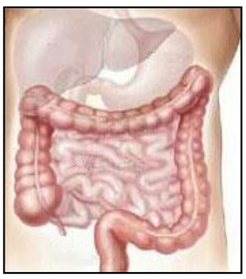
COLORECTAL CANCER RESEARCH UPDATES

Month Ending February 15, 2013



The following colorectal cancer research update extends from January 19th, 2013 – February 15th, 2013 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Avastin Plus Xeloda Helped Elderly Live Four Months Longer (Jan.21/13)

The phase III AVEX study is the first trial to prospectively evaluate the efficacy and safety of Avastin® (bevacizumab) specifically in elderly patients (≥70 years) with metastatic colorectal cancer (mCRC). The study met its primary endpoint of progression-free survival (PFS) – when Avastin was combined with Xeloda® (capecitabine) chemotherapy, people lived significantly longer without their disease getting worse compared to capecitabine alone. The trial is clinically important because the majority of people diagnosed with mCRC are elderly, but there is limited clinical data supporting the benefit of standard of care therapies in this population because they are under-represented in clinical trials. The AVEX study demonstrated that people aged 70 and older with metastatic colorectal cancer can derive progression-free survival benefit from Avastin plus capecitabine. The results are important and show that more can be done for these patients living with metastatic colorectal cancer."

Abstract 337. Cunningham D et al. Bevacizumab (Bev) in combination with capecitabine (Cape) for the first-line treatment of elderly patients with metastatic colorectal cancer (mCRC): Results of a randomized international phase III trial (AVEX). Saturday 26th January 2013, 2013 Gastrointestinal Cancers Symposium

2. Potential New Treatment for Some Types of Colon Cancer (Jan.21/13)

Researchers have identified a complex of proteins that promotes the growth of some types of colon and gastric (stomach) cancer, and shown that medications that block the function of this complex have the potential to be developed into a new treatment for these diseases. The complex of proteins, known as ***mTorc1*** (mammalian target of rapamycin complex 1), has previously been implicated in the development of some other cancers but this is the first time it has been shown to promote the growth of colon and gastric cancers that are associated with inflammation. Many types of colon and gastric cancer were associated with chronic inflammation. It has been previously shown that the immune system's inflammatory response can promote the growth of tumours. In the digestive system, persistent inflammatory conditions have been linked with tumour growth: patients who have stomach ulcers or gastritis (inflammation of the stomach lining) are more susceptible to gastric cancer, while inflammation of the colon, called colitis, is associated with an increased risk of developing colon cancer. The research team found that inflammation-associated gastric and colon cancers showed activation of mTorc1, an aggregate of proteins that signals inside cells to promote growth. Many cancer types depend on mTorc1 activity to grow, and there is considerable interest in the use of mTorc1 inhibitors to treat cancer. The growth of inflammation-associated colon and gastric cancers could be treated with mTorc1 inhibitors, maintains study author. "We were excited to discover that the growth of these cancers in laboratory models could be prevented by treatment with mTorc1 inhibitors that are already in clinical trials for other types of cancer," he said. "In the future, we hope that this finding might lead to better treatment options for colon and gastric cancers that are associated with inflammation. Since there are also other types of cancer that are associated with inflammation, we suspect that these could also be susceptible to treatment with mTorc1 inhibitors."

Thiem, Stefan et al., mTORC1 inhibition restricts inflammation-associated gastrointestinal tumorigenesis in mice. J Clin Invest. 2013;123(2):767–781. doi:10.1172/JCI65086.

3. FDA Approves New Use for Roche's Avastin in Colon Cancer Treatment (Jan.21/13)

The U.S. Food and Drug Administration approved the use of Roche's Avastin for patients whose colorectal cancer has worsened despite previous treatment with the drug. The new use will allow patients first treated with Avastin plus chemotherapy to be treated again with the biotechnology drug in combination with a different chemotherapy regimen. A pivotal clinical trial showed that such a treatment strategy improved survival. "The majority of people diagnosed with metastatic colorectal cancer receive Avastin plus chemotherapy as their initial treatment," Hal Barron, chief medical officer at Roche's Genentech unit, said in a statement. "These people now have the option to continue with Avastin plus a new chemotherapy after their cancer worsens, which may help them live longer than changing to the new chemotherapy alone." Avastin, also known as bevacizumab, is an antibody that blocks vascular endothelial growth factor, or VEGF, a protein tumours need to grow nutrient-providing blood vessels.

http://news.yahoo.com/fda-approves-roches-avastin-colon-cancer-treatment-232906822--finance.html

4. Phase III Trial of Neulasta Very Promising (Jan.26/13)

Amgen announced today results from Pegfilgrastim and Anti-VEGF Evaluation Study (PAVES), a Phase 3 trial which evaluated Neulasta® (pegfilgrastim) in 845 patients receiving FOLFOX or FOLFIRI and bevacizumab for the first-line treatment of locally-advanced or metastatic colorectal cancer. FOLFOX and FOLFIRI are two of the most commonly used chemotherapy regimens for colorectal cancer. The study met its primary endpoint, with **Neulasta** significantly reducing the incidence of febrile neutropenia. Febrile neutropenia is a low white blood cell count accompanied by a fever. In the study, the incidence of grade 3 or 4 febrile neutropenia in patients receiving Neulasta across the first four cycles of chemotherapy was 2.4% compared to 5.7% in the placebo group. A similar incidence of grade 3 or higher adverse events was seen in both arms of the trial (28% placebo; 27% Neulasta). "This analysis showed that PAVES met its primary endpoint, with Neulasta significantly reducing the incidence of febrile neutropenia in patients with colorectal cancer," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "In addition to providing new data on Neulasta, we believe PAVES will provide valuable information to the oncology community on commonly-used chemotherapy regimens." Follow-up results of PAVES looking at additional endpoints, including mature data on overall survival, overall response rate, time to progression and progression-free survival, will be presented at a future date.

http://wwwext.amgen.com/media/media_pr_detail.jsp?releaseID=1778221

5. What is CEA (Carcinoembryonic Antigen)? (Jan.23/13)

One of the easiest ways to track certain cancers is through a simple blood test called a tumor marker test. The presence of certain cancers can be confirmed by the specific proteins being shed into the blood. These proteins *are the tumor markers*. Carcinoembryonic antigen (CEA) is the protein linked to colorectal cancers. Every one of us has a little CEA in our blood. The presence of this protein in the blood alone does **not** mean you have colon cancer. The CEA blood test **cannot** be used to diagnose cancer, *only to track cancer after a diagnosis*. Your doctor probably checked your blood for this antigen when you were diagnosed. If elevated amounts of CEA were found in your blood at that time, your doctor can use it to monitor your response to treatment and watch for recurrence with future blood tests. False positive results -- results that are very high but do not indicate cancer growth -- can occur with CEA. One the main causes for inaccurately high readings is chemotherapy treatment. During chemotherapy, the drugs are supposed to target and kill the cancer cells. As these cells die, CEA is released into the bloodstream and can stay elevated for a few weeks following treatment. CEA levels may be elevated and signify a recurrence of cancer or a spread (metastasis) to another site in your body. The levels are considered elevated when they show above 4 nanograms per milliliter (ng/ml).

http://coloncancer.about.com/od/screening/a/Carcinoembryonic-Antigen-Cea.htm

6. Promising Data Regarding Reolysin (Jan.24/13)

Oncolytics Biotech presented promising phase 1 data for its cancer drug **Reolysin** at the ASCO Gastrointestinal Cancers Symposium in January. Reolysin was tested in combination with a cocktail of chemotherapy drugs called FOLFIRI in patients with metastatic colorectal cancer. The drugs produced a progression-free survival -- the amount of time it takes for the disease to progress or the patient to die -- of 7.4 months. Without a control group to compare it to and taking into account that there were only 21 patients in the study, it's difficult to interpret the PFS data. There was one partial response and nine patients who had stable disease among the 18 patients who were evaluable for response. Most impressive was that some of the patients that responded had previously progressed on irinotecan, the IRI in FOLFIRI. Oncolytics, in collaboration with the National Cancer Institute of Canada, has already started a phase 2 trial testing Reolysin in combination with **Roche**'s Avastin and a chemotherapy cocktail called FOLFOX compared to a control group that will get just FOLFOX and Avastin. Reolysin is being tested in multiple other clinical trials in different tumor types. The most advanced study is in a phase 3 trial in head and neck cancers

http://www.samachar.com/oncolytics-presents-promising-phase-1-data-in-colorectal-cancer-nb3dKvbfbia.html

7. New Drug Protects Against Side Effects of Chemo (Jan.23/13)

A drug developed in Sweden protects against the side effects of cancer treatments while strengthening the effects on the tumour. An international drug evaluation is now starting up on a larger group of patients. The results of the studies with the compound, known as **calmangafodipir**, were just published. The research was initiated on a substance called mangafodipir, which was used as a contrast media in magnetic resonance scans. But pharmacologists discovered that it also protected healthy cells in connection with cancer treatments. "We found that the substance could affect the formation of oxygen radicals, which are a cause of side effects in chemotherapy," says the lead author. For example, the number of white blood cells decreases drastically in almost all the patients, which opens the door to infections that could even be fatal. The researchers began with cell tests, and then went on to mice infected with cancer cells. The mice were treated with chemotherapy and were administered mangafodipir at the same time. Tumour formation decreased while white blood cells were protected. One problem was that a large portion of the manganese in the substance was released; as a consequence, the positive effect subsided. The free manganese can also be poisonous and cause brain damage. "We remade the substance and replaced a lot of the manganese with calcium. This yielded a more stable complex, which turned out to be even better at protecting cells, thereby increasing the anti-cancer effect," says Professor Andersson. The effect of mangafodipir was confirmed in a smaller study on patients with colon cancer, which was published in *Translational Oncology* in February 2012.

Karlsson, Jan Olof G., et al., Superior Therapeutic Index of Calmangafodipir in Comparison to Mangafodipir as a Chemotherapy Adjunct*. Translational Oncology, *2012; 5: 492-502 DOI: 10.1593/tlo.12238

SURGICAL THERAPIES

8. Administering Avastin Before Liver Surgery is Safe (Feb.7/13)

This study assessed the impact of preoperative neoadjuvant bevacizumab (Bev), also known as Avastin, on the outcome of patients undergoing resection for colorectal liver metastases (CLM). Thirteen nonrandomized studies with a total of 1431 participants were suitable for the review. There was no difference in overall morbidity and severe complications between the Bev treated group and the no Bev treated group (43.3% vs. 36.8%; 17.1% vs. 11.4%). Bev-related complications including wound and thromboembolic/bleeding events were also similar in the Bev treated group and no Bev treated group (14.4% vs. 8.1%; 4.1% vs. 3.8%, respectively). The incidence and severity of sinusoidal dilation (the dilation of the small blood vessels that supply blood and nutrients to the liver cells) were lower in patients treated with Bev than in patients treated without Bev (43.3% vs. 63.7%; 16.8% vs. 46.5%, respectively).

Authors concluded that Bev can be safely administered before hepatic resection in patients with CLM, and has a protective effect against hepatic injury in patients treated with oxaliplatin chemotherapy.

De-Bang Li, et al., Preoperative administration of bevacizumab is safe for pateitns with colorectal liver metastases. World J Gastroenterol 2013 February 7; 19(5): 761-768

RADIATION/INTERVENTIONAL RADIOLOGY

9. Radioactive Beads Help Colon Cancer Patients Live Longer (Jan.19/13)

Patients who received minimally invasive treatment with yttrium-90 (Y-90) radioactive beads (also referred to as microspheres and Theraspheres) to treat colorectal cancer that had spread to the liver lived almost a year longer compared to those who received the standard of care therapy. Researchers also determined that the Y-90 treatment was more successful in patients who hadn't been treated with bevacizumab (standard of care biologic therapy) for at least three months prior to the minimally invasive radioembolization therapy. "Patients with liver-dominant metastases from colorectal cancer should be offered radioembolization in addition to chemotherapy because it may offer a survival benefit compared with chemotherapy alone," said the lead author of the study. The treatment involves injecting Y-90 radioactive beads through a catheter into the arteries feeding the liver tumors. The beads lodge in the arteries and emit radiation to kill the tumors.

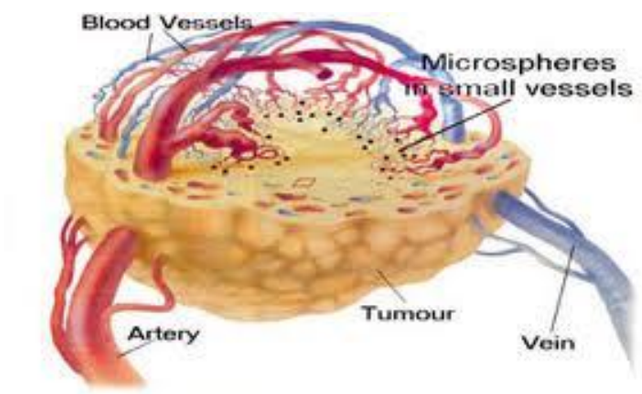


Image Source: ***http://www.mc.vanderbilt.edu/reporter/index.html?ID=2360***

The method allows high doses of radiation to be directed primarily to the tumors, rather than to healthy tissue. In the study, 39 patients underwent Y-90 radioembolization, 30 of whom had also received treatment with bevacizumab. Radioembolization patients who received treatment with bevacizumab within the previous three months had a median survival of 30.5 months after diagnosis with metastatic colorectal cancer but those who had either not received bevacizumab or had been treated more than three months previously had a median survival of 37.9 months, although the difference was not statistically significant. Taking into account all the study subjects, survival averaged about 11 to 12 months longer than historical survival estimates among patients who receive standard of care treatment with modern chemotherapy and biologics alone. Bevacizumab reduces arterial capacity. Patients who had received bevacizumab within three months of radioembolization were more likely to have therapy stopped early due to slow blood flow. This resulted in delivering less of the prescribed radiation to the tumors.

http://www.businesswire.com/news/home/20130119005001/en/Interventional-Treatment-Radioactive-Beads-Helps-Colon-Cancer

OTHER

10. Early & Missed Colorectal Cancers Common Among Older Patients with IBD (Jan.18/13

Older patients with inflammatory bowel disease (IBD) were at elevated risk for early or missed colorectal cancers following colonoscopy, according to recent results. Researchers evaluated data from 55,008 patients aged 67 years or older. All participants had been diagnosed with colorectal cancer (CRC) between 1998 and 2005, within 36 months of colonoscopy. The group included 304 patients with Crohn's Disease (CD) and 544 with Ulcerative Colitis (UC). CRC diagnosed between 6 and 36 months of colonoscopy was defined as early/missed CRC; when diagnosed within 6 months of the procedure, CRC was considered detected CRC. Researchers identified 3,589 early/missed CRCs, including 3,432 among those without IBD, 54 among patients with CD and 103 in those with UC. The rate of early/missed CRCs was 15.1% among patients with CD, 15.8% of those with UC and 5.8% of those without IBD. Investigators noted that early/missed CRCs were less likely to be located in the right colon in patients with IBD than in those without (54% of CRCs in those with CD; 52.1% in those with UC, vs. 68.4% in those without IBD). Results indicated increased risk for early/missed CRC in patients with either CD or UC compared with IBD-free patients. Other factors associated with increased early/missed CRC risk included female sex, family history of CRC, history of colon polyps and undergoing colonoscopy performed by a non-gastroenterologist. Investigators noted an inverse association between early/missed

CRC risk and inpatient colonoscopy. "In this population-based analysis … we found that the rate of early/missed CRCs among older IBD patients was three times as high as older non-IBD patients," the researchers wrote. "This finding provides additional evidence to support intensive surveillance colonoscopy for older IBD patients, as recommended by current guidelines."

Wang, Yize R, et al., Rate of Early/Missed Colorectal Cancers After Colonoscopy in Older Patients With or Without Inflammatory Bowel Disease in the United States. Am J Gastroenterol advance online publication 8 January 2013; doi: 10.1038/ajg.2012.429

11. Colorectal Cancer Prognosis and Response to Chemo Vary by Molecular Subtype (Jan.23/13)

Using a new classification system that categorizes colorectal cancers (CRC) by tumor gene expression patterns, researchers have determined that tumor prognosis and response to adjuvant chemotherapy in CRC vary according to molecular subtype. Researchers developed the molecular classification system based on gene expression data from 188 patients with CRC, and then validated the system in tumor samples from 543 patients with **stage II and III disease**. Subtypes were analyzed for correlation to clinical information, mutations in the kinome (protein kinases in the genome), known molecular marker status, and chemotherapy response. The analysis found that CRC consists of at least three major intrinsic **subtypes, A, B, and C**, based on three biological hallmarks of the tumor: epithelial-to-mesenchymal transition (a biologic change associated with more aggressive tumors), deficiency in mismatch repair genes (a tumor characteristic that leads to high rates of genetic alterations), and the rate of cell proliferation. These features are known to independently affect outcomes in patients with cancer. Of the samples analyzed,

- 21.5% belonged to subtype A,
- 62% to subtype B, and
- 16.5% to subtype C.

A 10-year follow-up found that patients with subtype C had the worst outcomes, showed no benefit from adjuvant chemotherapy, and had a mesenchymal gene expression phenotype. Patients with subtypes A and B had better outcomes, benefited from adjuvant chemotherapy, and had a more proliferative and epithelial phenotype. In addition, compared with subtype B, subtypes A and C had higher rates of mutation frequency in many genes, including those that play an important role in CRC development and growth, such as *KRAS*, *BRAF*, and PI3KCA. The classification system could be used to determine disease prognosis and individualized treatment plans. For instance, in stage II disease, clinical and pathological factors do not always accurately identify patients who face a high risk of relapse after surgery and might therefore benefit from additional therapy. Furthermore, currently available genomic classifiers such as Oncotype and ColoPrint are not linked to clear recommendations for postoperative chemotherapy. Finally, in patients with later-stage disease who have undergone treatment, currently available tests cannot help individualize therapy—the researchers' goal in developing the classification system. "There's no way to select treatment for individual patients. Currently, only *KRAS* has been established as a predictor of anti-*EGFR* treatment activity," said study co-author Josep Tabernero. "This study clearly shows that there are different subtypes in colorectal cancer with completely different biological and clinical characteristics," Tabernero said. "We hope that with continued research, we'll be able to develop new molecular tests based on this classification system, not only to identify patients needing more aggressive adjuvant treatment, but also to help us to predict which patients will respond to specific chemotherapy drugs and targeted agents, regardless of cancer stage." Researchers are currently validating the classification system in stage IV CRC. "I predict that in the next 2 or 3 years we and other research teams will have several gene expression signatures developed, informed by ours and other studies," Tabernero said.

Simon I, Roepman P, Schlicker A, et al. Association of colorectal cancer intrinsic subtypes with prognosis, chemotherapy response, deficient mismatch repair, and epithelial to mesenchymal transition (EMT). Presented at the 10th annual Gastrointestinal Cancers Symposium; January 24-26, 2013; San Francisco, CA. Abstract 333.

12. The Science Behind Metastasis (Jan.21/12)

The results of this study speak to the discovery of cells that herald the spreading (*metastasis*) of colon cancer. Scientists have found a definitive link between **stromal cell** activity and metastasis of colon cancer to other organs (lungs, brain, liver) within the body. If your doctor discovers increased stromal activity surrounding the colon cancer cells, there is an increased chance that the cancer is gearing up to spread. This sheds a whole new light on the risk of recurrence and may even alter how your doctor intends to treat the cancer. When colon cancer goes into remission - or is effectively "cured" many survivors agree on one remaining stressor - is my cancer going to come back? Watching every symptom and waiting on tenterhooks for recurrence is stressful. The hope is that this discovery can put many survivors' minds at rest in the near future.

Calon, Alexandre, et al., Dependency of colorectal cancer on a TGF-B-Driven program in stromal cells for metastasis initiation. Cancer Cell, Volume 22, Issue 5, 571-584, 13 November 2012

13. Blood Vessel Cells Coax Colorectal Cancer Cells To Become Stronger (Jan.31/13)

Blood vessels that supply oxygen and nutrients to tumors can also deliver something else -- a signal that strengthens nearby cancer cells, making them more resistant to chemotherapy, more likely to spread to other organs and more lethal. Working in human colorectal cancer cell lines and tumor samples, as well as mouse models, the researchers found that endothelial cells, which line the inside of blood vessels, can trigger changes in cancer cells without even coming into direct contact with them. This signaling by the endothelial cells causes colorectal cancer cells to take on the attributes of cancer stem cells, said senior author of the paper. "Cancer stem cells initiate and sustain tumor growth, promote metastasis and resistance to chemotherapy and have a variety of other attributes". "We've identified a new way that elements of a tumor's microenvironment, in this case endothelial cells, promote the conversion of malignant cells into cancer stem cells." The team found the blood vessel cells use a previously unknown method of activating the Notch molecular pathway in colorectal cancer cells to initiate that conversion. With much additional research, the team's findings could lead to more refined targeted therapies for metastatic colorectal cancer. Future studies will focus on other factors secreted by endothelial cells that promote cancer cell aggression. "It's clear that endothelial cells are more than just a conduit for blood delivery. In fact, in preliminary experiments, it appears that endothelial cells secrete more proteins than do cancer cells. This work, of course, requires validation."

Jia Lu, Jia, et al., Endothelial Cells Promote the Colorectal Cancer Stem Cell Phenotype through a Soluble Form of Jagged-1*. Cancer Cell*, 2013; DOI: 10.1016/j.ccr.2012.12.021

NUTRITION & HEALTHY LIFESTYLE

14. Physical Activity Cuts Mortality in Colorectal Cancer Survivors (Jan.23/13)

For patients with invasive, non-metastatic colorectal cancer, increased recreational physical activity is associated with reduced all-cause mortality, while prolonged sedentary time correlates with increased all-cause mortality. Researchers examined the correlation of pre-diagnosis and post-diagnosis recreational physical activity and sedentary leisure time with mortality among 2,293 adults diagnosed with invasive, non-metastatic colorectal cancer from a cohort of adults without colorectal cancer at baseline. During a maximum follow-up of 16.1 years after colorectal cancer diagnosis, the researchers found that 846 patients died—379 from colorectal cancer. Significantly lower all-cause mortality was seen for those who engaged in 8.75 or more metabolic equivalent (MET) hours per week of recreational activity versus less than 3.5 MET hours. Higher all-cause mortality was seen for those who spent six or more hours per day of leisure time sitting compared with fewer than three hours per day. "In conclusion, this study supports public health recommendations for recreational physical activity and the avoidance of sedentary time among colorectal cancer survivors," the authors write.

Campbell, Peter T, et al., Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. J of Clin Onc. Published online before print January 22, 2013.