2014 Symposium Highlights Treatment Advances for Multiple GI Cancers

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ALEXANDRIA, Va. – Research on the latest approaches for the diagnosis, treatment, and management of GI cancers was released today in advance of the 2014 Gastrointestinal Cancers Symposium being held January 16-18, 2014, at The Moscone West Building in San Francisco, CA.

Five top studies from the Symposium were featured in a presscast today:

- **Adding Ramucirumab to Standard Second-Line Chemotherapy Improves Survival for Patients with Metastatic Gastric Cancer**: Results of a global, phase III clinical trial of more than 600 patients suggest that combination therapy with the experimental targeted agent ramucirumab could become a new treatment option for previously treated gastric cancer, where there are few effective therapies that extend life.

- **Combination of Two Anti-Cancer Vaccines Improves Survival in Patients with Metastatic Pancreas Cancer**: In a phase II clinical trial of 90 patients, the anti-cancer vaccine CRS-207 was added to GVAX Pancreas as a treatment for metastatic pancreatic adenocarcinoma. This is the first randomized study to show improved overall survival for patients with metastatic pancreas cancer treated with immunotherapy.

- **Long-Lasting Response and Increased Progression-Free Survival with New Chemotherapy Combination for Patients with Treatment-Resistant Neuroendocrine Tumors**: Nearly all patients in this ongoing, phase II clinical trial experienced clinical benefit from the combination of capecitabine and temozolomide (CAPTEM), including tumor shrinkage and stalled tumor growth. CAPTEM was effective even in patients with carcinoid tumors, which are usually resistant to chemotherapy.

- **Oral Chemotherapy Equivalent to Infusional Chemotherapy for Patients with Stage II or III Rectal Cancer**: New findings from a phase III clinical trial indicate that combining pre-operative radiation with capecitabine is equally as effective as pre-operative 5-fluorouracil (5-FU). This is the largest clinical study showing there is no difference in clinical benefit between oral and infusional treatments; the study also showed that adding oxaliplatin to either treatment did not increase clinical response.
RAS Status Predicts Response to Combination Panitumumab Treatment in Patients with Metastatic Colorectal Cancer (mCRC): A genetic analysis of tumor samples collected as part of a large, phase III study demonstrates that tumors with RAS mutations are unlikely to benefit from the addition of panitumumab to second-line FOLFIRI chemotherapy. This analysis is the first to examine the effects of RAS mutations on second-line treatment.

“Three of the studies presented today demonstrate how advances in combination therapies can improve the prognosis of patients diagnosed with historically difficult to treat cancers,” said Smitha Krishnamurthi, MD, who moderated the presscast. “Two additional studies make strides in improving patients’ quality of life by providing an equally effective, but more convenient, treatment choice for patients with rectal cancer and by reducing unnecessary treatment for certain subsets of patients with advanced colorectal cancer. Together these five studies exemplify the type of breakthrough research being released at the 2014 GI Symposium.”

Gastrointestinal cancers include those of the colon/rectum, stomach, pancreas, esophagus, small intestine, anus and other digestive organs. It is estimated that 289,610 people in the U.S. will be diagnosed with these cancers in 2014 and 147,260 will die from them. [i]

The 2014 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.

Oncologist-approved patient information resources are available on ASCO’s cancer information website, Cancer.Net.

An interactive history of cancer research advances, including those in colorectal, pancreatic and stomach cancer, can be found at ASCO’s Cancer Progress website at www.cancerprogress.net.

ATTRIBUTION TO THE 2014 GASTROINTESTINAL CANCERS SYMPOSIUM IS REQUESTED IN ALL NEWS COVERAGE.

Adding the Targeted Therapy Ramucirumab to Standard Second-Line Chemotherapy Improves Survival, Quality of Life for Patients with Metastatic Gastric Cancer

The results of a global, phase III clinical trial in patients with metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma show that combining paclitaxel with the monoclonal antibody ramucirumab significantly increases overall survival by more than two months after progression on first-line therapy, compared to treatment with paclitaxel alone. Researchers also reported
significant improvements in progression-free survival and quality of life for patients who received the combination therapy. This is the largest clinical trial of second-line therapy in this patient population to date.

“A two-month survival gain for patients with gastric cancer receiving second-line therapy is a big improvement,” said lead study author Hansjochen Wilke, MD, Director of the Department of Oncology, Hematology and Center of Palliative Care at Kliniken Essen-Mitte in Essen, Germany. “This study shows that we can achieve more with targeted therapy and chemotherapy together than we can with chemotherapy alone. We’re also encouraged that this regimen not only improves survival but also offers patients a better quality of life.”

Gastric cancer is the second-leading cause of cancer death globally. Patients with advanced gastric cancer who progress after first-line therapy have a poor prognosis, with a median overall survival of approximately 3 to 3.5 months without second-line treatment. Currently, patients whose cancer progresses following first-line therapy receive either second-line chemotherapy with drugs such as docetaxel, paclitaxel, and irinotecan or best supportive care measures. Although 70 to 80 percent of patients receive second-line chemotherapy as part of standard practice in Japan, and live longer as a result, only an estimated 30 percent of patients in Europe and the United States receive an additional line of treatment. According to Dr. Wilke, this geographic difference in treatment may be attributed to the lack of large randomized clinical trials demonstrating clinical benefit of second-line chemotherapy in Western countries.

Ramucirumab is a human IgG1 monoclonal antibody that blocks the vascular endothelial growth factor receptor 2 (VEGFR-2), a common target for inhibiting angiogenesis. Because a tumor needs the nutrients delivered by blood vessels to grow and spread, the goal of anti-angiogenesis therapy is to essentially “starve” the tumor.

Six hundred sixty-five patients with metastatic GEJ or gastric adenocarcinoma who exhibited disease progression on or within four months after standard first-line platinum- and fluoropyrimidine-based combination chemotherapy were enrolled in this trial. Patients were randomized to receive either a combination of ramucirumab and paclitaxel or paclitaxel alone. Treatment was continued in four-week cycles until disease progression, unacceptable toxicity, or death.

The addition of ramucirumab to second-line paclitaxel treatment significantly improved response rates, overall survival, and progression-free survival. Overall, 28 percent of patients responded to treatment with ramucirumab and paclitaxel compared to 16 percent of patients treated with paclitaxel alone. The median overall survival was 9.6 months in the ramucirumab + paclitaxel group versus 7.4 months in the paclitaxel group. Median progression-free survival was 4.4 months
for the combination therapy compared to 2.9 months for paclitaxel alone. According to Dr. Wilke, patients who received ramucirumab and paclitaxel also reported a reduction in pain and other improvements in their quality of life.

The most common side effects of treatment with ramucirumab and paclitaxel include neutropenia, leukopenia, hypertension, anemia, fatigue, abdominal pain, and asthenia. Although neutropenia was more frequently reported in the ramucirumab + paclitaxel group, the incidence of febrile neutropenia was comparable to treatment with paclitaxel alone. All of these side effects were manageable, and very few patients discontinued treatment due to toxicities.

The researchers intend to retrospectively analyze tumor samples collected as part of this study in the hope of identifying biomarkers that may help define subgroups of patients more likely to benefit from ramucirumab treatment, as well as to investigate ramucirumab in the first-line setting. The U.S. Food and Drug Administration assigned ramucirumab a priority review designation in October 2013 as a second-line treatment for patients with advanced gastric cancer; a decision is expected in early 2014.

Study Identifies a Promising Vaccine Combination for Patients with Metastatic Cancer of the Pancreas

New findings from a randomized phase II study in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) suggest that treatment with two different anti-cancer vaccines, GVAX Pancreas followed by CRS-207, improves survival compared to treatment with GVAX alone. The greatest differences were seen in patients who received at least two doses of GVAX and at least one dose of CRS-207 and in those who received two or more prior treatment regimens.

“This is the first time a randomized study has shown that immunotherapy is effective in pancreatic cancer. This study is just a first step, and we believe we’ll be able to take this approach further,” said lead study author Dung T. Le, MD, an assistant professor of medicine at the Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center in Baltimore, Md. “Various chemotherapy drugs are used, but there are no standard treatment options for second- or third-line therapy in this setting. We’re excited these patients may soon have an alternative to chemotherapy that could come with fewer side effects.”

Advanced pancreatic cancer has a very poor prognosis. The best reported median survival of 11 months comes from first-line treatment with the chemotherapy regimen FOLFIRINOX. However, due to its side effects, only the fittest patients qualify for this treatment, and reported survival with other chemotherapy regimens is lower. For patients whose disease progresses despite first-line treatment, the median survival ranges from four to six months with second-line therapy, and two to
four months with third-line therapy.

The present study tested an innovative immunotherapy strategy that promises to improve outcomes for such patients and appears to be better tolerated than chemotherapy. The GVAX vaccine is composed of pancreatic cancer cells that have been genetically modified to secrete a protein called GM-CSF, which stimulates the immune system. The vaccine is given with a low-dose of a common cancer drug called cyclophosphamide to boost the effectiveness of the vaccine. The second vaccine, CRS-207, is a form of the bacterium *Listeria monocytogenes* that has been genetically modified to be safe for human use, while retaining its ability to stimulate the immune system. Specifically, CRS-207 has been engineered to stimulate an immune response against the protein mesothelin, which is present at high levels on pancreatic cancer cells. The combination of the two vaccines intends to stimulate an immune response against pancreas tumor cells, first with GVAX inducing a broad response against multiple tumor proteins and then with CRS-207 boosting immune response against the mesothelin protein. Essentially, this combinatorial vaccination approach enhances the patients’ natural immune system and trains it to recognize and attack pancreatic tumors.

Ninety patients with metastatic PDAC, the most common form of pancreatic cancer, were enrolled in the study and randomly assigned to treatment with GVAX followed by CRS-207 (arm A) or GVAX alone (arm B). Nearly all patients had previously received at least one prior course of chemotherapy.

At a planned interim analysis of the study, the median overall survival was significantly longer with the two-vaccine therapy compared to GVAX alone (6.1 months vs. 3.9 months). About 24 percent of patients in arm A were still alive after one year, compared with 12 percent in arm B. Among patients who received at least three doses of vaccine (about 70 percent of all patients), those in arm A who received 2 doses of GVAX and at least one dose of CRS-207 had a median overall survival of 9.7 months compared to 4.6 months with GVAX alone. Based on the benefit observed at this interim analysis, patients were allowed to cross over from arm B to arm A. The side effects of the vaccine were relatively mild, resolved quickly, and did not get worse with each dose of treatment (as is often the case with chemotherapy).
The GVAX/CRS-207 combination is one of several related immunotherapy strategies under clinical investigation. The researchers are about to open a large phase II study that will compare the vaccine combination versus CRS-207 alone versus chemotherapy as second-line or greater therapy for metastatic pancreatic cancer. They are also looking at combining GVAX/CRS-207 with immune checkpoint inhibitors such as ipilimumab and anti-PD-1/PD-L1. A study testing GVAX/ipilimumab as a maintenance treatment for patients whose disease became stable on FOLFIRINOX has recently opened.

**New, Rationally-Based Chemotherapy Combination Appears Highly Effective in Patients with Treatment-Resistant Neuroendocrine Tumors**

Interim results from an ongoing phase II clinical trial in patients with various types of advanced neuroendocrine tumors show that a new chemotherapy combination, CAPTEM, either stalled disease progression or shrank tumors in 95 percent of patients whose disease worsened after standard high-dose octreotide. CAPTEM includes a combination of capecitabine and temozolomide. The responses were long-lasting, with a median progression-free survival of 30 months, and most patients experienced only mild side effects. The authors believe that CAPTEM may eventually replace all other second-line therapies for advanced neuroendocrine tumors because its efficacy is far superior.

“In this study we’re seeing patients who had been given six months to live that are still alive eight years after starting CAPTEM. The regimen was effective even in patients with tumors that hadn’t responded to any other standard treatment, including chemotherapy, high-dose octreotide, small molecule inhibitors, radiation or surgery,” said lead study author Robert Fine, MD, an associate professor of medicine at New York Presbyterian Hospital-Columbia University Medical Center in New York, N.Y. “The rate of serious side effects was low with CAPTEM. We had no hospitalizations or treatment-related deaths.”

Neuroendocrine tumors begin in the hormone-producing cells of the body’s neuroendocrine system. Neuroendocrine cells are found throughout the body and perform specific functions, such as regulating air and blood flow through the lungs and controlling the speed at which food moves through the gastrointestinal tract. An estimated 7-9,000 people are diagnosed with a neuroendocrine tumor in the United States each year and the incidence is on the rise. Neuroendocrine tumors are often diagnosed at an advanced stage because they cause few symptoms until they reach a fairly large size.

A total of 28 patients with various subtypes of metastatic neuroendocrine tumors were treated as part of the study. All patients had so-called well or moderately differentiated tumors, which account
for most cases of neuroendocrine tumors. All patients’ diseases had either progressed despite standard therapy with high-dose octreotide or they were ineligible for this treatment based on a negative octreotide scan.

Nearly all patients experienced clinical benefit from CAPTEM — it caused tumor shrinkage in 43 percent of patients overall and stalled tumor growth in 54 percent of patients. Importantly, high response rates were observed in carcinoid and pituitary tumors, two very difficult-to-treat neuroendocrine tumor subtypes. Among the 12 patients with carcinoid tumors, 41 percent had tumor shrinkage; this finding is particularly striking since the typical response rate to chemotherapy for these patients is 0-4 percent. And among the four patients with pituitary tumors resistant to radiation therapy, chemotherapy, and surgery, two had complete remissions with CAPTEM, one had a 75 percent reduction in tumor size, and one has had stable disease for five years. At the latest data analysis, the median progression-free survival was close to 30 months, and more than four years for 25 percent of patients. The median overall survival was greater than 25 months.

CAPTEM combines two chemotherapy drugs — capecitabine and temozolomide. Because neuroendocrine tumors grow slowly, they are frequently resistant to chemotherapy. In lab studies of neuroendocrine tumor cells researchers discovered that 5-fluorouracil (5-FU) (a drug closely related to capecitabine) enhanced temozolomide’s anticancer activity three fold. With this insight, the researchers thoughtfully selected the doses and the order in which the two drugs are given to patients (capecitabine first, temozolomide second) to maximize the efficacy of the combination regimen. The prior oral 5-FU chemotherapy depletes thymidine stores which improves the temozolomide anti-tumor effect two-to-four-fold, according to Dr. Fine.

Dr. Fine stated that patients with neuroendocrine tumors should be able to get access to both temozolomide and capecitibine fairly easily, and insurance would likely cover the cost as there is scientific evidence supporting their use as single agents in this setting. In the meantime, his research team is working on ways to make CAPTEM even more effective (such as combining it with drugs that block the platelet-derived growth factor [PDGF] pathway). As temozolomide is a major treatment option for brain cancers and melanoma, Dr. Fine would like to have the regimen tested in brain tumors and melanoma.

**Pre-Operative Oral Capecitabine Chemotherapy Is Equivalent to Infusional 5-FU for Rectal Cancer; Adding Oxaliplatin Does not Improve Outcomes**

New findings from a four-arm phase III clinical trial in patients with stage II or stage III rectal cancer indicate that combining pre-operative (neoadjuvant) radiation with either capecitabine or 5-fluorouracil (5-FU) results in equivalent outcomes. Capecitabine is an oral drug similar to 5-FU. This study provides strong clinical evidence that using either 5-FU or capecitabine is acceptable in
The researchers also found that adding another chemotherapy drug, oxaliplatin, to either of these regimens did not provide further benefit but increased overall treatment toxicity.

“Doctors should feel reassured that they are not giving less effective therapy if they prescribe capecitabine,” said lead study author Carmen Joseph Allegra, MD, a professor of medicine at the University of Florida in Gainesville, Fla. “Oral capecitabine is certainly far more convenient for patients compared to infusional 5-FU. It means taking pills twice a day, rather than undergoing surgery to place an intravenous port and then wearing a pump on their belt for five weeks.”

Early stage rectal cancer is potentially curable with a combination of pre-operative chemotherapy, radiation therapy, surgery, and post-operative chemotherapy. Patients with operable stage II or stage III rectal cancer typically undergo chemotherapy and radiation therapy before surgery to shrink the tumor. Certain chemotherapy drugs, including 5-FU, capecitabine, and oxaliplatin, act as so-called radiosensitizers—they make the tumors more vulnerable to radiation. Only 5-FU is currently supported by randomized clinical trials data as a radiosensitizer in the preoperative treatment of rectal cancer. Although there hasn’t been any definitive data to support the use of capecitabine in this setting, many doctors suspected it would work as it is effective as an adjuvant treatment for metastatic colorectal cancers and in the adjuvant colon setting.

In this four-arm clinical trial, 1,608 patients were randomly assigned to receive five weeks of radiation therapy plus 5-FU (arm 1, 477 patients); 5-FU and oxaliplatin (arm 2, 329 patients); capecitabine (arm 3, 472 patients); or capecitabine and oxaliplatin (arm 4, 330 patients). Patients received one of these treatments for five weeks and about a month later underwent surgery to remove the tumor.

There were no significant differences between treatment arms in terms of local-regional control, disease-free survival, and overall survival. The three-year local-regional control rates ranged from 87.4 to 88.2 percent. In cases where surgeons were able to completely remove the tumor (about 95 percent of patients) and no traces of microscopic disease were detected, 2-4 percent of stage II patients and 4-11 percent of stage III patients had a local recurrence within three years after undergoing surgery. And in each of the treatment arms, about 80 percent of patients were still alive five years after surgery.

Infusional 5-FU and capecitabine had similar side effects. Patients who also received oxaliplatin, however, experienced significantly more diarrhea and fatigue.

Dr. Allegra commented that although capecitabine is more expensive than 5-FU, one has to take into account that the overall cost differential for the two therapies also depends on the cost of placing and maintaining the port and pump for 5-FU infusion.
RAS Status Predicts Response to Second-Line Treatment with Panitumumab for Metastatic Colorectal Cancer

New data from a phase III clinical trial shows that patients with metastatic colorectal cancer (mCRC) tumors that contain RAS mutations beyond KRAS exon 2 are unlikely to benefit from the addition of panitumumab to second-line FOLFIRI chemotherapy. Currently, doctors routinely test mCRC tumors for mutations in the KRAS gene at exon 2, which was previously shown to predict response to panitumumab treatment; however, the results of this study confirm the need to test for additional RAS mutations prior to administering panitumumab.

“By testing for RAS mutations, doctors will be able to better select among metastatic colorectal cancer patients and only recommend panitumumab treatment to those who are most likely to benefit,” said lead study author Marc Peeters, MD, PhD, a professor of oncology at Antwerp University Hospital in Edegem, Belgium. “These results confirm that it is RAS status that matters, not just KRAS, when determining if panitumumab therapy could be beneficial. For patients with a RAS mutation, these findings will spare them the costs and side effects of a treatment that will not improve their outcomes.”

Panitumumab is a fully human monoclonal antibody that blocks the epidermal growth factor receptor (EGFR), a protein known to promote the growth of colorectal cancer. Previous research has shown that EGFR inhibitors like panitumumab are not effective for colorectal tumors with mutations in the KRAS gene at exon 2, which occur in approximately 40 to 50 percent of mCRC patients. More recent studies have identified additional genetic biomarkers in the RAS family of genes that predict clinical response to panitumumab, most notably mutations in KRAS and NRAS gene exons (segments of a gene that contain information for producing a protein). Collectively, these mutations are referred to as RAS mutations.

In the present study, tumor samples from patients treated as part of a large, phase III study that were already known to be unmutated at KRAS exon 2 were assessed for other RAS mutations, specifically in KRAS exons 3 and 4 and NRAS exons 2, 3 and 4. The results indicate that 18 percent of these patients harbored one or more RAS mutations and that these mutations predicted clinical response to panitumumab treatment.

Among patients receiving both panitumumab and chemotherapy, both median overall survival (OS) and progression-free survival (PFS) was improved for patients with wild-type (unmutated) RAS tumors compared to those with RAS mutations (median OS: 16.2 months vs. 11.8 months; median PFS: 6.4 months vs. 4.8 months). For patients in the mutated RAS group, the addition of panitumumab to FOLFIRI resulted in no significant survival differences over FOLFIRI alone.
These findings support previously reported outcomes of panitumumab treatment based on RAS status in mCRC and provide the first published phase III data in a second-line setting. In addition, the results, combined with those of other trials, support the use of more comprehensive RAS testing to identify specific subgroups of patients for whom panitumumab and other anti-EGFR treatment is appropriate.

About ASCO:

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