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6th Annual ISGIO Conference – A Global Focus to Find a Cure



The International Society of Gastrointestinal Oncology held its 6th annual Gastrointestinal Oncology Conference in Philadelphia from October 1–3, 2009.

A GLOBAL FOCUS

The global reach of the Society was evident in the scope of countries from which the attendees and faculty came, including the U.S. and Canada, France, Spain, Italy, Greece, Romania, Japan, China, Korea, India, and Egypt.

“We have preeminent experts in gastrointestinal (GI) oncology coming to share their wisdom and their science with us today,” said John L Marshall, MD (Lombardi Comprehensive Cancer Center, Washington, DC), in opening the conference.

The conference included didactic and interactive presentations and case studies in all areas of gastrointestinal oncology as well as a session on emerging science covering oncogenes and cancer, current perspectives

on the role of cancer stem cells, and signaling pathways of survival.

SEEKING TO CURE GI CANCERS

Dr. Marshall provided an overall perspective on the goals of the ISGIO and GI physicians and researchers, which, he said, should be to find a cure for GI cancers.

“I will set the stage for why we are here by giving you a snapshot of my past week,” he
(continued on page 2)

Panitumumab Improves PFS in Patients with KRAS Wild-Type Metastatic CRC

First Large Randomized, Prospective Analyses of KRAS Status as Predictive Biomarker for Anti-EGFR Treatment in First- and Second-Line Metastatic CRC

PRIME TRIAL INTERIM ANALYSIS PRESENTED AT ANNUAL ISGIO CONFERENCE

■ OCTOBER 2, 2009, PHILADELPHIA, PA
In patients with KRAS wild-type metastatic colorectal cancer (CRC), the addition of panitumumab to first-line FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) chemotherapy statistically significantly improved progression-free survival (PFS), according to data from the phase III PRIME trial presented at the 6th annual ISGIO conference by Salvatore Siena, MD (Ospedale Niguarda Ca' Granda, Milan, Italy). PFS was 9.6 months with FOLFOX + panitumumab and 8.0 months with FOLFOX alone, translating to a 20% decrease in risk of progression for patients receiving the epidermal growth factor receptor (EGFR) inhibitor (hazard ratio .80

[95% confidence interval 0.66–0.97], $P = .02$), reported Dr. Siena, a PRIME trial investigator.

In patients whose tumors harbored mutated KRAS, however, panitumumab treatment resulted in a statistically significantly shorter PFS duration as compared with the FOLFOX-alone group (median, 7.3 vs. 8.8 months with vs. without panitumumab (HR = 1.29 [CI 1.04–1.62], $P = .02$). These findings confirm data from other studies showing no benefit of epidermal growth factor receptor (EGFR)-directed therapy in colorectal cancer patients with mutant KRAS tumor status.

The PRIME trial is an international, open-label, randomized phase III study in 1,183 patients receiving first-line treatment for metastatic CRC [Figure 3-1], in which KRAS status is prospectively analyzed as a predictive biomarker for anti-



Prof. Michel Ducreux

EGFR treatment efficacy. The ISGIO conference provided the first opportunity in the United States to hear the initial interim efficacy results of PRIME, following the presentation at the ECCO/ESMO European Congress in Berlin in late September. *(continued on page 3)*

REGISTER NOW!

2010
GASTROINTESTINAL
ONCOLOGY
CONFERENCE

Sept. 23–25, 2010
The Sheraton
Philadelphia City Center
Philadelphia, PA

6th Annual ISGIO Conference

(continued from page 1)

continued, "which may resonate with those of you who practice clinical oncology. We had a fairly busy week, including a site visit and seeing about 52 patients with GI cancers. About 25–30 of them had colon cancer, about 15–20 had pancreatic cancer, 5 had gastric cancer, and 5–6 had carcinoids or other GI tumor types. Their ages ranged from 34 to 82 years old and there was about an equal distribution of men and women. Then I looked for another piece of information and I realized that of the 52 patients, 42 of them will die under my care. That is what we are facing. That is not what is going on in the prostate or breast cancer clinic, but it is commonplace—it is accepted practice—in the area of GI oncology. We are here to change that number. We are not looking for the next drug or what will change things a little bit; we are really seeking to cure GI cancers.

We are not looking for the next drug or what will change things a little bit; we are really seeking to cure GI cancers.

— John L. Marshall, MD

"We need to focus our efforts with that goal in mind—not an additional 2 weeks of survival on the backs of costs or toxicity, but medicines that will make these cancers go away," Dr. Marshall declared, "and I charge that that is our goal as we move ahead."

In noting the failure of several large phase III trials to reveal treatments that will substantially improve patient outcomes, Dr. Marshall said, "the reason these trials have to be large is that we have decided to accept small differences as meaningful. We need to get away from that. We should not do another large phase III randomized trial unless we are sure to be successful. Find the

right patient population and focus on that group; if we spend the resources on a phase III randomized trial, we should be sure we are going to win.



Michel Ducreux, Michael Choti, Melanie Thomas

"The ISGIO plays a critical role in this process and I have been proud to be a part of that," he said, referring to his role as ISGIO's president for the 2008–2009 term. "It gives us a place to come and discuss this as a group. I'm pleased to say the ISGIO has maintained an active membership, it holds the annual meeting and has increasing participation in its journal, *Gastrointestinal Cancer Research (GCR)*, which is now available online and searchable through PubMed and EMBASE/Excerpta Medica.

"One of our roles at ISGIO is the role of mentorship and we plan to do more of that as we go along," Dr. Marshall stated. The ISGIO now has a Mentorship Program blog site at www.isgio.org, which is open for membership application.

This year saw a substantial increase in the number of abstracts submitted for presentation at the conference. Two abstracts selected for oral presentation covered phase III data presented for the first time in the U.S. (see article, Panitumumab Improves PFS in Patients with KRAS Wild-Type Metastatic CRC Receiving First- or Second-Line Chemotherapy, this issue).

Several abstracts were submitted by medical students and fellows who plan

to pursue GI oncology as their specialty. As stated by Waqar Haque, a medical student at M. D. Anderson Cancer Center in Houston, TX, who presented a



Waqar Haque

talk on radiation therapy for intrahepatic cholangiocarcinoma, "This conference provided a great opportunity for me to

present my first oral talk in front of a large and prestigious audience. I learned a lot while compiling the information and preparing my presentation, and about public speaking. I will be able to look back on this experience and build upon it for future presentations. Also, the talks given by numerous luminaries from all over the world provided good perspectives on how gastrointestinal cancers are treated around the globe. We were able to hear from different members of the multidisciplinary team as well—radiation oncologists, surgical oncologists, and medical oncologists." The meeting abstracts are available on ISGIO's web site.

The 7th annual meeting of the ISGIO will be held on September 23–25, 2010, in Philadelphia. Please mark your calendar and visit www.isgio.org for more information about the Society and its activities. ❖

ISGIO IMPRESSIONS



Jong-Inn Lee, MD, PhD
Korea Cancer Center Hospital
Seoul, Republic of Korea

At the ISGIO Annual Gastrointestinal Oncology Conference (October 1–3, 2009), Dr. Lee presented a poster titled, "Prognosis of Curatively Resected T4 Gastric Cancer: Significance of Combined Resection."

The conference was well organized and provided very comprehensive information in a tight schedule. I am a surgeon and also a basic researcher, so I found the presentations by Ju-Seog Lee from M. D. Anderson Cancer Center, on "Gastric Cancer Molecular Biology: East and West," and by John Giannios from Greece, on "Liposome-Formulated siRNA Against Msi1 and Docetaxel Treatment in an Animal Model of Advanced Gastric Adenocarcinoma Eradicates Cancer Stem Cells and Metastasis," very impressive. I hope to attend ISGIO's annual conference again next year.

Visit www.isgio.org for membership information, conference abstracts, and announcements of upcoming ISGIO events.

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Rae Bretana, Executive Editor
GI Oncology Review & Outlook
200 Broadhollow Rd., Suite 207, Melville, NY 11747
Phone: (631) 390-8390 Fax: (631) 393-5026
E-mail: rae.bretana@isgio.org

Panitumumab Improves PFS in KRAS Wild-Type Metastatic CRC (continued from page 1)

In this study, patients with metastatic CRC who had not received previous oxaliplatin or EGFR inhibitor therapy (adjuvant 5-fluorouracil was allowed) were treated with panitumumab 6 mg/kg q2wks plus FOLFOX4 q2wks (n= 593) or FOLFOX4 q2wks

in colorectal cancer. This is important to understand the results," he added. The subgroups Dr. Siena referred to were wild-type KRAS patients treated with/without panitumumab, and mutant KRAS patients treated with/without panitumumab.

interim OS data show a negative effect of anti-EGFR therapy. The biologic or clinical reason for the inferior effect

of panitumumab + FOLFOX on PFS and OS as compared with FOLFOX (continued on page 4)

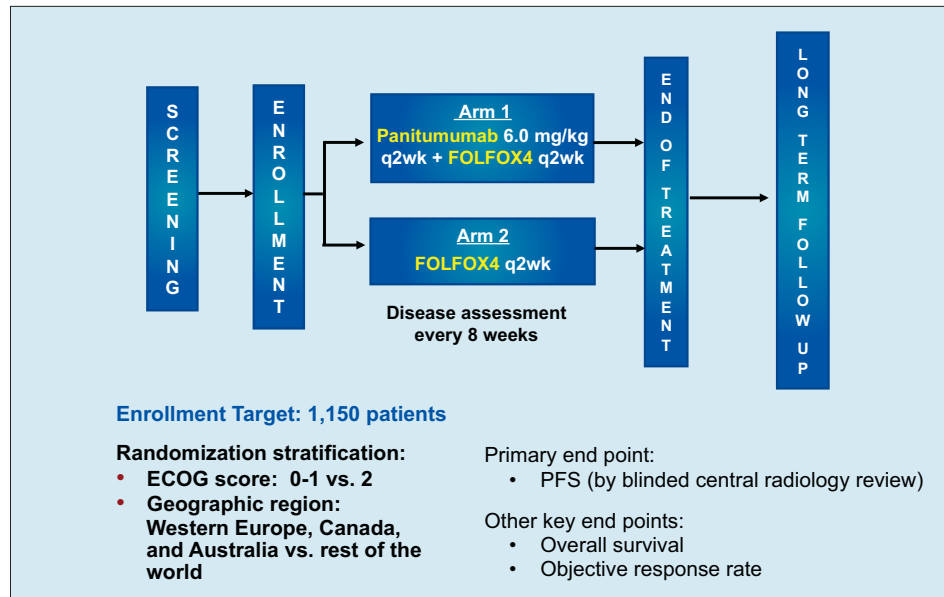


Figure 3-1. Trial schema and stratification factors for PRIME (Panitumumab Randomized trial in combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy).

alone (n=590). Documentation of EGFR and KRAS status was not required prior to study entry, but all patients had paraffin-embedded tumor tissue available for central biomarker testing. A total of 93% of tumors were analyzed for KRAS status — approximately 60% were wild type and 40% had mutated KRAS. In addition to PFS as the primary end point, other end points were overall survival (OS) and objective response rate.

Dr. Siena pointed out that approximately 70% of patients had metastases in the liver plus other sites. "The percentage of patients with liver-only disease was less than 20% in all subgroups, which is lower than in other phase III trials that evaluated EGFR-targeted monoclonal antibodies

In the wild-type KRAS patients, the PFS benefit of panitumumab was observed in all subgroups based on age, gender, colon vs. rectal tumor, and number and location of metastatic disease, except in those with ECOG performance status of 2, Dr. Siena said. Analysis of overall survival (OS) is ongoing; interim assessment shows a median OS of 18.8 months in the FOLFOX arm and the median has not been reached yet in the FOLFOX + panitumumab arm. Objective response rates by central review in wild-type KRAS patients were 48% and 55% (P= .068) in the two treatment groups, respectively (all partial responses).

In the mutant KRAS population, objective response rates were similar in the two treatment groups, whereas

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The International Society of
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2010 Gastrointestinal Oncology Conference

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ISGIO IMPRESSIONS



Ruth He, MD, Georgetown University Washington, DC

At the ISGIO Annual Gastrointestinal Oncology Conference (October 1-3, 2009), Dr. He presented a talk on "Mentoring Junior Faculty – Is It a Two-Way Street?"

I have enjoyed this conference a lot. It is relatively small in size, which has allowed a good amount of presenter/ attendee interaction. I appreciate the case presentations because they often raise controversial issues for discussion. Right now in the field of GI oncology, there are many areas that are not clear, or not totally "black and white," so it is interesting to hear the experts' opinions on managing those patients. I also like the interactive nature of the meeting. You can ask a lot of questions, and

the experts bring up points that are not necessarily obvious to everyone in the audience. Some of the presenters have mentioned their new data during their talks as well. This meeting has helped me to think differently, and I will be able to apply what I have learned to patients in real practice. In addition, I heard several interesting talks on basic and preclinical research related to GI cancers; in particular, I found the presentations on "A novel small molecule inhibitor of protein

kinase D blocks pancreatic cancer growth in vivo," and "Systemic delivery of liposome-incorporated adrenomedullin receptor small interfering RNA against tumor and its microenvironment reduced pancreatic tumor growth," very intriguing, as they showed the mechanisms behind the developed therapeutics and interesting preclinical data. These presentations have given me some ideas for my own projects.

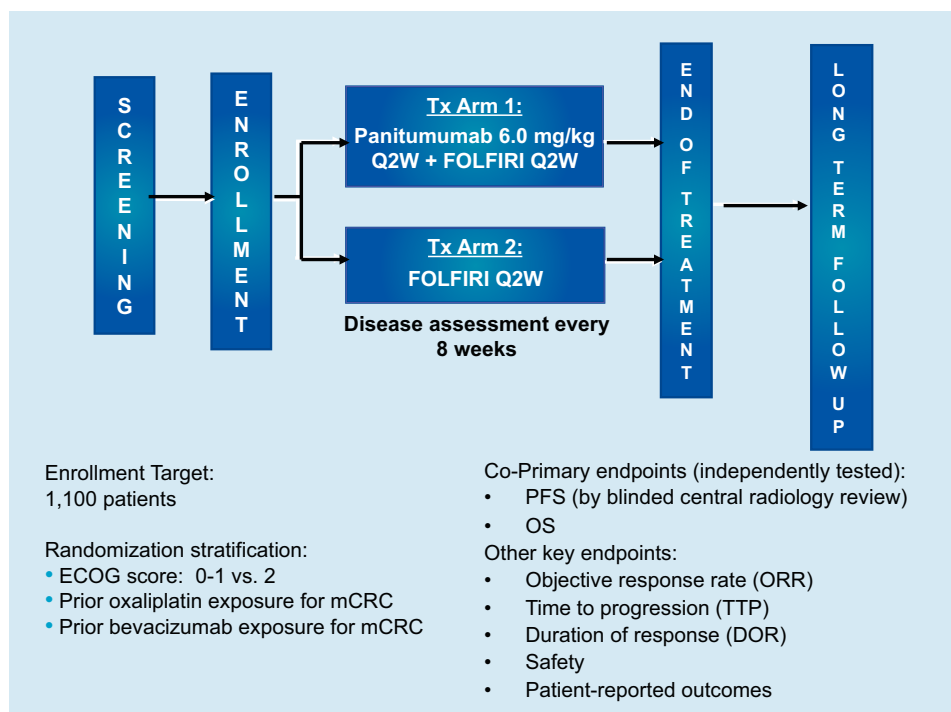


Figure 4-1. Phase III study of second-line FOLFIRI ± panitumumab in patients with metastatic colorectal cancer.

alone in patients with mutant KRAS tumors “remains unknown,” Dr. Siena stated.

“Panitumumab was well tolerated when administered with FOLFOX,” Dr. Siena said, “and the adverse events were as expected with an anti-EGFR antibody.” Grade 3–4 side effects that occurred more frequently with panitumumab than FOLFOX alone primarily comprised skin effects and mucosal toxicities (eg, diarrhea, mucositis). “What is most important,” he added, “is that adverse events were not different in the wild-type and mutant KRAS populations, and other side effects, such as neutropenia and febrile neutropenia, were not increased in the panitumumab arms.” Grade 3–4 infusion-related reactions attributed to panitumumab occurred in fewer than 1% of patients. Twelve panitumumab-treated patients had grade 3–4 hypomagnesemia, which was “not clinically significant,” according to Dr. Siena.

SECOND-LINE PANITUMUMAB + FOLFIRI IMPROVES PFS IN PATIENTS WITH WILD-TYPE METASTATIC CRC

In another phase III study, also reported for the first time in the U.S. during the annual ISGIO conference, the addition of panitumumab to second-line FOLFIRI (5-fluorouracil, leucovorin, irinotecan) chemotherapy resulted in a statistically significant improvement in PFS compared with FOLFIRI treatment alone in patients with KRAS wild-type metastatic CRC, as reported by Michel Ducreux, MD

(Institut Gustave-Roussy, Villejuif, France). Response rate also increased significantly ($P < .001$), from 10% with chemotherapy alone to 35% with FOLFIRI+ panitumumab for the wild-type KRAS group, he said.

In patients with KRAS wild-type metastatic CRC, the addition of panitumumab to first-line FOLFOX therapy led to a statistically significant 20% decrease in risk of progression.

These results are a “clear improvement for the patient,” according to Dr. Ducreux, one of the trial investigators.

A total of 1,186 patients with documented disease progression within 6 months of having received first-line treatment were enrolled in this second-line trial. KRAS analysis using a method that detects the seven most common mutations in codons 12 and 13 was conducted for 91% of the patients. Approximately 55% of patients had wild-type and 45% had mutated KRAS tumor status, similar to findings from the first-line PRIME trial. Patients were randomized to treatment with FOLFIRI q2wk alone ($n = 595$) or FOLFIRI plus panitumumab 6 mg/kg q2wks ($n = 591$), with stratification based on ECOG score and

previous exposure to oxaliplatin or bevacizumab for metastatic CRC [Figure 4-1].

Treatments the patients had received in the first-line setting were primarily FOLFOX (approx. 70% of patients) or FOLFOX + bevacizumab (approx. 20% of patients). Previous irinotecan treatment for metastatic disease and previous EGFR inhibitor therapy were exclusion criteria.

This trial included two co-primary end points of PFS and OS. “There was a statistically and clinically significant difference in PFS,” with a hazard ratio of 0.73 and P value of .004 favoring panitumumab + FOLFIRI treatment in patients with wild-type KRAS tumors, Dr. Ducreux said. Median PFS was 5.9 months in the panitumumab-treated patients and 3.9 months with FOLFIRI alone. “This difference in PFS in the wild-type KRAS patient,” he added, “was seen across all patient subgroups, even those with ECOG 2 or 1 performance status or in patients with liver-only vs. liver + other sites of metastases. These are very consistent data,” he reported.

At this time, analysis of OS duration in the wild-type KRAS patients shows no statistically significant difference but a trend in favor of adding panitumumab ($P = .12$), according to Dr. Ducreux.

These results are a “clear improvement for the patient,” according to Dr. Ducreux, an investigator in the second-line study of FOLFIRI ± panitumumab.

“It is interesting to look at the objective response rate in this population of patients,” he said. The 10% response rate in those receiving FOLFIRI alone, Dr. Ducreux pointed out, is consistent with data obtained in other studies of second-line FOLFIRI treatment. “With the addition of panitumumab in the KRAS wild-type patients, it was possible to obtain and certify an objective response rate which is quite good for second-line therapy in this setting,” he stated. Thirty-five percent (35%) of panitumumab-treated patients had a partial

response. All responses in this trial were confirmed by central review.

In patients with mutated KRAS tumor status, the addition of panitumumab to FOLFIRI treatment did not improve PFS or OS, but in contrast to the PRIME trial findings, had no deleterious effect on patient outcomes. Response rates were similar in the two treatment groups for the mutated KRAS patients, Dr. Ducreux reported, and toxicity observations were similar to those of the first-line PRIME trial, “with no major problem in terms of tolerability.”

ISGIO IMPRESSIONS



Sook Ryun Park, MD
National Cancer Center
Goyang, Republic of Korea

At the ISGIO Annual Gastrointestinal Oncology Conference (October 1-3, 2009), Dr. Park presented a talk on “Prognostic Value of Preoperative Clinical Staging Assessed by Computed Tomography in Resectable Gastric Cancer Patients: A Viewpoint in the Era of Preoperative Treatment.”

This is the first time I have attended an ISGIO annual meeting and I have found it to be very interesting. I am a junior staff member, so I have many questions regarding how I can best treat my patients, and at this conference, I have listened to several experts give their viewpoints on management of various types of GI cancers. The interactive voting and question and answer periods also promote interaction; being able to participate actively keeps you engaged. I am pleased that I was able to attend.