

The Gastrointestinal Cancers Symposium

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-- MEDIA WEBCAST TUESDAY, JANUARY 13, NOON (EST) --

ADVANCES IN THE TREATMENT OF GASTROINTESTINAL CANCERS

- Routine *KRAS* Testing in Patients with Metastatic Colorectal Cancer Could Save \$604 Million in Drug Costs Annually--**
- Gene Mutations Link GERD and Esophageal Cancer --**
- Octreotide LAR Slows Cancer Growth in Patients with Rare Neuroendocrine Tumors--**
- Genetic Variations May Predict Survival, Outcomes for People with Pancreatic Cancer --**

San Francisco, CA – New research on the treatment of gastrointestinal cancers was discussed today at a press briefing for the sixth annual Gastrointestinal Cancers Symposium, which is co-sponsored by the American Gastroenterological Association (AGA) Institute, the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO) and the Society of Surgical Oncology (SSO). The Symposium is being held from January 15 to 17 at the Moscone West Building in San Francisco.

“These studies address a pressing question in cancer care – how can we identify those patients who will benefit from treatment and differentiate them from those who will not?” said Jennifer C. Obel, M.D., a gastrointestinal cancers specialist, attending physician at NorthShore University HealthSystem, and moderator of the presscast. “In an era when the cost of cancer care continues to increase, the ability to tailor treatment to each patient’s disease could lead to improved outcomes and fewer side effects for patients, and significant cost savings.”

Gastrointestinal cancers include cancers of the esophagus, stomach, small intestine, colon, rectum, anus, pancreas and liver. More than 270,000 people are diagnosed with GI cancers in the United States every year, and more than 135,000 people die from them annually.

Studies highlighted in today’s presscast include:

- An economic analysis showing that routine testing for *KRAS* gene mutations in patients with metastatic colorectal cancer could save the U.S. health system up to \$604 million per year in the cost of the drug cetuximab (Erbix). Recent studies have shown that cetuximab is only effective in patients with the normal (wild-type) form of the *KRAS* gene.

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- Research finding for the first time that that specific mutations in the *EGF* gene may be able to predict esophageal cancer risk in people with gastroesophageal reflux disease (GERD), a key step in identifying which of the 20 million people with GERD in the United States may benefit from aggressive screening for esophageal cancer.
- A study finding that the drug octreotide LAR (Sandostatin LAR) slows cancer growth in patients with malignant neuroendocrine tumors of the lower small intestine, marking the first drug option for this rare cancer type.
- A study that identifies genetic variations that may predict survival and outcomes for people with pancreatic cancer. These early findings have the potential to spare patients from the side effects and high costs of aggressive surgery, chemotherapy and/or radiation when such treatment is unlikely provide any health benefit.

Information for Media: www.asco.org/GIpresskit09

Relevant Links on ASCO's Cancer.Net:

- [Cancer.Net Guide to Colorectal Cancer](#)
- [Cancer.Net Guide to Esophageal Cancer](#)
- [Cancer.Net Guide to Pancreatic Cancer](#)
- [Cancer.Net Guide to Neuroendocrine Tumor](#)
- [Clinical Trials](#)
- [Genetics](#)
- [Tumor Mutation Predicts Effectiveness of Cetuximab for Colorectal Cancer](#)
- [Financial Resources](#)

Using *KRAS* Testing to Avoid Unnecessary Treatment with Cetuximab (Erbix) for Metastatic Colorectal Cancer Could Result in Annual Cost Savings of \$604 Million

Researchers from the Jesse Brown Veterans Administration Hospital and Northwestern University in Chicago have shown that testing and treating patients with metastatic colorectal cancer based on their *KRAS* gene mutation status could yield significant cost savings for the United States health care system – up to \$604 million per year.

Previous studies have demonstrated that only patients whose tumors have the normal (wild-type) form of the *KRAS* gene respond to treatment with cetuximab (Erbix), a monoclonal antibody that blocks the epidermal growth factor receptor (EGFR) in tumors. Using a novel economic model, researchers evaluated the cost savings associated with limiting first-line cetuximab treatment to patients whose tumors have the normal form of the *KRAS* gene and avoiding unnecessary treatment in patients whose tumors have a mutated form of the gene.

“Personalizing cancer treatment based on gene status could spare thousands of people with colorectal cancer from side effects of treatments that are highly unlikely to improve their health, while saving the health care system substantial sums,” said Veena Shankaran, MD, a postdoctoral fellow at the Veterans Administration Center for the Management of Complex Chronic Care and Northwestern University’s Robert H. Lurie Comprehensive Cancer Center, and the lead author of the study. “Previous research has shown that treatment decisions for patients with metastatic colorectal cancer should be based on *KRAS* testing. Although a significant number of institutions are incorporating this, it’s not yet universal. Our findings show that *KRAS* testing is not only good medicine, it’s also good economics.”

The investigators used the American Cancer Society’s estimated incidence of metastatic colorectal cancer cases (28,724 in 2008) and determined that the cost of testing every newly diagnosed patient for *KRAS* mutations would be approximately \$13 million (\$452 per patient). They then estimated that the average newly diagnosed patient treated with cetuximab receives 24 doses, which yields a total drug cost of \$61,279 per patient. Researchers conservatively estimated that 35.6 percent of patients’ tumors have *KRAS* mutations (some studies have shown *KRAS* mutations occurring in up to 46 percent of metastatic colorectal cancers). Based on this, they projected that the cost savings from treating only patients with normal *KRAS* would be \$617 million; subtracting the costs of *KRAS* testing, researchers estimate a net savings of \$604 million.

The researchers said that future analyses would estimate cost savings associated with using *KRAS* testing to select patients for second- and third-line treatment with cetuximab, as well as treatment with panitumumab (Vectibix), another EGFR targeted therapy that is approved for metastatic colorectal cancer. They also plan to adapt their model to account for the treatment and hospitalization costs associated with side effects caused by these drugs in patients whose tumors have *KRAS* mutations.

Economic implications of *Kras* testing in metastatic colorectal cancer (mCRC)

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Background: Recent studies have demonstrated a benefit with the addition of cetuximab to FOLFOX or FOLFIRI in the first-line treatment of metastatic CRC. Subsequent correlative analyses have shown that this benefit is limited to patients whose tumors have wild type *Kras* status by PCR-based testing. Based on these results, patients with mutated *Kras* should no longer receive cetuximab in first or subsequent lines of therapy. In addition to avoiding unnecessary toxicity, tailoring therapy based on *Kras* will result in significant cost savings for the health care system. **Methods:** Using the 2008 American Cancer Society estimated incidence of metastatic CRC, the cost of *Kras* testing in all patients was determined. With the assumption that patients would receive first-line therapy with a cetuximab-containing regimen, the amount saved by withholding cetuximab in *Kras* mutants (excluding costs of managing drug toxicity) was calculated. Cost estimate for *Kras* testing was obtained from a commercial lab. **Results:** Based on an annual incidence of 28,274 new metastatic CRC cases, upfront *Kras* testing would cost \$13 million (\$452/patient). Using the average wholesale price of cetuximab (\$3,986/loading dose and \$2,491/weekly dose for a patient of average BSA (1.73m²)), drug cost is \$61,279/patient; this assumes an average of 24 doses per patient, as described in the CRYSTAL analysis (Van Cutsem, E. *ASCO* 2007). With the assumption that patients with mutated *Kras* (35.6% of all patients) would not receive cetuximab (other studies have found *Kras* mutation in up to 46% of patients), theoretical drug cost savings would be \$617 million; considering the cost of *Kras* testing, net savings would be \$604 million. **Conclusion:** To our knowledge, this is the first analysis to demonstrate cost savings by customizing therapy in a GI malignancy using a molecular test. Though cetuximab is used more commonly in second- and third-line therapy where treatment duration is shorter, *Kras*-based treatment selection is likely to result in cost savings across all lines of therapy. On a large scale, development of validated predictive molecular markers will not only spare patients ineffective and toxic therapies, but will also greatly reduce futile costs.

Disclosures for Research Team: Consultant or advisory role for ImClone Systems Incorporated; Research funding from ImClone Systems Incorporated

Mutations in *EGF* Gene Associated with Increased Esophageal Cancer Risk in People with Gastroesophageal Reflux Disease (GERD)

Researchers have identified specific mutations in the epidermal growth factor (*EGF*) gene that are associated with increased esophageal cancer risk in people with gastroesophageal reflux disease (GERD). This is the first study to examine *EGF* mutations as predictors of esophageal cancer risk in patients with GERD.

“We’ve known for some time that GERD is a risk factor for esophageal cancer, but our findings are the first to identify specific genetic markers that are linked with increased cancer risk in patients with GERD,” said Winson Y. Cheung, MD, a clinical research fellow working with the University of Toronto and the Harvard School of Public Health, and the lead author of the study. “While our findings will need to be validated in larger and more diverse patient groups, this is a first step in the right direction toward developing a test to identify which patients are at highest risk of esophageal cancer and would benefit from more aggressive screening. And because GERD is a common condition, the ability to single out patients at high risk of cancer could lead to better outcomes and significant cost savings.”

More than 16,000 cases of esophageal cancer were diagnosed in 2008. If detected early, the disease is generally curable, but screening is invasive and expensive (involving the insertion of an endoscopy into the esophagus), so it is not recommended for all patients with GERD. GERD is estimated to affect nearly 20 million people in the United States.

In this study, the researchers collected DNA samples from 309 patients being treated for esophageal adenocarcinoma (the most common type of esophageal cancer in North America) at Massachusetts General Hospital in Boston, and 275 healthy, matched controls. The investigators analyzed study participants’ genotypes and GERD history.

They found that patients who had the mutated *EGF* variant called G/G and experienced symptoms associated with GERD more than once a month were at a 10-fold increased risk of esophageal cancer, compared with those who had the A/A (normal, or wild-type) variant and did not have GERD. Esophageal cancer risk increased further among patients with the mutation who suffered from GERD more frequently or for a long period of time (more than 15 years). Patients with GERD and the genetic variant called A/G had an intermediate increase in risk.

Epidermal growth factor (*EGF*) gene polymorphism, gastroesophageal reflux disease (GERD) and risk of esophageal adenocarcinoma (EA)

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Introduction: Single nucleotide polymorphisms (SNPs) of key genes, such as *EGF A61G*, are associated with an elevated risk of EA, but the lack of full penetrance indicates that the effects of these SNPs on esophageal carcinogenesis are likely modified by additional genetic or environmental variables. Since GERD is an established risk factor for EA, we evaluated whether the association between *EGF* polymorphism and EA development is altered by the presence of GERD.

Methods: *EGF* genotyping of DNA samples was performed and GERD history was collected for 309 EA patients and 275 matched healthy controls. Associations between genotypes and EA risk were examined with adjusted logistic regression. Genotype-GERD relationships were explored using analyses stratified by GERD history and joint effects models that considered severity and duration of GERD symptoms. **Results:** Baseline characteristics were comparable between cases and controls except that *EGF* variants (*A/G* or *G/G*) were more common ($p=0.02$) and GERD was more prevalent ($p<0.001$) in cases than in controls. When compared to the *EGF* wild type *A/A* genotype, the *G/G* variant was associated with an increased risk of EA (OR 1.90; 95% CI, 1.2-3.0; $p=0.007$). Stratified analyses revealed that this correlation between *G/G* genotype and EA risk was evident only for the subset of patients with GERD (see table). In the joint effects models, the odds of EA was highest for *G/G* patients who either experienced frequent GERD of greater than 1 time per week (OR 21.8; 95% CI, 5.1-94.0; $p<0.001$) or suffered GERD for longer than 15 years (OR 22.4; 95% CI, 6.5-77.6; $p<0.001$). There was a highly significant interaction between the *G/G* genotype and the presence of GERD ($p=0.007$).

Conclusions: *EGF* polymorphism exerts its effect on EA susceptibility through an interaction with GERD. Performing *EGF* genotyping for patients with severe or longstanding GERD can help to identify individuals at the greatest risk of EA.

Risk of EA by <i>EGF A61G</i> polymorphism in the overall cohort and in GERD vs no GERD subsets					
	Number of Cases / Controls	Adjusted Odds Ratio of EA by <i>EGF A61G</i> Gene Polymorphism			
		<i>A/G</i> vs <i>A/A</i> Genotype		<i>G/G</i> vs <i>A/A</i> Genotype	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Entire Study Cohort	309 / 275	1.22 (0.8 - 1.8)	0.30	1.90 (1.2 - 3.0)	0.007
GERD Subset	205 / 62	1.52 (0.8 - 2.9)	0.21	3.39 (1.4 - 8.0)	0.005
No GERD Subset	104 / 213	0.93 (0.6-1.6)	0.79	0.67 (0.3 - 1.4)	0.30

EA, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; OR, odds ratio; CI, confidence interval

Disclosures for Research Team: Nothing to disclose

Ocreotide LAR Slows Cancer Growth in Patients with Rare Midgut Neuroendocrine Tumors – A Promising Drug Option for the Disease

A multi-institutional German research group has shown that the drug octreotide LAR (Sandostatin LAR) can slow tumor progression in patients with malignant neuroendocrine tumors of the midgut (the lower part of the small intestine), a rare form of cancer. While precise numbers are unknown, it is estimated that a few thousand cases occur in the United States each year.

Ocreotide LAR is a peptide that mimics the hormone somatostatin, which regulates the endocrine system and also affects cell proliferation and neural communication. It is currently approved in the United States to treat certain pituitary gland disorders and to reduce diarrhea caused by other types of benign gastrointestinal tumors. Other studies have indicated that octreotide LAR may be effective for treating malignant neuroendocrine tumors (NETs), but this is the first placebo-controlled trial to test this therapy.

“While malignant neuroendocrine tumors of the midgut are relatively rare, these findings are very good news for patients. We believe our study will change the way that this disease is treated, providing the first drug option for patients who cannot be cured by surgery,” said Rudolf Arnold, MD, a professor of internal medicine at Philipps University in Marburg, Germany, and the lead author of the study. “Looking ahead, we are also evaluating the ability of octreotide LAR to slow cancer progression in pancreatic and other neuroendocrine tumors. We are also investigating the molecular make-up of these tumors to determine why some patients do not respond to the drug.”

NETs of the digestive tract can occur in the stomach, pancreas, and large intestine as well as the midgut; they can be either malignant or benign. For patients with malignant midgut tumors that are still localized, the median survival is more than 10 years; for patients whose tumors have metastasized, most often to the liver, median survival is about five years. The standard treatment for these tumors is surgery; other therapeutic options include hepatic embolization, in case of liver metastases, or radioligand therapy, though both approaches carry significant side effects. Previous research has shown that chemotherapy and radiation are not effective.

The current study was a placebo-controlled, double-blind, randomized trial that enrolled 85 patients with newly-diagnosed disease. About 70 percent of the patients had surgery before enrollment in the trial to remove the primary tumor; the remainder had more advanced, inoperable disease. In total, 86 percent of participants had liver metastases. After six months of treatment, 64 percent of patients who received the drug experienced stable disease, versus 37.2 percent of patients who received the placebo. The median time to tumor progression in the octreotide LAR group was 14.3 months, compared with 6 months in the placebo group. Researchers also found that patients with localized disease responded to the drug better than patients with many metastases; about 30 percent of patients in the trial did not respond to the drug. Because the majority of the patients are still alive, it is too early to determine an overall survival benefit.

The side effects seen in the study were not severe and have been well-established. They include diarrhea, fatigue, fever, and bile stones. Five patients discontinued this trial because of side effects.

Placebo-controlled, double-blind, prospective, randomized study of the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID study group

R. Arnold, H. Müller, C. Schade-Brittinger, A. Rinke, K. Klose, P. Barth, M. Wied, C. Mayer, B. Aminossadati, PROMID Study Group

Introduction: Octreotide is currently used for the control of symptoms in patients with gastroenteropancreatic neuroendocrine tumors (NETs). However, the ability of long-acting somatostatin analogues to control the growth of well-differentiated metastatic NETs is a matter of debate. The analysis of the first randomized, double-blind, placebo-controlled, multicenter, Phase IIIb study of octreotide LAR in patients with metastatic NETs of the midgut is presented. **Methods:** Treatment-naïve patients with histologically confirmed locally inoperable or metastasized well-differentiated NETs and a Karnofsky index >60 were randomized to receive either octreotide LAR 30 mg/month (mo) or placebo for 18 mos, or until tumor progression or death. The primary endpoint was median time to tumor progression. Secondary endpoints included objective tumor response rate (WHO criteria), measured every 3 mos, as well as symptom control and overall survival. This was a planned interim analysis using the Lan-DeMets error spending approach. **Results:** Eighty-five patients (n=43 octreotide LAR; n=42 placebo) have been enrolled to date and data from 67 patients with tumor progressions and 16 deaths (n=7 octreotide LAR; n=9 placebo) are included here. Median time to tumor progression in the octreotide LAR and placebo groups were 14.3 mos and 6 mos, respectively (HR: 0.33; 95% CI: 0.20-0.57; P=0.000037). After 6 mos of treatment, stable disease was seen in 64% and 37.2% of patients treated with octreotide LAR and placebo, respectively. Due to the low number of observed deaths, median survival time could not be estimated. **Conclusions:** Octreotide LAR significantly lengthens median time to tumor progression compared with placebo in patients with metastatic NETs of the midgut. Patients treated with octreotide LAR had a 67% risk reduction of tumor progression compared with patients receiving placebo. Octreotide LAR demonstrates substantial tumor control and shows a more favorable antiproliferative response than placebo as nearly two-thirds of patients treated with octreotide LAR achieved stable disease at 6 mos.

Disclosures for Research Team: Honoraria from Novartis; Research funding from Novartis

Genetic Variations May Predict Survival, Outcomes for People with Pancreatic Cancer

A team of researchers from the University of Texas M.D. Anderson Cancer Center has found that certain genetic variations may be able to predict response to treatment and survival in patients with pancreatic cancer. It is the first study to look at the role of variations in genes responsible for DNA “mismatch repair” (MMR) in pancreatic cancer outcomes. Pancreatic cancer has proven very difficult to treat, and five-year survival is just 5 percent.

“Some patients who are treated for pancreatic cancer do better than others, and these findings help us to understand why this is the case,” said Donghui Li, PhD, lead author and professor in the Department of GI Medical Oncology at the University of Texas M.D. Anderson Cancer Center in Houston. “As we dig deeper into genetics and personalized medicine, we are gaining new insights into the sophisticated and subtle genetic differences between those patients who will respond to certain treatment and those who will not. Such findings will eventually help us to select the best suitable treatment for each patient in order to achieve maximum efficacy.”

Mismatch repair is a process by which errors that occur when DNA is being made are fixed. If the DNA errors are overwhelming, mismatch repair will trigger cell death. Certain chemotherapeutic agents, like gemcitabine, bind to the DNA of cancer cells. When mismatch repair does not function properly, the DNA error that was caused by the binding of the drug cannot be corrected and cell death cannot be triggered. In this study, investigators examined 15 different genotypes (also known as single nucleotide polymorphisms, or SNPs) in eight genes that encode DNA MMR proteins that help repair DNA damage caused by cancer treatment; this enables cancer cells to become resistant to cancer treatment.

The study included 154 patients with potentially operable pancreatic adenocarcinomas who were already enrolled in clinical trials evaluating the benefit of preoperative radiation and chemotherapy with gemcitabine (Gemzar). DNA analysis was performed on patients’ blood samples to determine their genetic profiles.

Patients were divided into groups based on the number of unfavorable genotypes were present. Unfavorable genotypes were defined by their association with poor response to therapy, lower likelihood the tumor could be surgically removed, or reduced overall survival. The researchers found that median survival times decreased as the patients’ number of unfavorable genotypes increased, ranging from 36.2 months for patients with two unfavorable genotypes, to 8.3 months for patients with six to seven unfavorable genotypes. For patients who had only zero or one unfavorable genotype, 80 percent (20 out of 25) were still alive three to five years after being diagnosed.

Researchers also identified specific combinations of MMR gene variations that increased the likelihood that tumors could be surgically removed or that they would respond to chemotherapy and radiation therapy.

Effects of DNA mismatch repair gene polymorphisms on clinical outcome of pancreatic cancer

D. Li, X. Dong, L. Jiao, Y. Li, D. B. Evans, H. Wang, J. L. Abbruzzese

Purpose: To demonstrate whether genetic variations in DNA mismatch repair (MMR) affect clinical response to gemcitabine, tumor resectability and overall survival of patients with pancreatic cancer. **Patients and Methods:** We evaluated 15 single-nucleotide polymorphisms (SNPs) of eight MMR genes (EXO1, MLH1, MSH2, MSH3, MSH6, PMS1, TREP1, and TP73) in 154 patients with potentially resectable pancreatic adenocarcinoma. All patients were enrolled in 2 phase II clinical trials for preoperative gemcitabine-based chemoradiation at M.D. Anderson from 1999 to 2006. Associations of genotypes with tumor response to therapy (change of tumor size by radiological evaluation at restaging), margin-negative tumor resection and overall survival were evaluated using logistic regression and Cox proportional regression models. **Results:** Five, six and ten genotypes were significantly associated with tumor response to preoperative chemoradiation, tumor resectability, and overall survival, respectively, in univariable analysis. For example, tumor became larger in 27.3% of the TP73 GA/AA genotype carriers versus 5.7% of the GG carriers at the restaging CT evaluation after completion of the chemoradiation (P<0.001). Eighty three percent of the TP73 Ex2+4G>A GG genotype carriers compared to 51.5% of the GA/AA genotype carriers reached margin-negative tumor resection (P<0.001). TREP1 EX14-460C>T and TP73 Ex2+4G>A genotype remained as significant predictors for tumor response, MLH1 IVS12-169C>T and TP73 for tumor resectability, and EXO1 R354H, TREP1 and TP73 for overall survival in multivariable models including all clinical factors and genotypes examined. A strong combined genotype effect on each clinical endpoint was observed. For example, 20 of the 25 patients with 0-1 adverse genotypes were alive, those with 2, 3, 4, 5, and 6-7 adverse genotypes had median survival time of 36.2, 23.9, 16.3, 13.0, and 8.3 months, respectively (P<0.001). **Conclusion:** SNPs of MMR genes have a potential value as predictors for clinical response to gemcitabine-based therapy, and as prognostic markers for tumor resectability and overall survival of patients with resectable pancreatic cancer.

Disclosures for Research Team: Nothing to disclose

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Moderator Dr. Obel had nothing to disclose.

ATTRIBUTION TO THE 2009 GASTROINTESTINAL CANCERS SYMPOSIUM IS REQUESTED IN ALL NEWS COVERAGE