DRUGS / SYSTEMIC THERAPIES

1. Avastin Not Effective in Treatment of Early Stage Colon Cancer (Sept. 19/10)

Adding Avastin (bevacizumab) to chemotherapy for early stage colon cancer didn’t reduce the risk that cancer would return. In fact, preliminary results of the AVANT trial found that chemotherapy alone worked better in preventing recurrences of stage III and high-risk stage II colon cancer, according to a news release from Roche, who were the sponsors of the international clinical trial. This is the second trial in which adding Avastin to chemotherapy after surgery for early stage colon cancer failed to show a disease-free survival benefit. The C-08 trial found that, although Avastin did improve disease-free survival during the first year of treatment, the benefit had disappeared by the third year. The results of the AVANT trial have been eagerly awaited since conclusions of the similar C-08 trial were announced in 2009. After their surgery was over, the Phase III AVANT study randomly assigned 3,451 patients with stage III or high-risk stage II colon cancer to one of three arms:

- FOLFOX (continuous infusion 5-FU, leucovorin, and oxaliplatin) chemotherapy alone for 24 weeks, followed by observation for 24 weeks.
- FOLFOX plus Avastin for 24 weeks, followed by 24 weeks of Avastin alone.
- XELOX (oral Xeloda and oxaliplatin) in combination with Avastin for 24 weeks, followed by 24 weeks of Avastin alone.

The primary aim of AVANT was to find out if adding Avastin to standard chemotherapy improved the percentage of people alive without a cancer recurrence three years after treatment began (disease-free survival). Researchers also wanted to measure overall survival at five years and the safety of adding Avastin to chemo. Researchers claimed that it was becoming increasingly clear that the effects of Avastin are different in the metastatic vs. the early disease settings for patients with colon cancer. Avastin is Health Canada approved to treat colorectal cancer that has spread beyond the colon or rectum (metastatic), where it does improve survival time.

**Anti-VEGF Therapy**

Therapies that inhibit VEGF (vascular endothelial growth factor - a protein believed to be one of the most potent sources of angiogenesis, or the development of new blood vessels) may have multiple effects on angiogenesis (tumor growth and delivery of other types of therapy. These effects may include:

- Reducing the tumor's blood supply by potentially causing existing small blood vessels in the tumor to die.
- Preventing the development of new blood vessels in the tumor.
- Facilitating the delivery of chemotherapy to the tumor cells by potentially making mature tumor vessels, which tend to be leaky, behave more like normal vessels.


2. **NSAID Vioxx did Not Help Stage II or III Colorectal Cancer Patients**  
(Sept. 30/10)

Results from this study indicate that Vioxx (rofecoxib) did not improve survival for Stage II-III colorectal cancer patients when administered following surgery and adjuvant treatment. This study was closed early due to cardiac safety concerns of Vioxx; reported results represent 7.4 months of the intended three to five years of drug exposure. Vioxx belongs to the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDS). Vioxx inhibits the COX-2 enzyme, which plays a role in inflammation. The COX-2 enzyme is over expressed in many colorectal cancers, suggesting that inhibitors of this enzyme may play a role in prevention or treatment. Some studies, however, have linked COX-2 inhibitors with an increased risk of cardiovascular problems. Vioxx was withdrawn from the market due to safety concerns over elevated risk of cardiovascular problems associated with long-term use. In the current Phase III randomized study (initiated before Vioxx was withdrawn from the market), researchers evaluated whether Vioxx could improve survival among patients with Stage II or III colorectal cancer. Eligible patients had undergone surgical removal of their cancer as well as adjuvant (post surgical) treatment. The study was originally designed to include 7,000 patients who would receive either Vioxx or a placebo for three to five years. The study was terminated early due to the withdrawal of Vioxx related to cardiac toxicity concerns. Of the intended 7,000 patients, 2,327 patients were enrolled, and treatment duration was truncated from three to five years to approximately seven months. Patients treated with Vioxx did not experience a statistically significant improvement in survival or recurrence rate compared with placebo. In addition, patients whose tumors expressed COX-2 did not appear to experience a benefit from Vioxx versus placebo. The researchers concluded that Vioxx given for seven months did not improve survival with Stage II or III colorectal cancer when compared with placebo. Nevertheless, the role of COX-2 inhibitors in colorectal cancer is still being investigated, with safety precautions to minimize cardiovascular complications.


3. **Algae Chemical Being Tested to Treat Colorectal Cancer**  
(Oct. 3/10)

Scientists say that the algae living in the waters of the Florida Keys may provide a drug to fight colon cancer. Largazole, named for the blue-green algae beds of Pickles Reef, off Key Largo, has shown great potential against the deadly disease, according to University of Florida scientists. The oceans have been a largely untapped source of drugs, but now many compounds extracted from marine organisms are being researched. So far, only two marine-based drugs have been approved by the U.S. Food and Drug Administration. Prialt, a non-narcotic painkiller derived from the venom of cone snails, is used to treat severe chronic pain in people failed by standard drugs. Yondelis, made from orange sea squirts that grow on the roots of mangroves in the Florida Keys, is used to treat advanced soft tissue sarcoma abroad. Although developed in the United States, Yondelis has yet to receive FDA approval for sarcoma, but it is approved for women with relapsed ovarian cancer.
4. Vectibix Delays Progression of Metastatic Disease in Colorectal Cancer Patients  

Among patients with previously treated, metastatic colorectal cancer, the addition of the targeted therapy Vectibix® (panitumumab) to chemotherapy delayed cancer progression. This benefit was only observed in patients whose tumors did not contain a mutation in the KRAS gene. Targeted therapies are anticancer drugs that interfere with specific pathways involved in cancer cell growth or survival. Some targeted therapies block growth signals from reaching cancer cells; others reduce the blood supply to cancer cells; and still others stimulate the immune system to recognize and attack the cancer cell. Depending on the specific “target,” targeted therapies may slow cancer cell growth or increase cancer cell death. Vectibix inhibits cancer cell growth and survival by targeting a protein known as the epidermal growth factor receptor (EGFR). Vectibix has been approved for the treatment of EGFR-expressing metastatic colorectal cancer that has progressed on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Vectibix appears to benefit only those patients whose cancers do not contain a mutation in a gene known as KRAS. KRAS mutations occur in an estimated 40-50% of metastatic colorectal cancers and can be identified by testing a sample of tumor tissue. Two recently published Phase III clinical trials reported on the safety and efficacy of Vectibix in combination with chemotherapy for metastatic colorectal cancer. One of the trials evaluated Vectibix in the first-line (initial) treatment of metastatic colorectal cancer, and the other evaluated Vectibix in the second-line treatment of metastatic colorectal cancer. The study that evaluated Vectibix in newly diagnosed, metastatic colorectal cancer was known as PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy). The study enrolled 1,183 patients. Study participants were assigned to receive treatment with FOLFOX4 chemotherapy alone or FOLFOX4 plus Vectibix.

- Among patients without KRAS mutations, the addition of Vectibix delayed cancer progression. Progression-free survival was **9.6 months** among patients treated with chemotherapy plus Vectibix compared with 8.0 months among patients treated with chemotherapy alone. Overall survival was **23.9 months** among patients treated with chemotherapy plus Vectibix versus 19.7 months among patients treated with chemotherapy alone, but this result did not meet the criteria for statistical significance, suggesting that it could have occurred by chance alone.
Among patients with KRAS mutations, the addition of Vectibix worsened outcomes. Progression-free survival was 7.3 months among patients treated with chemotherapy plus Vectibix compared with 8.8 months among patients treated with chemotherapy alone.

To evaluate the effectiveness of Vectibix in the second-line treatment of metastatic colorectal cancer, researchers conducted a Phase III study among 1,186 previously treated patients. Study participants were assigned to receive treatment with FOLFIRI chemotherapy alone or FOLFIRI plus Vectibix.

- Among patients without KRAS mutations, progression-free survival was 5.9 months among patients treated with chemotherapy plus Vectibix compared with 3.9 months among patients treated with chemotherapy alone. Overall survival was 14.5 months among patients treated with chemotherapy plus Vectibix versus 12.5 months among patients treated with chemotherapy alone, but this result did not meet the criteria for statistical significance either, suggesting that it could have occurred by chance alone.
- Among patients with KRAS mutations, the addition of Vectibix did not improve progression-free or overall survival.

In both studies, side effects of Vectibix included skin rash, low magnesium levels, and diarrhea. These studies indicate that the addition of Vectibix to chemotherapy delays cancer progression among patients with either newly diagnosed or previously treated metastatic colorectal cancer. Because the benefit only applies to patients whose cancer does not contain a KRAS mutation, these studies also highlight the importance of KRAS testing prior to treatment with this type of targeted therapy.

**Anti-EGFR Therapies (Vectibix and Erbitux)**

**EGFR Signaling Pathway**

**KRAS and BRAF Mechanisms in Action**

- Anti-EGFR therapies (such as vectibix and erbitux) are commonly used in treating patients with metastatic colorectal cancer.
- These therapies heavily rely on blocking the EGFR signaling pathway.
- Recent data strongly suggest the evaluation of downstream markers, such as KRAS and BRAF, are important in selecting which patients will respond to therapy.
- Patients with mutations in the KRAS and BRAF genes are less likely to respond to anti-EGFR therapies.
- Both KRAS and BRAF are prone to mutations in colorectal carcinomas (CRC).
- The combined mutational analysis of both KRAS and BRAF could be used to prospectively select metastatic colorectal cancer patients most likely to benefit from EGFR-targeted treatment. Monoclonal antibodies approved to treat mCRC are
Avastin® (bevacizumab), a monoclonal antibody and anti-angiogenesis drug, blocks the growth of blood vessels to the tumor.

Erbitux® (cetuximab) and Vectibix® (panitumumab) block the effect of hormone-like factors that promote cancer cell growth and binds specifically to the human epidermal growth factor receptor (EGFR).

Both Erbitux (cetuximab) and Vectibix (panitumumab) have proven to be effective in providing clinical benefit in approximately 10% to 20% of patients.


Variation of Sulindac May Help Prevent Colorectal Cancer (Oct. 6/10)

A drug called sulindac has been used for many years as a way to prevent colon cancer. It's a non-steroidal anti-inflammatory drug (NSAID), which means it's in the same category of drugs as ibuprofen and aspirin. Unfortunately, sulindac and other NSAIDs that reduce colon cancer risk can have negative side effects with long-term use, including kidney damage and bleeding in the gastrointestinal tract. Now, researchers at Stony Brook University School of Medicine have found that a new derivative of sulindac, called phospho-sulindac, may be better at preventing colon cancer and with fewer side effects. So far, the researchers have tested the compound only in animals. Future studies to determine if the drug is safe and effective for colon cancer prevention in humans too, are being planned.


Erbitux Does Not Help Early Stage Colorectal Cancer Patients (Oct. 11/10)

Adding the targeted drug cetuximab, or more commonly referred to as erbitux, to a three-drug chemotherapy regimen for first-line treatment of metastatic colorectal cancer does not improve response rate, progression-free survival or overall survival, according to the results of this study. Results from the NORDIC VII study included 566 patients from Sweden, Denmark, Norway, Finland and Iceland who were randomly assigned to either a combination of 5-fluorouracil plus folinate plus oxaliplatin (NORDIC FLOX), FLOX plus cetuximab until disease progression, or FLOX intermittently plus continuous cetuximab. Among the whole study population, there were no statistically significant differences between the treatment groups in terms of response rate, progression-free survival or overall survival, the NORDIC VII researchers found. The lack of significant benefit also applied to sub-groups of patients with mutant and wild-type versions of the KRAS gene. Some recent studies have shown that the beneficial effect of cetuximab was limited to the group of patients without KRAS-mutations. However, unexpectedly, researchers could not find a significant clinical effect in this specific group either. The results do not support the use of cetuximab in first line when given together with an oxaliplatin regimen. The results of trials combining cetuximab with an irinotecan regimen, as well as results from panitumumab-studies in first line, seem to be more positive, according to the researchers. However, they conclude that these drugs are not fully established as part of standard first-line treatment of metastatic colorectal cancer. The results of this study add to a growing body of evidence regarding the role of cetuximab in the treatment of patients with metastatic colorectal cancer in the first-line setting.
7. **Imprime PGG Plus Erbitux Can Double Response in Patients** (Oct. 12/10)

A combination of Biothera’s Imprime PGG and cetuximab (Erbitux) doubled the overall response rates for second- and third-line metastatic colorectal cancer patients participating in a Phase Ib/Ila clinical trial. The completed trial results were released at the 35th European Society for Medical Oncology (ESMO) Congress. The sequential, dual-arm, open-label, dose-escalation study evaluated the safety and efficacy of Imprime PGG plus cetuximab and irinotecan (Arm #1) or Imprime PGG plus cetuximab alone (Arm #2). The 32-patient trial was conducted in Asia. In both arms of the trial, patients were dosed with Imprime PGG in combination with standard doses of cetuximab and irinotecan. Imprime PGG was safe and well tolerated.

**Study Arm 1 Results**

This portion of the study compared the combination of Imprime PGG, cetuximab and irinotecan to the standard of care of cetuximab and irinotecan alone for these late-stage patients. The trial results from this Arm demonstrated a doubling of the historical overall response rate and a two-month extension in the time to progression of these patients, compared with cetuximab and chemotherapy.

**Study Arm 2 Results**

This portion of the trial compared the combination of Imprime PGG and cetuximab with cetuximab monotherapy. Chemotherapy was not administrated to avoid the unintentional destruction of immune cells that are integral to Imprime PGG’s mechanism of action. The trial results from this Arm demonstrated a doubling of the historical overall response rate and the time to progression of these patients, compared with cetuximab monotherapy.

**Subpopulation Results**

The study also retrospectively looked at subpopulations of the colorectal cancer patients based on those whose tumors expressed wild type versus mutated KRAS genes. In the wild type KRAS patient population, responses were even more pronounced. The results of this dual arm study demonstrate the proof of concept that Imprime PGG is a novel drug that engages and directs innate immune cells to kill cancer. Imprime PGG’s ability to engage the innate immune system opens the door to numerous new therapeutic combinations with monoclonal antibodies targeting the vast majority of cancers.

**About Imprime PGG**

Imprime PGG® is a novel immunotherapy that works synergistically with anti-tumor monoclonal antibodies to activate the largest population of the body’s immune cells (neutrophils) to kill cancer cells. Imprime PGG is currently in multiple Phase II clinical trials for lung and colorectal cancer. While some immunomodulatory drugs trigger a broad proinflammatory response, Imprime PGG selectively targets and activates neutrophils without inducing systemic pro-inflammatory cytokines that are attributed to adverse reactions. As a platform therapeutic in oncology, Imprime PGG has the potential to improve patient response rates for existing monoclonal antibody therapies in approved indications, create new indications for these drugs and enhance the efficacy of development-stage monoclonal antibody drugs.

8. **Interstitial Lung Disease and CRC Chemotherapies** (Oct. 12/10)

Interstitial lung disease is a rare and potentially fatal complication of chemotherapy in patients with colon and rectum cancer. Oxaliplatin plus 5-fluorouracil (5-FU) and leucovorin (FOLFOX) or irinotecan plus 5-FU and leucovorin (FOLFIRI) are current standard first-line treatments of colorectal cancer (CRC). Interstitial lung disease (ILD) is a rare adverse event of chemotherapy that may result in respiratory failure and death. There are a small number of case reports of chemotherapy-induced ILD following FOLFOX or FOLFIRI. This retrospective safety study evaluated clinical features of ILD associated with FOLFOX or FOLFIRI in 11 patients with CRC. The results of this study suggested that oxaliplatin might have a greater effect on the onset of ILD than the other treatments in this study. Previous case studies have reported oxaliplatin-induced ILD. The results also suggest that preexisting
pulmonary disorders increase the risk. ILD is a rare, life-threatening complication of chemotherapy for CRC that may occur during or after chemotherapy. Early diagnosis and treatment are critical. Researchers recommend termination of the suspected chemotherapy culprit agent plus follow-up is generally advised. Low-dose corticosteroids may be given for patients with less severe ILD, or steroid pulse therapy with methylprednisolone may be required for patients with more severe ILD.

**Interstitial Lung Disease:**

Interstitial lung disease—sometimes called restrictive lung disease—refers to a group of lung problems. When you have interstitial lung disease, your lungs become inflamed and scarred. You may find it harder to take deep breaths. Or you may have a dry cough and mild chest discomfort. Interstitial lung disease develops in steps:

- First, the alveoli are injured and the lungs become inflamed.
- Then scarring of the lungs develops. The lungs may become stiff.
- With enough damage from scarring, oxygen can’t easily move through interstitium.
