

The Gastrointestinal Cancers Symposium

January 22-24, 2010

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STUDIES ADVANCE DETECTION AND TREATMENT OF GASTROINTESTINAL CANCERS

**-- Simple Blood Test Detects Early Colorectal Cancer and Adenomas;
Early-Detection Test Developed for Pancreatic Cancer;
Researchers Identify Hereditary, Predictive Gene Variation for Aggressive Gastric
Cancer;
Adjuvant XELOX Slows Colon Cancer Progression in Patients of All Ages, Including
Those over 70 --**

ORLANDO, Fla. – New research on the treatment of gastrointestinal cancers was released today in advance of the seventh annual Gastrointestinal Cancers Symposium, being held January 22-24, 2010, at the Orlando World Center Marriott.

Four significant studies were highlighted today in a presscast (press briefing via live webcast):

- *Simple blood test detects colorectal cancer and colorectal adenomas:* A new test for blood levels of the CD24 protein is more than 90 percent sensitive and specific for detecting colorectal cancer, and more than 80 percent accurate at detecting potential precancers, called adenomas. These findings may prove useful for identifying patients who would benefit most from colonoscopy.
- *New test for early detection of pancreatic cancer:* Researchers report on a promising immunoassay that detects early-stage pancreatic cancers with a high degree of accuracy. The assay identifies and quantifies blood levels of the PAM4 protein – a unique antigen present in almost 90 percent of pancreatic cancers and precancers. Pancreatic cancer is typically diagnosed at a late stage, when it is more difficult to treat.
- *Inherited gene variation predicts aggressive gastric cancer:* For the first time, researchers report the identification of an inherited genetic variation – located on the *CD44* gene – that is linked to increased risk of recurrence in patients with gastric (stomach) cancer.
- *Adjuvant XELOX chemotherapy regimen slows colon cancer progression in patients of all ages, including those 70+:* Adjuvant (post-surgical) treatment with capecitabine and oxaliplatin (XELOX) is more effective than standard 5-fluorouracil and leucovorin (5-FU/LV) for slowing the progression of stage III colon cancer among patients of all ages, including those age 70 and older – findings that may prompt more aggressive treatment for older patients in otherwise good health.

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“Growing understanding of molecular biology has helped us make enormous progress in screening, detection and treatment for gastrointestinal cancers,” said Robert P. Sticca, MD, Chairman of the Department of Surgery and Professor at the University of North Dakota School of Medicine and Health Sciences, who moderated the presscast. “These studies describe long-awaited approaches, such as an early detection test for pancreatic cancer and a blood test for colon cancer. Other studies presented today will help us to better personalize treatment for gastric and colon cancers based on patients’ age and genetic factors.”

Gastrointestinal cancers include those of the colon/rectum, stomach, pancreas, esophagus, small intestine, anus and other digestive organs. More than 275,000 people in the U.S. are diagnosed with these cancers each year, and nearly 136,000 people die from them.

The Gastrointestinal Cancers Symposium is co-sponsored by the American Gastroenterological Association (AGA) Institute, the American Society for Clinical Oncology (ASCO), the American Society for Radiology Oncology (ASTRO) and the Society of Surgical Oncology (SSO).

More information for media: [2010 GI Cancers Symposium Press Kit](#)

Relevant links on ASCO’s patient website, www.Cancer.Net

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General Poster Session C
Sunday, January 24, 2010
7:00-8:00 AM EST

Lead Author: Sarah Kraus, PhD
Tel Aviv Souraski Medical Center
Tel Aviv, Israel

Simple Blood Test Detects Early Colorectal Cancer and Adenomas

Researchers have developed the first reliable blood test for detecting colorectal adenomas and colorectal cancers – findings that may prove useful for identifying patients who would benefit most from colonoscopy. The test examines blood levels of the CD24 protein, which is produced early in the multistep process of colorectal cancer development and may be involved in the spread of tumor cells.

“Screening is effective for early colorectal cancer detection and prevention, but for a range of reasons, many people are reluctant to undergo colonoscopy. Most people, however, are willing to have a blood test,” said lead author Sarah Kraus, PhD, who heads a research laboratory at Tel Aviv Souraski Medical Center in Israel. “The CD24 blood test holds promise for identifying the patients at risk for colorectal cancer and could help guide the best use of colonoscopy resources.”

Colonoscopy and stool testing for occult blood are currently the primary methods for detecting colorectal cancer and colorectal adenomas (growths that have the potential to progress to cancer). However, colonoscopy remains underutilized in the U.S., and the stool blood test is not very sensitive.

In this study, Dr. Kraus and her colleagues examined the sensitivity (ability to accurately detect an abnormality) and specificity (ability to differentiate cancer or adenomas from other diseases) of the CD24 blood test in 150 patients undergoing colonoscopy. They found that the CD24 test was 92.3 percent sensitive and specific for detecting colorectal cancer, and 84.2 percent sensitive and 89.2 percent specific for detecting adenomas.

Dr. Kraus noted that larger studies are needed to validate these findings before the blood test can be widely used for colorectal cancer screening. The test is expected to be relatively inexpensive (less than \$50).

Use of a simple blood test evaluating the level of CD24 protein to detect subjects with adenomas

Authors: S. Kraus, I. Naumov, D. Kazanov, S. Shapira, E. Shmueli, A. Hallak, I. Shafat, F. Kastrinos, A. I. Neugut, N. Arber

Background: CD24 is a cell surface protein and P-selectin ligand, involved in cell adhesion and metastasis. Using gene expression array we have shown that CD24 expression is associated with colorectal cancer (CRC) (Sagiv E, et al. *Gastroenterology* 2006; 131:630-9). The data was confirmed by IHC staining showing expression of CD24 in ~90% of adenomas and adenocarcinomas. The aim of the study was to evaluate CD24 protein expression in peripheral blood lymphocytes (PBLs) from normal, adenoma, and CRC subjects. **Methods:** We initially recruited 150 consecutive subjects attending Tel Aviv Souraski Medical Center. Each consented individual underwent colonoscopy. PBLs were isolated from blood samples and protein extracts were subjected to SDS-PAGE and Western blotting using anti-CD24. The samples were also externally evaluated. A second validation trial was conducted which included 73 consecutive subjects. Band intensities were scanned and tested for statistical significance. Sensitivity and specificity for CD24 was calculated using receiver operating characteristic (ROC) curves. The study was approved by the Israel Ministry of Health. **Results:** Among the patients that we first analyzed, 63 had colorectal cancer (CRC), 19 had adenomas, and 68 had normal colonoscopies. The sensitivity and specificity of the CD24 test for distinguishing CRC from normal subjects was 70.5% (95% CI, 54.8-83.2%) and 83.8% (95% CI, 74.6-92.7%), respectively, and for the detection of advanced adenomas was 84.2% (95% CI, 60.4-96.4%) and 73.5% (95% CI, 61.4-83.5%), respectively. The results obtained in the external evaluation slightly varied. Improved values were achieved in the validation trial. Thus, the sensitivity for the detection of CRC was 92.3% (95% CI, 63.9-98.7%), with similar specificity, whereas the specificity for detecting adenomas was higher, 89.2%(95% CI, 74.6-96.9%).

Conclusions: This blood test is the first of its kind to be able to detect adenomas. It can also successfully distinguish CRC from healthy subjects. CD24 may serve as a new potential and promising blood biomarker for the early detection and CRC surveillance. **Disclosures:** Nothing to disclose.

General Poster Session B
Saturday, January 23, 2010
11:20 AM-12:50 PM EST

Lead Author: David V. Gold, PhD
Garden State Cancer Center
Belleville, N.J.

Researchers Develop Early-Detection Test for Pancreatic Cancer

Researchers have developed a novel immunoassay for detecting early-stage pancreatic cancer that identifies and quantifies blood levels of the PAM4 protein – a unique antigen present in almost 90 percent of pancreatic cancers and precancers.

“Most patients with pancreatic cancer are diagnosed when the disease is advanced and more difficult to cure,” said lead author David V. Gold, PhD, a member of the Garden State Cancer Center in New Jersey. “In this study, we found that the PAM4 protein is quite accurate at identifying patients with pancreatic cancer and, if validated in larger studies, would be a promising tool for detecting this disease in its earlier, more treatable stages, before it spreads to other organs.”

The PAM4 antibody (also called clivatuzumab) used in this assay reacts with a protein produced by pancreatic cancer cells. The protein is not detectable in normal pancreatic cells and is rarely detected in a non-cancerous condition, called pancreatitis (inflammation of the pancreas), making it highly specific for pancreatic cancer. (Pancreatic cancer is initially often difficult to distinguish from pancreatitis.)

The researchers evaluated an immunoassay for the PAM4 protein in 68 patients who had pancreatic cancer surgery and 19 healthy controls. They found that the test was 62 percent sensitive for detecting stage 1 pancreatic cancer (disease confined to the pancreas), 86 percent sensitive for stage 2 disease (disease which has spread to nearby organs) and 91 percent sensitive for stage 3/4 cancers (local and distant spread). The assay was 81 percent sensitive for detecting all stages of pancreatic cancer.

The investigators concluded that these promising data warrant further evaluation to determine how the test can improve the management of patients with pancreatic cancer. If these results are confirmed, it may become possible to test people at risk for pancreatic cancer (patients with a history of tobacco use, or those with genetic or other medical factors) on a yearly basis, to enhance the chance of early detection. Currently, just 7 percent of pancreatic cancer cases are detected at an early stage, before the cancer has spread to other parts of the body. The survival rate for early-stage pancreatic cancer is 20 percent, compared with just 1.8 percent for those diagnosed when the disease has metastasized.

The investigators noted that the clivatuzumab antibody may also prove useful for treating the disease by acting as a carrier for agents (such as radioactive isotopes) that can target and kill cancer cells.

The PAM4 serum enzyme immunoassay (EIA) for detection of early-stage pancreatic carcinoma

Authors: D. V. Gold, M. Goggins, G. Newsome, D. E. Modrak, M. Liu, D. M. Goldenberg

Background: Pancreatic cancer is almost universally lethal because of not being detected early enough for implementing effective treatment. Our goal has been the development of a serum assay that detects early-stage pancreatic carcinoma (PC) with high sensitivity and specificity. The PAM4 mAb identifies a unique biomarker having high specificity for a mucin glycoprotein expressed by PC. While identified in almost 90% of PC and its precursor lesions by immunohistochemistry, the antigen is not detectable in normal pancreas and rarely in pancreatitis. Thus, its presence in the blood of PC patients is the basis for our evaluating its role for early detection of this disease.

Methods: The PAM4-based EIA was employed for detection and quantitation of this biomarker in the serum of patients who had surgical resection of PC (n = 68) and healthy volunteer controls (n = 19). **Results:** We previously reported use of an EIA for quantitation of PAM4-antigen in the serum. The assay demonstrated a sensitivity and specificity of 77% and 95%, respectively, for PC (*J Clin Oncol.* 2006;24:252-8). However, at the time, we did not have information on tumor size and stage of disease. We now provide evidence that the PAM4 serum immunoassay detects early PC with sensitivity rates of 62% and 86% for early stages I and II, respectively. Stage I specimens could be divided, based on tumor size, into stage IA (n = 13) and stage IB (n = 8), with detection rates of 54% and 75%, respectively; however, the number of specimens within each subgroup are small. As expected, the sensitivity for

detection of advanced, stage III and IV, PC patients was high (91%). Overall, the sensitivity and specificity for discrimination of all stages of PC versus healthy volunteers were 81% and 95%, respectively, calculated by ROC curve analysis (AUC of 0.92 ± 0.03 ; 95% CI = 0.84-0.97). **Conclusions:** The PAM4-EIA can detect a high percentage of early stage I and stage II PC. These data warrant evaluation of this biomarker assay's impact on the management of patients with pancreatic carcinoma. **Disclosures:** David Goldenberg, Employment/Leadership Position, Immunomedics, Stock Ownership, Immunomedics.

**General Session II
Friday, January 22, 2010
10:50-11:05 AM EST**

**Lead Author: Thomas Winder, MD
University of Southern California
Los Angeles, Calif.**

Researchers Identify Hereditary, Predictive Genetic Variation for Aggressive Gastric Cancer

Investigators report for the first time that they have identified an inherited genetic variation in patients with gastric (stomach) cancer that predicts more aggressive disease. Researchers found that patients with this variation – located on the *CD44* gene – experienced recurrence more than three times sooner than patients without this variation.

“If our findings are confirmed in larger, prospective clinical trials, testing for the *CD44* variation could help us identify patients who would benefit from more aggressive treatment, as well as facilitate the development of therapies targeting this genetic variation,” said lead author Thomas Winder, MD, a postdoctoral research fellow at the University of Southern California.

The *CD44* gene regulates the production of a protein associated with cell adhesion (the loss of which is associated with cancer development) and metastasis in digestive cancers. Altered *CD44* may also make cancer cells more resistant to chemotherapy or radiation therapy.

In this study, Dr. Winder and his colleagues analyzed the association between the presence of the *CD44* variation and the time to recurrence in 104 patients with localized gastric cancer at the University of Southern California. They found that patients who had the *CD44* variation had a significantly shorter time to recurrence (2.1 years) compared to those without this variation (7 years).

Because the genetic variation is inherited, it is theoretically possible that this finding could be used to develop a genetic test to predict an individual’s risk of developing gastric cancer before it develops. However, Dr. Winder cautioned that epidemiological studies need to be conducted to further characterize and confirm the role of this genetic variation in gastric cancer development.

Germline polymorphism in the CD44 gene is associated with clinical outcome in localized gastric adenocarcinoma

Authors: T. Winder, W. Zhang, D. Yang, Y. Ning, P. O. Bohanes, A. Pohl, G. Lurje, H. Lenz

Background: The loss of cell adhesion is a significant event in human cancer development. CD44 is a transmembrane glycoprotein serving as the principal transmembrane hyaluronate receptor, which is associated with adhesion and metastasis in gastrointestinal carcinomas. Moreover, a gastric cancer stem cell population with CD44 as their defined surface marker has been identified showing increased resistance for chemotherapy- or radiation-induced cell death. Previously, our group showed that germline polymorphisms in angiogenesis pathway may serve as independent molecular prognostic markers in patients with localized gastric adenocarcinoma. Here we tested the hypothesis whether germline variations in CD44 will predict clinical outcome in patients with localized gastric adenocarcinoma. **Methods:** Between 1992 and 2008 peripheral blood samples were obtained from 104 patients (41 females and 63 males with a median age of 57 years; range = 26-85) with localized gastric cancer at University of Southern California medical facilities. The median time to recurrence (TTR) was 2.2 years (95% CI: 1.7-4.4 years). The median OS was 4.5 years (95% CI: 3.4-5.7 years) with median follow-up of 3.3 years (range 0.1-14.6). DNA was isolated and four cell-adhesion related, potentially functional polymorphisms within the CD44 gene (rs8193, rs187116, rs4755392, rs7116432) were analyzed using PCR-restriction fragment length polymorphism. **Results:** Patients carrying at least one G allele (GG; AG) at the CD44 +4883G > A gene locus (rs187116) had a significantly shorter median TTR of 2.1 years compared to 7.0 years TTR for patients with AA (p = 0.036, log-rank test). After adjusting for covariates (chemotherapy, N-category, race) in the multivariate analysis, patients with AA alleles remained significantly associated with TTR, compared to the other patients carrying at least one G allele (GG; AG) (adjusted p-value = 0.019). No statistical significant association was found between TTR and the other three tested SNP’s (rs8193, rs4755392, rs7116432). **Conclusions:** For the first time we have identified a germline polymorphism in the CD44 gene associated with clinical outcome in patients with localized gastric adenocarcinoma. Our exploratory data warrant future confirmatory trials. **Disclosures:** Nothing to disclose.

**Oral Abstract Session:
Cancers of the Colon and Rectum
Sunday, January 24, 2010**

11:20-11:35 AM EST

Lead Author: Daniel G. Haller, MD

**Abramson Cancer Center at the
University of Pennsylvania
Philadelphia, Pa.**

Adjuvant Capecitabine Plus Oxaliplatin More Effective than 5-FU and Leucovorin in Improving Disease-Free Survival in Patients of All Ages, Including Those 70 and Older

Summary includes updated data not in the abstract

A randomized phase III study has shown that post-surgical (adjuvant) treatment with the capecitabine and oxaliplatin (a combination called XELOX) is more effective than standard 5-fluorouracil and leucovorin (5-FU/LV) therapy for slowing the progression of stage III colon cancer among patients of all ages, including those age 70 and older. Previous data have suggested that older patients may not benefit from or be able to tolerate aggressive adjuvant treatment with newer chemotherapy drugs, beyond 5FU/LV.

“These findings indicate that patients with stage III colon cancer benefit more from the newer, XELOX adjuvant treatment regimen than from traditional adjuvant chemotherapy, and that this benefit persists among older patients. While treatment decisions should be made on an individual basis, these findings shed important new light on how we can best treat otherwise healthy patients age 70 and older,” said lead author Daniel G. Haller, MD, Professor of Medicine and Deenie Greitzer Professor of Gastrointestinal Oncology at the Abramson Cancer Center at the University of Pennsylvania.

In this study, 1,886 patients with stage III colon cancer were randomly assigned to receive XELOX or 5-FU/LV chemotherapy following surgery. After 3 years, 71 percent of patients in the XELOX group did not experience disease progression compared with 67 percent of the 5-FU/LV group, a difference that was statistically significant. Among patients younger than 70, 72 percent of patients in the XELOX group did not experience disease progression after three years versus 69 percent of those in the 5-FU/LV group. The corresponding figures for patients age 70 and older were 66 percent and 60 percent, respectively. Analysis of overall survival is ongoing.

The use of newer chemotherapy drugs in the adjuvant setting for older patients with stage III colon cancer has been a topic of controversy, and these findings contradict conclusions from two recent studies. The first, a 2009 retrospective meta-analysis of six clinical trials, found that elderly patients with stage III colon cancer did not experience improved disease-free survival or longer overall survival after receiving therapy that included newer drugs such as oxaliplatin, irinotecan and capecitabine, compared to 5FU/LV controls. In addition, the prospective MOSAIC trial recently reported that adjuvant treatment with oxaliplatin and 5-FU/LV did not provide additional benefit for elderly patients. These data have prompted some clinicians to decide against using these drugs for their older patients. In addition, German clinical guidelines were amended based on these previous studies, and a European trial examining adjuvant treatment for colorectal cancer – PETACC-8 – was amended to exclude patients over age 70. According to the authors of the current study, these new data are strong enough to recommend that patients should be evaluated on an individual basis for XELOX therapy, regardless of age.

Efficacy findings from a randomized phase III trial of capecitabine plus oxaliplatin versus bolus 5-FU/LV for stage III colon cancer (NO16968): No impact of age on disease-free survival (DFS)

Authors: D. G. Haller, J. Cassidy, J. Taberero, J. A. Maroun, F. G. De Braud, T. J. Price, E. Van Cutsem, M. Hill, F. Gilberg, H. Schmoll

Background: Adjuvant capecitabine is at least equivalent to bolus i.v. 5-FU/LV for DFS and overall survival (OS) in stage III colon cancer. NO16968 compared XELOX with bolus i.v. 5-FU/LV (standard regimen at study start) for stage III colon cancer. In a planned safety analysis, XELOX had an acceptable safety profile (Schmoll et al. JCO 2007). In a recent analysis of the ACCENT database, investigators concluded that newer adjuvant regimens are not associated

with significant efficacy benefits versus 5-FU/LV in patients (pts) ≥ 70 years (McCleary et al. ASCO 2009). We examined DFS across age groups in NO16968. **Methods:** Pts were randomized to either XELOX (capecitabine 1000 mg/m² bid d1–14 + oxaliplatin 130 mg/m² i.v. d1, q3w x8) or bolus i.v. 5-FU/LV regimens: Mayo Clinic (LV 20 mg/m² + 5-FU 425 mg/m² d1–5, q4w x6) or Roswell Park (LV 500 mg/m² + 5-FU 500 mg/m² d1, w1–6 in 8w cycles x 4). Each center's preferred 5-FU/LV regimen was selected at study start and used in all pts treated. **Results:** 1,886 pts were randomized between Apr 2003 and Oct 2004. 1,864 were evaluable in the previously reported safety analysis. After a median follow-up of 57 months, 1,886 pts are evaluable for DFS (primary endpoint), which was significantly superior for XELOX at 3, 4, and 5 years (Table). Analysis of 3-year DFS in pts < 70 and ≥ 70 years showed a similar advantage of XELOX over 5-FU/LV. **Conclusions:** XELOX is superior to bolus 5-FU/LV for DFS as adjuvant treatment for stage III colon cancer. These findings confirm the benefits shown with oxaliplatin plus 5-FU combinations in stage III pts in the MOSAIC and NSABP C-07 trials. Additionally, efficacy benefits seem to be maintained in pts ≥ 70 years and differ from the ACCENT meta-analysis and MOSAIC. It is reasonable to evaluate each pt for XELOX therapy on individual merits, regardless of age. OS data are currently immature; follow-up is ongoing and updates will be reported when available. **Disclosures:** Daniel Haller, Consultant or Advisory Role, sanofi-aventis, Hoffmann-La Roche, Honoraria, sanofi-aventis, Hoffmann-La Roche, Research Funding, Hoffmann-La Roche; James Cassidy, Consultant or Advisory Role, sanofi-aventis, Hoffmann-La Roche, Honoraria, sanofi-aventis, Hoffmann-La Roche, Research Funding, sanofi-aventis, Hoffmann-La Roche; Josep Taberero, Consultant or Advisory Role, sanofi-aventis, Hoffmann-La Roche; Jean Maroun, Consultant or Advisory Role, Hoffmann-La Roche, Honoraria, Hoffmann-La Roche, Research Funding, Hoffmann-La Roche; Filippo De Braud, Consultant or Advisory Role, sanofi-aventis, Honoraria, sanofi-aventis, Hoffmann-La Roche; Timothy Price, Consultant or Advisory Role, sanofi-aventis, Hoffmann-La Roche; Eric Van Cutsem, Consultant or Advisory Role, Hoffmann-La Roche, Research Funding, Hoffmann-La Roche; Frank Gilberg, Employment/Leadership Position, Hoffmann-La Roche, Stock Ownership, Roche Connect and Roche Genusschein, Hans-Joachim Schmoll, Consultant or Advisory Role, Hoffmann-La Roche, Honoraria, Hoffmann-La Roche, Stock Ownership, Hoffmann-La Roche, Research Funding, Hoffmann-La Roche.

	3-year DFS		4-year DFS	5-year DFS
Total population				
XELOX	71.0%	HR 0.80; p=0.0045	68.4%	66.1%
5-FU/LV	67.0%		62.3%	59.8%
Analysis by age group				
<70 years	HR 0.79 (95% CI 0.66–0.94)			
≥ 70 years	HR 0.87 (95% CI 0.63–1.18)			

Disclosures for 2010 Gastrointestinal Cancers Symposium News Planning Team

Daniel Chung, MD: Consultant for Myriad Labs; Honoraria from Ipsen

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