The following colorectal cancer research update extends from January 18th, 2014 – March 14th, 2014 inclusive and is intended for informational purposes only.

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**DRUGS / SYSTEMIC THERAPIES**
1. 2014 GI ASCO Summaries (Jan. 16/14)

*Oral Drug is as Effective as Infusional Drug for Rectal Cancer when Combined with Radiation therapy Before Surgery.* According to this study, patients with stage II or stage III rectal cancer who received radiation therapy and chemotherapy with either capecitabine, a pill taken by mouth, or 5 FU, a drug given by infusion, before surgery had similar results. The study also showed that adding oxaliplatin (Eloxatin) to either treatment did not provide any additional benefits. ASCO GI, Abstract 390

*Beyond KRAS: Testing Tumors for Other Genetic Mutations Helps Personalize Treatment for Metastatic Colorectal Cancer.* Currently doctors routinely test metastatic colorectal cancer tumours for specific genetic mutations in the KRAS gene before recommending treatment with panitumumab (Vectibix) or other similar drugs. The results of this study show that other changes in the RAS family of genes, which includes KRAS, occur in about 18% of patients and also affect how well panitumumab works. ASCO GI, Abstract #LBA387

*Phase III GCR-3 Trial* for pre-operative (neoadjuvant) treatment of rectal cancer tipped the balance in favour of induction chemotherapy followed by chemoradiotherapy and then surgery vs. the standard approach of chemoradiotherapy followed by surgery and then adjuvant radiotherapy in patients with
locally advanced rectal cancer. Locoregional and distant recurrence, pathologic CR rates and overall survival were similar between the two approaches out to five years. Although a large Phase III randomized trial is needed to definitely find the best approach this trial showed less acute toxicity and better compliance to chemotherapy with the indication approach vs the standard approach. ASCO GI Abstract 383.

**Phase III Cairo 3 Trial** provided guidance on how big a treatment holiday to give patients followed by induction therapy. Maintenance treatment with Xeloda and Avastin after 6 cycles of CAPOX-B (Xeloda, Oxaliplatin, Avastin) significantly prolonged time to disease progression. There was an overall survival benefit for maintenance treatment in patients with synchronous disease who had a resection of the primary tumour and in patients with a complete or partial response on induction treatment. Koopman et al ASCO GI 2014 LBA

http://www.cancer.net/research-and-advocacy/research-summaries?field_page_topic_tid_2=468&field_page_topic_tid_268&date_filter=%5D%5D&year%5D=2014&Apply

2. **Aspirin Did Not Extend Survival in PIK3CA-Mutant Colorectal Cancer** (Jan.30/14)

Regular aspirin use did not improve outcomes among patients with colorectal cancers with mutations in the PIK3CA gene, suggest new data from the largest study yet of aspirin use in this patient population. Regular aspirin use was reported by 26% of the 185 patients studied, researchers reported at the annual Gastrointestinal Cancers Symposium sponsored by the American Society of Clinical Oncology. Users and nonusers were statistically indistinguishable with respect to a variety of recurrence- and survival-related outcomes. In this new study, the investigators performed targeted exome sequencing of tumors from patients with stage I to IV colorectal cancer treated at the Moffitt Cancer Center and Royal Melbourne Hospital to identify the cohort with PIK3CA mutations. The primary colorectal cancer tumor was right sided in 107 patients, left sided in 77 patients, and of unknown location in 1 patient. With a median follow-up of 46 months, aspirin users and nonusers had statistically indistinguishable overall survival. There was no benefit in terms of recurrence-free survival among patients with stage II and III disease.


3. **FOLFIRI Plus Panitumumab (Vectibix) Effective in mCRC** (Jan.30/14)

FOLFIRI chemotherapy plus panitumumab appears safe and effective for the second-line treatment of patients with KRAS wild-type metastatic colorectal cancer, according to long-term study results. Evaluated data from 1,186 patients who had received one prior treatment for metastatic colorectal cancer. Half the patients received 6 mg/kg panitumumab (Vectibix, Amgen) plus FOLFIRI every 2 weeks, and the other half received FOLFIRI alone. Patients in the panitumumab arm with KRAS wild-type tumors demonstrated significantly improved median PFS compared with patients in the FOLFIRI arm (6.7 months vs. 4.9 months). Researchers also observed a trend toward improved median OS in patients assigned panitumumab (14.5 months vs. 12.5 months). Thirty-six percent of patients assigned panitumumab responded to treatment compared with 10% of patients assigned FOLFIRI alone. Toxicities associated with treatment were comparable to those observed with anti-epidermal growth factor receptor therapy, researchers said. “These data confirm the primary efficacy and safety findings of this trial and support panitumumab-FOLFIRI as a second-line treatment of wild-type KRAS metastatic colorectal cancer,” the researchers wrote.


4. **Maintenance Chemo Delays Progression in Metastatic CRC** (Jan.30/14)

Maintenance treatment with capecitabine (Xeloda) and bevacizumab (Avastin) significantly delayed disease progression, compared with observation, in patients with metastatic colorectal cancer. There was also a trend toward improved overall survival, although this did not reach statistical significance, according to final results from the CAIRO3 trial, which were presented at the 2014 Gastrointestinal Cancers Symposium. Specifically, the study demonstrated that providing maintenance treatment with capecitabine plus bevacizumab after induction therapy with bevacizumab, capecitabine, oxaliplatin, and bevacizumab (CAPOX-B) significantly prolonged time to disease progression. It also prolonged the time from randomization to progression after the reintroduction of CAPOX-B.


5. **Avastin Efficacy in mCRC May Be Dependent on Primary Tumor Resection** (Mar. 1/14)

Avastin plus 5FU-based chemo is standard treatment for first-line and second-line metastatic colorectal cancer (mCRC). However, to date, there is no current biomarker predictive for the benefit of bevacizumab (avastin) use for these patients. Preclinical data suggest that the presence of the primary tumour could
be involved in less efficient antitumour activity of antiangiogenic agents (such as avastin), but no clinical data currently support this hypothesis. In this study, researchers performed a retrospective analysis of factors associated with overall survival (OS) in a study cohort of 409 mCRC patients. Analyses were used to assess the influence of primary tumour resection and avastin use on OS. They evaluated associations linking avastin use and OS among patients who previously underwent or did not undergo primary tumour resection. Results were externally validated in a second independent cohort of 328 mCRC patients. In the study cohort, avastin use and resection of the primary tumour were associated with improved OS. However, subgroup analyses indicate that avastin did not influence survival of patients bearing a primary colorectal tumour. By contract, the survival benefit of avastin was restricted to patients who previously underwent primary tumour resection. Similar results were observed in the validation cohort. The researchers concluded that the addition of avastin to chemotherapy is associated with improvement of OS only in patients with primary tumour resection. The data support the rationale to validate prospectively the influence of primary tumour resection on avastin antitumour effect in synchronous mCRC.


6. Avastin is Safe to Use in Patients Over 70 (Mar.7/14)

Bevacizumab (Avastin) improves survival when added to chemotherapy in metastatic colorectal cancer (mCRC). In this study, researchers assessed the safety and efficacy of avastin in mCRC patients > 70 years old (YO) vs. those < 70 (YO). M CRC patients treated from 2005-2012 who received chemotherapy plus avastin were included. The primary end point was safety; secondary objectives were progression-free survival (PFS) – the amount of time it took before the patient’s cancer got worse – and overall survival (OS). Data was collected retrospectively. Three hundred eight patients with 20.5 month median follow up were included. The researchers noted that OS and PFS were similar in younger and older patients. They concluded that in their patient population, avastin is safe and effective in older as well as younger patients.


**SURGICAL THERAPIES**

7. Intensive Monitoring Ups Surgical Treatment of CRC Recurrence (Jan.30/14)

For patients who have undergone curative surgery for primary colorectal cancer, intensive monitoring is associated with increased surgical treatment of recurrence compared with minimum follow-up, but does not reduce the number of deaths. Researchers examined the effect of scheduled blood measurement of carcinoembryonic antigen (CEA) and computed tomography (CT) as follow-up for 1,202 eligible patients who underwent curative surgery for primary colorectal cancer. Participants were randomized to CEA only (300 patients), CT only (299 patients), CEA+CT (302 patients), or minimal follow-up (follow-up only in case of symptom occurrence; 301 patients). After a mean of 4.4 years of observation, the researchers detected recurrence in 199 participants (16.6%) overall. Surgical treatment of recurrence with curative intent was undertaken in 5.9% of the cohort overall, with rates of 2.3% in the minimum follow-up group, 6.7% in the CEA group, 8% in the CT group, and 6.6% in the CEA+CT group. There was no significant difference in the number of deaths between the combined intensive monitoring groups (CEA, CT, CEA+CT, 18.2%) and the minimum follow-up group (15.9%; difference, 2.3%; P = 0.27). Among patients who had undergone curative surgery for primary colorectal cancer, intensive imaging or CEA screening each provided an increased rate of surgical treatment of recurrence with curative intent compared with minimal follow-up; there was no advantage in combining CEA and CT,” the authors write.

Primrose, John N., et al., Effect of 3 to 5 Years of scheduled CEA and CT follow up to detect recurrence of colorectal cancer – the FACS randomized clinical trial. JAMA. 2014; 311(3): 263-270.

**SCREENING**

8. Repeat Colonoscopy Examined In Patients With Polyps Referred For Surgery Without Biopsy-Proven Cancer (Feb.1/14)

A new study reports that in the absence of biopsy-proven invasive cancer, a second colonoscopy done at an expert center may be appropriate to reevaluate patients referred for surgical resection. In the study, 71 percent of the lesions referred for surgery were noncancerous polyps (growths in the colon) and were treatable endoscopically. In 26 percent of cases, previous removal was attempted by the referring physician but was unsuccessful. Endoscopic treatment was performed as an outpatient procedure without serious adverse events, and hospital admission for overnight observation was necessary in only six percent of patients. Endoscopic resection (removal) of colorectal precancerous polyps is an integral part of colorectal cancer screening and prevention programs. Limitations of endoscopic polyp resection include adverse events such as bleeding and perforation, significant local recurrence rates, and technical
inability to resect some lesions. Large flat and sessile lesions can be particularly difficult to resect endoscopically; these lesions are often treated surgically. However, surgical resection entails significant morbidity and is associated with a low but significant risk of serious adverse events even when performed at expert centers. Recent studies have demonstrated that endoscopic mucosal resection (EMR) of large sessile and flat lesions is technically feasible and can be performed with a low risk of adverse outcomes by gastroenterologists specifically trained in this technique. EMR is a technique in which a needle is passed through the endoscope and a liquid solution is injected under the area of interest, in effect "lifting" the abnormal tissue and separating it from the deeper intestinal layers. The abnormal lesion is then removed ("resected") with a snare; the tissue is subsequently retrieved and sent to a pathologist for evaluation. This was a single center, retrospective study at Stanford University, Palo Alto, Calif. The study objective was to analyze the results of routine repeat colonoscopy in patients referred for surgical resection of colon polyps without biopsy-proven cancer. Electronic records of all patients referred to a colorectal surgery practice and an interventional colonoscopy clinic between December 2010 and March 2013 were reviewed. During this period, standard practice was to schedule all patients referred for colorectal surgery of colon polyps without biopsy-confirmed cancer for a repeat colonoscopy because the institution's colorectal surgery team believed strongly that surgical treatment of endoscopically resectable adenomas (precancerous polyps) is unnecessarily aggressive. Colonoscopy was performed by an endoscopist with extensive experience in EMR, having performed more than 1,000 EMR procedures in the past 10 years. At the repeat colonoscopy, EMR was attempted when the lesion did not have definite features of deeply invasive cancer (converging folds, firm consistency with a surface pit pattern suggestive of invasion, non-lifting not because of previous endoscopic interventions). All patients were evaluated for procedural adverse events with a phone call or clinic visit at least 10 days after the procedure. There were 38 lesions in 36 patients; 71% of the lesions referred for surgery were noncancerous polyps and were treatable endoscopically. In 26% of cases, previous removal was attempted by the referring physician but was unsuccessful. Endoscopic treatment was performed as an outpatient procedure without serious adverse events, and hospital admission for overnight observation was necessary in only six percent of patients. The researchers noted that the major limitation of endoscopic treatment was a high local recurrence rate of 50%, although in keeping with results from other studies, recurrences were successfully treated on follow-up colonoscopy. The favorable results in this study suggest that most lesions currently referred for surgery are amenable to endoscopic treatment. According to the researchers, the decision of whether to refer a patient to an interventional colonoscopy center versus surgical resection may depend on multiple factors, including whether the endoscopist who performed the initial colonoscopy believes that reasonable endoscopic methods to remove the polyp have been exhausted. However, endoscopist inexperience or an unwillingness to tackle technically challenging lesions because of time constraints or perceived risk may also contribute to the decision.


9. Pill Camera to Screen for Colon Cancer Approved in the U.S. (Feb. 4/14)

An ingestible pill camera to help screen for polyps and early signs of colon cancer has been approved for use in the U.S. Given Imaging Ltd.'s PillCam Colon was originally touted as an alternative to traditional colonoscopy procedures, but the company's research found images taken by the mini-camera aren't as clear as those taken during the more invasive procedure. The U.S. Food and Drug Administration approved the device for patients who have experienced an incomplete colonoscopy. The company estimates 750,000 U.S. patients are not able to complete the procedure each year, due to anatomy issues, previous surgery or various colon diseases.

PillCam Colon is designed to transmit images for about 10 hours. (Courtesy Given Imaging)

The newly approved capsule has two miniature colour video cameras, a battery and light source. Once the patient ingests the capsule, it is designed to transmit images for about 10 hours. Data is transferred
from the device to a computer to be compiled. A doctor later reviews and reports the results. Risks of the procedure include capsule retention, aspiration and skin irritation. Before the capsule is excreted, patients should not be near powerful electromagnetic fields, such as those created by an MRI device. The PillCam Colon is commercially available in Canada, Japan, Europe, Latin America, Australia and parts of Asia and Africa. Given Imaging also develops technology to visualize, diagnose and monitor the digestive system, including with its PillCam, a swallowed capsule endoscope.


**NUTRITION & HEALTHY LIFESTYLE**

10. **Study Shows High Fibre Diet Reduces Risk of Colon Problems**  (Jan.30/14)

Previous research has suggested that a diet rich in fibre may reduce the risk of colon inflammation and cancer. But new research suggests that niacin, also known as vitamin B3, may also help protect against these conditions. The research team, including co-author Dr. Vadivel Ganapathy of the Medical College of Georgia at Georgia Regents University, says their findings help explain why a diet high in fibre can reduce the risk of colon-related health conditions and suggests that niacin - supplements already used to regulate cholesterol - can keep the colon healthy for people who have low-fibre diets. To reach their findings the investigators conducted a mouse study. From this, they discovered that mice that were missing a receptor called Gpr109a were more likely to develop inflammation and cancer of the colon. But on giving niacin to mice who had no healthy colonic bacteria - because it had been destroyed by antibiotics - the researchers found the vitamin pushed immune cells into an anti-inflammatory mode. To explain the mechanisms of the study findings, co-author Dr. Nagendra Singh, of the Cancer Center at Georgia Regents University, begins by noting that good bacteria in the colon flourish on fibre. The digestion of fibre leads to the production of butyrate - a short-chain fatty acid. Previous research by Dr. Singh revealed that butyrate activates the Gpr109a receptor. But he says that this only seems to happen in the colon and that a high-fibre diet significantly increases butyrate levels in this area. Butyrate triggers the Gpr109a receptor in immune cells - macrophages and dendritic cells - in the colon. Dr. Singh explains that these immune cells produce anti-inflammatory molecules and transmit signals to T cells - white blood cells that play a major role in the immune system - which also causes the T cells to produce anti-inflammatory molecules. Additionally, epithelial cells that line the colon are triggered by butyrate to produce cytokines - soluble proteins that help wound healing. Dr. Singh notes that this process is crucial when it comes to healing intestinal inflammation that is found in medical conditions such as Crohn's disease and ulcerative colitis. Dr. Ganapathy says that in order for a person's colon to be protected, they need to have the Gpr109a receptor alongside a high intake of fibre to produce butyrate, which activates the receptor. But Dr. Singh notes that their findings suggest high doses of niacin may have a similar effect, which is good news for individuals who have a diet low in fibre. "We think mega-doses of niacin may be useful in the treatment and/or prevention of ulcerative colitis, Crohn's disease, and colorectal cancer as well as familial adenomatous polyposis, or FAP, a genetic condition that causes polyps to develop throughout the gastrointestinal tract." The researchers say they are looking to carry out clinical trials to determine whether niacin supplements may help reduce the risk of intestinal inflammation and colon cancer in patients already using them for cardiovascular health.

http://www.medicalnewstoday.com/articles/271406.php

11. **Nutrition & Exercise Guidelines for Cancer Survivors**  (Feb.6/14)

New research finds many cancer survivors are obese and not physically active, which could make it harder to keep their cancer under control. Researchers in Canada analyzed data from more than 114,000 adults. They found fewer than 22% of Canadian cancer survivors were physically active - the lowest rates were in men and women who had survived colorectal cancer and women who survived melanoma and breast cancer. Results also show nearly one in five cancer survivors was obese, and one in three was overweight. Fewer than 22% of the cancer survivors were physically active, over 18% were obese (body mass index [BMI] ≥ 30 kg/m2), and another 34% were overweight (BMI 25-30 kg/m2). In the light of the above findings, Women Fitness (WF) team of health experts bring you information related to help cancer survivors and their families make informed choices related to nutrition and physical activity. For survivors at risk for unintentional weight loss, including those who are already malnourished or those who receive directed treatment to the gastrointestinal tract, it is crucial to maintain energy balance or prevent weight loss. Most cancer therapies, including surgery, radiation, and chemotherapy, can significantly affect nutritional needs, eating habits, and digestion. Individualized nutritional therapies may include:

- For survivors with decreased appetite, consuming smaller, more frequent meals without liquids can help increase food intake.
- For survivors who cannot meet nutritional requirements through food alone, fortified and commercially prepared or homemade nutrient-dense beverages or foods may improve the energy and nutrient intake.

http://www.medicalnewstoday.com/articles/271406.php
12. Grape Seed Shows Promise in the Fight Against Colorectal Cancer  
(Feb.18/14)

University of Adelaide research has shown for the first time that grape seed can aid the effectiveness of chemotherapy in killing colon cancer cells as well as reducing the chemotherapy’s side effects. Published in the prestigious journal PLOS ONE, the researchers say that combining grape seed extracts with chemotherapy has potential as a new approach for bowel cancer treatment - to both reduce chemotherapy on colon cancer cells in culture by 26%.

"Our experimental studies have shown that grape seed extract reduced chemotherapy-induced inflammation and damage and helped protect healthy cells in the gastrointestinal tract," says Dr Cheah. "While this effect is very promising, we were initially concerned that grape seed could reduce the ability of chemotherapy to kill cancer cells, but was also more potent than the chemotherapy we tested at one concentration." Co-author and project leader Professor Gordon Howarth says: "Grape seed is showing great potential as an anti-inflammatory treatment for a range of bowel diseases and now as a possible anti-cancer treatment. These first anti-cancer results are from cell culture and the next step will be to investigate more widely." Fellow co-author and joint leader researcher Dr Sue Bastian, says: "These findings could be a boost to the wine grape industry as its value adds to what is essentially a by-product of the winemaking process."


13. Lifestyle Interventions Can Improve Health Outcomes In Patients At Risk of Colorectal Cancer  
(Mar.14/14)

Direct interventions in diet and physical activity among patients at risk of colorectal cancer can lead to significantly improved weight reduction, helping tackle a major risk factor for the disease, a new study led...
by the University of Dundee has shown. The BeWEL study led by the University of Dundee looked at whether interventions to encourage patients at increased risk for colorectal cancer to make a sustained effort to reduce weight and improve physical activity would have an impact on health measures. The researchers who carried out the new study said it showed that significant and sustained weight loss, improvements in blood pressure and blood glucose as well as changes in diet and physical activity could be achieved over a one-year period through an intervention consisting of regular meetings with lifestyle counselors and monthly phone calls. This intervention resulted in an average weight loss of 3.50kg in the intervention group, 2.7kg greater than patients who were only given a weight loss booklet only. The researchers say the findings show the importance of combining evidence-based cancer prevention messages with cancer screening programs to deliver the strongest benefits to patients. Results of the study have been published online by the British Medical Journal. ‘Weight management programs in secondary care are common in the context of diabetes but they do not feature in the cancer screening setting, despite the fact that obesity is a risk factor in colorectal and other cancers,’ said Annie Anderson, Professor of Public Health Nutrition at the University of Dundee and lead author of the research paper. ‘The potential for healthcare systems, including hospitals and clinic, to promote appropriate diet, physical activity and body weight is an area that is underdeveloped. The BeWEL study had a high response rate indicating that patients are interested in lifestyle change and over 90% of participants kept going in the trial for a one year period’.