

# The Promise of Biological and Molecular-orientated Treatments for Colon Cancer

a report by

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Colorectal cancer is one of the most common malignancies and the second leading cause of death from cancer in the western world, representing one million new cases and half a million deaths annually worldwide. Since the mid-1980s, both the incidence and mortality rates of colorectal cancer have decreased, due at least in part to increased rates of screening and polyp removal.

The five-year survival rate for colorectal cancer is 90% if detected early when still localised, but only 39% of colorectal cancers are found at this stage. Nearly one-quarter of patients have metastatic disease at diagnosis, with a five-year survival rate lower than 10%.

After the acceptance of irinotecan- and oxaliplatin-based combination therapies as a standard of care, treatment options now extend beyond conventional chemotherapy and routinely include biological agents targeting angiogenesis and the epidermal growth factor receptor (EGFR) system (bevacizumab [BEV] and cetuximab [CET]). The addition of BEV and CET to chemotherapy in the treatment of metastatic colorectal cancer (MCRC) has resulted in an increase in progression-free survival (PFS) and overall survival (OS).<sup>1</sup>

## Bevacizumab – Mechanism of Action and Clinical Efficacy

BEV (Avastin®) is a recombinant, humanised monoclonal antibody against vascular endothelial growth factor (VEGF) that is used to inhibit VEGF action in vascular endothelial cells and then inhibit angiogenesis, upon which solid tumours depend for growth and metastasis.<sup>2</sup>

Calvani et al.<sup>3</sup> have shown that serum-starved colon cancer cells differentially respond to autocrine production of VEGF with the activation of hypoxia-inducible factor-1 alpha (HIF-1 alpha) and survival under hypoxic conditions. Abrogation of VEGF or VEGF receptor 2 (VEGFR2)/KDR, but not VEGFR1/Fit-1, was sufficient to inhibit VEGF-mediated induction of HIF-1 alpha and survival in sensitive HCT116 colon cancer cells, but not in resistant HT29.

These results suggest that a VEGF/KDR/HIF-1 alpha autocrine loop differentially promotes survival of hypoxic colon cancer cells. They also show that colon cancer cells may be intrinsically sensitive or resistant to anti-VEGF strategies, which may cause the therapeutic action of BEV.<sup>3</sup>

A phase III study that evaluated BEV in patients with advanced colorectal cancer was performed by Hurwitz et al.<sup>4</sup> This randomised, multicentre study evaluated the OS in 402 subjects with MCRC who were randomised to receive irinotecan, 5-fluorouracil (5-FU), leucovorin (IFL) plus BEV (5mg/m<sup>2</sup> every two weeks) compared with 411 patients who were randomised to receive IFL plus placebo.

The median duration of OS, the primary end-point of this study, was 20.3 months for those in the BEV group and 15.6 months in the placebo group (p<001) (see *Figure 1*).

One-year survival rates were 74.3 and 63.4% for those who received IFL plus BEV and IFL plus placebo, respectively. Secondary end-points were a 10.6-month PFS (IFL plus BEV) compared with a 6.2-month PFS (IFL plus placebo) (see *Figure 2*).

BEV also has activity in the second-line setting but not in the third-line setting. Results from the Bevacizumab Regimens Investigation of Treatment Effects and Safety (BRiTE) registry and from the post-marketing study (BEAT) suggest that BEV is similarly effective at increasing PFS when administered in combination with all regimens of chemotherapy. In addition, retrospective analyses demonstrate that surgery with curative intent can be performed in about 20% of patients on BEV.

In addition, BEV has been studied in combination with 5-FU, leucovorin and oxaliplatin (FOLFOX) as second-line treatment in 829 patients with MCRC who progressed despite previous therapy with 5-FU/IFL and irinotecan. Median survival times in patients treated with FOLFOX plus BEV were 12.5 months versus 10.7 months for patients treated with FOLFOX alone.<sup>5</sup>

By way of first-line treatment, the randomised trial Three Regimens of Eloxatin Evaluation (TREE-2) compared three oxaliplatin-based regimens with or without the addition of BEV. Recently reported results showed an

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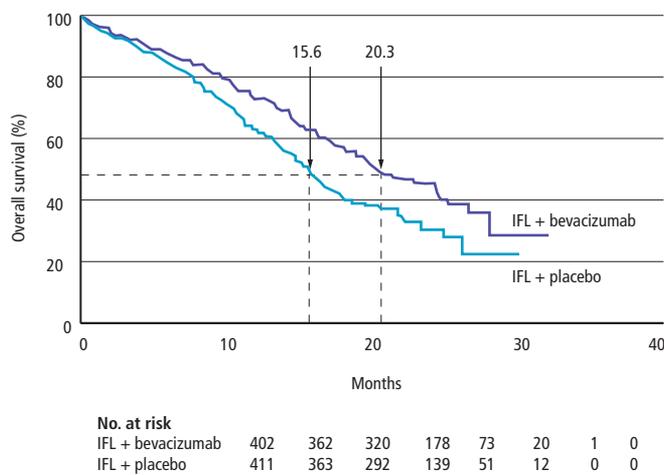
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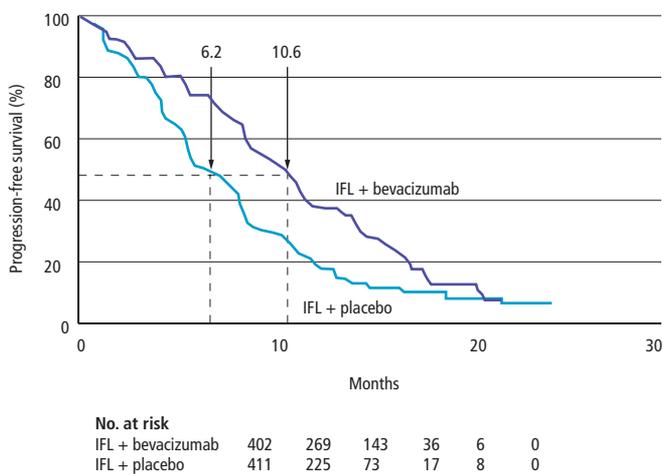
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**Figure 1: Kaplan-Meier Estimates of Survival**



**Figure 2: Kaplan-Meier Estimates of Progression-free Survival**



overall response rate (RR) in patients randomised to receive FOLFOX plus BEV versus FOLFOX alone of 52 and 41%, respectively. This study was also important in that it demonstrated that capecitabine could be combined successfully with oxaliplatin and BEV in American patients, resulting in a 48% RR and a 10.3-month median time to progression.<sup>6</sup>

On the other hand, an international phase III trial (NO16966) was initiated to estimate the efficacy of capecitabine and oxaliplatin (XELOX) and FOLFOX-4 for the first-line treatment of MCRC. The study was later corrected to compare BEV and chemotherapy with placebo and chemotherapy. The data suggest that XELOX was as operative as FOLFOX-4 (PFS: hazard ratio [HR] 1.04, 97.5% confidence interval 0.93–1.16). Also, BEV/chemotherapy (pooled XELOX or FOLFOX) significantly prolonged PFS (HR 0.83;  $p=0.0023$ ) compared with placebo and chemotherapy (XELOX/FOLFOX). In subgroup analysis, the addition of BEV to XELOX (9.3 versus 7.4 months, HR 0.77;  $p=0.0026$ ) and FOLFOX-4 (9.4 versus 8.6 months, HR 0.89;  $p=0.1871$ ) increased PFS compared with respective placebo arms. The adverse events were comparable between therapy arms.<sup>7</sup>

In addition, Politano et al.<sup>8</sup> executed a retrospective review. Patients with MCRC treated with BEV outside of a clinical trial and any infusional

5-FU/IFL regimen off protocol (i.e. FOLFIRI/BEV or FOLFOX/BEV) at the University of Texas MD Anderson Cancer Center between February 2004 and September 2005 were included. Pre-specified characteristics of tumour burden, age, severe toxicity and front-line regimen efficacy were analysed. Eighty-seven patients treated with the specified front-line regimens were selected. Seventy-six per cent of the eligible patients were treated with a second cytotoxic agent. In spite of equal therapy durations, patients with a better response of stable disease were significantly less likely to receive a third-line regimen than patients with a partial response (68 versus 95%, odds ratio 8.2;  $p=0.02$ ) due to declining performance status (86%) or patient preference (14%). This was in correlation with a decreased two-year OS (86 versus 55%). Tumour burden, age and development of toxicity were not associated with a different utilisation of a second-line regimen. Therefore, failure to obtain a response to initial chemotherapy for MCRC results is to be connected with decreased utilisation of the second-line regimen.<sup>8</sup>

In conclusion, BEV is currently approved for the first-line treatment of MCRC combined with 5-FU-based chemotherapy and is currently being tested in combination with standard therapies for a range of indications. In fact, the addition of BEV to fluoropyrimidine chemotherapy, with or without irinotecan or oxaliplatin, in both the first- and second-line treatment of MCRC improved median PFS by 4.7 months and 2.1 months, respectively. The tolerability of BEV is acceptable. Common adverse events are hypertension, rash, fever, headache, thrombotic events, proteinuria and haemorrhage. Incidence of any serious adverse events occurred with low frequency. Only severe hypertension was significantly higher with BEV than with the placebo patients. In the EU, the dosage for therapy of MCRC is 5mg/kg once every two weeks administered as an intravenous infusion. Treatment should be continued until progression.

### Cetuximab – Mechanism of Action and Clinical Efficacy

The EGFR is a member of the ErbB group of receptors. It is composed of extracellular domains, including a ligand-binding region, hydrophobic transmembrane domain and tyrosine kinase-containing cytoplasmic region. Activation of the EGFR by endogenous ligands results in a conversion in the receptor, allowing it to enter into dimers and other oligomers. Dimerisation causes stimulation of intracellular tyrosine kinase, protein phosphorylation and activation of various cell signals that determine gene transcription. The EGFR is expressed on normal human cells, but higher levels of expression of the receptor have also been shown to be associated with malignancy in a variety of cancers.

Cetuximab (Erbix<sup>®</sup>) is a chimeric human-murine monoclonal antibody that binds competitively and with high affinity to EGFR. Binding of the antibody to the EGFR prevents activation of the receptor by endogenous ligands and results in elimination of cell multiplication, increased apoptosis and reduced invasiveness, angiogenesis and metastasis.<sup>9</sup>

A randomised, multicentre study in patients with EGFR-positive, irinotecan-refractory MCRC was undertaken (the Bowel Oncology with Cetuximab Antibody (BOND) trial). In this study, 329 patients were randomised in a 2:1 ratio to receive CET (400mg/m<sup>2</sup> first infusion, then 250mg/m<sup>2</sup> weekly) plus irinotecan (arm A;  $n=218$ ) or CET alone (arm B;  $n=111$ ) with the option to switch to the combination of CET with irinotecan after failure of CET as a single agent.

The RR in the combination therapy group (arm A) was significantly higher than that in the monotherapy group (arm B) (22.9 versus 10.8%;  $p=0.007$ ). The median time to progression was also significantly greater in the combination therapy group (4.1 versus 1.5 months;  $p<0.001$ ). No survival benefit for arm A was observed over arm B. Nevertheless, CET was demonstrated to have clinically significant activity when given alone or in combination with irinotecan, and it consequently received US Food and Drug Administration (FDA) approval for use in patients whose disease is refractory to irinotecan with tumours expressing EGFR.<sup>10</sup>

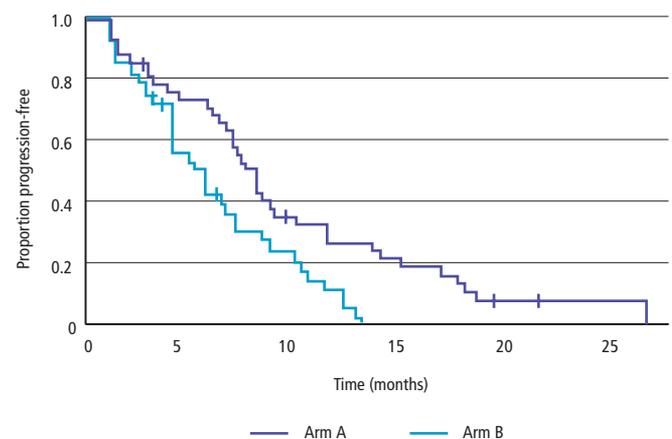
VEGF and EGFR have different mechanisms of action. The feasibility of administering BEV and CET in combination was addressed in the BOND-2 study. All patients had not been treated previously with CET or BEV. Patients in arm A received irinotecan at the same dose and schedule as last given prior to study entry, plus CET 400mg/m<sup>2</sup> loading dose, then weekly CET 250mg/m<sup>2</sup> plus BEV 5mg/kg administered every other week. Patients in arm B received the same CET and BEV as those in arm A but without irinotecan.

Forty-three patients received CET, BEV and irinotecan (CBI) and 40 patients received CET and BEV alone (CB). For the CBI arm, time to tumour progression (TTP) was 7.3 months and the RR was 37%; for the CB arm, TTP was 4.9 months and the RR was 20% (see Figure 3). The OS for the CBI arm was 14.5 months and the OS for the CB alone arm was 11.4 months (see Figure 4). In conclusion, CET and BEV can be administered concurrently with a toxicity that seems to be identical to that which would be expected from the two drugs alone. This combination plus irinotecan also seems to be feasible. The action seen with the addition of BEV to CET, or to CET plus irinotecan, seems to be advantageous in this setting. Combination of biologicals is feasible, but financial considerations constitute a problem.<sup>11</sup>

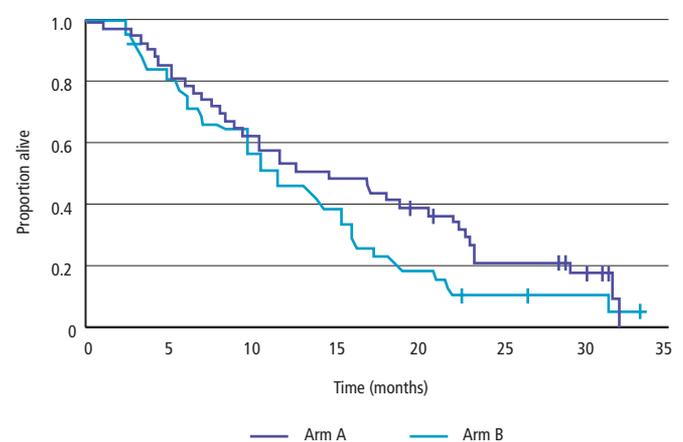
The CAIRO2 study is another randomised phase III trial on capecitabine, oxaliplatin and BEV with or without CET in previously untreated advanced colorectal cancer patients. In all, 755 patients were randomly allocated to therapy with capecitabine, oxaliplatin and BEV with or without CET. The primary end-point was PFS. The incidence of dermatological toxicity was significantly higher in arm B compared with arm A. This difference was attributed to CET utilisation. In addition, in comparison with capecitabine, oxaliplatin and BEV, CET in first-line treatment of advanced colorectal cancer appears to be favourable and feasible.<sup>12</sup>

A randomised study that was conducted by the National Cancer Institute of Canada Clinical Trials Groups, in collaboration with the Australasian Gastro-Intestinal Trials Group, also investigated data from between December 2003 and August 2005, and 572 patients who had colorectal cancer expressing immunohistochemically EGFR and who had been previously treated with fluoropyrimidine, irinotecan and oxaliplatin or had contraindications to treatment with these drugs. Patients received an initial dose of 400mg/m<sup>2</sup> of CET followed by a weekly infusion of 250mg/m<sup>2</sup> plus best supportive care (287 patients) or best supportive care alone (285 patients). The addition of CET was associated with a significant improvement in OS (HR for death 0.77, 95% CI 0.64–0.92;  $p=0.005$ ) and in PFS (HR for disease progression or death 0.68, 95% CI 0.57–0.80;  $p<0.001$ ). The median OS was 6.1 months in the CET group and 4.6 months in the group assigned to supportive care alone. Partial responses occurred in 23 patients (8%) in the first group but in none in the second group. The disease was stable in an additional 34.4% of

**Figure 3: Kaplan-Meier Estimates of Time to Tumour Progression – Arm A (CBI) versus Arm B (CB)**



**Figure 4: Kaplan-Meier Estimates of Survival – Arm A (CBI) versus Arm B (CB)**



patients assigned to CET and in 10.9% of patients assigned to supportive care alone ( $p<0.001$ ). CET treatment was associated with an acne-form rash. A rash of grade 3 or higher was correlated with an increase in survival (HR for death 0.33; 95% CI 0.22–0.50;  $p<0.001$ ).

Therefore, CET improves OS and PFS and preserves quality-of-life measures in patients with colorectal cancer for whom other treatments have failed.

CET has also been evaluated as a component of first-line therapy in patients with advanced colorectal cancer. A phase II study analysed the efficacy and safety of CET plus standard oxaliplatin-based chemotherapy (FOLFOX-4) in the first-line treatment of EGFR-expressing MCRC. In the clinical study, patients received CET on day one of a 14-day cycle (initial dose 400mg/m<sup>2</sup> during week one, then 250mg/m<sup>2</sup> weekly) followed by FOLFOX-4 (oxaliplatin 85mg/m<sup>2</sup> on day 1; IFL 200mg/m<sup>2</sup> on days one and two, followed by 5-FU 400mg/m<sup>2</sup> bolus then 600mg/m<sup>2</sup> intravenous infusion during 22 hours on days one and two). The pre-clinical studies confirmed the supra-additive activity of CET to oxaliplatin. In the clinical study, 43 patients were included, with a median age of 65 years (range 43–78 years). RRs were 79% (unconfirmed) and 72% (confirmed), with 95% disease control. Median PFS and median duration of response were 12.3 and 10.8 months,

respectively. Ten patients (23%) underwent resection with curative intent of previously unresectable metastases. After a median follow-up of 30.5 months, median OS was 30 months. CET did not increase the characteristic toxicity of FOLFOX-4 and was generally well tolerated. In conclusion, CET in combination with FOLFOX-4 is a highly active first-line treatment for MCRC, showing encouraging RR and median PFS and OS values. The treatment resulted in a high resectability rate, which could potentially result in an improved cure rate. The correct placing of the CET, oxaliplatin and fluoropyrimidine combinations in first-line treatment of MCRC has to be assessed in phase III trials.<sup>13</sup>

All studies show that CET can increase OS in patients with refractory MCRC and that CET has encouraging activity in second-line treatment. Promising action has also been evaluated in first-line treatment in combination with FOLFIRI and FOLFOX, but new clinical studies are needed to determine the combination and sequence of these drugs. CET is generally well tolerated. Dermatological toxicity (acne-form rash) is the most frequent problem associated with CET. The rash typically appears on the face, neck and chest. The intensity of the acne-form rash seems to be correlated to drug activity. Infusion reaction (hypotension, airway obstruction and cardiac arrest) may occur during

first-line treatment with CET and requires immediate interruption of the infusion. In addition, the dosage for therapy is 400mg/m<sup>2</sup> initially, followed by 250mg/m<sup>2</sup> weekly.

## Conclusions

Randomised studies have shown that survival or time to TTP of MCRC is improved when BEV is used in combination with cytotoxic drugs (5-FU with or without irinotecan or oxaliplatin). CET was approved for therapy on the basis of a large, randomised phase II study, but its therapeutic contribution in MCRC needs to be clarified. According to recommendations on the use of molecular-targeted agents in combination with chemotherapy for MCRC, BEV should be considered in first-line treatment of patients with a good performance status and CET in third-line treatment.

More recent studies estimate promising CET action in second-line treatment after oxaliplatin-based therapy failure and with first-line chemotherapy, where increased RRs seen with adding cetuximab to first-line therapy for MCRC may increase the chances for curative surgery in a population for whom the treatment would otherwise be palliative.<sup>14</sup> ■

1. Klein B, Gottfried M, Targeted agents to improve treatment results in colon cancer: bevacizumab and cetuximab, *J BUON*, 2007;12(Suppl. 1):127–36.
2. McCormack PL, Keam SJ, Bevacizumab: a review of its use in metastatic colorectal cancer, *Drugs*, 2008;68(4):487–506.
3. Calvani M, Trisciuglio D, Bergamaschi C, et al., Differential involvement of vascular endothelial growth factor in the survival of hypoxic colon cancer cells, *Cancer Res*, 2008;68(1):285–91.
4. Hurwitz H, Fehrenbacher L, Novotny W, et al., Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer, *N Engl J Med*, 2004;350:2335–42.
5. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al., Cetuximab for the treatment of colorectal cancer, *N Engl J Med*, 2007;357(20):2040–48.
6. Hochster HS, Hart LL, Ramanathan RK, et al., Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: final analysis of the TREE-study, *Proc Am Soc Clin Oncol*, 2006;24(148s), abstract 3510.
7. Tyagi P, Grothey A, Commentary on a phase III trial of bevacizumab plus XELOX or FOLFOX4 for first-line treatment of metastatic colorectal cancer: the NO16966 trial, *Clin Colorectal Cancer*, 2006;6(4):261–4.
8. Politano S, Overman M, Pathak P, et al., Second-line chemotherapy use in metastatic colon cancer varies by disease responsiveness, *Clin Colorectal Cancer*, 2008;7(1):55–9.
9. Harding J, Burtneis B, Cetuximab: an epidermal growth factor receptor chimeric human-murine monoclonal antibody, *Drugs Today (Barc)*, 2005;41(2):107–27.
10. Cunningham D, Humblet Y, Siena S, et al., Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer, *N Engl J Med*, 2004;351:337–45.
11. Saltz LB, Lenz HJ, Kindler HL, et al., Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study, *J Clin Oncol*, 2007;25(29):4557–61.
12. Tol J, Koopman M, Rodenburg CJ, et al., A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG): an interim analysis of toxicity, *Ann Oncol*, 2008;13 (Epub ahead of print).
13. Tabernero J, Van Cutsem E, Diaz-Rubio E, et al., Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer, *J Clin Oncol*, 2007;25(33):5225–32.
14. Ree AH, Bratland A, Dueland S, Molecular targeted therapy in colorectal cancer, *Tidsskr Nor Laegeforen*, 2008;128(2):190–93.

## Related Articles

### Targeted Agents to Improve Treatment Results in Colon Cancer – Bevacizumab and Cetuximab

Klein B, Gottfried M

*J BUON*, 2007;12(Suppl. 1):127–36.

The addition of bevacizumab (BEV) and cetuximab to chemotherapy in the treatment of metastatic colorectal cancer (MCRC) has resulted in an increase of progression-free survival (PFS) and overall survival. BEV is usually given in the first- and second-line setting, but not in the third-line setting. Cetuximab increases PFS in the second-line setting, as seen in the EPIC study. In the first-line setting (CRYSTAL study), cetuximab increased PFS. Combination of biologicals is feasible (BOND-2), but financial considerations constitute a problem. BEV is approved for first- and second-line treatments, and cetuximab is approved in patients failing irinotecan. ■

### Second-line Chemotherapy Use in Metastatic Colon Cancer Varies by Disease Responsiveness

Politano S, Overman M, Pathak P, et al.

*Clin Colorectal Cancer*, 2008;7(1):55–9.

Improved survival of patients with metastatic colorectal cancer (CRC) has been shown to correlate with increased utilisation of the three active cytotoxic chemotherapeutic agents. It is unclear which patient, disease and treatment characteristics are associated with the utilisation of a second-line regimen. Subsequently, 87 sequential patients treated with the specified front-line regimens were identified and 76% were treated with a second-line regimen. Patients with a better response were significantly less likely to receive a third cytotoxic agent than patients with a partial response. This was associated with a decreased two-year overall survival. ■