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-- PRESS BRIEFING SUNDAY, JANUARY 21, 7:30 AM (EST) --

ADVANCES IN THE TREATMENT OF COLORECTAL CANCER

**-- Use of Bevacizumab as First-Line Treatment with Oxaliplatin-Based Therapy
Extends Survival in Metastatic Colorectal Cancer;**

Benefit to Adding Oxaliplatin to Preoperative Treatment for Rectal Cancer;

Need for Improvement in Doctor-Patient Communication About Colorectal Cancer Treatment --

Orlando, FL—New research on the treatment of colorectal cancer was discussed today at a press briefing at the 2007 Gastrointestinal Cancers Symposium, co-sponsored by the American Gastroenterological Association (AGA), the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO), and the Society of Surgical Oncology (SSO). The fourth annual symposium is being held at the Orlando World Center Marriott in Orlando, Florida, from Friday, January 19 to Sunday, January 21.

“The colorectal cancer research community is continuing to study new therapy combinations for all stages of disease, in order to determine which regimens provide the best overall results for patients,” said Robert Bresalier, MD, Chair of Gastrointestinal Medicine and Nutrition at the University of Texas M.D. Anderson Cancer Center, and moderator of the briefing. “Colorectal cancer is the third most common cancer among men and women, and it is critical that we work to reduce the toll of this disease. In addition, we are looking for new ways to improve patient experiences during and after treatment, and striving to better educate patients about the risks, benefits, and potential side effects associated with treatment.”

Nearly 149,000 new cases of colorectal cancer were diagnosed in the U.S. in 2006, and just over 55,000 people died of the disease.

Studies include:

- A phase III study showing that the addition of bevacizumab (Avastin) to first-line oxaliplatin-based chemotherapy extends survival in metastatic disease.
- A phase III study demonstrating that the addition of oxaliplatin (Eloxatin) to preoperative fluorouracil (5FU)-based chemotherapy and radiation for rectal cancer is safe and does not significantly increase toxic side effects, and could eventually prove to be an important new tool for the treatment of this disease.

- A survey of physicians and of patients who received chemotherapy following surgery for colorectal cancer found that patients are more willing than physicians expect to accept a relatively modest treatment benefit from adjuvant therapy, and that patients' expectations of potential side effects often differ from what they actually experience, highlighting the need for better communication between oncologists and patients.

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**January 21, 12:30 – 1:45 PM
Palms Ballroom**

**Lead Author: Leonard Saltz, MD
Memorial Sloan-Kettering Cancer Center
New York, NY**

First-Line Use of Bevacizumab with Oxaliplatin-Based Chemotherapy Improves Progression-Free Survival in Patients with Advanced Colorectal Cancer

Note: This summary contains updated data not in the abstract.

The first study to evaluate the addition of bevacizumab (Avastin) to oxaliplatin-based chemotherapy as a first-line treatment in patients with advanced metastatic colorectal cancer shows that bevacizumab improves progression-free survival. The study was one of the largest ever conducted in metastatic colorectal cancer.

This phase III trial involved 1,401 patients receiving chemotherapy with either capecitabine (Xeloda) plus oxaliplatin (Eloxatin) (a regimen known as XELOX) or 5-fluorouracil and leucovorin plus oxaliplatin (a regimen known as FOLFOX4), who were randomized to receive either bevacizumab or a placebo in addition to the chemotherapy. Progression-free survival was 8.0 months in the chemotherapy plus placebo group, compared with 9.4 months in patients who received chemotherapy plus bevacizumab.

Overall side effects for the groups were similar. These effects were due primarily to oxaliplatin-based therapy and included neuropathy (pain, numbness, and tingling), lowered resistance to infection, fatigue, and diarrhea. The only side effect that was clearly increased by bevacizumab was elevated blood pressure, which was easily controlled with medication.

“Although previous studies have not examined its use in the first-line setting, oxaliplatin-based chemotherapy plus bevacizumab is nonetheless currently a widely used first-line treatment regimen in standard practice in the United States for advanced colorectal cancer,” said Leonard Saltz, MD, Professor of Medicine and member of the Gastrointestinal Oncology Service at Memorial Sloan-Kettering Cancer Center, and the study’s lead author. “This is the first study to examine this regimen’s use as first-line treatment. These data validate its continued use in standard practice.” Dr. Saltz is the U.S. principal investigator for this trial; the European principal investigator is James Cassidy, MD, MSc, Cancer Research UK Professor of Oncology at Glasgow University in Scotland.

Abstract # 238

Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC)

L. B. Saltz, S. Clarke, E. Diaz-Rubio, W. Scheithauer, A. Figer, R. Wong, S. Koski, M. Lichinitser, T. Yang, J. Cassidy

Background: The addition of Bev to standard chemotherapy for MCRC has been shown to improve progression-free survival (PFS) and overall survival in several randomized clinical trials [Hurwitz H et al. N Eng J Med 2004;350:2335-42, Kabbinavar FF et al. J Clin Oncol 2005;23:3697-705, Giantonio BJ et al. J Clin Oncol 2005;23(Suppl. 16S):1s(#2)]. NO16966 is the first phase III trial to evaluate the efficacy of Bev in combination with the standard chemotherapy regimen FOLFOX4 and the XELOX regimen in the first-line treatment of MCRC. **Methods:** 1,401 pts were randomized to receive FOLFOX4 (oxaliplatin, 5-FU, leucovorin as described previously) [De Gramont A et al. J Clin Oncol 2000;18:2938-47] or XELOX (oxaliplatin 130 mg/m² iv, capecitabine 1,000 mg/m² bid oral d1-14, q3w) plus Bev (5mg/kg to FOLFOX, 7.5mg/kg to XELOX) or placebo (Pla) in a 2x2 factorial design. The complete trial design has been reported previously. Efficacy is reviewed by an independent review committee. **Results:** Median PFS for XELOX-Bev + FOLFOX4-Bev was 9.3 months vs. 8.0 months for XELOX-Pla + FOLFOX4-Pla (p=0.0023, HR 0.83, 97.5% CI, 0.72-0.95). Although the protocol specified study drug treatment until disease progression (PD), only 56% of patients were treated in this manner, and 50% of patients discontinued for reasons unrelated to PD. Median PFS on specified study treatment was 10.4 months for chemotherapy + Bev vs. 8.1 months for chemotherapy + Pla (HR 0.63, p<0.0001). Heterogeneity was detected in subgroups. No unexpected toxicity has been reported. Additional efficacy data, including independently reviewed data and subgroup analyses will be presented at the meeting. **Conclusions:** This large, international phase III trial demonstrates that the addition of Bev to oxaliplatin-based chemotherapy regimens significantly improves PFS.

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**January 21, 9:45 – 11:30 AM
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**Lead Author: Carlo Aschele, MD, PhD
E.O. Ospedali Galliera
Genoa, Italy**

First Study to Examine Addition of Oxaliplatin to Preoperative Chemotherapy and Radiation for Rectal Cancer Finds the Treatment Safe

A multi-institutional Italian study (called Studio Terapia Adiuvante Retto, or STAR) has shown that oxaliplatin (Eloxatin) can be added to a standard preoperative fluorouracil-based chemoradiotherapy regimen for rectal cancer, with increased frequency and severity of acute toxicity but without major unexpected adverse events, and without affecting the dosage of radiotherapy or the ability to perform surgery.

Chemotherapy and radiation are sometimes offered before surgery for colon and rectal cancers to shrink tumors, making them easier to remove. The addition of oxaliplatin has been shown to increase the efficacy of chemotherapy in both early-stage and metastatic colon cancer, either following or as a substitute for surgery, but it was not known whether it was safe and effective to add oxaliplatin to chemotherapy and radiation regimens given prior to surgery.

This study reports preliminary safety data from the first 250 patients, and will ultimately report on the efficacy of the approach. Approximately half of the patients received standard 5FU chemotherapy and radiation before surgery, while the other half received the chemoradiotherapy regimen combined with oxaliplatin therapy. The large majority of patients in both groups had surgery following preoperative treatments. The study was an open-label, multicenter, randomized phase III trial with the primary purpose of comparing the activity (pathological response rate) and efficacy (overall and disease-free survival) of preoperative chemoradiotherapy with and without oxaliplatin.

Although oxaliplatin regularly resulted in more severe acute toxicity, there were no major unexpected adverse events. The most common side effects were diarrhea (59% in the oxaliplatin group versus 47% in the control group), neurosensory problems (40% vs. 0%), nausea (36% vs. 19%), and vomiting (24% vs. 6%). With the exception of a slight increase in severe (grade 3 or 4) diarrhea, none of the side effects were severe enough to result in major changes in the treatment program.

“These data show that adding oxaliplatin to preoperative chemotherapy and radiation for rectal cancer is safe and could, if proven effective, provide an important new tool for treating this disease,” said Carlo Aschele, MD, PhD, Attending Physician and Lead Clinician in Colorectal/Gastrointestinal Cancer in the Department of Medical Oncology and Cancer Prevention, E.O. Ospedali Galliera in Genoa, Italy, and the study's lead author. “The doses of oxaliplatin used in this study are in the same range as those used in the treatment of metastatic cancer, and thus are likely to be active in this population of patients as well. Our group is continuing to enroll patients in the study to determine whether the addition of oxaliplatin improves both tumor response and overall and disease-free survival in these patients.”

Abstract #233

Pre-operative FU-based chemoradiation +/-weekly oxaliplatin in locally advanced rectal cancer. Preliminary safety findings of the STAR (Studio Terapia Adiuvante Retto)-01 randomized trial

C. Aschele, C. Pinto, G. Rosati, G. Luppi, A. Bonetti, S. Miraglia, G. Silvano, S. Artale, L. Boni, L. Cionini, on behalf of STAR Network Investigators.

Introduction: Oxaliplatin (OXA) significantly enhances the efficacy of 5-Fluorouracil (FU)-based chemotherapy (CT) in metastatic and radically resected, early stage colon cancer. Weekly OXA, at systemically active doses, can be added to preoperative FU-based pelvic chemoradiation (CRT) (Aschele, Ann Oncol 2005).

Methods: An open-label, multicenter, randomized, phase III trial was launched to compare the efficacy (disease-free and overall survival) and activity (pathological response rate) of infused FU (225 mg/msq/day) concomitant to external-beam pelvic radiation (50.4 Gy in 28 daily fractions) (Arm A) to that of the same regimen plus weekly OXA (60 mg/msq weekly x 6) (Arm B). TME surgery is scheduled 6-8 weeks after completing CRT. FU-based adjuvant CT (4 cycles) is planned in both arms. Eligible patients (pts) have resectable tumors located within 12 cm from the anal verge and radiological evidence of perirectal fat or regional nodes involvement. **Results:** 410 pts (median age 63 years; males/females: 66/34 %; cT3/cT4: 66/18 %; cN+: 56 %; median distance from the anal verge: 6 cm) were randomized between 11/2003 and 10/2006 at 40 Italian centers. Toxicity data from the first 250 randomized pts are reported in the table. CRT was completed by 89 % and 74 % of pts in arm A and B, respectively.

The median cumulative dose of delivered radiotherapy was 50.4 Gy in both arms. 120 of 123 pts in arm A and 109 of 112 pts in arm B were operated with a median interval from the end of treatment to surgery of 7.3 and 7.4 weeks, respectively. **Conclusions:** This analysis provides the first comparative toxicity data showing that OXA, at systemically active doses, can be safely added to standard FU-based CRT with an increased frequency and severity of acute toxicity but without major unexpected adverse events and without affecting the ability to deliver full RT doses and to perform surgery.

Toxicity, %	arm A		arm B	
	overall	grade III-IV	overall	grade III-IV
diarrhoea	47	7	59	17
stomatitis	9	1	13	2
nausea	19	0	36	1
vomiting	6	0	24	2
neutropenia	7	0	11	1
thrombocytopenia	3	0	11	0
neurosensory	0	0	40	1
fatigue	14	0	23	1

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**Lead Author: Neil Love, MD
Research To Practice
Miami, FL**

**Study Finds Need for Improvement in Doctor-Patient Communication About
Risks and Benefits of Colorectal Cancer Treatment**

Note: This summary contains updated data not in the abstract.

A survey of patients who had previously received chemotherapy following surgery for colorectal cancer (called “adjuvant” chemotherapy) found that although patients are generally satisfied with their care, better communication between oncologists and patients is needed regarding the benefits and potential side effects of therapy. The study also found that clinical investigators and practicing medical oncologists may underestimate patients’ willingness to undergo therapy for even a modest treatment benefit.

The study surveyed 150 patients treated with adjuvant chemotherapy for colorectal cancer within the past five years. Twenty-three clinical investigators and 150 practicing medical oncologists also participated in a corresponding survey. Patients listened to an audio educational program about adjuvant chemotherapy; based on the risks and benefits discussed in the program, patients were asked whether they would be willing to undergo the same adjuvant chemotherapy they received previously for varying reductions in risk of cancer recurrence. The patients were also asked about their experiences with treatment and their clinical care.

Of these patients, 36% said they would choose to be treated again with the same therapy for a 1% absolute reduction in the risk of cancer recurrence and 57% would be treated again for a 3% reduction. By contrast, clinical investigators and medical oncologists predicted that far fewer patients would wish to be treated for those same benefits.

The patient survey also found that the side effects of treatment differed from what patients expected, suggesting that communication from physicians regarding the potential toxicities of therapy were not as clear or accurate as it could have been, or that patients are receiving inaccurate information from other sources. Additionally, the survey found that 60% of patients were not offered the opportunity to participate in a clinical trial, but that 81% of those patients wished they had received such information.

“This survey demonstrates that patients may be far more willing to receive cytotoxic therapy for what others might view as modest potential treatment benefits,” said Neil Love, MD, a medical oncologist who is President of Research to Practice, an oncology education company in Miami, and the study’s lead author. “The findings underscore the importance of better communication between physicians and patients to ensure that physicians clearly understand patient expectations regarding treatment, and so that patients receive clear and accurate information about the risks and benefits of therapy.”

Abstract #239

How well do we communicate with our patients? A survey of patients who received adjuvant chemotherapy for colorectal cancer

N. Love, C. Bylund, N. J. Meropol, J. Marshall, S. A. Curley, L. M. Ellis, A. Grothey, H. Lenz, L. B. Saltz, M. Elder

Background: In 2005 our pilot survey of colorectal cancer (CRC) survivors demonstrated that some patients wish to receive adjuvant chemotherapy (AC) for modest benefits. This project attempted to validate those findings and examine the experiences of patients with CRC (Pts) who received AC previously. **Methods:** Between May 2006 and August 2006, we recruited from oncology practices and advocacy groups a sample of 100 Pts who had received AC for CRC in the last 5 years. Pts were asked to complete a survey of their experiences with AC and to evaluate a pilot audio educational program on AC featuring interviews with clinical investigators (CIs) and Pts. Based on the risks and benefits of AC discussed in the audio program, Pts were asked whether they would undergo the same AC again for varying absolute treatment benefits. They were also asked about information they received from their medical oncologist (MO) prior to AC and how that compared to their experiences. Concurrently, we asked similar questions in a survey of 23 CRC CIs and 150 practicing MOs. **Results:** Of these Pts, 40% would choose to be treated for a 1% absolute reduction in recurrence risk (ARRR), and 62% would opt for treatment for a 3% ARRR. Pts who received oxaliplatin (OX) responded similarly to those who did not. CIs and MOs underestimated the percentage of Pts willing to receive AC for a modest benefit (Table). Whereas 75% of Pts rated their MO highly for overall care, 48% found AC more difficult than expected based on discussions with their MO, although the majority of Pts experienced less alopecia and GI toxicity than anticipated. **Conclusions:** Although Pts participating in this type of

survey may have more proactive treatment attitudes than a general Pt population, these findings suggest an opportunity to improve communication between MO and Pts and demonstrate the need for educational interventions to provide supplemental information about treatment options.

Pts electing AC and related physicians predictions by ARRR							
ARRR	Pts electing AC				OX vs No C.	CI prediction (n=23)	MO prediction (n=150)
	Total (N=100)	OX (n=4)	No C. (n=52)				
1%	40%	38%	42%	P = 0.63	10%	14%	
3%	62%	60%	63%	P = 0.76	29%	28%	
5%	70%	73%	67%	P = 0.55	59%	52%	
10%	88%	88%	88%	P = 0.88	83%	72%	

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