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ERRATA

In the previous issue of Colorectal Cancer Update (Vol 2, Issue 3), the oxaliplatin dose in NSABP-C-08 and the MOSAIC trial was incorrectly stated as 85 mg. The correct oxaliplatin dose is 85 mg/m^2.

HOW TO USE THIS MONOGRAPH

This is a CME activity that contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ColorectalCancerUpdate.com** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**.

Colorectal Cancer Update: A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Colorectal cancer is among the most common cancers in the United States, and the arena of colorectal cancer treatment continues to evolve. Published results from ongoing clinical trials lead to the emergence of new therapeutic agents and regimens and changes in indications, doses and schedules for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well-informed of these advances.

To bridge the gap between research and patient care, *Colorectal Cancer Update* utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe ongoing clinical trials in colorectal cancer and their potential impact on patient care.
- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment.
- Develop and explain a management strategy for patients with colorectal cancer in the adjuvant and metastatic settings.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 4

Upon completion of this activity, participants should be able to:

- Describe the design and scientific rationale for the planned trial comparing infusional 5-FU, leucovorin and oxaliplatin to capecitabine and oxaliplatin with or without bevacizumab in patients with metastatic colorectal cancer.
- Develop a treatment strategy for patients with metastatic colorectal cancer that incorporates irinotecan, oxaliplatin, 5-FU and capecitabine.
- Review some of the ongoing clinical trials in pancreatic cancer and gastrointestinal stromal tumors (GIST).
- Consider the implications of the MOSAIC trial on the selection of adjuvant therapy for patients with colorectal cancer.
- Review the results from the Phase III trial evaluating IFL with or without bevacizumab in patients with metastatic disease.

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

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As a provider accredited by the ACCME, it is the policy of Research To Practice to require the disclosure of any significant financial interest or any other relationship the sponsor or faculty members have with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Charles D Blanke, MD, FACP	Grants/Research Support: Pfizer Inc, Aventis Pharmaceuticals Consultant: Bayer Corporation, RITA Medical Systems Inc, Pfizer Inc, Roche Laboratories Inc, Bristol-Myers Squibb Company
Robert B Diasio, MD	Consultant and Honorarium: Pfizer Inc, Roche Laboratories Inc, Sanofi-Synthelabo Inc, Genentech Inc
Patrick J Flynn, MD	Honorarium: Sanofi-Synthelabo Inc, Aventis Pharmaceuticals

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bevacizumab	Avastin™	Genentech Inc
capecitabine	Xeloda®	Roche Laboratories Inc
celecoxib	Celebrex®	Pfizer Inc
cetuximab	Erbitux®	ImClone Systems and Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
doxorubicin hydrochloride	Adriamycin®	Pfizer Inc
5-fluorouracil, 5-FU	Various	Various
gemcitabine	Gemzar®	Eli Lilly & Company
hydrochlorothiazide	Various	Various
ifosfamide	IFEX®	Bristol-Myers Squibb Company
imatinib mesylate	Gleevec®	Novartis Pharmaceuticals Corporation
irinotecan	Camptosar®	Pfizer Inc
leucovorin	Various	Various
oxaliplatin	Eloxatin®	Sanofi-Synthelabo Inc

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Editor's Note

Extraordinary Cases

"After 75 years and millions of dollars in grants being offered to doctors and scientists, you mean to tell me that no cure for cancer could be found? Maybe no one wants to see cancer cured because they will lose money."

– Audience Participant
Breast Cancer Patients' Perspectives Meeting
Miami, Florida, September 14, 2003

The seemingly rapid progress in clinical research for cardiovascular disease and HIV has added to the frustration of cancer patients and oncologists who are hoping to see quicker progress. One of my favorite questions for interviewees for a breast, lung, prostate or colorectal cancer CME program is, "Where do you think clinical research is likely to be in 10 years?" Invariably, the answer relates to targeted therapy and the identification of predictors of response to systemic agents.

Is this research focus a reason for hope or just more hype to keep angry critics like the woman quoted above in abeyance? Two cases presented in this program create a strong argument that perhaps current approaches to targeted cancer therapy may provide some of the answers we have pursued for so long.

Dr Charles Blanke describes a 40-year-old man with an end-stage, heavily pretreated gastrointestinal stromal tumor (GIST) who traveled across the country to participate in an early Phase II study of imatinib (Gleevec®) in a final desperate attempt at remission. Within weeks, a pelvic tumor that was causing severe bladder compression and intense pain requiring narcotics "melted away," and three years later, the cancer has yet to recur and the patient is doing extremely well.

Dr Patrick Flynn describes another patient whose clinical course provides intriguing hints of future progress in oncology. After the surgical removal of a primary colon cancer, this mother of two teenagers received the disheartening news that she had unresectable retroperitoneal lymphadenopathy.

Hoping to contribute to the well-being of future cancer patients, she sought participation in a clinical trial and enrolled in a study and was randomized to bevacizumab, 5-FU and leucovorin. Within months, the tumor was in complete remission. Currently, two years later, she is asymptomatic and continues to have no evidence of disease while still receiving bevacizumab.

Will oncology waiting rooms 10 or 20 years from now be filled with patients like

these or will we continue to struggle with relatively toxic interventions that provide modest antitumor benefits? Clearly, targeted biologic interventions like imatinib and bevacizumab are the focal points of a great deal of clinical research, but perhaps the identification of predictors of response in the tissue or serum will be even more important than the discovery of new agents.

In the last issue of our series, Dr Norman Wolmark discussed the challenge of finding a predictor of response to bevacizumab. However, he noted that in the landmark clinical trial presented by Dr Herbert Hurwitz at the 2003 ASCO meeting, the addition of bevacizumab to IFL conferred a major survival advantage, even in the absence of a tissue target that predicted response.

Investigators often cite the example of trastuzumab in breast cancer to emphasize the critical role of predictors of response with targeted therapies. It is fascinating to consider that the pivotal breast cancer clinical trial by Slamon et al would not have demonstrated a survival benefit if the study had been done in unselected patients rather than in women with HER2-positive breast cancer.

It is pleasant to fantasize of a time in the future when most cancer patients will have clinical courses like the patients of Drs Blanke and Flynn. To accomplish this formidable task, clinicians and patients must continue their commitment to participate in clinical trials. Hopefully, cancer survivors will then be able to feel a sense of relief, rather than frustration, at the pace of cancer clinical research.

—Neil Love, MD

Targeted therapies in gastrointestinal cancers

"Despite surgical, radiotherapeutic, and chemotherapeutic advances, a large proportion of gastrointestinal (GI) cancers remain incurable. An improved understanding of the molecular pathogenesis of cancer has promulgated the development of novel agents designed to target critical pathways involved in cancer development and progression. ...

"Evidence suggests that novel agents can be administered alone or in combination with standard therapies with little additional toxicity. The results of ongoing and future research efforts will clarify the optimal use and survival benefit of targeted therapies for patients with GI malignancies."

EXCERPT FROM: Gill S et al. **New targeted therapies in gastrointestinal cancers.** *Curr Treat Options Oncol* 2003;4(5):393-403. **Abstract**

Select publications

Demetri GD et al. **Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors.** *N Engl J Med* 2002;347(7):472-80. **Abstract**

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646**.

Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21(1):60-5. **Abstract**

Charles D Blanke, MD, FACP

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Edited comments by Dr Blanke

SWOG-S0303: Phase III trial in patients with locally advanced metastatic or recurrent colorectal cancer

This trial will address two important questions. First, is capecitabine and oxaliplatin equivalent to infusional 5-FU and oxaliplatin? Oxaliplatin has moved into the front-line treatment of patients with metastatic colorectal cancer. We are interested in exploring whether the infusional 5-FU component of the regimen is necessary or whether it can be substituted by an oral fluoropyrimidine, like capecitabine.

Secondly, can we improve survival with the addition of bevacizumab? Bevacizumab was recently shown to improve the median survival associated with chemotherapy by about five months. Therefore, we will also randomly assign patients to bevacizumab or placebo. I think capecitabine and oxaliplatin will be at least equivalent to infusional 5-FU and oxaliplatin. We're hoping that bevacizumab improves median survival substantially.

Potential synergy from combining bevacizumab with cytotoxic therapy

"Given the potentially cytostatic nature of anti-VEGF therapy, use of this class of drugs may be optimized by combinations with more classical cytotoxic therapy. Most anti-VEGF agents, including bevacizumab, should increase local tumor apoptotic rates as one of their primary mechanisms for inhibiting tumor growth. In addition, most traditional cytotoxic and antiproliferative agents have been shown to be anti-angiogenic. …

"This effect may be mediated by direct effects against the endothelial cell and/or by reducing tumor production of pro-angiogenic factors. Thus, the mechanisms behind anti-angiogenic and antitumor agents may be more complex and inter-related than usually presumed."

SOURCE: Fernando NH, Hurwitz HI. **Inhibition of vascular endothelial growth factor in the treatment of colorectal cancer**. *Semin Oncol* 2003;30(Suppl 6):39-50. **Abstract**

Rationale for SWOG-S0303

When a survival advantage was demonstrated with the combination of 5-FU, leucovorin and irinotecan, we moved away from standard 5-FU to triple therapy. For several years, we used irinotecan with bolus 5-FU and leucovorin (IFL). It was the best therapy we had to offer, and it was better than standard 5-FU alone. Rich Goldberg headed up N9741, the trial that compared bolus IFL to infusional 5-FU, leucovorin and oxaliplatin (FOLFOX). FOLFOX proved to be markedly better and less toxic. Whether the infusional 5-FU or oxaliplatin was responsible for the difference is not clear; however, FOLFOX was clearly better, and we chose it as the control arm for SWOG-S0303.

Since capecitabine is as effective — perhaps a little more effective — and less toxic than 5-FU alone, it seemed like a logical combination with oxaliplatin. In addition, Phase II data indicate that capecitabine in combination with oxaliplatin has a very high response rate and a favorable median survival.

Phase III Randomized Study of Fluorouracil, Leucovorin Calcium, and Oxaliplatin versus Capecitabine and Oxaliplatin with or without Bevacizumab in Patients with Locally Advanced, Metastatic, or Recurrent Colorectal Cancer Approved Protocol-Not Yet Active

Protocol ID: SWOG-S0303
Projected Accrual: 2,200 patients

Eligibility: Patients with locally advanced, recurrent or metastatic colorectal adenocarcinoma that has not been treated with chemotherapy

Treatment:
ARM 1: [oxaliplatin + infusional 5-FU + leucovorin ± bevacizumab]
ARM 2: [oxaliplatin + capecitabine ± bevacizumab]

Study Contacts:
Charles Blanke, MD, Study Coordinator
Tel: 503-494-1556
Southwest Oncology Group

Heinz-Josef Lenz, MD, Study Coordinator
Tel: 323-865-3955; 1-800-872-2273
Southwest Oncology Group

SOURCE: NCI Physician Data Query, October 2003.

ASCO 2003 Phase II capecitabine/oxaliplatin trials: Response rate for first-line therapy in patients with metastatic disease

Abstracts from Proc ASCO 2003	Number of patients	Response rate
Van Custem E et al. **Abstract 1023**	96	45%
Grothey A et al. **Abstract 1022**	71	49%
Makatsoris T et al. **Abstract 1447**	36	31%
Carreca T et al. **Abstract 2939**	21	43%

Phase II study of capecitabine plus oxaliplatin

"Combining capecitabine and oxaliplatin yields promising activity in advanced colorectal cancer. ...

"The main toxicity is diarrhea, which is manageable with appropriate dose reductions.This combination may be preferable compared to a standard combination with infusional fluorouracil/leucovorin as it is more convenient and practical with similar efficacy. Thus, phase III trials are needed to clarify its role in the treatment of chemotherapy-naive advanced colorectal cancer patients."

SOURCE: Zeuli M et al. **Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer.** *Ann Oncol* 2003;14(9):1378-82. **Abstract**

Bevacizumab in the nonprotocol setting

If bevacizumab were available today, I would definitely use it as second-line therapy in a nonprotocol setting. FOLFOX tends to be my first-line regimen because I have the most experience and excellent results with it. If there were no trial to offer a patient with disease that had failed FOLFOX, I would probably recommend 5-FU and irinotecan with bevacizumab. The question of whether to use bevacizumab as first-line therapy is still unanswered, although there are other experts who would use it right now.

If a patient had received first-line irinotecan, I would consider an oxaliplatin-based regimen plus bevacizumab in a nonprotocol situation, but we don't have data yet. From the ECOG trial evaluating bevacizumab and oxaliplatin as second-line therapy, we know that it's safe, and the efficacy data should be reported soon.

Clinical benefits of adding bevacizumab to 5-FU/leucovorin

"This relatively small, randomized, phase II trial compared the safety and efficacy of bevacizumab (at two dose levels) plus FU/LV versus FU/LV alone as first-line therapy for metastatic colorectal cancer. …

"These preliminary results suggest that bevacizumab, in combination with FU/LV, increases response rate, prolongs time to progression, and prolongs survival compared with FU/LV alone in patients with metastatic colorectal cancer. …

"...ECOG-sponsored trial (E3200) will study single-agent bevacizumab and bevacizumab plus FU/LV/oxaliplatin in patients who have progressed after previous chemotherapy with FU/LV/CPT-11."

EXCERPT FROM: Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21:60-5. **Abstract**

Phase III Randomized Study of Oxaliplatin, Fluorouracil and Leucovorin Calcium with or without Bevacizumab versus Bevacizumab Only in Patients with Previously Treated Advanced or Metastatic Colorectal Adenocarcinoma Closed Protocol

Protocol IDs: E-3200, CTSU
Projected Accrual: 880 patients

Eligibility: Patients with advanced or metastatic colorectal cancer that has been treated with a fluoropyrimidine-based regimen and an irinotecan-based regimen, either alone or in combination

Treatment:
ARM 1: [oxaliplatin + infusional 5-FU + leucovorin + bevacizumab] every 2 weeks
ARM 2: [oxaliplatin + infusional 5-FU + leucovorin] every 2 weeks
ARM 3: bevacizumab every 2 weeks

Study Contact:
Bruce Giantonio, MD, Protocol Chair
Tel: 215-662-8756, Fax: 215-243-3268
Eastern Cooperative Oncology Group

SOURCE: NCI Physician Data Query, October 2003.

Celecoxib and chemotherapy-related toxicity

We recently reported preliminary results from a Phase II trial evaluating IFL in combination with celecoxib. Interestingly, there may be a dramatic reduction in chemotherapy-related toxicity. The incidence of diarrhea — particularly severe diarrhea — decreased, and there may also be a reduction in myelosuppression. It's too early to tell whether there will be an improvement in efficacy.

Dr Edward Lin reported that celecoxib might improve capecitabine-associated toxicity. If celecoxib could prevent the hand-foot syndrome, even if it didn't improve efficacy, it would be a worthwhile addition. Other preliminary data indicate that celecoxib may affect oxaliplatin-mediated neurotoxicity, which would be a huge breakthrough. We're discussing whether we should evaluate that in a formal trial.

Approaches to adjuvant therapy

Dr de Gramont's presentation at ASCO demonstrated an advantage in disease-free survival for adjuvant FOLFOX. It was a modest improvement of roughly five percent, but it's not a particularly toxic regimen, so I think it was enough to offer to patients. In 2003, it is reasonable to offer adjuvant FOLFOX to patients with Stage III disease. It is also reasonable to discuss whether patients with Stage II disease should receive chemotherapy and, if they are going to be treated, it is reasonable to consider oxaliplatin, although that would be aggressive.

Data will soon emerge regarding the adjuvant irinotecan trial. The preliminary data indicate that that trial is negative, which is difficult to explain. Based on the current data, I would not offer irinotecan in the adjuvant setting, but I definitely would like to see additional follow-up from the CALGB trial.

MOSAIC trial: 3-year disease-free survival for adjuvant chemotherapy

	FOLFOX	LV5FU2	Hazard ratio
Overall (n=1123, 1123)	77.8%	72.9%	0.77 [0.65-0.92], p<0.01
Stage III (n=672, 675)	71.8%	65.5%	0.76 [0.62-0.92]
Stage II (n=451, 448)	86.6%	83.9%	0.82 [0.57-1.17]

LV5FU2= (leucovorin 2-hour infusion + 5-FU bolus and 22-hour continuous infusion) days 1-2 every 2 weeks x 6 months. FOLFOX=(LV5FU2 + oxaliplatin day 1) every 2 weeks x 6 months

SOURCE: de Gramont A. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized MOSAIC trial.** Presented at: Annual Meeting of the American Society of Clinical Oncology; May 31 – June 3, 2003; Chicago, IL. **Abstract 1015**

Current research in pancreatic cancer

Pancreatic cancer remains the malignant neoplasm with the shortest five-year survival of the gastrointestinal tumors. Essentially, we don't have good treatments. Standard chemotherapy offers about a five percent remission rate and a few weeks of improvement in median survival.

This is the era of doublet therapy. We have gemcitabine, which I use all the time off protocol. It's being evaluated in combination with a number of other chemotherapeutic agents, but also with some targeted therapies. In the chemotherapeutic arena, there is emerging data on its use with the platinums — particularly cisplatin and, even more promising, oxaliplatin.

Finally, there is emerging data for gemcitabine in combination with either bevacizumab or cetuximab (C225). There was a small trial that combined bevacizumab with gemcitabine, which had some nice biologic correlates. There was presumed clinical benefit, and the regimen was actually very well-tolerated.

Bevacizumab (B) plus gemcitabine (G) in advanced pancreatic cancer (PC)

"Vascular endothelial growth factor (VEGF) is commonly over-expressed in PC, and VEGF expression appears to be an important predictor of survival in PC pts. VEGF may also be an autocrine growth factor for PC. In preclinical models, anti-VEGF antibodies inhibit the growth of pancreatic tumors. …

"BG is an active combination in PC. The median TTP of 5.5 months and estimated 1-year survival of 54% are encouraging."

SOURCE: Kindler HL et al. **Bevacizumab (B) plus gemcitabine (G) in patients (pts) with advanced pancreatic cancer (PC).** *Proc ASCO* 2003;**Abstract 1037.**

Gastrointestinal stromal tumor (GIST)

GISTs weren't recognized six or seven years ago, but now they are one of the most common soft-tissue sarcomas. Somewhere between 5,000 and 10,000 GISTs are diagnosed in the United States every year. The usual clinical presentation is GI bleeding. These tumors become enormously large, auto-ulcerate and outgrow their blood supply. They do not respond to standard cytotoxic chemotherapy, including agents that are active in other sarcomas (i.e., doxorubicin, ifosfamide or gemcitabine).

Studies were conducted at Oregon Health & Science University in patients with chronic myeloid leukemia (CML) utilizing the drug imatinib mesylate. It turns out that patients with GISTs have a genetic defect, which leads to the activation of a gene and subsequent protein production that is very similar to the one seen in CML.

Basic science research indicated that the KIT oncoprotein could be inhibited by imatinib. Therefore, we conducted a Phase II trial with imatinib and found a 65 percent response rate with GIST. Three years later, more than half of the patients in that original trial are alive and well, although some patients relapsed or progressed in about 15 to 18 months.

Efficacy of imatinib mesylate in GIST: Results of randomized, multicenter study

"Our study demonstrates, in a large series of patients with advanced gastrointestinal stromal tumors, that imatinib is effective in most patients. ...

"Advanced gastrointestinal stromal tumors are unresponsive to conventional chemotherapy. The high rate of response to imatinib in these patients with bulky disease who had no response to cytotoxic chemotherapy is not only remarkable, but also supports the hypothesis that dysregulated KIT kinase activity is important in human gastrointestinal stromal tumors."

SOURCE: Demetri GD et al. **Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors.** *N Engl J Med* 2002;347:472-80. **Abstract**

Select publications

Publications discussed by Dr Blanke

Benjamin RS et al. **Phase III dose-randomized study of imatinib mesylate (STI571) for GIST: Intergroup S0033 early results.** *Proc ASCO* 2003;**Abstract 3271.**

Benson AB et al. **Bevacizumab (anti-VEGF) plus FOLFOX4 in previously treated advanced colorectal cancer (advCRC): An interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO* 2003;**Abstract 975.**

Borner MM et al. **Phase II study of capecitabine and oxaliplatin in first- and second-line treatment of advanced or metastatic colorectal cancer.** *J Clin Oncol 2002;20(7):1759-66.* **Abstract**

Blanke CD et al. **A phase II trial of celecoxib (CX), irinotecan (I), 5-fluorouracil (5FU), and leucovorin (LCV) in patients (pts) with unresectable or metastatic colorectal cancer (CRC).** *Proc ASCO* 2002;**Abstract 505.**

Carreca I et al. **Oral capecitabine plus oxaliplatin (XELOX regimen) in elderly patients with advanced colorectal carcinoma (ACC). Southern Italy Cooperative Oncology Group (SICOG 0108) phase II study.** *Proc ASCO 2003;***Abstract 2939.**

de Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized MOSAIC trial.** *Proc ASCO* 2003;**Abstract 1015.**

Goldberg RM et al. **N9741: Oxaliplatin (Oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Updated efficacy and quality of life (QOL) data from an intergroup study.** *Proc ASCO* 2003;**Abstract 1009.**

Grothey A et al**. Randomized phase II trial of capecitabine plus irinotecan (CapIri) vs capecitabine plus oxaliplatin (CapOx) as first-line therapy of advanced colorectal cancer** (ACRC). *Proc ASCO 2003;***Abstract 1022.**

Heinrich MC et al. **PDGFRA and KIT mutations correlate with the clinical responses to imatinib mesylate in patients with advanced gastrointestinal stromal tumors (GIST).** *Proc ASCO* 2003;**Abstract 3274.**

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646.**

Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21(1):60-5. **Abstract**

Kindler HL et al. **Bevacizumab (B) plus gemcitabine (G) in patients (pts) with advanced pancreatic cancer (PC).** *Proc ASCO* 2003;**Abstract 1037.**

Lin E et al. **Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity.** *Oncology (Huntingt)* 2002;16(12 Suppl 14):31-7. **Abstract**

Makatsoris T et al. **A phase II study of capecitabine and oxaliplatin as first line treatment for advanced colorectal carcinoma (CRC). A Hellenic Cooperative Oncology Group (HeCOG) study.** *Proc ASCO 2003;***Abstract 1447.**

Lin EH et al. **Celecoxib attenuated capecitabine induced hand-and-foot syndrome (HFS) and diarrhea and improved time to tumor progression in metastatic colorectal cancer (MCRC).** *Proc ASCO* 2002;**Abstract 2364.**

Saltz LB et al. **Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group.** *N Engl J Med* 2000;343(13):905-14. **Abstract**

Scheithauer W et al. **Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer.** *J Clin Oncol* 2003;*21(7):1307-12.* **Abstract**

Van Cutsem E et al. **XELOX: Mature results of a multinational, phase II trial of capecitabine plus oxaliplatin, an effective 1st line option for patients (pts) with metastatic colorectal cancer (MCRC).** *Proc ASCO 2003;***Abstract 1023.**

von Mehren M et al. **High incidence of durable responses induced by imatinib mesylate (Gleevec) in patients with unresectable and metastatic gastrointestinal stromal tumors (GISTs).** *Proc ASCO* 2002;**Abstract 1608.**

Zeuli M et al. **Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer.** *Ann Oncol 2003;14(9):1378-82.* **Abstract**

Robert B Diasio, MD

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Edited comments by Dr Diasio

MOSAIC trial

The MOSAIC adjuvant trial compared the de Gramont regimen (infusional 5-FU and leucovorin) to the FOLFOX4 regimen (infusional 5-FU, leucovorin and oxaliplatin). Approximately 1,100 patients per arm were enrolled in the trial; about one-third had Stage II disease and two-thirds had Stage III disease.

After three and one-half years, there was a relative disease-free survival risk-reduction of 23 percent associated with FOLFOX4. Some concerns were raised about using disease-free survival as an endpoint because most United States adjuvant trials have utilized overall survival, which requires a longer time to obtain meaningful data. However, the disease-free survival from the MOSAIC trial was comparable to the disease-free survival in some of the earlier United States adjuvant trials.

This trial represents the first evidence that the addition of another agent to 5-FU and leucovorin has a benefit in the adjuvant setting. As with almost all of the other adjuvant studies conducted, the benefit is in patients with Stage III disease, not Stage II disease. Tantalizing data, however, suggests that patients with Stage II disease also benefited, but it was not a statistically significant benefit.

FOLFOX4 was very tolerable. The major problem was neurotoxicity — 12 percent of the patients receiving FOLFOX4 experienced Grade III neurotoxicity (e.g., functional impairment in manual dexterity). It must be emphasized, however, that the neurotoxicity was rapidly reversible.

After 12 months, only one percent of the patients had neurotoxicity. A strategy to manage oxaliplatin-associated neurotoxicity — involving the administration of calcium and magnesium before and after oxaliplatin — was presented at ASCO 2002.

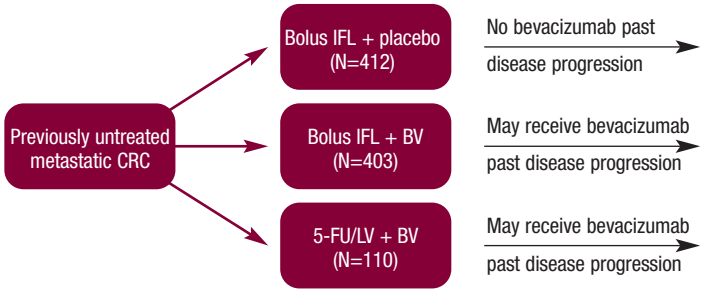
Bevacizumab in combination with IFL in patients with metastatic disease

Results of the Phase III study evaluating the combination of bevacizumab and IFL were presented as a late-breaking abstract at the ASCO 2003 GI Plenary Session. In patients with metastatic disease, a 4.7-month increase in median overall survival was observed when bevacizumab was added to IFL.

The toxicities associated with bevacizumab were minimal, mainly mild hypertension. In all cases, the hypertension was managed with antihypertensive drugs that were administered on an outpatient basis. Another toxicity we need to be aware of is perforation of the GI tract.

Six patients out of the 400 treated with bevacizumab were noted to have evidence of perforations. No similar events occurred in the patients treated with IFL and placebo. Overall, the toxicity profile was not a major limitation to the use of bevacizumab — a very impressive agent that provides a marked benefit when administered with IFL.

Phase III trial comparing IFL with or without bevacizumab (BV)



SOURCE: Hurwitz H. **Bevacizumab (Avastin, a Monoclonal Antibody to Vascular Endothelial Growth Factor) Prolongs Survival in First-Line Colorectal Cancer (CRC): Results of a Phase III trial of Bevacizumab in Combination with Bolus IFL (Irinotecan, 5-Fluorouracil, Leucovorin).** Presented at: Annual Meeting of the American Society of Clinical Oncology; May 31 – June 3, 2003; Chicago, IL. **Abstract 3646.**

Mechanism of action of bevacizumab

Bevacizumab is a chimerized antibody — more than 90 percent of it is humanized and a relatively small part is murine. This particular antibody is capable of complexing with the vascular endothelial growth factor (VEGF) released by the tumor.

A number of different factors upstream of the tumor are thought to stimulate VEGF. Following its release, VEGF acts downstream on receptors within endothelial cells in the blood vessels; this potentially increases vascularization of the area within the tumor and influences metastases. Bevacizumab couples with the released VEGF and prevents it from working at the endothelial sites.

Efficacy results from Phase III trial of bevacizumab (BV) in combination with bolus irinotecan, 5-fluorouracil, leucovorin (IFL) as first-line therapy in patients with metastatic colorectal cancer

	IFL/placebo	IFL/BV	*p*-value
Median survival (months)	15.6	20.3	0.00003
Progression-free survival (months)	6.24	10.6	<0.00001
Objective response rate (CR + PR)	35%	45%	0.0029
Duration of response (months)	7.1	10.4	0.0014

SOURCE: Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a Phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646.**

NSABP-C0-8: Proposed adjuvant trial

The planned adjuvant bevacizumab trial (NSABP-C-08) has gone through several iterations, and questions remain about the design. One of the current considerations is to compare the FLOX regimen to a FOLFOX regimen, although it's not clear at this point which of the FOLFOX regimens should be compared.

The MOSAIC trial evaluated FOLFOX4, but most United States cooperative group studies now incorporate FOLFOX6 and even FOLFOX7. There's also interest in evaluating the CAPOX regimen, a combination of capecitabine and oxaliplatin. The proposed NSABP-C0-8 may compare the Roswell Park regimen of 5-FU administration to a FOLFOX regimen and to CAPOX, each administered with or without bevacizumab.

Phase III Trial Comparing Weekly Bolus 5-Fluorouracil (5-FU) plus Leucovorin (LV) and Oxaliplatin (FLOX) ± Bevacizumab with Two Weekly Infusional 5-FU plus LV and Oxaliplatin (FOLFOX) ± Bevacizumab with Capecitabine plus Oxaliplatin ± Bevacizumab for the Treatment of Patients with Stages II or III Carcinoma of the Colon Proposed Protocol

Protocol ID: NSABP-C-08
Expected Accrual: 5,015 patients over 3.5 years

Randomization
ARM 1: FLOX ± bevacizumab
ARM 2: FOLFOX6 ± bevacizumab
ARM 3: CAPOX ± bevacizumab

SOURCE: NSABP Annual Meeting, Orlando, Florida, June 2003.

First-line therapy for patients with metastatic colorectal cancer

When treating patients with advanced colorectal cancer, we have three very active drugs: 5-FU, irinotecan and oxaliplatin. The comparative studies,

however, are difficult to evaluate because N9741 compared the Saltz regimen (bolus 5-FU) to FOLFOX (infusional 5-FU). Although we are comparing apples and oranges in N9741, I think oxaliplatin still shows some improvement. My bias is to treat patients with a FOLFOX regimen first-line.

Historically, most of us have used FOLFOX4, but the convenience of FOLFOX6 and FOLFOX7 makes them much more appealing. In the university setting, we are using FOLFOX6 at the moment. We were impressed with the data on FOLFOX7 presented at ASCO 2003, which involves a higher oxaliplatin dose and, if necessary, stopping the regimen and using intermittent therapy — something that goes against our traditional teaching in oncology. However, as reported at ASCO 2003, FOLFOX7 can be administered intermittently with very positive results compared to FOLFOX4 administered continuously.

To summarize, I would use an oxaliplatin-containing regimen as first-line therapy in a patient with metastatic colorectal cancer. Since I'm more familiar with FOLFOX6, I would probably use that regimen. Then, if the patient's disease progressed in the future, I would consider irinotecan.

CAPOX in patients with metastatic disease

At ASCO 2003, Van Cutsem reported on a Phase II trial evaluating the combination of capecitabine and oxaliplatin (CAPOX). This small trial (n=96) demonstrated an overall median survival of 19.5 months. A number of trials that will be conducted by the United States cooperative groups (i.e., NSABP, SWOG, ECOG) will evaluate the CAPOX regimen because it avoids the problem American oncologists have with infusional 5-FU.

CAPOX is a worthwhile alternative that should be discussed with patients. Some oncologists don't have an infusional service available for the administration of infusional 5-FU, and they ask what they should do. I initially say, "We have very exciting data with CAPOX; I don't recommend it up front, and there are caveats to be emphasized in terms of diarrhea when using capecitabine." I have treated patients with CAPOX, and I have recommended that oncologists use it in select situations. It's a much easier way to administer 5-FU, and the data on overall survival is very impressive from the small Phase II study.

Capecitabine/oxaliplatin (XELOX) in first-line metastatic colorectal cancer

"…oral capecitabine (Xeloda®) is replacing IV 5-FU/LV monotherapy in 1st line MCRC based on superior activity and improved safety compared with bolus 5-FU/LV. Tumor-activated capecitabine was designed to mimic infused 5-FU and, with advantages in convenience and patient preference, should also replace 5-FU/LV in combination. ...

"XELOX has comparable efficacy and safety to the IV FOLFOX regimens in 1st line MCRC…"

EXCERPT FROM: Van Cutsem E et al. **XELOX: Mature results of a multinational, Phase II trial of capecitabine plus oxaliplatin, an effective 1st line option for patients (pts) with metastatic colorectal cancer (MCRC).** *Proc ASCO* 2003;**Abstract 1023.**

Phase II trial of capecitabine and oxaliplatin (CAPOX) as first-line therapy in patients (n=96) with metastatic colorectal cancer

Response rate		**Grade III/IV toxicity (cont)**	
Investigator	55%	Nausea/vomiting	13%
Independent review	45%	Asthenia	9%
Median overall survival	19.5 months	Neuropathic pain	6%
Grade III/IV toxicity		Neutropenia	7%
Sensory neuropathy	16%	Thrombocytopenia	4%
Diarrhea	16%		

SOURCE: Van Cutsem E et al. **XELOX: Mature results of a multinational, Phase II trial of capecitabine plus oxaliplatin, an effective 1st line option for patients (pts) with metastatic colorectal cancer (MCRC).** *Proc ASCO* 2003;**Abstract 1023.**

Select publications

Publications discussed by Dr Diasio

Andre T et al. **FOLFOX7 compared to FOLFOX4. Preliminary results of the randomized optimox study.** *Proc ASCO* 2002; **Abstract 1016.**

Cunnigham D et al. **Cetuximab (C225) alone or in combination with irinotecan (CPT-11) in patients with epidermal growth factor receptor (EGFR)-positive, irinotecan-refractory metastatic colorectal cancer (MCRC).** *Proc ASCO* 2003;**Abstract 1012.**

de Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized MOSAIC trial.** *Proc ASCO* 2003;**Abstract 1015.**

de Gramont A et al. **Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French Intergroup study.** *J Clin Oncol* 1997;15(2):808-15. **Abstract.**

Gamelin E et al. **Prevention of oxaliplatin peripheral sensory neuropathy by Ca+ gluconate/ Mg+ chloride infusions: A retrospective study.** *Proc ASCO* 2002;**Abstract 624.**

Garay CA et al. **Randomized trial of bolus plus infusional 5-FU/leucovorin (LV5FU2) with/without oxaliplatin (FOLFOX4) after sequential fluoropyrimidine and CPT-11 in the treatment of advanced colorectal cancer (ACRC).** *Proc ASCO* 2003;**Abstract 1019.**

Goldberg RM et al. **N9741: Oxaliplatin (Oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Updated efficacy and quality of life (QOL) data from an Intergroup study.** *Proc ASCO* 2003;**Abstract 1009.**

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646.**

Rothenberg ML et al. **Final results of a phase III trial of 5-FU/leucovorin versus oxaliplatin versus the combination in patients with metastatic colorectal cancer following irinotecan, 5-FU, and leucovorin.** *Proc ASCO* 2003;**Abstract 1011.**

Smith RE et al. **The occurrence of severe enteropathy among patients with stage II/III resected colon cancer (CC) treated with 5-FU/leucovorin (FL) plus oxaliplatin (FLOX).** *Proc ASCO* 2003;**Abstract 1181.**

Van Cutsem E et al. **XELOX: Mature results of a multinational, phase II trial of capecitabine plus oxaliplatin, an effective 1st line option for patients (pts) with metastatic colorectal cancer (MCRC).** *Proc ASCO* 2003;**Abstract 1023.**

Patrick J Flynn, MD

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Edited comments by Dr Flynn

MOSAIC adjuvant trial: LV5FU2 with or without oxaliplatin

Aimery de Gramont presented data from the adjuvant trial comparing 5FU/leucovorin to 5FU/leucovorin + oxaliplatin (FOLFOX4), which resulted in a disease-free survival difference at three years. He was emphatic that the difference would not disappear with longer-term follow-up, but I've seen such differences erode in other adjuvant trials. Dr de Gramont's zeal is admirable in some ways but problematic in others. We should not be quite so dogmatic until we've had a more robust follow-up. I trust his numbers, but the duration of follow-up concerns me because it's fairly brief.

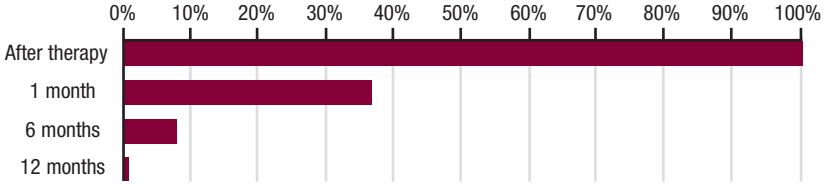
The information provided about the toxicity of 5FU/LV/oxaliplatin suggested there were a considerable number of patients treated on the FOLFOX4 regimen who developed fairly major neuropathy. They provided data that it was ameliorated over time, and the majority of patients had minimal neuropathy one year post-therapy, but I'm hesitant to recommend any therapy that causes neuropathy that interferes with my patients' daily lives until the data is published and the follow-up is longer. The data are very interesting, but I personally hope this regimen is not rapidly adopted as standard therapy at this time.

Oxaliplatin-associated neuropathy

"Oxaliplatin has become an integral part of various chemotherapy protocols, and in advanced colorectal cancer in particular. While oxaliplatin has only mild hematologic and gastrointestinal side effects, its dose-limiting toxicity is a cumulative sensory neurotoxicity that resembles that of cisplatin with the important difference of a more rapid and complete reversibility. The reversibility of neurotoxicity has been assured in long-term follow-up of patients who have received adjuvant oxaliplatin-based chemotherapy."

SOURCE: Grothey A. **Oxaliplatin-safety profile: neurotoxicity.** *Semin Oncol* 2003;30(4 Suppl 15):5-13. **Abstract**

MOSAIC adjuvant trial: Patients with Grade III neuropathy (n=137/1,108) on FOLFOX4



SOURCE: de Gramont A. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized MOSAIC trial.** Presented at: Annual Meeting of the American Society of Clinical Oncology; May 31 – June 3, 2003; Chicago, IL.

Median dose intensity, disease-free survival and toxicity of FOLFOX4 versus LV5FU2

	FOLFOX4 (n=1123)*	LV5FU2 (n=1123)*
Median follow-up	37.2 months (26-53)	37.1 months (26-53)
Median relative dose intensity		
Oxaliplatin	81%	NA
5-FU	85%	98%
Primary endpoint		
3-year DFS (ITT)	77.8%	72.9%
Toxicity		
Neutropenia (>Grade III)	41.0%	4.7%
Febrile neutropenia	0.7%	0.1%
Neuropathy (Grade III)	12.4%	1.0%
All-cause mortality	0.5%	0.5%

*Total number of patients in the intent-to-treat analyses. Efficacy and safety data not available for all patients.

SOURCE: de Gramont A. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized MOSAIC trial.** Presented at: Annual Meeting of the American Society of Clinical Oncology; May 31 – June 3, 2003; Chicago, IL. **Abstract 1015.**

Clinical experience with oxaliplatin

Oxaliplatin is a much easier drug to use than American oncologists thought 10 years ago. The neuropathy and the cold dysesthesias aren't quite as challenging if we warn patients ahead of time to not drink really cold beverages and grab something out of the freezer with their bare hands. I have very few patients with metastatic disease who come in complaining of significant side effects. I attend to the development of neuropathy and do not let patients go forward with worsening neuropathy to the point that it interferes with ambulation or

function. If they're responding, they may not be quite as honest about reporting symptoms as I'd like.

Outside of a formal clinical trial, I'm still using the original published FOLFOX4 regimen. I established relationships in my area with a couple of home-care companies that provide us with the pumps and do the authorization and the billing for the patients, so those responsibilities do not fall to my nurses. It's a very simple therapy to administer now that the orchestration of the people in charge of the pump is routine.

In talking with my colleagues, I believe there is more concern about use of pumps than there ought to be. Pumps are not that difficult to manage, and patient acceptance is not problematic. Nonetheless, there's still a significant tendency for American oncologists to resist the use of ambulatory pumps.

Prolonged survival with the addition of bevacizumab to IFL in metastatic disease

A trial presented at ASCO 2003 evaluated IFL — the Saltz regimen — with and without bevacizumab. Originally, there was an additional arm combining 5FU/leucovorin plus bevacizumab, because at the time the trial opened it had not been established that irinotecan improved response rates in metastatic colorectal cancer.

The addition of bevacizumab — a monoclonal antibody to vascular endothelial growth factor — involved more patient visits but had relatively minimal toxicity. The 4.7-month improvement in overall survival with bevacizumab is a solid breakthrough in the treatment of colorectal cancer.

In a nonprotocol setting, I would use bevacizumab with the Saltz regimen because that's where we have data. I'm very hopeful that in the very near future we're going to have data combining bevacizumab with other regimens using oxaliplatin.

The FOLFOX4 regimen in the North Central Cancer Treatment Group protocol clearly had a better response rate and duration of response when it was compared to IFL, but IFL plus bevacizumab resulted in overall survival very similar to FOLFOX4. We don't know if adding bevacizumab to FOLFOX4 results in additional benefit, and we don't know the nature of the toxicities. In a nonprotocol situation, I would not utilize bevacizumab in combination with FOLFOX4.

Deciding between FOLFOX4 and IFL plus bevacizumab will require a lengthy discussion with patients, and I don't know which option patients will choose. With bevacizumab, patients have to be willing to be on pumps. This regimen is something new that's a challenge to talk to patients about, but it's a great option to have. We have two regimens that produced a major improvement in overall survival. Those are the kinds of problems oncologists would like to have more often.

Tolerability of bevacizumab in combination with IFL

The most noticeable side effect associated with bevacizumab was that about one-quarter of patients developed problems with hypertension, but this was relatively simple to treat. Usually, something as simple as a diuretic, like hydrochlorothiazide, could be used to treat the hypertension. It wasn't a significant problem to manage.

Combining bevacizumab with IFL raised concerns about whether there'd be many patients with renal injury resulting in proteinuria. In my experience, that's pretty rare in patients treated with bevacizumab. Another concern was whether bevacizumab would cause more problems with bleeding or thrombosis, and there really wasn't a demonstrable difference in the two arms.

A very small number of patients had GI perforations, and that will have to be addressed in larger studies. Gastrointestinal perforations occurred in about one to two percent of patients, and it's something that we need to be aware of when it's used more broadly in clinical practice.

Select Grade III/IV adverse events in the Phase III trial comparing IFL with or without bevacizumab

	IFL + placebo (n=397)	IFL + bevacizumab (n=393)
Diarrhea		
Grade III	24%	29%
Grade IV	1%	4%
Bleeding		
Grade III	2.5%	2.3%
Grade IV	0%	0.8%
Hypertension		
Grade III	2.3%	10.9%
Grade IV	0%	0%
Leukopenia		
Grade III	23%	25%
Grade IV	8%	12%
Any thromboembolic event	16.1%	19.3%
Any GI perforation	0%	1.5%

SOURCE: Hurwitz H. **Bevacizumab (Avastin, a Monoclonal Antibody to Vascular Endothelial Growth Factor) Prolongs Survival in First-Line Colorectal Cancer (CRC): Results of a Phase III trial of Bevacizumab in Combination with Bolus IFL (Irinotecan, 5-Fluorouracil, Leucovorin).** Presented at: Annual Meeting of the American Society of Clinical Oncology; May 31 – June 3, 2003; Chicago, IL. **Abstract 3646.**

Select publications

Publications discussed by Dr Flynn

de Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized MOSAIC trial.** *Proc ASCO* 2003;**Abstract 1015.**

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646.**

Post-test: Colorectal Cancer Update, Issue 4, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. Which of the following is not one of the arms in the planned SWOG-S0303 trial for patients with metastatic colorectal cancer?
   a. Infusional 5-FU, leucovorin, oxaliplatin and placebo
   b. Infusional 5-FU, leucovorin, oxaliplatin and bevacizumab
   c. Capecitabine, oxaliplatin and placebo
   d. Capecitabine, oxaliplatin and bevacizumab
   e. Bevacizumab alone

2. Which of the following is being evaluated in patients with pancreatic cancer?
   a. Bevacizumab
   b. Taxanes
   c. Platinums
   d. All of the above
   e. None of the above

3. Imatinib is being evaluated as adjuvant therapy in patients with gastrointestinal stromal tumors (GIST).
   a. True
   b. False

4. The MOSAIC trial demonstrated a disease-free survival and overall survival benefit for adjuvant FOLFOX4.
   a. True
   b. False

5. In patients with metastatic colorectal cancer, Phase III randomized trial results are available for bevacizumab in combination with which of the following agents:
   a. Irinotecan
   b. Oxaliplatin
   c. Capecitabine
   d. All of the above
   e. None of the above

6. The addition of bevacizumab to IFL resulted in 4.7 month improvement in median overall survival compared to IFL alone in patients with metastatic disease.
   a. True
   b. False

7. In the Phase III trial evaluating IFL with or without bevacizumab, which of the following was the most frequently occurring side effect associated with bevacizumab?
   a. Bleeding
   b. GI perforations
   c. Hypertension

8. NCCTG-N9741 evaluated which of the following regimens?
   a. IFL
   b. FOLFOX4
   c. IROX
   d. All of the above
   e. None of the above

9. In a small Phase II trial, first-line therapy for metastatic colorectal cancer with CAPOX demonstrated an overall median survival of 19.5 months.
   a. True
   b. False

10. In the MOSAIC adjuvant trial, oxaliplatin-associated Grade III peripheral neuropathy continued to be a persistent problem in the majority of patients one year after completion of FOLFOX4.
    a. True
    b. False

Post-test Answer Key: 1e, 2d, 3a, 4b, 5a, 6a, 7c, 8d, 9a, 10b

Evaluation Form: Colorectal Cancer Update, Issue 4, 2003

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

GLOBAL LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe ongoing clinical trials in colorectal cancer and their potential impact on patient care 5 4 3 2 1
- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment 5 4 3 2 1
- Develop and explain a management strategy for patients with colorectal cancer in the adjuvant and metastatic settings 5 4 3 2 1

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 4

Upon completion of this activity, participants should be able to:

- Describe the design and scientific rationale for the planned trial comparing infusional 5-FU, leucovorin and oxaliplatin to capecitabine and oxaliplatin with or without bevacizumab in patients with metastatic colorectal cancer 5 4 3 2 1
- Develop a treatment strategy for patients with metastatic colorectal cancer that incorporates irinotecan, oxaliplatin, 5-FU and capecitabine 5 4 3 2 1
- Review some of the ongoing clinical trials in pancreatic cancer and gastrointestinal stromal tumors (GIST) 5 4 3 2 1
- Consider the implications of the MOSAIC trial on the selection of adjuvant therapy for patients with colorectal cancer 5 4 3 2 1
- Review the results from the Phase III trial evaluating IFL with or without bevacizumab in patients with metastatic disease 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Charles D Blanke, MD, FACP	5 4 3 2 1	5 4 3 2 1
Robert B Diasio, MD	5 4 3 2 1	5 4 3 2 1
Patrick J Flynn, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Evaluation Form: Colorectal Cancer Update, Issue 4, 2003

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What other faculty would you like to hear interviewed in future educational programs?

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