue, improved emotional well-being.	Diarrhoea, nausea, hair loss, sweating, stomach cramps, watery eyes, low blood counts. Fortnightly administration in hospital can cause disruption to normal life.
Oxaliplatin	In combination with 5FU/FA, it may shrink liver metastases and enable resection of liver metastases. Improved survival when added to 5FU/FA (19 months vs. 14 months).	Diarrhoea, nausea, hair loss, low blood counts, tingling in fingers and feet. Fortnightly administration in hospital can cause disruption to normal life.

Monoclonal Antibodies

Bevacizumab and cetuximab are both monoclonal antibodies. Monoclonal antibodies are drugs that recognise and bind to specific proteins (receptors) that are found on the surface of particular cancer cells or in the bloodstream. Monoclonal antibodies can then destroy these cancer cells while causing little harm to normal cells.

Bevacizumab

Bevacizumab can stop some cancers from developing new blood vessels by blocking a protein called VEGF (Vascular Endothelial Growth Factor). This reduces the cancer's supply of oxygen and nutrients, which causes the tumour to shrink, or at least to stop growing. Bevacizumab is currently used as a first line treatment for patients with metastatic colorectal cancer in combination with 5-flourouracil/folinic acid (5-FU/FA) or 5-FU/FA plus irinotecan.

Cetuximab

Cetuximab locks onto the protein EGFR (Epidermal Growth Factor Receptor) and may prevent the cancer cell from growing and dividing. Cetuximab is currently licensed for use in combination with irinotecan to treat colorectal cancer that has metastasised after previous failure of irinotecan including therapy. Therefore, cetuximab offers a new treatment if a patient's tumour has progressed after receiving irinotecan or if they are unsuitable for treatment with irinotecan alone.

CancerBACUP argues strongly that NICE should recommend that bevacizumab and cetuximab are available on the NHS for the treatment of patients with metastatic colorectal cancer in accordance with their licences for the following reasons:

1. Bevacizumab and cetuximab can extend survival for patients with metastatic colorectal cancer

The goal of treatment of metastatic colorectal cancer is to slow the growth of the tumour and to prevent it spreading further. Bevacizumab and cetuximab are more effective in achieving this than alternative treatments.

Studies have shown a meaningful improvement in survival rates for bevacizumab given with 5-FU/FA or 5-FU/FA plus irinotecan. A study by Hurwitz, Fehrenbacher, Novotny et al showed the median survival time for bevacizumab with bolus 5-FU/FA plus irinotecan as 20.3 months compared to 15.6 months for a placebo with bolus 5-FU/FA plus irinotecan. The median time of progression free survival was 10.6 months compared to 6.2 months with the placebo⁴.

Results from trials on patients with metastatic colorectal cancer at the Royal Marsden Hospital, which carried out a randomised clinical trial found that cetuximab has clinically significant activity when given alone or in combination with irinotecan in patients with irinotecan-refractory colorectal cancer. The trial involved 329 patients whose disease had progressed during or within three months after treatment with an irinotecan-based regimen to receive either cetuximab and irinotecan (at the same dose and schedule as in a prestudy regimen [218 patients]) or cetuximab monotherapy (111 patients). The median survival time was 8.6 months in the combination-therapy group and 6.9 months in the monotherapy group.⁵

⁴ Hurwitz, Fehrenbacher, Novotny et al 'Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for metastatic colorectal cancer', *The New England Journal of Medicine*, 3 June 2004, Vol 350 No 23

⁵ *The New England Journal of Medicine*. Jul 22 2004 Vol 351(4):337-45.

2. Bevacizumab and cetuximab can provide better quality of life for patients with metastatic colorectal cancer

CancerBACUP's contact with patients suggests that quality of life is a very important endpoint from the perspective of many patients when considering treatment options.

Targeted compounds such as bevacizumab and cetuximab have the potential of being less toxic and may even reverse acquired drug resistance in some patients. The side effects of bevacizumab and cetuximab are generally mild and patients do not appear to experience side effects common to traditional chemotherapy such as hair-loss and neutropenia. The possible side effects that may be seen are mild skin rashes, tiredness, nausea, fatigue, diarrhoea and in the case of bevacizumab, an increase in cases of high blood pressure.

Bevacizumab and cetuximab increase active treatment options and provide patients and physicians the potential option to extend life as well as managing symptoms in a sizeable proportion of patients. Through our conversations with patients, it is clear that some are willing to try any kind of treatment that offers them the chance of additional survival time. As with all anti-cancer treatments, potential clinical benefits must be set against the risk of unwanted side-effects. This is an important trade-off from the patient's perspective, and it is essential to avoid over-generalising about patients' preferences.

Declaration of interest

CancerBACUP has received sponsorship from Roche, the manufacturer of bevacizumab, and Merck Pharmaceuticals, the manufacturer of cetuximab, for several publications and projects.

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