

The Gastrointestinal Cancers Symposium

January 19-21, 2012

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2012 GASTROINTESTINAL CANCERS SYMPOSIUM REVEALS NEW ADVANCES AIMED AT IMPROVING TREATMENT, PROGNOSIS AND DETECTION OF GI CANCERS

ALEXANDRIA, Va. – New research into the treatment, prognosis and early detection of gastrointestinal cancers was released today in advance of the ninth annual Gastrointestinal Cancers Symposium being held January 19-21, 2012, at The Moscone West Building in San Francisco, Calif.

Four important studies were highlighted today in a live precast:

- *Biomarkers Promising for Detecting Barrett's Esophagus Patients at High Risk for Esophageal Cancer:* Newly found biomarkers could eventually improve early detection of esophageal cancer in patients with Barrett's esophagus (BE), a condition that significantly increases esophageal cancer risk. Using a special microscope, researchers identified three optical biomarkers in cells of the esophagus lining, which enabled them to stratify patients' risks of progressing to cancer.
- *New Test Shows Promise for Detecting Early Stage Pancreatic Cancer:* A new blood-based biomarker test correctly identified nearly two-thirds of patients with early stage pancreatic cancer, which has historically been extremely difficult to detect. When combined with another tumor marker commonly used to monitor disease progression, the new test found 85 percent of patients with pancreatic cancer.
- *Study Finds Prognostic Factors for Rare Neuroendocrine Tumors, Suggests Everolimus May Be More Beneficial Than Previously Shown:* Researchers re-analyzing the results of a large phase III study of patients with advanced neuroendocrine tumors (NET) found certain factors predict which individuals are at greatest risk for neuroendocrine tumor progression and more likely to need active therapy. The re-analysis also showed that combining the drug everolimus (Afinitor) with another drug, octreotide, halted tumor growth for a longer period that previously shown, compared to octreotide alone.

–More–

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- *Multi-Targeted Drug Improves Survival in Certain Patients With Metastatic Colorectal Cancer:* An international phase III trial showed that single-agent treatment with the investigational drug regorafenib significantly improves survival and delays cancer progression in patients with metastatic colorectal cancer that has progressed despite other approved treatments, as compared to treatment with placebo and supportive care. Regorafenib is a novel, oral agent that targets multiple biological pathways involved in cancer development and growth.

“Research continues to focus on improving the lives of patients with gastrointestinal cancers in a number of ways, as we better understand how cancer develops and progresses, and develop new therapies and methods of early detection,” said Morton Kahlenberg, MD, who moderated the presscast. “At this conference, we will see the results of new studies showing novel approaches to earlier detection and treatment in some of our deadliest and hardest to treat cancers.”

Gastrointestinal cancers include those of the colon/rectum, stomach, pancreas, esophagus, small intestine, anus and other digestive organs. In 2012, nearly 285,000 people in the U.S. will be diagnosed with these cancers and more than 142,000 will die from them.¹

The 2012 Gastrointestinal Cancers Symposium 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).

Information for Media: www.asco.org/GIpresskit

Oncologist-Approved Patient Information Resources from Cancer.Net, ASCO’s Patient Website:

- [Guide to Colorectal Cancer](#)
- [Guide to Esophageal Cancer](#)
- [Guide to Neuroendocrine Cancer](#)
- [Guide to Pancreatic Cancer](#)

An interactive history of cancer research advances, including those in colorectal and pancreatic cancer, can be found at www.cancerprogress.net.

¹ *Cancer Facts & Figures 2012*. Atlanta, GA; American Cancer Society: 2012.

General Poster Session A
Thursday, January 19, 2012
11:45 PM - 01:45 PM PT
05:15 PM – 06:45 PM PT

Lead Author: Randall Brand, MD
University of Pittsburgh
Pittsburgh, PA

Biomarkers Promising for Detecting Barrett’s Esophagus Patients at High Risk for Esophageal Cancer

A study has identified new biomarkers that could eventually improve early detection of esophageal cancer in patients with Barrett’s esophagus (BE), a condition that significantly increases esophageal cancer risk. Using a special type of high-powered microscope, researchers identified three “optical biomarkers,” specific nano-scale changes in cells of the lining of the esophagus, which enabled them to stratify patients’ risks of progressing to cancer.

“If subsequent testing proves successful, our approach could lead to simpler and more effective ways of monitoring for patients with Barrett’s esophagus. Such a monitoring program would identify a subset of high-risk Barrett’s patients who need more intensive surveillance, and who could also be candidates for therapy to destroy the precancerous tissue,” said lead researcher Randall Brand, MD, professor of medicine at the University of Pittsburgh.

The incidence of esophageal adenocarcinoma in the U.S. is increasing faster than any other type of cancer – approximately 400 percent in the last three decades. If detected early, 5-year survival can be as high as 90 percent; advanced esophageal adenocarcinoma has a 5-year survival rate of 13 percent. Barrett’s esophagus, which is estimated to affect about 1 to 2 percent of the U.S. population (approximately 3 to 6 million people), is a pre-malignant condition involving a change in the epithelium lining of the esophagus, also known as intestinal metaplasia. Individuals with longstanding gastroesophageal reflux disease (GERD) are at increased risk for BE.

Currently, patients with Barrett’s esophagus are monitored for the presence of dysplasia or early stage cancers through the use of endoscopy and biopsies. The recommended surveillance method consists of multiple random biopsies of the esophagus every one to two centimeters along the length of the area of the esophagus affected by BE every three years, if no abnormality is identified. However, this practice may miss abnormal cells (dysplastic cells) that indicate unseen high-grade dysplasia or an undetected small esophageal adenocarcinoma. “Our ultimate goal is to identify all patients with high-grade dysplasia and early cancers to allow early treatment, when therapy is most effective and the least invasive,” said Brand. “The problem is that sometimes intestinal metaplasia from a patient with high-grade dysplasia looks normal under a traditional microscope.”

In the study, researchers retrospectively examined archived tissue from 60 patients with Barrett’s esophagus who underwent biopsies. Of these, 33 were known to have only intestinal metaplasia, meaning no dysplasia or cancer, while 27 patients had high-grade dysplasia or cancer. The investigators examined cells from biopsy specimens that only had intestinal metaplasia from both groups of patients: those who had no dysplasia and those who had high-grade dysplasia or cancer were diagnosed on a different biopsy specimen.

Using a special type of microscope, called spatial-domain low-coherence quantitative phase microscopy (SL-QPM), the researchers examined these samples for extremely small changes in the cell that cannot be seen by a conventional microscope. They found at least three new features that are based on the use of light to detect abnormalities in cells that distinguished patients with Barrett’s esophagus who had no cancer from those who had high-grade dysplasia/cancer. These include:

- Average optical path length of the cell nucleus, or the density of the cell nucleus
- Intra-nuclear entropy, or the random structure of the cell nucleus
- Intra-nuclear uniformity, or the texture uniformity of the cell nucleus

Using these biomarkers, the researchers developed a prediction model that resulted in 89 percent sensitivity (meaning they correctly detected 89 percent of cases of high grade dysplasia/adenocarcinoma), and 76 percent specificity (correctly identifying 76 percent of patients with non-cancer) in distinguishing Barrett's patients with high-grade dysplasia/adenocarcinoma from those without dysplasia by only looking at cells that under a traditional microscope are non-cancerous.

According to Brand, if a standard pathology examination identifies any form of dysplasia, the patient will immediately undergo treatment. These patients would not require this special imaging test. However, this test may be used for the majority of patients with Barrett's esophagus whose pathology examination showed non-dysplastic intestinal metaplasia or was ambiguous for dysplasia. Ultimately, the researchers hope the new technique would be "a simpler, more sensitive and accurate approach," requiring only two or three random biopsies and "may also allow for the identification of a subset of Barrett's patients who require less frequent monitoring."

The researchers plan to expand the study population and test additional optical biomarkers as well to improve on the current sensitivity and specificity. In the long-term, they plan on a multi-center trial using previously collected specimens at other centers to validate their results.

Abstract # 14

Title: Use of optical biomarkers from nondysplastic metaplastic cells on the detection of high-grade dysplasia and adenocarcinoma from Barrett's esophagus.

Authors: Randall Brand, Sumera Rizvi, Jon M. Davison, Rajan Bista, Kevin Staton, Douglas Hartman, Kenneth Fasanella, Kevin McGrath, Yang Liu; University of Pittsburgh, Pittsburgh, PA; University of Pittsburgh Medical Center, Pittsburgh, PA; University of Pittsburgh, Pittsburgh, PA.

Background: Patients with Barrett's esophagus (BE), defined as presence of intestinal metaplasia (IM) in the esophagus, require surveillance due to an increased risk of developing esophageal adenocarcinoma (EAC). The biggest challenge in the current surveillance methodology (i.e., Seattle protocol) is random sampling with the inability to identify those patients with non-dysplastic BE on surveillance who have occult high grade dysplasia (HGD) or will eventually progress to HGD or EAC. We propose a novel approach based on the concept of field effect to detect HGD or EAC through the analysis of non-dysplastic IM, thus identifying a high risk BE population. Our group uses a unique microscope – spatial-domain low-coherence quantitative phase microscopy (SL-QPM) to detect changes in nuclear structure as small as 0.9 nm, a scale 1000 times smaller than what conventional microscopy detects. We hypothesize that the SL-QPM-derived optical biomarkers of non-dysplastic IM would distinguish BE patients with EAC/HGD from those without neoplasia.

Methods: We performed a retrospective study of 60 BE patients who underwent Seattle protocol biopsies: 33 BE patients with IM only and 27 BE patients with HGD or EAC (21 HGD, 6 EAC). H&E stained slides with non-dysplastic IM on review by an expert pathologist were used. The distance between the selected IM biopsy and HGD/EAC was 1 to 4 cm. Forty to 60 columnar cells from each case were analyzed.

Results: We identified three optical biomarkers (nuclear optical path length, intra-nuclear uniformity, entropy) that can distinguish non-dysplastic BE from patients with HGD and EAC with statistical significance ($P < 0.01$). A prediction model combining all three optical biomarkers can distinguish BE patients with HGD/EAC from those with IM only at 89% sensitivity and 76% specificity (accuracy = 0.87).

Conclusions: The accurate assessment of nanoscale optical biomarkers by SL-QPM is a promising approach for detecting dysplastic/neoplastic Barrett's epithelium from non-dysplastic IM. This approach could potentially simplify BE surveillance by identifying a subset of high-risk BE patients that warrant intensive surveillance.

Disclosures: Nothing to disclose

General Poster Session B
Friday, January 20, 2012
11:45 PM - 01:45 PM PT
05:15 PM - 06:45 PM PT

Lead Author: David Gold, PhD
Garden State Cancer Center
Belleville, NJ

New Test Shows Promise for Detecting Early Stage Pancreatic Cancer

A study shows that a test using a monoclonal antibody to detect a cancer marker, the PAM4-protein, in the blood correctly identified nearly two thirds of patients with early stage pancreatic cancer. When combined with CA19-9, another tumor marker that is commonly used to monitor the course of the disease, the new test was able to detect 85 percent of patients with pancreatic ductal adenocarcinoma (PDAC), which makes up approximately 90 percent of all pancreatic cancers.

Based on the test's ability to correctly identify cancers already known in patients in the study, researchers say that the test may hold promise for early detection of pancreatic cancer in individuals at high risk for the disease. In addition, the test – in uncovering the PAM4-protein – opens up the possibility of personalized treatment for patients with pancreatic cancer with the use of PAM4-based imaging and therapy.

“Early detection, in addition to better therapeutics, is urgently needed for patients with pancreatic cancer,” said lead author David V. Gold, PhD, director of laboratory administration and a senior member of the Garden State Cancer Center in Morris Plains, NJ. “Pancreatic cancer symptoms are vague, and the disease tends to develop and grow silently. By the time it is detected, it has often spread to other parts of the body, making it nearly impossible to cure. These study results are extremely encouraging and may eventually lead to improved detection of the disease in high-risk individuals.”

Patients with early-stage pancreatic cancer have a five-year survival rate of approximately 22 percent, compared to only 1 to 2 percent for those with advanced disease. About 44,000 new cases of pancreatic cancer are diagnosed annually in the U.S., and there are an estimated 38,000 deaths. While the CA19-9 test is routinely used for monitoring pancreatic cancer progression, no test is currently approved by the U.S. Food and Drug Administration for detection and diagnosis of pancreatic cancer.

Gold and his colleagues previously developed the PAM4 blood serum-based test for the detection and diagnosis of PDAC. In earlier research, they demonstrated the test could identify 13 of 21 patients (62 percent) with stage 1 pancreatic cancer.

In the current study, the investigators expanded the research on the use of the PAM4-protein test to include 602 individuals, separated into four groups: patients with pancreatic cancer, including PDAC and other forms of the disease; those with cancers of the surrounding organs; patients with benign pancreatic disease, such as pancreatitis; and healthy adults.

The researchers found that the test detected 76 percent of individuals overall with PDAC, and 85 percent of such individuals when it was combined with the CA19-9 test. Among these, the test accurately detected 64 percent of patients with stage 1 disease, and 85 percent of individuals with advanced disease when the test was combined with the CA19-9 test. In cancers of surrounding organs, the investigators found that about half of patients with extrahepatic biliary (50 percent) and periampullary (48 percent) adenocarcinomas tested positive for the PAM4-protein. Gold said that the latter finding was not unexpected because these cancers originated in closely related organs.

For comparison, 19 percent of patients with benign pancreatic disease and 23 percent with chronic pancreatitis tested positive for the PAM4-protein. “These results demonstrate that reactivity of the PAM4 antibody is highly restricted to PDAC, with the biomarker present at the earliest stages of neoplastic development,” Gold said. “To

the best of our knowledge, there are no biomarkers or target antigens that are expressed at a similarly high frequency and concentration in PDAC, and which show such specificity.”

In future research, the investigators plan to use the test to screen patients who are considered at high risk for pancreatic cancer – such as individuals with chronic pancreatitis, sudden onset diabetes or those with a family history of PDAC – for the presence of PDAC at an early stage of tumor growth.

Abstract # 151

Title: Detection of early-stage pancreatic ductal adenocarcinoma (PDAC): Sensitivity, specificity, and discriminatory properties of the serum-based PAM4-immunoassay.

Authors: D. V. Gold, J. Gaedcke, B. M. Ghadimi, M. Goggins, R. H. Hruban, M. Liu, G. Newsome, D. M. Goldenberg; Center for Molecular Medicine and Immunology/Garden State Cancer Center, Morris Plains, NJ; University Medical Center, University of Goettingen, Goettingen, Germany; The Johns Hopkins Medical Institutions, Baltimore, MD; New York University Medical Center, New York, NY.

Background: We recently reported that a serum-based enzyme immunoassay employing the PAM4 antibody was able to correctly identify 82% of patients with known PDAC and, importantly, that this assay had promising sensitivity for detecting early-stage disease. We now extend these findings in a much larger patient population that includes over 600 sera from both malignant and benign diseases of the pancreas and surrounding tissues.

Methods: In a blinded analysis, sera from patients with confirmed PDAC (N=298), other cancers (N=99), benign disease of the pancreas (N=126), and healthy adults (N=79) were evaluated by enzyme immunoassay for concentration of PAM4-antigen levels.

Results: Overall sensitivity for detection of PDAC was 76%, with 64% of stage-1 patients testing positive and a higher sensitivity (85%) for advanced disease. For the most part, sera from patients with neuroendocrine tumors of the pancreas or cancers of other origin (squamous, GIST, etc.) did not have elevated levels of the PAM4-antigen. Approximately half of the patients with ampullary (48%) and extrahepatic biliary (50%) adenocarcinomas had positive levels of circulating PAM4-antigen. Of 126 patients diagnosed with benign conditions of the pancreas, only 24 (19%) were positive and, in particular, 18 of 80 (23%) patients with chronic pancreatitis (CP) were positive. ROC curve analysis demonstrated a statistically significant difference between the PDAC and CP groups ($P < 0.0001$), with an area under the curve of 0.84 ± 0.02 (95% CI: 0.79 – 0.89). The positive- and negative-likelihood ratios for differentiating PDAC from benign conditions of the pancreas were 4.00 and 0.30, respectively.

Conclusions: The PAM4-immunoassay detects nearly two-thirds of stage-1 PDAC patients, and does so with high discriminatory power with respect to benign pancreatic disease. Our results provide a rationale for longitudinal surveillance of patients considered at high-risk for PDAC (e.g., familial pancreatic cancer, new-onset diabetes, etc.) with the PAM4 assay. (Supported in part by NIH grants CA096924, CA120432 and CA62924, and the Turpin Foundation.)

Disclosure: David M. Goldenberg, Sc.D., M.D., Employment/Leadership Position with Immunomedics, Stock Ownership with Immunomedics

Oral Abstract Session
Friday, January 20, 2012
01:45 PM - 03:15 PM PT

Lead Author: James Yao, MD
University of Texas' M. D. Anderson Cancer Center
Houston, TX

Study Finds Prognostic Factors for Rare Neuroendocrine Tumors, Suggests Everolimus May Be More Beneficial Than Previously Shown

Researchers re-analyzing the results of a large phase III study of patients with advanced neuroendocrine tumors (NET) found that certain factors, such as bone metastases, having NETs that originate in the lung, and elevated levels of the blood biomarker chromogranin A predict which individuals are at greatest risk for neuroendocrine tumor progression and are more likely to need active therapy. The re-analysis also showed that combining the drug everolimus (Afinitor) with another drug, octreotide, halted NET growth for a much longer period than previously reported, compared to octreotide treatment alone.

“We have identified important prognostic factors that can help physicians to better determine the optimal treatment for patients with neuroendocrine tumors, which can have a widely variable course of progression,” said lead author James Yao, MD, assistant professor and deputy chair of gastrointestinal oncology at the University of Texas' M.D. Anderson Cancer Center in Houston. “The findings will also improve our ability to stratify patients in future randomized trials on neuroendocrine tumors.”

In the original phase III study, called RADIANT-2, investigators showed that a combination of everolimus and the drug octreotide led to a median 5.1 months longer delay in cancer progression compared to treatment with octreotide alone. That study included 429 patients with advanced NET that began in the gastrointestinal tract, lungs or other non-pancreas locations in the body (all of which are referred to as carcinoid syndrome). According to Yao, the study was found to have imbalances in its patient randomization, which put many more patients with a poor prognosis in the everolimus arm and potentially altered the results of the study, suggesting that everolimus may have a greater benefit than investigators originally reported.

In the current re-analysis, Yao's team analyzed the original phase III results to both identify and adjust for randomization imbalances. The original study had an increased risk for such imbalances, Yao said, because the appropriate prognostic factors needed to stratify patients had not been well defined at the start of the study. As part of their re-analysis, the investigators used standard statistical methods to first identify prognostic factors that predicted both good and bad outcomes in the trial, and found that certain factors were associated with a greater likelihood of NET progression. For example, patients with bone metastases had a 1.52 times greater risk than those without bone metastases for disease progression, while those individuals whose cancer originated in the lung had a 1.55 times greater risk of progression. Other factors included baseline chromogranin A and World Health Organization performance status, which measured patients' functional status.

The researchers found that after using these prognostic indicators to correct for the randomization imbalances, the reduction in risk of NET progression changed from 23 percent to 38 percent, meaning that the original study data may have underestimated the effectiveness of the drug. They plan to conduct a larger study to confirm these results.

Everolimus is one of two drugs approved in the last year by the U.S. Food and Drug Administration for treating advanced pancreatic neuroendocrine tumors, but it has been uncertain whether the drug was also effective in treating neuroendocrine tumors that do not originate in the pancreas.

Advanced neuroendocrine tumors arise from neuroendocrine cells spread and can arise in nearly any part of the body with these cells. The incidence of neuroendocrine tumors has increased over five-fold from 1 per 100,000

people per year to 5.25 per 100,000 per year over the last three decades. Low to intermediate grade NETs are generally less aggressive tend to be curable in early stages with surgery. Advanced NETs are more aggressive and incurable, and most patients will die from the disease. Median overall survival is approximately four years for patients with advanced disease. Though NETs tend to progress at a slower pace than cancers that do not arise from neuroendocrine cells, they are also generally more resistant to treatment. There are currently no U.S. Food and Drug Administration-approved therapies for controlling neuroendocrine tumors arising outside of the pancreas.

Abstract # 157

Title: Multivariate analysis including biomarkers in the phase III RADIANT-2 study of octreotide LAR plus everolimus (E+O) or placebo (P+O) among patients with advanced neuroendocrine tumors (NET).

Authors: J. C. Yao, J. D. Hainsworth, E. M. Wolin, M. E. Pavel, E. Baudin, D. Gross, P. Ruzniewski, P. Tomassetti, A. Panneerselvam, S. Saletan, J. Klimovsky; University of Texas M. D. Anderson Cancer Center, Houston, TX; Sarah Cannon Research Institute, Nashville, TN; Cedars-Sinai Medical Center, Los Angeles, CA; Charite-Universitätsmedizin, Berlin, Germany; Institut Gustave Roussy, Villejuif, France; Hadassah-Hebrew University Medical Center, Jerusalem, Israel; Hôpital Beaujon, Paris, France; University of Bologna, Bologna, Italy; Novartis Pharmaceuticals, Florham Park, NJ.

Background: In this large phase III trial, median progression-free survival (PFS) improved by 5.1 mo with E+O compared to P+O in patients (pts) with NET associated with carcinoid syndrome. Randomization imbalances including WHO performance status (PS), and primary site favoring P+O confounded primary analysis. Chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) are important biomarkers in NET. Analyses were performed to identify prognostic factors and adjust for randomization imbalances.

Methods: Pts were randomized to E+O (n=216) or P+O (n=213). Potential prognostic factors including baseline CgA ($\leq 2 \times \text{ULN}$ vs $> 2 \times \text{ULN}$), baseline 5-HIAA (\leq median vs $>$ median), age (< 65 vs ≥ 65), gender, race, WHO PS (0 vs 1, 2), primary site (lung vs other), prior somatostatin analog use (yes vs no), duration from diagnosis (< 6 mo, 6-24 mo, 2-5 yr, > 5 yr), and organs involved (liver, bone) were assessed in univariate analysis using the log rank test and a stepwise regression using Cox proportional hazards model.

Results: Randomization resulted in significant imbalance in baseline CgA (median [ng/mL], 251 E+O vs 137 P+O). Median PFS (mo) was significantly longer for pts with nonelevated CgA (27 vs 11; $P < .001$) and nonelevated 5-HIAA (17 vs 11; $P < .001$). Analyses also indicated age (14 vs 12; $P = .01$), WHO PS (17 vs 11; $P = .004$), liver involvement (14 vs not reached; $P = .02$), bone metastases (8 vs 15; $P < .001$), and lung as primary site (11 vs 14; $P = .06$) as potentially prognostic. Multivariate analysis indicated that significant prognostic factors for PFS included baseline CgA (HR, 0.47; CI, 0.34-0.65; $P < .001$), WHO PS (HR, 0.69; CI, 0.52-0.90; $P = .006$), bone involvement (HR, 1.52; CI, 1.06-2.18; $P = .02$), and lung as primary site (HR, 1.55; CI, 1.01-2.36; $P = .04$). Adjusted for covariates, a 38% reduction in risk of progression was observed for E+O (HR, 0.62; 95% CI, 0.51-0.87; $P = .003$).

Conclusions: In the phase III RADIANT-2 trial, baseline CgA levels, WHO PS, lung as primary site, and bone involvement were important prognostic factors. Exploratory analysis adjusted for these prognostic factors indicated significant benefit for everolimus therapy.

Disclosures: **James Yao, MD**, Consultant or Advisory Role with Ipsen, Pfizer, Endo Pharmaceuticals, Novartis, Honoraria from Novartis, Research Funding from Genentech, Novartis; **Edward M. Wolin, MD**, Consultant or Advisory Role with Novartis; **Marianne E. Pavel, MD**, Consultant or Advisory Role with Novartis; **Eric Baudin, MD**, Consultant or Advisory Role with Novartis; **David Gross, MD**, Consultant or Advisory Role with Novartis, Honoraria from Novartis, Research Funding from Novartis; **Philippe Ruzniewski**, Consultant or Advisory Role with Pfizer, Ipsen and Novartis, Honoraria from Pfizer, Ipsen and Novartis, Research Funding from Pfizer, Ipsen and Novartis; **Ashok Panneerselvam**, Employment/Leadership Position with Novartis; **Stephen Saletan, MD**, Employment/Leadership Position with Novartis; **Judith Klimovsky, MD**, Employment/Leadership Position: Novartis, Stock Ownership with Novartis.

Oral Abstract Session
Saturday, January 21, 2012
02:30 PM - 04:00 PM PT

Lead Author: Axel Grothey, MD
Mayo Clinic
Rochester, MN

Multi-Targeted Drug Improves Survival in Certain Patients with Metastatic Colorectal Cancer

An international phase III trial shows that single-agent treatment with the investigational drug regorafenib significantly improves survival and delays cancer progression in patients with metastatic colorectal cancer that has progressed despite other approved treatments, as compared to treatment with placebo and supportive care. Regorafenib is a novel, oral agent that targets multiple biological pathways involved in cancer development and growth.

“When standard therapies for patients with metastatic colorectal cancer stop working, and the cancer continues to worsen, most patients only survive a few months,” said lead author Axel Grothey, MD, professor of oncology at the Mayo Clinic in Rochester, MN. “So it’s exciting that this is the first time an agent has shown a statistically significant overall survival benefit, in some cases adding many more months of life, in these patients in a randomized phase III study.”

Regorafenib inhibits a number of pathways involved in tumor progression, including those involved in cell proliferation and angiogenesis – the process by which tumors develop a blood supply necessary to survive and grow in the body. These may include VEGFR, PDGFR-beta, and KIT, among others.

The trial, called CORRECT, was a randomized phase III study of patients whose metastatic colorectal cancer progressed despite standard treatments. In the trial, 760 patients from 105 centers were randomized to receive best supportive care plus either regorafenib or placebo. Best supportive care involves treatment to address the symptoms of cancer, rather than to improve the overall disease outcomes; it includes therapies such as antibiotics, analgesics, radiation therapy for pain from bone metastases, and corticosteroids.

At the second interim data analysis, the researchers found that the median overall survival was 6.4 months for regorafenib and 5.0 months for placebo – a 29 percent increase in overall survival. They also found a substantial difference in disease control rate (DCR): 44 percent in the regorafenib group versus 15 percent for placebo. DCR is defined as the percentage of patients who have a partial or complete response to a drug, or stable disease.

“Tumors that progress after first-, second- and even third-line treatment have developed elaborate mechanisms and pathways that enable them to resist chemotherapy and sustain their growth. Using a multitargeted drug alone, without chemotherapy, is a novel approach for overcoming some of the tumor’s defenses and sparing patients the side effects of additional chemotherapy,” Grothey said.

According to Grothey, regorafenib appears more effective in stabilizing disease and delaying tumor growth, rather than in shrinking tumors. He said that a subset of patients in the trial have responded particularly well to regorafenib, continuing to have stable disease for a relatively long time; research is ongoing to find ways to identify these individuals. “The current era in oncology is about individualizing therapy and not treat every patient the same way,” he said. “We’d like to find biomarkers that could tell us exactly which patients will likely benefit from treatment with regorafenib.”

Abstract # LBA385

Title: Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies.

Authors: Axel Grothey, Alberto F. Sobrero, Salvatore Siena, Alfredo Falcone, Marc Ychou, Heinz-Josef Lenz, Takayuki Yoshino, Frank Cihon, Andrea Wagner, Eric Van Cutsem, on behalf of the CORRECT Study Team; Mayo Clinic, Rochester,

MN; Ospedale San Martino, Genova, Italy; Ospedale Niguarda Ca' Granda, Milan, Italy; University of Pisa, Pisa, Italy; CRLC Val d'Aurelle, Montpellier, France; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; National Cancer Center Hospital East, Kashiwa, Japan; Bayer HealthCare Pharmaceuticals, Montville, NJ; Bayer Pharma AG, Berlin, Germany; University Hospital Gasthuisberg, Leuven, Belgium.

Background: Regorafenib (BAY 73-4506) is an oral multi-kinase inhibitor of a broad range of angiogenic, oncogenic and stromal kinases. The CORRECT trial was conducted to evaluate efficacy and safety of regorafenib in pts with mCRC who had progressed after all approved standard therapies.

Methods: Enrollment criteria included documented mCRC and progression during or ≤ 3 months after last standard therapy. Pts were randomized 2:1 to receive regorafenib (160 mg od po, 3 weeks on/1 week off) plus BSC, or placebo (PL) plus BSC. Pts continued on treatment until progression, death, or unacceptable toxicity. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), safety and quality of life.

Results: From May 2010 to March 2011, 760 pts were randomized (regorafenib: 505; PL: 255). Baseline characteristics were balanced. Preliminary results are available from a pre-planned formal interim analysis. The estimated hazard ratio (HR) for OS was 0.773 (95% CI: 0.635, 0.941; 1-sided $p=0.0051$). Median OS was 6.4 mos (95% CI: 5.9, 7.3) for regorafenib and 5.0 mos (95% CI: 4.4, 5.8) for PL. The estimated HR for PFS was 0.493 (95% CI: 0.418, 0.581; 1-sided $p < 0.000001$). Median PFS was 1.9 mos (95% CI: 1.88, 2.17) for regorafenib and 1.7 mos (95% CI: 1.68, 1.74) for PL. ORR was 1.6% for regorafenib and 0.4% for PL. DCR was 44% for regorafenib and 15% for PL ($p < 0.000001$). Since the pre-specified OS efficacy boundary was crossed (1-sided nominal α : 0.0093), the Data Monitoring Committee recommended to unblind the study and pts on PL were allowed to cross over. The most frequent grade 3+ AEs in the regorafenib arm were hand-foot skin reaction (17%), fatigue (15%), diarrhea (8%), hyperbilirubinemia (8%), and hypertension (7%). Updated results will be presented.

Conclusions: Statistically significant benefit in OS and PFS was observed for regorafenib over PL in pts with mCRC who have failed all approved standard therapies. No new or unexpected safety signal was found.

Disclosures: **Axel Grothey, MD**, Consultant or Advisory Role with Bayer; **Alberto F. Sobrero, MD**, Consultant or Advisory Role with Merck, Bayer, Amgen, Roche, sanofi-aventis, Honoraria from Merck, Bayer, Amgen, Roche, sanofi-aventis; **Salvatore Siena, MD**, Consultant or Advisory Role with AstraZeneca, Merck Serono, Celgene, Amgen, Roche and sanofi-aventis; **Alfredo Falcone, MD**, Consultant or Advisory Role with Merck, Amgen and Roche; Honoraria from Merck, Amgen and Roche, Research Funding from Merck, Amgen and Roche; **Marc Ychou, MD, PhD**, Consultant or Advisory Role with Bayer, Honoraria from Bayer, Research Funding from Bayer; **Heinz-Josef Lenz, MD**, Consultant or Advisory Role with Bayer, Research Funding from Bayer; **Takayuki Yoshino, MD**, Honoraria from Chugai Pharma, Yakult; **Frank Cihon**, Employment/Leadership Position with Bayer; **Andrea Wagner**, Employment/Leadership Position with Bayer; **Eric Van Cutsem, MD, PhD**, Research Funding from Bayer.

2012 Gastrointestinal Cancers Symposium News Planning Team

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