The following colorectal cancer research update extends from January 15th, 2011 – February 18th, 2011 inclusive and is intended for informational purposes only.

**DRUGS / SYSTEMIC THERAPIES**

1. **New Phase I Study from Lorus Therapeutics**  
   (Jan. 16/11)

   The biotech company Lorus has announced the enrollment of the first cancer patient in a Phase I clinical study evaluating its small molecule anticancer drug candidate **LOR-253**. The open-label, dose escalation study will enroll patients with advanced or metastatic solid tumors for which no effective therapy is currently available, or whose cancer has not responded to conventional or standard therapies. The primary objectives of the study are to determine the maximum tolerated dose and recommended Phase II dose of LOR-253. Additional study objectives include the safety profile, anti-tumor activity, and pharmacokinetics of LOR-253. The study will be conducted under the direction of Dr. Andrea Cercek and Dr. Leonard Saltz in New York City at the Memorial Sloan Kettering Cancer Center, which is a recognized world leader in the investigation of novel cancer therapies. The study plans to enroll approximately 22-37 patients during the dose escalation stage. In addition, up to 10 patients will be added at the recommended Phase II dose level for assessment of tumor biomarkers related to the anticancer mechanism of LOR-253. Preference will be given to enrolment of patients with colorectal cancer and non-small cell lung cancer in this expanded treatment group, based on the strong anticancer efficacy of LOR-253 against these cancer types in preclinical studies. LOR-253 is a first in class drug, being the first clinical-stage compound to stimulate KLF-4 (Kruppel-like factor 4), a tumor suppressor factor which is characteristically deficient in a variety of cancers, including colorectal cancer and lung cancer, and so represents a new approach to cancer therapy. The study is listed in clinicaltrials.gov and can be accessed by clicking the following:


2. **Gene Discovered Hindering Oxaliplatin Action**  
   (Jan. 16/11)

   The drug, oxaliplatin, is widely used in the treatment of colorectal cancer. It is used in early disease, following surgery in those cancers that are likely to recur. It is also used in advanced disease to slow progression of the cancer where it has spread to other parts of the body. However, a significant number of patients experience serious side effects, including prolonged damage to the nervous system, creating an urgent need to identify genes that are responsible for drug sensitivity or resistance, which results in directing therapy to those most likely to benefit. Nerve damage, or neurotoxicity, associated with oxaliplatin is most commonly manifested as pain or a loss of sensation in the hands and feet and can severely affect a patient's quality of life and ability to work. These symptoms are experienced in some form by the majority of patients receiving this drug and, for some patients, can be permanent. Researchers examined the role of individual cancer genes to influence the sensitivity or resistance of colon cancer cells grown in laboratory culture. According to the study, researchers identified 27 genes
that, when silenced, altered the sensitivity of colon tumor cells to oxaliplatin, causing damage to the cancer cells’ DNA and inhibiting the cancer cells’ ability to reproduce and survive. This study has also shown that diverse gene networks also play a role in the ability of the drug to impact colon tumors. These 27 genes, whose loss of function significantly affect the effectiveness of oxaliplatin, may be promising therapeutic biomarkers for oxaliplatin.

Pelham, Robert J, et al., Functional Genomics Reveals Diverse Cellular Processes that Modulate Tumor Cell Response to Oxaliplatin. Molecular Cancer Research, online publication. doi: 10.1158/1541-7786.MCR-10-0412

3. Erbitux Shows Long Term Survival Benefit When Administered with Folfox  (Jan. 19/11)

Results of the Phase II OPUSa study demonstrate an association between early tumor shrinkage and long-term median overall survival (OS) of more than 2 years for patients with KRAS wild-type metastatic colorectal cancer (mCRC) treated with erbitux (cetuximab) plus FOLFOX standard chemotherapy. This correlation was not seen in the chemotherapy-alone arm of the study. The study was presented at the annual Gastrointestinal (GI) Cancers Symposium of the American Society of Clinical Oncology (ASCO). This latest data shows that the majority of patients (69%) with KRAS wild-type mCRC demonstrated tumor shrinkage of 20% or more in the first 8 weeks of 1st line treatment with Erbitux and FOLFOX. These patients experienced a long-term median OS of 26.2 months. Patients treated with FOLFOX chemotherapy alone whose tumors shrank by 20% or more in the same period (46%) experienced median OS of only 21.8 months. These results support recent findings from the Phase III CRYSTALb trial, which found that early tumor shrinkage achieved with Erbitux in combination with FOLFIRI standard chemotherapy led to a long-term median OS of 2.4 years (28.3 months). The OPUS and CRYSTAL studies show, for the first time in colorectal cancer, that there is a correlation between early tumor shrinkage during the first weeks of treatment and extended survival. This effect seems to be unique to treatment with chemotherapy and Erbitux since a similar association was not observed with chemotherapy alone in this analysis, nor has it been proved for any other colorectal cancer treatment, according to the investigators. The result is medically relevant for improving patient care through the personalized medicine approach with Erbitux. Further Erbitux data to emerge from ASCO GI came from the randomized Phase II CORE.1.2.002 study that included 152 patients. The results showed that administration of Erbitux every second week in combination with FOLFOX resulted in sustained efficacy and safety in the treatment of mCRC patients with KRAS wild-type tumors, which were equivalent to the results demonstrated with the weekly administration. Response rates of 51% and 63% were seen in the weekly administration group and in the group where Erbitux was given every second week, respectively. There was no significant difference between the two groups.

Plessevaux H, et al., ASCO GI, Abstract No. 398 and Ciuleanu T, ASCO GI, Abstract No. 494

4. New Phase I/II Trial Initiated for Kras-Mutant Patients  (Jan. 20/11)

4SC AG, a drug discovery and development company, has announced the dosing of their first patient in the Phase I/II SHORE study with the oral pan-histone deacetylase, or HDAC, inhibitor called resminostat as a second-line treatment for patients with advanced and metastatic colorectal KRAS-mutant cancer. SHORE is a randomized, open-label, multi-centre, two-arm Phase I/II study in 70 patients that will evaluate the efficacy, safety and pharmacokinetics of resminostat, in combination with FOLFIRI, a chemotherapy regimen for the treatment of colorectal cancer, versus FOLFIRI alone in the control arm. In the combination arm of the study patients will be treated with the maximum tolerated dose of resminostat in combination with FOLFIRI, which will be determined through an initial dose-escalation phase, evaluating 200mg, 400mg, 600mg and 800mg of resminostat together with FOLFIRI in approximately 20 patients. The primary endpoint of the study is to determine the progression free survival (PFS). The secondary endpoints include progression free survival rate (PFSR) after eight weeks and every eight weeks thereafter, the analysis of time-to-progression (TTP), overall survival (OS), analysis of drug safety, tolerability, pharmacokinetics and the investigation of biomarkers, the company added. By evaluating the efficacy of resminostat in patients carrying KRAS-mutant tumours,
investigators hope to open a second-line treatment option for this colorectal cancer patient population where there is an increased unmet medical need since they cannot be treated with current EGFR targeting agents. More information may be found by clicking on the following link:
http://www.clinicaltrials.gov/ct2/show/NCT01277406?term=resminostat&rank=1

Figure 1: Studies evaluating KRAS mutation status in colorectal cancer patients demonstrate that KRAS mutations are strongly correlated with lack of response to cetuximab and panitumumab (anti-egfr therapies), shorter progression-free survival (PFS) and shorter overall survival, thereby requiring additional approved therapies for third line treatment of advanced colorectal cancer.

http://www.clinicaltrials.gov/ct2/show/NCT01277406?term=resminostat&rank=1

5. Clinical Trial Involving Tivozanib Yielded Positive Results at ASCO GI  (Jan. 21/11)

Aveo Pharmaceuticals announced that previously reported positive data from its Phase 1b clinical trial evaluating tivozanib, its lead product candidate designed to optimally block the VEGF pathway by inhibiting all three VEGF receptors, in combination with FOLFOX6, a standard chemotherapy regimen, in patients with advanced gastrointestinal (GI) cancers was presented at the American Society of Clinical Oncology (ASCO) 2011 Gastrointestinal Cancers Symposium. Results from this study showed the combination was tolerable and safe at the full recommended tivozanib dose (1.5 mg/day) and schedule and standard FOLFOX6 dose; and, partial responses in more than a third (35%) of patients evaluated and disease control in 82% of patients. Tivozanib’s unique characteristics allow it to be combined with other anti-cancer agents at full dose and schedule. Tivozanib, an investigational new drug, is designed to optimally block the VEGF (vascular endothelial growth factor) pathway by inhibiting all three VEGF receptors. Each of the three receptors of the VEGF pathway play an important role in angiogenesis (the formation of new blood vessels), which is critical in cancer cell growth. Tivozanib’s high level of potency across VEGF receptors 1, 2 and 3 is designed to provide the most complete blockade of the VEGF pathway. Tivozanib’s high level of selectivity for VEGF receptors 1, 2 and 3 is designed to minimize off-target toxicities, and its oral, one capsule, once-daily administration may enhance convenience for patients. Tivozanib has also demonstrated the ability to be combined with
both targeted therapies and chemotherapies at the full dose. More information may be found at http://www.clinicaltrials.gov/ct2/show/NCT01210846?term=tivozanib&rank=8

Jac, Jaroslaw, et al., A Phase Ib, open-label, dose-escalation study of tivozanib and folfox6 in patients with advanced gastrointestinal (GI) tumors. ASCO 2011 GI Symposium. Abstract #549

6. AVANT Study Finds No Benefit From Avastin in Stage III Colon Cancer (Jan. 24/11)

A second randomized clinical trial has confirmed what the first one found — adding Avastin to standard chemotherapy does not reduce recurrences after surgery for stage III colon cancer. The AVANT trial compared standard FOLFOX chemotherapy to either FOLFOX plus Avastin (bevacizumab) or XELOX plus Avastin. Chemo was given for 6 months, and Avastin was added during that time and for another 6 months after chemo ended. Nearly 2,870 stage III patients took part in the study. Much like the C-08 trial, there was a temporary benefit during the year that patients received Avastin, but it didn’t last. By the end of three years the percentage of people who were alive and cancer-free was slightly less in the two Avastin arms. At three years, disease-free survival was:

- 76% in the FOLFOX only arm
- 73% in the FOLFOX plus Avastin arm
- 75% in the XELOX plus Avastin arm

FOLFOX chemotherapy combines oxaliplatin with leucovorin and continuous infusion 5-FU. XELOX combines oral Xeloda (capecitabine) with oxaliplatin. Although it is too early to be certain, there was a trend toward poorer survival in those patients who received Avastin with their chemotherapy. It is not clear why this might be. There was no serious additional toxicity due to Avastin. When cancer did recur, the sites of recurrence weren’t different among the three arms, with most initially in the liver, leading researchers to believe that there wasn’t a “rebound” after Avastin was stopped. AVANT included collecting tissue and studying a number of biomarkers to see if there might be some subgroups where adding Avastin to chemo might be beneficial. Those results are not yet complete. In presenting the trial results at the 2011 GI Symposium, Aimery De Gramont concluded,

- The addition of bevacizumab to FOLFOX4 or XELOX did not improve disease-free survival in the adjuvant treatment of Stage III colon cancer.
- Immature overall survival data suggest a potential detriment. Continued follow-up is ongoing.
- Bevacizumab treatment effect was not constant over time.
  - In the first year, there was a transient favorable effect, consistent with what was found in C-08.
  - The treatment effect became unfavorable after one year, which is different than what C-08 discovered. In C-08 there was no difference between arms after one year.
- Bevacizumab is the third agent, after irinotecan and cetuximab, with proven efficacy in metastatic colorectal cancer and no observed benefit in the adjuvant treatment of colon cancer.

Figure 2: Avastin consists of a group of large proteins called monoclonal antibody (Mab). These agents are similar to the antibodies the body’s own immune system normally makes when we have a bacterial or viral infection but, in this case, it has been made in a laboratory and attacks specific targets on cancer cells. In the case of Avastin, the target (otherwise called the antigen) is a protein called Vascular Epidermal Growth Factor (VEGF). Avastin binds to VEGF, rendering it unable to then bind with its receptor which in turn by blocking the formation of new blood vessels then interferes with the growth of the tumour (see
When cancer cells spread to another part of the body they try to form a lump or tumour mass. In order to do this, they need to rapidly stimulate the local blood vessels and capillaries to grow into the tumour mass in order to nourish the cancer cells with food and oxygen (a process called angiogenesis). They achieve this by releasing a chemical into the surrounding tissues called Vascular Epidermal Growth Factor (see image above). Avastin, being a monoclonal antibody which attaches to circulating VEGF, effectively blocks its ability to bind to its receptors in the tissues of the body, most importantly those surrounding tumours. Avastin, therefore, interferes with the tumour’s ability to recruit new blood vessels reducing their ability to grow and spread to other areas of the body. As this process is universal to most bowel tumours, there is no requirement to perform extra laboratory tests on the cancer cells prior to Avastin therapy. There is also evidence that Avastin enhances the effect of chemotherapy. It is thought they make tumour vessels less “leaky” and so allows chemotherapy to reach the tumour more effectively.

DeGramont et al., AVANCE: results from a randomized, three-arm multinational phase III study to investigate bevacizumab plus either oxelox or Folfox4 versus folfox4 alone as adjuvant treatment for colon cancer, 2011 GI Cancers Symposium, Abstract 362.

7. Chemo Delay Puts Lives at Risk in Colon Cancer (Jan. 24/11)

The results of this study suggest that delaying adjuvant (post-operative) chemotherapy for colon cancer by more than four weeks increases the mortality risk, beginning with a 12% increase at eight weeks. The results of the analysis indicate a significant adverse association between time to adjuvant chemotherapy and survival in colorectal cancer. The level of evidence from the study, with knowledge that this relationship will not be subjected to prospective assessment, provides sufficient proof of an adverse association, according to the lead investigator. Two types of factors can contribute to delays in the onset of chemotherapy: patient-related factors — such as postoperative complications and variations in recovery — and logistical issues, including institution-specific delays and inefficiencies. To characterize the impact of delays in chemotherapy on outcomes in colorectal cancer, researchers performed a systematic review of the medical literature and a meta-analysis (a method designed to increase the reliability of research by combining and analyzing the results of all known trials of the same product or experiments on the same subject) of relevant data. The reviewers identified studies that had a clearly defined measure of the time from surgery to initiation of adjuvant chemotherapy for patients with colorectal cancer and that evaluated the impact of the time interval on overall and disease-free survival. Moreover, they included only those studies that adequately described the relevant prognostic factors in the groups compared. All nine studies showed an increase in the hazard for overall survival with increasing delays to the start of adjuvant chemotherapy. Similar associations were seen in an overall analysis and a separate analysis of the incremental impact per each four-week delay.


8. Phase I Results of ARQ 197 c-MET Inhibitor (Jan. 24/11)

Phase 1 results of a clinical trial among patients with metastatic colorectal cancer (CRC) treated with ARQ 197, a selective small molecule inhibitor of the c-MET receptor tyrosine kinase, in combination with irinotecan and cetuximab were presented at ASCO 2011 Gastrointestinal Cancers Symposium showing that this combination was well tolerated and demonstrated encouraging anti-tumor activity in patients with relapsed metastatic CRC. Among nine patients treated, one had a complete response, two had partial responses and five had stable disease. The systemic exposure of ARQ 197 with this combination regimen was consistent with previous observations, and no dose-limiting toxicities were observed. These results provide important support for the ongoing Phase 2 randomized study of this combination. The ongoing Phase 2 study of ARQ 197 in CRC is enrolling patients with the wild-type form of the KRAS gene who have received front-line systemic therapy. The primary objective of the trial is progression-free survival. Secondary objectives include overall survival and objective response rate. Approximately 150 patients will be enrolled at clinical trial sites in the U.S. and Europe. The trial is being conducted by Daiichi Sankyo Pharma Development, the global development arm of Daiichi Sankyo, the co-developer with ArQule of ARQ 197 outside of certain countries in Asia. ARQ 197 is an orally available, selective inhibitor of c-Met, a receptor tyrosine kinase that is currently in Phase 2 and Phase 3 clinical trials and is not yet approved for commercial sale. In healthy adult cells, c-Met is present in normal levels to
support natural cellular function, but in cancer cells, c-Met is inappropriately and continuously activated for unknown reasons. When abnormally activated, c-Met plays multiple roles in aspects of human cancer, including cancer cell growth, survival, angiogenesis, invasion and metastasis.

Eng, C. et al., Phase I results of the randomized, placebo controlled, phase I/II study of the novel oral c-MET inhibitor, ARQ 197, irinotecan and cetuximab in patients with wild type kras metastatic colorectal cancer who have received front line systemic therapy. 2011 GI Cancers Symposium, Abstract No. 527

9. Bone Drugs Reduce Risk of CRC   (Jan. 25/11)

Postmenopausal women taking oral bisphosphonates for osteoporosis had almost a 50% reduction in the risk of colorectal cancer, according to data from a large cohort study. The case-control study, conducted among over 1,800 Israeli women, found that the magnitude of the risk reduction increased with length of time women were on antiresorptive therapy — topping out at almost 80% with more than three years of bisphosphonate use. The findings add to the growing body of evidence of a chemopreventive potential for bisphosphonates. The same group previously reported a reduction in the risk of breast cancer among women taking the bone-friendly drugs. The importance of these findings is that the colon is a tumor site that is less hormonally driven [compared with breast cancer] and therefore there is a better chance that what we actually see, in this association study, is a true effect of the drug, according to the researchers. To examine the association between bisphosphonate use and colorectal cancer, investigators analyzed data from the Molecular Epidemiology of Colorectal Cancer (MECC) study, an epidemiologic study of newly diagnosed colorectal cancer in northern Israel from 1998 to 2004. The analysis included 933 postmenopausal women who developed colorectal cancer and 933 matched female controls. The analysis identified several factors that had significant associations with a reduced risk of colorectal cancer, including:

- Aspirin use for more than three years
- Statin use for more than a year
- Postmenopausal hormone therapy
- Use of bisphosphonates for more than a year

Any use of bisphosphonates was associated with a 33% reduction in the risk of colorectal cancer. The magnitude of the benefit ranged from no benefit for less than a year of use to 50% for a year or more of treatment, 49% for more than two years, and 61% for more than three years.
10. **Reducing Hypersensitivity Reactions from Oxaliplatin Therapy** (Jan. 26/11)

Oxaliplatin is a third-generation platinum compound and a key agent for the management of colorectal cancer, both in early and late stage disease. Patients treated with oxaliplatin are at risk for hypersensitivity reactions (allergic reactions). Researchers designed a modified premedication regimen to prevent oxaliplatin-related hypersensitivity reactions and assessed if this approach was effective. A retrospective cohort study of patients with advanced colorectal cancer who received modified FOLFOX6 (mFOLFOX6) was performed. Patients received routine premedication with dexamethasone 8 mg and granisetron 3 mg for the first five cycles of mFOLFOX6. From the sixth cycle onward, cohort (group) 1 received the same premedication, and cohort 2 received modified premedication (diphenhydramine 50 mg orally, followed by dexamethasone 20 mg, granisetron 3 mg, and famotidine 20 mg). Researchers compared the incidence of hypersensitivity reactions, duration of treatment, and reasons for treatment withdrawal between the two cohorts. A total of 181 patients were studied (cohort 1, 81; cohort 2, 100). Hypersensitivity reactions developed in 16 patients (20%) in cohort 1 and 7 (7.0%) in cohort 2. The median number of cycles increased from 9 in cohort 1 to 12 in cohort 2. Apart from progressive disease, neurotoxicity was the reason for discontinuing treatment in 20% of the patients in cohort 1, as compared with 53% in cohort 2. Researchers concluded that increased doses of dexamethasone and antihistamine significantly reduced oxaliplatin-related hypersensitivity reactions. This effective approach should be considered for all patients who receive FOLFOX, allowing treatment to be completed as planned.

*Kidera, Yasuhiro, et al., High dose dexamethasone plus antihistamine prevents colorectal cancer patients treated with modified Folfox6 from hypersensitivity reactions induced by oxaliplatin. International J of Clinical Oncology. Doi: 10.1007/ss10147-010-0170-6*
11. **KRAS Mutation May Promote Lung Mets in Patients with Curatively Resected Colorectal Cancer**  
(Jan. 31/11)

Analyzing KRAS mutation status has become routine clinical practice in the management of advanced colorectal cancers to determine if patients have a chance to benefit from therapy with EGFR monoclonal antibodies, such as cetuximab (erbitux) and panitumumab (vectibix). The identification of KRAS mutations as a negative predictive factor for cetuximab and panitumumab therapy, however, does not appear to be the end of the story for KRAS. Results from this study suggest that KRAS mutations are associated with a higher propensity of colorectal cancers to form lung and brain metastases, a finding which could eventually help gain insight into the biology of site-specific metastases. In addition, it has to be pointed out that, potentially, not all KRAS mutations have the same biologic effect with regard to their value as negative predictive biomarkers. Results of a recent retrospective analysis of several trials conducted with cetuximab suggested that a specific KRAS mutation at codon 13 (G13D) might not be associated with resistance to EGFR antibodies (as summarized in the January Clinical Research Updates).


12. **IROX Not Superior to Folfiri In First Line Therapy for Advanced Colorectal Cancer**  
(Jan. 31/11)

According to the results of this study, a new regimen of irinotecan plus oxaliplatin (mIROX) failed to demonstrate superior activity over high-dose 5FU/folinic acid and irinotecan (Folfiri) in patients with advanced colorectal cancer. Nor was the IROX regimen tolerated as well as Folfiri, which remains the standard of care.


13. **Avastin Increases the Number of Fatal Events**  
(Feb.1/11)

A team of researchers at Stony Brook University School of Medicine in New York published a paper in JAMA showing that patients who receive Avastin (bevacizumab), in combination with chemotherapy are at increased risk of side effects that may lead to death. Lead author Dr. Vishal Ranpura and his colleagues reported that the risk of fatal adverse events varied according to the type of chemotherapy agents used in conjunction with Avastin. There were also suggestions that the risk might vary by tumor type and dose of Avastin, but results were not definitive. The randomized trials reviewed in this analysis involved more than 10,200 patients. Overall fatal events in patients who received Avastin was low--2.5% compared to 1.7% of patients who did not receive it. However, the increased risk was more than three times higher in patients who received Avastin in combination with platinum or taxane chemotherapy agents such as carboplatin and paclitaxel. The most common fatal event, accounting for nearly one-quarter of the total, was hemorrhage. This finding will most likely affect overall usage of Avastin. Because the most significant benefits from Avastin are seen, thus far, in colorectal cancer, it may be that the drug is used with less frequency for treating lung or breast cancers, where the risk may not outweigh the benefits.

Although many trials have shown the efficacy of preoperative chemoradiotherapy (CRT) or postoperative CRT compared with surgery alone, the optimal sequence of radiotherapy and surgery for the treatment of locally advanced rectal cancer is unclear. The authors of this study reported the final results of this randomized phase 3 trial comparing preoperative CRT with postoperative CRT using the oral chemotherapeutic agent capecitabine (better known as xeloda) in survival, local control, sphincter preservation, and toxicity for the treatment of locally advanced rectal cancer. Patients with locally advanced rectal cancer (cT3, potentially resectable cT4 or N+) were randomly assigned to receive preoperative or postoperative CRT. CRT consisted of 50 Gy/25 fractions and concurrent capecitabine (1,650 mg/m²/day). Patients then went on to receive surgery - total mesorectal excision. From March 2004 to April 2006, 240 patients were enrolled. After a median follow-up time of 52 months, the 3- and 5-year disease-free survival, overall survival, and cumulative incidence of local recurrence were similar between both arms. However, for the patients with low-lying tumors, the preoperative CRT arm had a higher rate of sphincter preservation (68% v.s. 42%). Acute and late complication rates were similar between both arms. According to the authors of the study, although significant benefit of preoperative CRT in local control and survival was not demonstrated, the data showed that increased rate of sphincter preservation was possible in low-lying tumors without jeopardizing local control and surgical complication by preoperative CRT.