The following colorectal cancer research update extends from March 19th, 2011 – April 8th, 2011 inclusive and is intended for informational purposes only.

**DRUGS / SYSTEMIC THERAPIES**

1. **KRAS Mutations Match in Primary Tumour and Liver Mets**  
   
   If there is a KRAS mutation in the primary colon or rectal tumor, there is almost always a matching mutation when that tumor spreads to the liver. Researchers in the Netherlands tested both tumors for KRAS mutations in over 300 patients whose cancer had spread to their livers. They found about a third of patients had KRAS mutations and KRAS status matched in 96% of the cases, making it possible to test either tumor to make decisions about treatment with Erbitux® (cetuximab) or Vectibix® (panitumumab). Out of 305 tumors:

   - 108 had a KRAS mutation in either the primary colorectal or metastatic liver tumor (35.4%)
   - KRAS mutations didn’t match in 11 of the 108 (3.6%)
   
   Of those:

   - 5 had a wild-type (normal) primary and KRAS mutation in the liver metastasis
   - 1 had a KRAS mutated primary and the liver met was wild-type
   - 5 had different KRAS mutations in the primary and liver tumors.

   Researchers in the Netherlands concluded: “We observed a high concordance of KRAS mutation status of 96.4% between primary colorectal tumours and their corresponding liver metastases. In only six patients (2.0%), the discordance was clinically relevant. In this largest and most homogenous study to date, we conclude that both primary tumours and liver metastases can be used for KRAS mutation analysis”.

   The KRAS gene provides instructions for making a protein called K-Ras that is involved primarily in regulating cell division. Through a process known as signal transduction, the protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide or to mature and take on specialized functions (differentiate).

   The KRAS gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. The KRAS gene produces a protein that plays an important role in cell division, cell differentiation, and the self-destruction of cells (apoptosis). In colorectal cancer, mutations in the kras gene prohibit metastatic colorectal cancer patients from accessing anti-egfr therapies such as vectibix and erbitux because evidence shows that these therapies are not effective when administered to patients who have an identified kras mutation.  

2. Administering Folfox 6 with Avastin in Non-optimally resectable Liver Mets  (Mar. 29/11)

Researchers maintain that in patients with colorectal liver metastases (CLM), a complete resection (R0) significantly improves overall survival (OS). In this study, investigators present the results of a phase II trial of FOLFOX6 + bevacizumab (avastin) in patients with non-optimally resectable CLM. Patients received six cycles of FOLFOX6 + five of bevacizumab. Patients who still did not qualify for surgery received six additional cycles of each. A PET-CT was performed at baseline and again within 1 month after initiating treatment. From September 2005 to July 2009, 21 patients were enrolled. An objective response (OR) was documented in 12 cases. Thirteen patients underwent radical surgery (61.9%). Six patients (46.1%) experienced minor post-surgical complications. After a median 38.8-month follow-up, the median OS was 22.5 months. Investigators noted that those patients who achieved at least 1 unit reduction in Standard uptake value (SUV)max on PET-CT had longer progression-free survival (PFS – time before disease got worse - 22 v.s. 14 months). Researchers therefore concluded that FOLFOX6 + bevacizumab does not increase post-surgical complications and yields high rates of resectability. Early changes in PET-CT values appear to be predictive of longer PFS.

*Bertolini, F. et al., Folfox6 and bevacizumab in non-optimally resectable liver metastases from colorectal cancer. British J of Cancer (2011) 104, pp. 1079-1084

3. Effect of Simvastatin on Erbitux Resistance with KRAS Mutations (Mar. 29/11)

Metastatic colorectal cancer (CRC) patients with KRAS mutations are resistant to treatment with cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor. Statins have reported antitumor activity, but it is unknown whether a well known statin – simvastatin - can reverse cetuximab resistance in KRAS mutant CRC. In the study, human CRC cells with KRAS mutations or with BRAF were used to test the effect of cetuximab, simvastatin, and cetuximab plus simvastatin on cell proliferation and cell death. Addition of simvastatin to cetuximab reduced cell proliferation of KRAS mutant but not of BRAF mutant CRC cells. Treatment of KRAS mutant cells with simvastatin reduced BRAF activity and induced cell death (apoptosis). Treatment with cetuximab and simvastatin reduced the growth of tumors originating from KRAS mutant cells compared with cetuximab; treatment with cetuximab alone or in combination with simvastatin had no effect on the growth of BRAF mutant tumors. Researchers concluded that simvastatin may overcome cetuximab resistance in colon cancer cells with KRAS mutations by inducing cell death (apoptosis). ***Please note that this is an early and limited study which requires additional testing in human subjects to confirm the effect of simvastatin administered in combination with cetuximab in KRAS mutant patients.


4. Addressing the Hypersensitivity to Cold Caused by Oxaliplatin  (Apr.4/11)

For patients receiving chemotherapy treatment that consists of oxaliplatin, a common side effect is hypersensitivity to cold. It happens in approximately 95% of patients, wherein the drug causes increased sensitivity to cool or cold temperatures from the first infusions, resulting in tingling in the extremities. To help remedy the unwanted side effect, patients will put gloves on before opening the fridge, avoid the refrigerated section in supermarkets and avoid coming in contact with cool temperatures or objects. This known side effect is so uncomfortable that some patients reduce or even stop their chemotherapy. No preventative treatment is currently available. In this study however, a team of researchers have shown that, as is the case in humans, administration of oxaliplatin in mice increases sensitivity to cold. A molecule already marketed in France for the treatment of angina has been shown to restore the excitation thresholds of cold-sensitive neurons (nerve cells) to normal levels. The molecule is known as Ivabradine and it was not only able to restore the normal excitation threshold of cold-activated neurons, but it did not affect other populations of sensory neurons, such as touch receptors. This molecule, already used in the clinic to treat angina, could be a promising preventative treatment against the acute neurotoxicity induced by oxaliplatin in colorectal cancer patients. Additional testing is required before the agent is administered as a prophylactic in the prevention of oxaliplatin-induced cold hypersensitivity.

*Descoeur, Juliette, et al., Oxaliplatin-induced cold hypersensitivity is due to remodeling of ion channel expression in nociceptors. EMBO Molecular Medicine, online publication, March 23, 2011.
5. **Venlafaxine for the Prevention of Oxaliplatin-Induced Neuropathy** (Apr. 5/11)

The most serious side effects limiting use of the chemotherapeutic agent oxaliplatin are acute sensory neuropathy, which is typically triggered by cold exposure, and cumulative, chronic peripheral neuropathy. Finding strategies that improve neurotoxicity without affecting the anti-tumor activity of oxaliplatin is an important goal, and various approaches have been tried. In a previous small study, (Durand et al) investigators found that a 50-mg dose of oral venlafaxine protected against acute neurosensory toxicity in patients receiving an oxaliplatin infusion. To explore this finding further, the researchers conducted a randomized, double-blind, placebo-controlled phase III trial to evaluate the efficacy of venlafaxine in managing oxaliplatin-induced acute neurotoxicity. From October 2005 to May 2008, the study enrolled eligible adult patients with cancer who reported acute neurotoxicity following biweekly treatment with oxaliplatin. A total of 48 patients were included in the study; 72.9% of patients had colorectal cancer. At inclusion, patients had similar oxaliplatin exposure and similar intensity of symptoms. The symptoms shared by the patients included burning, cold-evoked pain, pins and needles. After baseline assessment, patients were randomized to treatment groups.

- **Group A** (n = 24) received venlafaxine immediate release (50 mg) 1 hour prior to oxaliplatin infusion (day 1 of chemotherapy), followed by venlafaxine extended release (37.5 mg twice daily) on day 2 through day 11.
- **Group B** (n = 24) received placebo 1 hour prior to oxaliplatin infusion, followed by placebo (twice daily) on day 2 through day 11. Venlafaxine and placebo were withheld on days 12 and 13. Study treatment resumed on day 14 (day 1 of the next cycle), following the same protocol as for cycle 1, and continued as long as oxaliplatin therapy continued.

During study treatment, on day 1 through day 5 of chemotherapy, patients rated their symptoms over the previous 12 hours, rated their functional impairment (0–10), and estimated relief of symptoms experienced with treatment (0%–100%). Neurosensory symptoms were reevaluated 3 months after discontinuing treatment. The primary endpoint was the percentage of patients with 100% relief of acute neuropathy. Secondary endpoints were the percentage of responders (patients with ≥ 50% relief of symptoms), and percentage of patients with grade 0 and grade 3 neuropathy at 3 months. Of 48 patients randomized, 20 from group A and 22 from group B were analyzed for neurotoxicity. The data revealed the following:

- that **a significantly greater number of patients receiving venlafaxine experienced 100% relief of acute neuropathy (31.3% vs 5.3%)**
- the responder rate also was **significantly greater with venlafaxine (68.8% vs 26.3%)**
- Additionally, **venlafaxine improved pins and needles and functional status and was associated with a lower rate of grade 3 neuropathy (0% vs 33.3%)**

Venlafaxine caused no grade 3 or 4 adverse events. The investigators maintained that although small, this phase III trial provides important evidence on the clinical activity of venlafaxine in preventing oxaliplatin-induced acute neurotoxicity. Larger prospective trials are needed to confirm the efficacy of complementary treatment with venlafaxine in ameliorating this often treatment-limiting side effect of oxaliplatin.


6. **Stronger Chemo + Immune Boost May Help Metastatic Colorectal Cancer Patients** (Apr. 7/11)

By giving more intensive chemotherapy along with drugs designed to boost the body’s own immune system, researchers were able to roughly double survival time for patients with advanced, metastatic colorectal cancer compared to patients receiving standard chemotherapy alone. In fact, the trial, whose results are being presented at the annual meeting of the American Association for Cancer Research in Orlando, was stopped early because of the promising findings. “With this study, we have produced for the first time strong proof-of-concept that chemo-immunotherapy may be active and more efficacious than standard [chemotherapy] in metastatic colon cancer patients,” said study lead author Dr. Pierpaolo Correale. The standard of care right now for patients with colorectal cancer that has spread to other regions is to use one of two dual-drug combinations of chemotherapy alone, or use them alongside a newly developed monoclonal antibody treatment such as Avastin (bevacizumab) or Erbitux (cetuximab). These approaches...
can boost overall survival to about 20 to 22 months. For this study, the research team randomized 130 patients to receive either chemotherapy alone (with a regimen known as FOLFOX) or to receive FOLFOX plus drugs to ramp up the immune system (this regimen is known as GOLFIG). The chemo/immune boost approach involves first giving patients the chemo gemcitabine plus standard FOLFOX chemotherapy (oxaliplatin, levofolinic acid and 5-FU/GOLF) that targets and kills the cancer cells in a number of ways -- all the while sending off signals alerting the immune system to the cancer. This is then followed up with the administration of signaling molecules called cytokines that spur key immune cells into action. Another immune-boosting cancer drug, called adesleukine, is also given to help boost the population of immune cells targeted against tumor cells. At the time of data collection, the patients treated with this approach have survived an average 16.5 months without a relapse, compared with just 7.5 months in the chemo-only group. But the study began in 2005, before the advent of drugs like Avastin or Erbitux, meaning that investigators do not yet know if GOLFIG would outperform regimens that include those medications. This needs to be looked at. On the other hand, many patients do not see a benefit from biological agents such as Erbitux or Avastin because they have the wrong genetic profile. "Essentially, we have a very problematic subset of patients with metastatic colorectal cancer which are limited to two lines of chemotherapy and [perhaps] one biological agent," said Dr. Igor Astsaturov, assistant professor of medical oncology at the Fox Chase Cancer Center in Philadelphia. "For those patients, which are about one-third of the overall patient population, this [new finding] will be particularly welcome news," Astsaturov said, while adding the caution that the results are still preliminary. However, clinical use of the protocol may be delayed further by the fact that "there is no direct commercial interest of pharmaceutical companies," noted Correale, who is nevertheless planning larger trials. The costs associated with GOLFIG, he added, are "four-to-five times lower than that produced by the current use of Avastin or Erbitux with apparently similar therapeutic results." Because this study was presented at a medical meeting, the findings should be viewed as preliminary until they are published in a peer-reviewed journal.