The following colorectal cancer research update extends from May 16th, 2011 – June 24th, 2011 inclusive and is intended for informational purposes only.

DRUGS / SYSTEMIC THERAPIES

1. **EGFR-Targeted Therapies Like Erbitux & Vectibix Bind to Decoy Receptor**  (May 19/11)

Researchers at Yale School of Medicine have found that cancer drugs designed to target the epidermal growth factor receptor (EGFR), such as Erbitux and Vectibix, to inhibit cancer cell growth may not work because they also bind to a related receptor, serum sEGFR, with the same affinity. This may explain why these drugs were shown to be ineffective in two phase III clinical trials involving patients with colorectal cancer and suggests people get screened for sEGFR levels to determine if they will benefit from treatment with the drug. sEGFR concentrations vary widely in people with cancer and change in those taking the drug. Reagents designed to measure blood sEGFR also measure alpha-5 integrin, present on the surface of tumor cells which leads researchers to hypothesize that sEGFR plays a role in metastasis.


2. **Biothera Initiates Dosing in a Phase III Trial in Colorectal Cancer Patients**  (May 19/11)

Biothera began dosing patients in a Phase III trial evaluating Imprime PGG® in combination with cetuximab (Erbitux®) as a potential new treatment for recurrent or progressive KRAS wild-type colorectal cancer. The trial design is built on data obtained in the company’s previous clinical studies in colorectal cancer. Biothera has reviewed these results, as well as the protocol for the Phase III study, with the U.S. Food and Drug Administration. The endpoints for the study are designed to include an opportunity for accelerated approval based on interim data. Late stage colorectal cancer patients who can neither tolerate nor benefit from chemotherapy represent a large unmet clinical need. Based on previous trials, the company is confident that the combination of Imprime PGG and cetuximab will prove effective in treating this disease and further extending the survival and quality of life in these patients. The open-label, randomized study will enroll up to 795 patients and will be conducted in over 50 locations worldwide, including the U.S., Europe and South America. Patients will be randomized to one of two study arms in a 2:1 ratio. A total of 530 subjects in Arm 1 will receive Imprime PGG and cetuximab and a total of 265 subjects in Arm 2 will receive cetuximab alone. The patients must have received at least two prior chemotherapeutic regiments and cannot have been previously treated with cetuximab or panitumumab. The primary endpoint for the study is overall survival. Secondary endpoints are progression-free survival, tumor response and quality of life. Imprime PGG® is a novel immunomodulatory drug in development as a cancer therapy. Neutrophils are the most abundant immune cell in the body and normally responsible for pathogen killing, but not anti-tumor activity. In preclinical cancer models, however, Imprime PGG has been shown to bind to neutrophils and harness their killing ability to reduce tumor growth and enhance long-term survival. This targeted mechanism is synergistic with multiple
anti-tumor monoclonal antibodies, demonstrating the potential to improve patient outcomes in a wide range of cancer indications.


3. DNA Repair Plays a Role in Colon Cancer Recurrence  (May 24/11)

A new study shows a person's DNA repair system may play a role in determining if their cancer will recur. Investigators found colorectal cancer patients with defects in mismatched repair -- one of the body's systems for repairing DNA damage -- have lower rates of recurrence and better survival rates. About 15% of colorectal cancers are associated with mismatch repair defects. Researchers say it has never been clear whether these mismatches are linked to cancer recurrence rates, time-to-recurrence and site of recurrence. They also have been unclear about whether such defects affect responses to chemotherapy. Investigators from the Mayo Clinic in Rochester, Minn., analyzed data from more than 2,000 clinical trial patients who had been treated after surgery with chemotherapy that included 5-fluorouracil (5-FU) -- a standard drug used in colorectal cancer. The patients had either stage II or stage III colon cancer. Whether or not mismatch repair status influences response to 5-FU has been debatable. Results from this study, however, showed treatment with 5-FU reduced recurrence rates in stage III patients regardless of mismatch repair status but not stage II patients. The investigators also compared the effects of 5-FU-based therapy in patients thought to have inherited mismatch repair defects versus those whose defects that occurred sporadically. They found 5-FU appeared to reduce recurrences only in those with inherited defects. Investigators concluded that the data demonstrate that patients with defective mismatch repair colon cancers have a statistically significant reduction in their rates of tumor recurrence, a delayed time to recurrence, and better survival rates.


4. Primary Tumor Response to Preoperative Chemoradiation With or Without Oxaliplatin  (May 25/11)

Seven hundred forty-seven patients with resectable, locally advanced (cT3-4 and/or cN1-2) adenocarcinoma of the mid-low rectum were randomly assigned to receive pelvic radiation and concomitant infused fluorouracil (5FU) either alone (arm A, n = 379) or combined with oxaliplatin (arm B, n = 368). Overall survival was the primary end point. Investigators concluded that adding oxaliplatin to fluorouracil-based preoperative chemoradiotherapy significantly increases toxicity without affecting primary tumor response. Longer follow-up is needed to assess the impact on efficacy end points.

Aschele, Carlo, et al., Primary Tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Onc. Published online before print. Doi: 10.1200/JCO.2010.34.4911

5. Avastin in First Line Therapy Comparing Folfiri and Xeliri  (May 30/11)

The antivascular endothelial growth factor monoclonal antibody bevacizumab (better known as avastin) with infusional 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) is a standard first-line treatment option for metastatic colorectal cancer. However, clinical data for capecitabine and irinotecan (XELIRI) with bevacizumab are limited. A retrospective study was conducted on 139 patients with metastatic colorectal cancer to assess the efficacy and safety of first-line bevacizumab in combination with XELIRI or FOLFIRI. Primary endpoints were overall response rate (ORR), disease control rate and radical resection rate. Secondary endpoints included overall survival (OS), progression-free survival (PFS) and safety. According to the investigators, no significant differences in efficacy were observed between patients administered XELIRI or FOLFIRI with bevacizumab. The ORR, median OS and PFS and recorded adverse events (AEs) were comparable to those previously reported, with no new or unexpected AEs observed. Investigators concluded that bevacizumab is similarly efficacious and well tolerated when administered with XELIRI or FOLFIRI.


6. Study Shows No Benefit from Adding Erbitux to Standard Chemo  (Jun. 3/11)
According to the results of this study, the targeted therapy cetuximab (better known as erbitux) does not improve progression-free survival (PFS) or overall survival (OS) when added to standard chemotherapy as a first-line treatment for advanced colorectal cancer. The unexpected results of the COIN trial show that even patients without KRAS mutations in their tumour (the sub-group that showed a benefit from this therapy in other trials) did not benefit from the addition of cetuximab. And, in a second part of the COIN study, investigators commented that for the majority of patients with a normal platelet count before starting treatment, taking breaks from standard chemotherapy might improve quality of life (less time on chemotherapy, fewer hospital visits, and reduced side-effects) without compromising survival. The COIN study enrolled nearly 2500 previously untreated patients with advanced colorectal cancer from 111 hospitals across the UK and Ireland to investigate whether the addition of a monoclonal antibody (cetuximab) to standard chemotherapy might improve survival, and to establish whether taking treatment holidays from standard chemotherapy might improve quality of life without compromising survival. Patients were randomly assigned to a continuous combination of oxaliplatin and fluoropyrimidine, the same continuous combination plus cetuximab, or the same combination chemotherapy in an intermittent schedule. Apart from a modest increase in the rate of tumour shrinkage, cetuximab had no significant benefit on PFS or OS. Interestingly, even patients with a KRAS wild-type (normal) gene in their tumour (who in theory should have benefited from the addition of cetuximab) did not differ in their OS or PFS. The authors say: “The use of cetuximab in combination with oxaliplatin and capecitabine in first-line chemotherapy in patients with widespread metastases cannot be recommended. However, the trial showed the powerful effect of the presence of specific mutations in the tumour on prognosis and this should influence future clinical trials in bowel cancer.” The COIN trial also assessed whether it might be possible to shorten the duration of initial chemotherapy to 12 weeks and then restart on disease progression by comparing standard continuous chemotherapy with the same chemotherapy given with planned treatment holidays (intermittent chemotherapy). Findings showed that intermittent chemotherapy did not increase or significantly decrease survival. However, platelet count before starting intermittent chemotherapy was identified as a potentially valuable predictor of survival and quality of life. A raised platelet count resulted in a 5-month reduction in survival and impaired quality of life, whereas for the three-quarters of patients with normal platelet counts, time off chemotherapy was associated with improved quality of life (less time on chemotherapy, fewer hospital visits, and reduced neuropathy and hand-foot syndrome [redness, swelling, tenderness, and peeling of palms and soles]) with similar survival. The authors remark: “There seems to be a large subpopulation of patients for whom intermittent therapy provides similar survival benefit and the results of this trial provide a basis for discussion of options between patients and clinicians.”

http://www.medicalnewstoday.com/releases/227421.php

7. **VEGF-C and VEGF-D Identified as Biomarkers for Avastin Resistance** (Jun.4/11)

Circadian Technologies Limited (ASX: CIR) announced the presentation of data at the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago associating resistance to Avastin® with increases in plasma VEGF-C and D concentrations. Resistance to Avastin® is a frequent occurrence in the treatment of certain cancers such as colorectal cancer with resulting loss of response and disease progression. The study, which was led by Drs Lieu and Kopetz at The University of Texas MD Anderson Cancer Center showed that increases in VEGF-family markers in patients with metastatic colorectal cancer are associated with Avastin® resistance. In particular, VEGF-C increases were seen in patients prior to and at the time of disease progression while receiving Avastin® and chemotherapy. The data show that the VEGF-family ligands, other than VEGF itself, are associated with Avastin®-containing chemotherapy resistance in patients with metastatic colorectal cancer and investigators are planning prospective confirmatory studies to further evaluate and validate these findings.

http://www.reuters.com/article/2011/06/06/idUS196530+06

8. **Breast Cancer Drug Lapatinib Helpful in Colon Cancer** (Jun. 4/11)

A new treatment for colon cancer that combines a chemotherapy agent approved to treat breast cancer and a cancer-fighting antibody is now ready to proceed to clinical trials. Researchers tested lapatinib, a targeted chemotherapy agent currently approved for breast cancer treatment, in a new combination with artificial antibodies that mimic a natural cancer-fighting protein produced in the human body. The monoclonal
antibodies mapatumumab and lexatumumab act similarly to TRAIL -- tumor necrosis factor [TNF]-related apoptosis-inducing ligand -- a naturally occurring molecule in the body that tells a cell it is time to die. TRAIL sets a process in motion that targets and shuts down tumor cells and keeps them from spreading. The TRAIL receptors -- death receptors -- on the cancer cells respond to TRAIL by dying. The artificial antibodies act as surrogates of TRAIL by activating the same signaling pathway resulting in tumor cell death. The monoclonal antibodies have an advantage over TRAIL because they remain active in the body for a longer period of time. TRAIL receptor antibodies last for less than 30 minutes, while the artificial monoclonal antibodies last for about 9 days. Although the antibodies can act similarly to TRAIL, they do not completely substitute for TRAIL and ultimately which one gets used in what situation is still being tested in clinical trials. But for the purpose of these new advances, either one works. Lapatinib (also known as Tykerb) increases the amount of "death receptor" protein available for TRAIL to do its job -- killing off cancerous cells. The researchers tested the lapatinib and monoclonal antibody combination in mice. Separately, the two treatments did not increase tumor cell suppression -- but when the drugs were administered together, the researcher found that cell death escalated.


9. Xeloxgem (Xeloda + Oxaliplatin + Gemcitabine) In Second Line Therapy (Jun. 4/11)

Capecitabine plus oxaliplatin (XELOX) is an effective second-line regimen for advanced colorectal cancer (CRC) patients pretreated with irinotecan. Previous studies have shown supra-additive anti-tumor activity of gemcitabine (GEM) when administered with oxaliplatin. Researchers investigated the dose, toxicity, and efficacy of a second-line XEOXGEM regimen in CRC patients pretreated with irinotecan. Patients with metastatic or recurrent CRC who failed after a first-line irinotecan-containing regimen received escalating doses of gemcitabine followed by capecitabine and oxaliplatin on a 21-day cycle. Ten (26.3%) and 23 (60.5%) patients experienced partial response and stable disease, respectively. The median progression-free survival and overall survival were 5.4 months and 17.7 months respectively. Researchers concluded that the XELOXGEM triplet combination is an active and safe second-line regimen for advanced CRC patients pretreated with irinotecan.


10. Adding Oxaliplatin to 5FU/Leucovorin in Stage II Colon Cancer (Jun. 6/11)

In this study, researchers investigated the addition of Oxaliplatin to 5FU/Leucovorin in patients with stage II colon cancer. The analysis includes 4,883 patients with stage II and III colon cancer (2009 with stage II disease) treated using 5FU/Leucovorin regimens, and 3,788 patients with stage II and III colon cancer (991 with stage II disease) treated with FU/L + Oxaliplatin. Patients from 4 NSABP trials were included. Only in one of the trials (C-07) was there random assignment to Oxaliplatin. Overall, there was a highly significant benefit of Oxaliplatin for DFS (disease free survival) and OS (overall survival) in patients with stage II and III disease combined. According to the researchers, the effect of Oxaliplatin remained significant for DFS and OS in stage III. For stage II, Oxaliplatin did not significantly improve outcomes.


11. Erbitux + Folfiri As First Line Therapy for MCRC (Jun. 6/11)

Cetuximab (better known as erbitux) is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR). In phase III studies, cetuximab has been shown to improve outcomes when added to standard chemotherapy for treatment of metastatic colorectal cancer. The Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) study showed reductions in risk of progression and tumor response in patients who received cetuximab in addition to a chemotherapy regimen of irinotecan, infusional fluorouracil, and leucovorin (FOLFIRI). In particular, the benefits of cetuximab appeared to be limited to patients whose tumors were wild-type at the KRAS gene. This study is an updated analysis of
the CRYSTAL study that evaluates outcomes after a longer follow-up time and in a larger number of patients evaluated for KRAS status. In addition, the significance of the BRAF gene, which is a downstream effector of KRAS was evaluated. This was a retrospective subgroup analysis of KRAS mutation status in patients enrolled in an open-label, randomized, multicenter, phase III study of cetuximab plus FOLFIRI or FOLFIRI alone as first-line treatment for metastatic colorectal cancer. Among patients whose tumors were wild-type for KRAS, cetuximab plus FOLFIRI resulted in significantly reduced risk of disease progression (median progression free survival [PFS], 9.9 vs 8.4 months;), significantly improved overall survival (23.5 vs 20.0 months;), and significantly increased odds of response (best overall response rate 57.3% vs 39.7%;) compared with FOLFIRI alone. Among patients with wild-type KRAS, those in the cetuximab plus FOLFIRI group who developed early acne-like rash had significantly prolonged survival time compared with those who did not develop early acne-like rash (26.4 vs 19.1 months). Among patients with mutations in KRAS, the addition of cetuximab did not improve PFS, overall survival, or best overall response. KRAS mutations were associated with worse overall survival in both treatment groups compared with wild-type. Treatment effect and KRAS mutation status were associated with significant interaction effects for PFS, overall survival, and best overall response. A total of 60 of 999 (6%) tumor samples evaluated for both BRAF and KRAS had BRAF V600E mutations. All but 1 patient with BRAF were wild-type for KRAS. Patients who were wild-type for both genes who received cetuximab plus FOLFIRI had significantly reduced risk of disease progression and significantly increased odds of response compared with FOLFIRI alone, but overall survival no longer differed significantly between treatment groups. BRAF mutation status was not associated with a significant treatment interaction effect, but was associated with worse outcomes in both treatment groups. KRAS mutation status was not associated with differences in safety outcomes.