# COLORECTAL CANCER ASSOCIATION OF CANADA

## COLORECTAL CANCER RESEARCH
### Week Ending October 31, 2008

The following colorectal cancer research update extends from October 18 – October 31, 2008 inclusive and is intended for informational purposes only.

## DRUGS

1. **Continuing Avastin Beyond Initial Progression Is Associated With Prolonged Overall Survival In mCRC** (Oct. 19/08)

   Continuing Avastin beyond the time when advanced crc gets worse helps patients, according to new study reports. Patients who continued to receive avastin with a new chemotherapy regimen after their cancer first progressed lived almost 12 months longer than patients who got more chemo but stopped avastin. Both groups did better than those who had no further treatment at all. The BRITE (Bevacizumab Regimens: Investigation of treatment Effects and Safety) observed progress of 3 groups of patients when their cancer got worse after their first chemotherapy treatments. All patients had avastin as part of their first chemo, some continued it beyond that first cancer progressing. The 3 groups included:

   - No further treatment with either chemotherapy or avastin and overall survival was 12.6 months
   - Chemotherapy but no further avastin with overall survival being 19.9 months
   - Change in chemotherapy and continued avastin with an overall survival of 31.8 months

   Patients were treated in almost 250 different places in the US. Lead investigator from the Mayo Clinic suggests that continued treatment with avastin beyond initial progressive disease could play an important role improving the overall success of therapy for patients who have metastatic colorectal cancer.

   ***Grothey, Axel, et al., Bevacizumab Beyond First progression Is Associated With prolonged Overall Survival in Metastatic Colorectal Cancer: Results From a Large Observational Cohort Study (BRITE), J of Clinical Oncology, Early Release, October 14, 2008.***

2. **Dose Finding Study of Erlotinib Combined to Capecitabine (Xeloda) and Irinotecan in Pretreated Advanced Colorectal Cancer Patients** (Oct. 21/08)

   An Italian study evaluated the maximum tolerated dose and the dose limiting toxicity of erlotinib when combined to irinotecan and capecitabine in pre-treated metastatic colorectal cancer patients. 21 patients were treated in cohorts of three. The results documented that erlotinib at the dose of 100 mg per day, irinotecan 180 mg/m2 and capecitabine 1,500 mg/m2 per day for 14 days has an acceptable safety profile and appears suitable for further phase II studies.

   ***Bajetta, Emilio, Dose finding study of erlotinib combined to capecitabine and irinotecan in pretreated advanced colorectal cancer patients. Cancer Chemotherapy and Pharmacology. On-line edition: 1432-0843. October 21, 2008***

3. **Avastin + Folfox – CRC Phase III Trial to Continue** (Oct. 22/08)

   Based on the results of a planned interim analysis, Genentech has announced the continuation of the National Surgical Adjuvant Breast and Bowel Project (NSABP) – an ongoing Phase III study (NSABP C-08) of Avastin plus chemotherapy (folfox) in patients with early stage colon cancer will continue as planed so as to determine the effect and survival benefit of avastin. The NSABP's decision to continue the trial was based on a recommendation from an independent Data Monitoring Committee after a planned interim analysis. NSABP C-08 is a randomized, multi-center Phase III study designed to evaluate the effect of folfox chemotherapy with or without avastin on disease free survival in patients with resected stage II or III adenocarcinoma of the colon. The trial is being conducted primarily in the United States. Patients enrolled in the two arm study were randomized after surgery to receive either folfox alone for 6 months **or** avastin in combination with folfox for 6 months followed by an additional 6 months of avastin monotherapy. Overall survival is a secondary endpoint of the study.

   ***www.gene.com/gene/news/press-releases***

**4. Picoplatin in Combination with 5FU and Leucovorin (Folpi) Has Potential Neuropathy Sparing Effect in CRC** (Oct. 23/08)

The new generation platinum agent picoplatin added to the combination of 5FU and leucovorin (folpi) provides similar platinum dose intensity to the combination of oxaliplatin with 5FU and leucovorin while showing less frequent and severe neurotoxicity for treatment of metastatic colorectal cancer in patients who have had no prior chemotherapy. Results of a randomized, controlled, phase 2 study were presented at the 20th International Symposium of the European Organization for Research and treatment of Cancer (EORTC), the National Cancer Institute (NCI), and the American Association for Cancer Research (AACR). Standard treatment of patients with advanced crc is associated with significant oxaliplatin-related neurotoxicity. In single-agent trials of picoplatin, the same type of neurotoxicity that has been reported with other platinum agents, was not seen, and this created the possibility that in crc, where oxaliplatin is part of the standard therapy, picoplatin could be substituted. The current study had the standard regimen of infusional 5FU plus leucovorin every 2 weeks in both treatment groups. 51 patients received oxaliplatin and 50 patients received picoplatin. Both treatment groups had similar response rates and non neurological toxicities were similar. **Of note, however, neuropathy of grade 2 or greater was reported in 27% in the folfox group and 9% of folpi patients, and grade 3 or 4 neuropathies were seen in 5% and 0% of patients respectively.**

***Preliminary Results of a Phase II Study of Picoplatin in Combination With 5 Fluorouracil and Leucovorin (FOLPI) as a Potential Neuropathy-Sparing First Line Therapy for Colorectal Cancer (CRC) , Abstract 210. Presented at EORTC-NCI-AACR***

**5. Celecoxib Active in Colorectal Adenoma Chemoprevention: presented at UEGW** (Oct. 23/08)

Celecoxib appears to have efficacy for prevention of colorectal adenoma that persists for 5 years after a 3 year initial treatment, according to a study presented at the 16th United European Gastroenterology Week (UEGW). The most pronounced protection seen with celecoxib was against advanced adenomas, especially in high risk patients. The primary objective of the study was to evaluate the effect of celecoxib 400 mg once daily or placebo in subjects with new adenomas after baseline polypectomy at year 1 and/or year 3. Patients with a history of cardiovascular disease were not excluded from the trial. A total of 1,561 patients were randomized to double-blind treatment with either celecoxib 400 mg or placebo for 36 months. All patients underwent colonoscopy at 1 and 3 years. By December 2004, 3 years after its initiation, the study was discontinued due to safety concerns raised in other studies of celecoxib. More than 1,000 patients continued to be followed off-treatment for 2 years. The primary objective of the extension phase was to evaluate safety and efficacy of celecoxib 400 mg at year 5. Overall, 17% of patients in both treatment arms were low-dose aspirin users. Celecoxib prevented polyp recurrence up to 3 years, regardless of aspirin use. At 5 years, the researchers observed an 11% reduction in the cumulative rate of new adenomas. In aspirin nonusers, celecoxib use was associated with a reduction of 13%, whereas aspirin users showed a slight increase of 6% as compared with placebo

***Prevention of Sporadic Colorectal Adenomatous Polyps Study – Chemopreventive Effectiveness and Safety of Celecoxib Two Years After Treatment Cessation. Abstract OP388.*** **Presented at UEGW**

**6. Clinical Trial: Vaccine Therapy after Surgery** (Oct. 28/08)

Researchers are attempting to develop a vaccine that will stimulate the body's immune response to destroy cancer cells in the body and prevent cancer from returning after surgery so as to remove metastatic tumours. Vaccines and immune responses in patients are being studied where colorectal cancer has spread beyond the original cancer to the liver or lungs. Researchers are looking for patients who have completed surgery for a clinical trial of **PANVAC-VF.** Patients must meet the following criteria in order to quality:

- Had surgery to completely remove metastatic tumours in their liver or lungs
- Have no sign of remaining cancer
- Received chemotherapy for at least 2 months before or after their surgery

Patients will randomly receive vaccine treatment in one of 2 ways:

**(i)** **Autologous DC:** White blood cells will be removed from the patient's own blood and the dendritic cells (DC) treated in the lab with the two vaccines being used for the trial (PANVAC-V and PANVAC-F). On the first day of trial treatment, patients will receive their own dendritic cells, which have been prepared with PANVAC-V, by an injection under the skin. On the second day, their dendritic cells treated with PANVAC-F will be injected. The second-day treatment will be repeated 1, 7, and 11 weeks later.

**(ii)** **Sargramostin:** Patients will not have their own dendritic cells injected. Instead they will receive PANVAC-V on the first day of treatment and PANVAC-F at the beginning of the 4th, 8th, and 12 weeks. They will also receive sargramostim (GM-CSF) for three days with each vaccine treatment.

PANVAC-V is vaccinia-CEA-MUC-1-TRICOM vaccine. PANVAC-F is fowlpox-CEA-MUC-1-TRICOM vaccine. The primary goal of the study is to determine how many patients are alive and cancer-free 2 years after treatment. Immune response will also be measured. The study is being conducted at cancer centers in Washington DC, Houston, Durham and Winston-Salem, NC, Portland OR, Tampa and Charleston, SC.

***http://fightcolorectalcancer.org/research***

***http://clinicaltrials.gov/ct/show/NCT00103142***

## 7. Kras Mutation Affects Outcomes with Erbitux in Colorectal Cancer (Oct. 27/ 08)

Erbitux therapy is a type of targeted therapy called a monoclonal antibody. It works by binding to a protein receptor located on many cancer cells called the **epidermal growth factor receptor (EGFR)**. EGFR is involved in cellular growth and replication, and by targeting EGFR, the spread of cancer can be reduced or delayed. Response to erbitux and other drugs may be influenced by mutations in specific genes. If gene mutations are found to predict response to treatment, information about a patient's genetic status may help doctors select the best treatment for that patient. Kras is a gene that may influence response to erbitux. Recent studies have indicated that Kras mutations affect responses to any agents targeting the EGFR pathway. Researchers continue to further refine these new findings and ultimately individualize therapy for these patients. Researcher centers recently conducted a clinical trial to evaluate the effects of Kras mutation status on response and survival among patients with colorectal cancer treated with erbitux. This study included 394 patients who had received treatment with either erbitux or supportive care only (treatment to relieve symptoms but not treat the disease). Samples of tissue from the cancer were tested for Kras mutations and outcomes were analyzed according to these mutations. Among individuals who did not have mutations within their Kras gene, overall survival was significantly improved if they had received treatment with erbitux (9.5 months) compared to best supportive care (4.8 months). Progression-free survival was also improved among patients with no mutations in their Kras gene if they received treatment with erbitux vs. supportive care only. Among patients with mutations in their Kras gene, there was no difference in overall survival or progression-free survival between patients treated with erbitux or supportive care, regardless of treatment group. Among patients treated with supportive care only, there were no differences in overall survival or progression free survival. The researchers concluded that colorectal cancer patients with Kras mutations do not benefit from treatment with erbitux, whereas those without Kras mutations achieve significantly improved survival with erbitux compared to supportive care. These results confirm prior studies evaluating this issue.

**Karapetis C, et al., Kras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer. New England Journal of Medicine. 2008: 359: 1757-1765**

## 8. Celldex Presents Results from Phase I Studies of CDS-1307 (Oct. 31/08)

Celldex Therapeutics announced initial results from multi center Phase I clinical trials of its cancer vaccine candidate, **CDX-1307**, combined with GM-CSF, at the International Society for the Biologic therapy of Cancer annual meeting in San Diego. Researchers believe that specific immunotherapy combinations will provide even more potent clinical effects and based on the safety and immunogenicity seen in these dose escalation studies, Celldex is now evaluating CDX-1307 in combination with the experimental Toll-Like Receptor agonists that the Company recently accessed. CDX-1307 is a **dendritic cel**l targeted immunotherapy designed to focus the immune system against hCG Beta which is frequently expressed in epithelial tumours and has been associated with poor prognosis. The phase I studies are open label, dose escalating clinical trials in patients with incurable breast, bladder, pancreatic, or **colorectal cancer,** all tumours that can express hCG Beta. The studies evaluated the safety and immunogenicity of multiple dosing of CDX-1307 alone and in combination with GM-CSF at multiple dose levels. Despite advanced disease in the majority of patients, 2 patients experienced stable disease for at least 6 months and a minor response was seen in a patient with pancreatic cancer.

***www.celldextherapeutics.com***

**9. EntreMed's ENMD-2076 Demonstrates Tumor Regression In Human Colon Cancer Model** (Oct. 24/08)

EntreMed announced the presentation of preclinical data for its Aurora A/angiogenesis kinase inhibitor, ENMD-2076 at the 20th EORTC-NCI-AACR Annual Meting held in Geneva, Switzerland. ENMD-2076 is a novel, oral, kinase inhibitor with potent activity against Aurora A and a number of tyrosine kinases linked to cancer and inflammatory diseases. ENMD-2076 demonstrated strong antitumour effects in a xenograft model of human colon cancer. ENMD-2076 exerts its effects through multiple mechanisms of action, including antiproliferative activity and the inhibition of angiogenesis. ENMD-2076 has demonstrated substantial dose-dependent efficacy as a single agent, including tumour regression, in multiple xenograpft models (e.g. breast, **colon**, leukemia). Aurora kinases are key regulators of the process of mitosis, or cell division, and are often over-expressed in human cancers. In addition to the Aurora A isoform, ENMD- 2076 has been shown to inhibit a distinct profile of angiogenic tyrosine kinase targets. ENMD- 2076 is currently in a phase 1 clinical study in advanced cancer patients.

***www.medicalnewstoday.com/articles/126642.php***

**10. Oxford Says Cancer Drug May Increase Patient Survival** (Oct. 24/08)

Oxford BioMedica said that a cross trial analysis of its experimental drug **TroVax** in **colorectal**, renal and prostate cancer showed a positive correlation between immune response and patient survival. The effect was strongest in colorectal patients. There are 2 late stage prospective colorectal trials taking place.

***www.reuters.com/news***

## SURGERY

**11. Adjuvant Chemotherapy After Resection of Colorectal Cancer Metastases** (Oct. 22/08)

This month's J of Clinical Oncology reports on a pooled analysis of randomized trials on adjuvant chemotherapy after curative resection of metastases from colorectal cancer. Adjuvant systemic chemotherapy administered after surgical resection of colorectal cancer metastases may reduce the risk of recurrence and improve survival, but its benefit has never been demonstrated. Dr. Emmanuel Mitry and colleagues from Italy evaluated 2 large randomized trials. The 2 phase 3 trials included Federation Francophone de Cancerologie Digestive Trial 9002 and the European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia trial. Both trials had to close prematurely because of slow accrual, but both trials showed a trend favouring adjuvant chemotherapy (chemotherapy administered after surgery). After complete resection of colorectal liver or lung metastases, patients were randomly assigned to chemotherapy. Adjuvant chemotherapy was independently associated with both progression free survival, and overall survival. Dr. Mitry's team concludes: This pooled analysis shows a marginal statistical significance in favor of adjuvant chemotherapy with a 5FU bolus-based regimen after complete resection of crc metastases.

***Mitry, E., et al., Adjuvant Chemotherapy After Resection of Colorectal Cancer Metastases. J Clinical Oncology 2008: 26(30): 4906-11***

**12. Preoperative Iron Supplementation and Intraoperative Transfusion During Colorectal Cancer Surgery** (Oct.31/08)

This study investigated whether giving an iron preparation to anemic patients before colorectal cancer surgery improves their anemia and reduces the need for intraoperative blood transfusion. Among 569 patients who underwent colorectal cancer surgery between 1998 and 2003, 32 anemic patients were studied who received iron supplementation for at least 2 weeks preoperatively (group A) and 84 anemic patients who did not (group B). Anemia was defined as a low Hb level at first presentation. Hb levels were similar at first presentation between the 2 groups but significantly different immediately before surgery. There were no significant differences in intraoperative blood loss between the groups, but significantly fewer patients in group A needed an intraoperative blood transfusion. Researchers concluded that iron supplementation for at least 2 weeks before colorectal cancer surgery increases Hb values in anemic patients and reduces the need for intraoperative transfusion.

***Okuyama, M., et al., Preoperative iron supplementation and intraoperative transfusion during colorectal cancer surgery. Surg Today. 205; 35(1):36-40***

## RADIATION

### 13. Diagnostic Value of FDG-PET in Recurrent Colorectal Carcinoma – A Meta-Analysis (Oct. 18/08)

The purposes of this study were to evaluate the diagnostic value of Positron Emission Tomography (PET) using fluor-18-deoxyglucose (FDG) in recurrent colorectal carcinoma with a meta analysis. All the published studies in English relating the diagnostic value of FDG-PET in the detection of recurrent colorectal cancer were collected. 27 studies were included in the meta-analysis. Pooled sensitivity and specificity for FDG-PET detecting distant metastasis or whole body involvement in recurrent CRC were 0.91 and 0.83. Pooled sensitivity and specificity for FDG-PET detecting liver metastasis were 0.97 and 0.98. Pooled sensitivity and specificity for pelvic metastasis for local regional recurrence were 0.94 and 0.94. Researchers concluded that FDG-PET is valuable for the assessment of recurrent colorectal carcinoma.

***Zhang, C et al., Diagnostic value of PDG-PET in recurrent colorectal carcinoma: A meta-analysis. International J of Cancer. Published online. Ijc23926. October 18, 2008***

## OTHER

### 14. BRAF: Another Gene Found Linked to Lack of Erbitux/Vectibix Response (Oct. 27/08)

Another mutated gene has been discovered that appears to cause resistance to treatment with the EGFR inhibitors erbitux and vectibix. Only a fraction of patients who receive erbitux or vectibix respond to it. There is now convincing evidence that the 30-40% of crc patients whose tumours have mutated Kras genes don't benefit, but what about others who have normal or wild-type Kras and don't respond either? Researchers in Italy have found that about 12% of wild type patients have a mutation in their tumour's BRAF gene, and these patients showed no response to erbitux or vectibix. Testing 113 crc tumours from patients who had been treated with either erbitux or vectibix, they found 30% had a Kras mutation. Going further, they tested the remaining 79 tumours for a mutation in BRAF. Patients with mutated BRAF showed no response to the EFGR inhibiting drugs. None had tumours shrink, and they had a shorter time until their cancer got worse and shorter survival. All of the patients who did respond to erbitux or vectibix had normal or wild type BRAF. In a laboratory experiment, cells that contained mutated BRAF had a dramatically reduced response to erbitux and vectibix, but when they were also treated with the BRAF inhibitor **sorafenib** (nexavar), the cells died. Lead researcher comments: These findings suggest that combination therapy that simultaneously blocks EGFR and BRAF in patients with BRAF-mutated tumours may be a useful approach to increase the number of patients who could benefit from anti-EGFR therapy, but that remains to be assessed in a clinical trial. The lead researcher went on to say that in the cohort, 52% of non responsive patients did not have mutations in either gene. This means further molecular markers are needed to better define patients who are unlikely to benefit from EGFR targeted treatment.

***Di Nicolantonio, F, et al., Abstract #247: BRAF Mutations in Colorectal Cancer Cause Resistance To Anti-EGFR Therapy, Study Finds. ECCO-the European Cancer Organization. EORTC-NCI-AACR Symposium.***

### 15. NCCN Updates Guidelines to Include KRAS Testing (Oct. 31/08)

The National Comprehensive Cancer Network (NCCN) has updated their Clinical Practice Guidelines in Oncology for Colon cancer to include testing tumours from patients with metastatic colon cancer for the Kras gene. The guidelines also now say that erbitux and vectibix should only be given to patients whose tumours have normal (wild type) Kras. Version 3-2008 includes the following changes:

- **Updates:** "The Guidelines were updated to version 3-2008 to represent the addition of Kras gene testing in the workup of all patients with stage IV disease. Erbitux and vectibix are only indicated for patients with tumours that express the wild type Kras gene."
- **COL-5:** Workup for suspected or proven metastatic adenocarcinoma from the large bowel includes "Determination of tumor Kras gene status."
- **COL-9 and COL-10:** Recurrence with documented metachronous metastases now includes the note"*Determination of tumour Kras gene status."

- **COL-10 (1 of 6)**: Now has "(Kras wild type gene only)" after every mention of erbitux or vectibix.

Similar changes have been made for rectal cancer in the guidelines. The NCCN Clinical Practice Guidelines in Oncology are the recognized standard for cancer care. Multidisciplinary panels of experts continuously update the guidelines to reflect new evidence. Panels address cancer prevention, detection, workup and diagnosis, treatment and supportive care.
Patients who have been diagnosed with stage IV colorectal cancer or recurrent colorectal cancer should talk to their doctors about Kras testing. **The NCCN Guidelines now call for that testing to be part of the initial workup before deciding on a treatment plan.**

***www.C3:Research&Treatment.com***

## NUTRITION

### 16. Calcium, Dairy Foods, Vitamin D, and Colorectal Cancer Risk: The Fukuoka Colorectal Cancer Study (Oct. 18/08)

Evidence supporting a protective role of calcium and vitamin D in colorectal cancer has been accumulating in Western populations, but it is limited in Asian populations whose intake of calcium is relatively low. The association of intakes of these nutrients was investigated with colorectal cancer risk in the Japanese. Higher levels of dietary vitamin D were significantly associated with decreased risk of colorectal cancer among those who had fewer chances of sunlight exposure at work or in leisure. A decreased risk of colorectal cancer associated with high calcium intake was observed among those who had higher levels of vitamin D intake or among those who had a greater chance of daily sunlight exposure, but not among those with medium or lower intake of vitamin D or among those with potentially decreased sunlight exposure. The results add to support for a joint action of calcium and vitamin D in the prevention of colorectal carcinogenesis.

***Mizoue, T, et al., Calcium, Dairy Foods, Vitamin D and Colorectal Cancer Risk: The Fukuoka Colorectal Study. Cancer Epidemiology, Biomarkers & Prevention. 2008; 17(10):2800-7***

### 17. No Connections Between Acrylamide and GI Cancers (Oct. 31/08)

Acrylamide is produced when carbohydrate-rich foods are cooked at high temperatures. Foods like French fries, potato chips, cakes, and even coffee contain high levels of acrylamide. It has been classified as a probable carcinogen based on animal studies where cancer resulted from very high doses. However, human studies have not always produced clear answers. After a 13 year study, epidemiologists in the Netherlands found no increase in the number of colorectal or other gastrointestinal cancers in those people who ate foods with high amounts of acrylamide. However, there appeared to be a connection with the amount of acrylamide rich foods eaten in some subgroups with colorectal cancer, including the obese, the less physically active, and older people. Despite the good news about acrylamide and colorectal cancer, people shouldn't feel safe eating foods that are rich in the chemical. Other than coffee, which has consistently shown no connection with cancer, most foods that contain acrylamide also are high in fat and calories and contribute to obesity. And obesity does increase colorectal cancer risk.

***Hogervorst et al., The Journal of Nutrition, Vol 138, Issue 12, November 2008.***

### 18. Surgeons Discover That Vitamin C and Other Antioxidants Reduce Infections, Pulmonary Failure, And Abdominal Wall Complications in Trauma Patients (Oct. 18/08)

In a study presented at the 2008 Clinical Congress of the American College of Surgeons, Bryan A. Cotton reported that "Implementation of high dose antioxidant protocol (vitamins C, E and selenium) resulted in a reduction of pulmonary complications, in general as well as infectious complications, including central line and catheter related infections." Dr. Cotton, who is assistant professor of surgery at Vanderbilt University Medical center, Nashville, TN, also observed a remarkable decrease in abdominal wall complications including abdominal compartment syndrome and surgical site infections. He and his colleagues demonstrated that high dose antioxidant protocol resulted in a stunning 28% reduction in mortality in acutely injured patients, as well as reducing the patient's length of stay in both the hospital and intensive care unit. They learned that antioxidants work by addressing the overwhelming oxidative stress that is created. He explained that any time a patient has an acute injury, an operation, or some kind of infection,

it places a huge stress on the body. This stress can result in injured oxygen molecules called free radicals being released in the body. These molecules roam around, causing considerable damage at the cellular level. This damage is called oxidative stress. Dr. Cotton said that past research by some renowned scientists in this field has shown a depletion in the store of antioxidants in critically stressed, critically injured patients. Essentially, it appears that antioxidants work as a team in mopping up some of the oxidative stress waste byproducts, reducing the stressors that cause harm. Antioxidants are like an army of molecular warriors that rush to the site of an injury to fight infection. In the course of doing battle on the front lines, however, most troops are lost early on. When infectious insurgents rise up later on, patients are highly vulnerable to infections. Depletion of antioxidants is one of the mechanisms that explains why we are vulnerable. Antioxidant therapy replenishes those troops to help keep us safe.

***www.medicalnewstoday.com***