Table of Contents

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 and the website, ColorectalCancerUpdate.com, where you will find 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 3

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

- Counsel patients with metastatic colorectal cancer about the use of oxaliplatin- or irinotecan-containing chemotherapy regimens.
- Discuss the advantages of neoadjuvant chemotherapy in patients with colorectal cancer who have resectable liver metastases.
- Evaluate the potential future role for bevacizumab in the treatment of colorectal cancer in the metastatic and adjuvant setting.
- Describe the rationale and design of the planned NSABP trial of preoperative capecitabine for primary rectal cancer.
- Describe the planned NSABP-C-09 trial in order to counsel patients about eligibility for participation.
- Consider the implications of the MOSAIC trial for incorporation of oxaliplatin-containing regimens as adjuvant therapy for colorectal cancer.

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Norman Wolmark, MD	No financial interests or affiliations to disclose
John Zalcberg, MB, BS, PhD, FRACP	**Honorarium:** Sanofi-Synthelabo Inc, Roche Laboratories Inc, Novartis Pharmaceuticals Corporation, Pharmacia Corporation, Aventis Pharmaceuticals Inc **Board Member:** Progen Industries
Yehuda Patt, MD	**Grants/Research Support:** Roche Laboratories Inc, Sanofi-Synthelabo Inc, Pharmacia Corporation **Honorarium:** Roche Laboratories Inc, Sanofi-Synthelabo Inc
Lawrence D Wagman, MD, FACS	No financial interests or affiliations to disclose

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bevacizumab	Avastin™	Genentech Inc
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
dexamethasone	Various	Various
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
epoetin alpha	Procrit®	Ortho Biotech Products
floxuridine	Various	Various
5-fluorouracil, 5-FU	Various	Various
gemcitabine	Gemzar®	Eli Lilly & Company
interferon-alpha-2b	Various	Various
irinotecan	Camptosar®	Pfizer Inc
leucovorin	Various	Various
morphine sulfate	MS Contin®	Purdue Frederick Co
oxaliplatin	Eloxatin®	Sanofi-Synthelabo Inc
peginterferon-alpha-2a	Pegasys®	Hoffman-La Roche Inc
trastuzumab	Herceptin®	Genentech Inc

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Editor's Note

Visit to the Magic Kingdom

Florida residents, like myself, usually find that after about a dozen trips, Disney World becomes a tiresome experience. However, my June 2003 sojourn to the Contemporary Hotel in Orlando included a thrill-a-minute ride on what might be called, "Dr Norm's wild ride into the future." Specifically, the NSABP meeting — just weeks after a breathtaking series of colorectal cancer research presentations at ASCO in Chicago — featured discussions of a number of new visionary trials that are about to be launched in this disease.

At the helm of this adventure was, of course, NSABP chairman, Dr Norman Wolmark. A past guest on our breast cancer series, Dr Wolmark is passionate about clinical research, and his enthusiasm for the new wave of bold Phase III colorectal trials was obvious. He implored me to carry the message of protocol accrual to practicing oncologists.

An interesting feature to many of these new studies is the central role of colorectal surgeons. To that end, this issue includes an interview with surgical oncologist Dr Lawrence Wagman, who presented to the NSABP membership a proposed new trial, protocol C-09, which will randomize patients with resectable or ablatable hepatic metastases to intrahepatic FUDR or not, with all patients receiving systemic oxaliplatin and capecitabine.

While the NSABP patiently waits for its C-07 adjuvant trial to provide additional information on the potential value of oxaliplatin in adjuvant therapy, the new adjuvant study, C-08, incorporates oxaliplatin into all three major initial randomization arms. As discussed on this program by Dr John Zalcberg, a major part of the impetus to study adjuvant oxaliplatin is the data presented at ASCO by Dr Aimery DeGramont on the MOSAIC trial. (Figures 1a, b). This study demonstrated an impressive disease-free survival advantage for the FOLFOX4 regimen, and Dr Zalcberg is optimistic that this benefit will eventually translate into a survival advantage.

Figure 1a: MOSAIC adjuvant trial schema

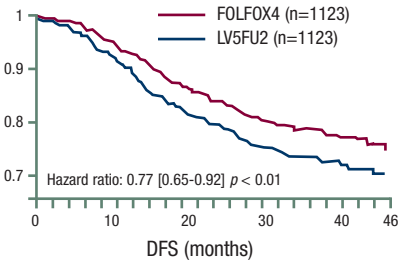
ARM 1: FOLFOX4: Oxaliplatin 85 mg + (LV 200 mg/m^2 followed by bolus 5-FU 400 mg/m^2 + 22-hour infusional 5-FU 600 mg/m^2 for 2 consecutive days) q 2 weeks x 6 months

ARM 2: LV 200 mg/m^2 followed by bolus 5-FU 400 mg/m^2 + 22-hour infusional 5-FU 600 mg/m^2 for 2 consecutive days q 2 weeks x 6 months

DERIVED FROM: Presentation, A DeGramont, ASCO 2003, Chicago, Illinois

The second proposed randomization on C-08 is perhaps the most breathtaking part of the Phase III NSABP panorama. Patients will be randomized to control or the anti-VEGF agent, bevacizumab, bringing the vision of Judah Folkman and others into "prime time." Dr Zalcberg discusses the key new database that led to this design, groundbreaking trial data presented by Dr Herbert Hurwitz at ASCO demonstrating a prolongation of progression-free and overall survival in patients receiving bevacizumab on an IFL background (Figure 2).

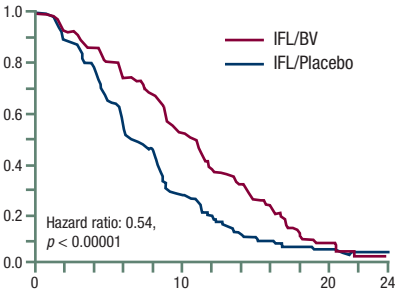
Figure 1b: MOSAIC trial — Disease-free survival



23% risk reduction in the FOLFOX4 arm

DERIVED FROM: Presentation, A DeGramont, ASCO 2003, Chicago, Illinois

Figure 2: Progression-free survival (IFL/bevacizumab versus IFL alone)



DERIVED FROM: Presentation, H Hurwitz, ASCO 2003, Chicago, Illinois

The other interviewee for this issue, Dr Yehuda Patt, presents and discusses a case history that was rare five years ago but now is becoming more common. Because of the dramatic tumor response this patient experienced while receiving oxaliplatin and capecitabine, Dr Patt is considering hepatic resection or ablation of the remaining liver disease. This situation also fits the C-09 trial discussed by Dr Wagman.

In his interview, Dr Wolmark cites the initial positive NSABP adjuvant trials* in 1993 as the last major turning point in colorectal cancer research. My visit to the Magic Kingdom revealed that 2003 is clearly the next milestone year in the treatment of this disease.

—Neil Love, MD

*Wolmark N et al. **The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: Results from National Surgical Adjuvant Breast and Bowel Project protocol C-03.** *J Clin Oncol* 1993;11(10):1879-87. **Abstract**

Norman Wolmark, MD

Chairman, Department of Human Oncology,
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Professor and Chairman, Department of Human Oncology,
Drexel University College of Medicine

Chairman, National Surgical Adjuvant Breast
and Bowel Project

Edited comments by Dr Wolmark

Bevacizumab as first-line therapy for metastatic disease

The ASCO meeting was very exciting in terms of the research data in colorectal cancer. For the first time in my memory, the session for colorectal cancer had a larger audience than the breast cancer session. Certainly, the prolongation in overall survival for humanized monoclonal antibody to VEGF bevacizumab, was impressive, and I think it exceeded even the most enthusiastic expectations.

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

DERIVED FROM: 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.**

The Phase II data for bevacizumab weren't nearly as exciting as that, and I think it brings up a good point, because it's simply assumed that bevacizumab in breast cancer, for example, is not effective. It's very important that we not confuse no effect for no contest. I don't look upon bevacizumab as negative in breast cancer. That trial was asking a great deal of bevacizumab in advanced breast cancer, and it showed an increased response rate. Fortunately, there is an

ongoing first-line trial in advanced disease that will further elucidate the role of this agent in breast cancer. We're also very excited about the potential of bringing bevacizumab into the adjuvant breast setting.

Identifying a target for bevacizumab

There are other adjuvant colorectal trials being planned with bevacizumab. The Intergroup is currently discussing a bevacizumab monotherapy trial in patients with Dukes B colorectal cancer. We'd like to demonstrate a clear benefit in the adjuvant setting and determine the degree of benefit. We haven't identified a target for bevacizumab — one that we could use to restrict its use to a subset of the population — but clearly that's a goal.

It's often pointed out that if we had conducted the trastuzumab trials on the entire population of patients with breast cancer, we would not have seen an effect. Fortunately, there was a target that could be measured. On the other hand, even without a target, the survival advantage of bevacizumab is clear, so if we find a target, the effects may be impressive.

Proposed NSABP-C-08 adjuvant colorectal trial

For many months, we've been discussing bevacizumab in the adjuvant setting for colorectal cancer and have proposed NSABP-C-08, a three-by-two factorial adjuvant study for Dukes B and C — Stages II and III — colon cancer. It will compare weekly bolus 5-FU/leucovorin/oxaliplatin (FLOX) plus or minus bevacizumab, to every-two-week infusions of 5-FU/leucovorin/oxaliplatin (FOLFOX) plus or minus bevacizumab, to capecitabine/oxaliplatin (CAPOX) plus or minus bevacizumab.

Phase III Trial Comparing Weekly Bolus 5-fluorouracil (5-FU) plus Leucovorin (LV) and Oxaliplatin (FLOX) ± Bevacizumab with 2 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: FOLFOX-6 ± Bevacizumab
ARM 3: CAPOX ± Bevacizumab

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

We included the capecitabine/oxaliplatin combination because we are committed to bringing oral regimens into the adjuvant setting. We conducted trial C-06, comparing leucovorin-modulated 5-FU to oral UFT. However, despite a unanimous ODAC recommendation, UFT was not approved in advanced disease. It's unclear what the status of UFT will be if C-06 demonstrates

noninferiority. Some are skeptical about the possibility of the CAPOX arm demonstrating superiority in C-08, but we've been surprised before and no doubt will be again.

Bevacizumab is to be administered for one year in C-08, which is an empirical choice. We don't really know the optimal duration — one year parallels the duration with which trastuzumab has been used, and until we have data proving otherwise, we have to start somewhere.

ECOG-3200 Phase III Trial of FOLFOX4/Bevacizumab, FOLFOX4* or Bevacizumab in Patients with Previously Treated Advanced Colorectal Cancer: Interim Toxicity Analysis

	FOLFOX4 + bevacizumab N=75		FOLFOX4 N=73		Bevacizumab N=75	
	Grade III	Grade IV	Grade III	Grade IV	Grade III	Grade IV
Hemorrhage	3%	0%	0%	0%	3%	0%
Thrombosis/embolism	4%	0%	1%	0%	1%	0%
Hypertension	8%	1%	1%	0%	7%	0%
Febrile neutropenia	1%	0%	3%	0%	0%	0%
Neuropathy	4%	0%	3%	0%	0%	0%
Fatigue	8%	0%	14%	1%	4%	1%

*FOLFOX4 = biweekly administration of oxaliplatin 85 mg/m^2 on day 1; leucovorin 200 mg/m^2 IV 2 hours and fluorouracil 400 mg/m^2 IV bolus followed by fluorouracil 600 mg/m^2 CIV for 22 hours on days 1 and 2.

DERIVED FROM: 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.**

Oxaliplatin-associated neurotoxicity

Neurotoxicity is a major concern with oxaliplatin, but in the MOSAIC trial the Grade III neurotoxicity was reversible in the majority of cases. The data presented at ASCO regarding the use of magnesium and calcium to decrease the neurotoxicity is based on preclinical studies by Erick Gamelin. His hypothesis is that oxalate associated with oxaliplatin is responsible for the neurotoxicity, and that these agents can reduce neurotoxicity. It's an interesting hypothesis, but the studies need to be done. A number of neuroprotective agents are being considered, and hopefully one can be found that can attenuate the neurotoxicity without diminishing efficacy.

Proposed NSABP adjuvant trial comparing capecitabine to observation in frail elderly patients

Margaret Kemeny presented a proposed adjuvant trial to assess the effectiveness of capecitabine in treating the elderly. It's an interesting study, but the eligibility criteria present a dilemma. Rather than an age cutoff, I would

prefer we target individuals who are not eligible for standard adjuvant chemotherapy regimens. An age cutoff does not reflect that and "frail" is not a readily measurable discriminate. You don't want to eliminate a significant proportion of the population who might be eligible and who would tolerate and benefit from the regimen simply because one cannot clearly define the population.

NSABP-R-04: Preoperative radiation therapy with capecitabine

R-04 is a two-by-two trial designed to determine if oral capecitabine can replace prolonged venous infusion 5-FU during radiotherapy in preoperative therapy. Initially, we were going to compare UFT to venous infusion, but when it became apparent UFT would not be on the market and the data relative to capecitabine and radiotherapy became available, we embraced that regimen.

Erythropoietin was added because we found in our previous colorectal trial that over 20 percent of the patients required transfusions. As proposed, patients on the erythropoietin arms will receive it whether or not they are anemic, but we are still discussing that with the FDA, and it could change.

The regimen of radiation therapy plus capecitabine as outlined in R-04 has an acceptable toxicity. The data relative to response rates are not extensive, but small studies have shown significant pathologic complete responses more impressive than those we saw in NSABP-R-03. The data justify studying this combination in the preoperative setting in order to determine the efficacy once and for all.

Select publications

Publications discussed by Dr Wolmark

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.**

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

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

Giantonio BJ et al. **Bevacizumab (anti-VEGF) plus IFL (irinotecan, fluorouracil, leucovorin) as front-line therapy for advanced colorectal cancer (advCRC): Results from the Eastern Cooperative Oncology Group (ECOG) Study E2200.** *Proc ASCO* 2003;**Abstract 1024.**

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.**

Smith RE et al. **UFT/leucovorin vs 5-FU/leucovorin in colon cancer.** *Oncology (Huntingt)* 2000;14(10 Suppl 9):24-7. **Abstract**

John Zalcberg, MB, BS, PhD, FRACP

Director, Division of Haematology and
Medical Oncology, Peter MacCallum Cancer Centre

Edited comments by Professor Zalcberg

MOSAIC adjuvant trial: FOLFOX4 versus the DeGramont regimen

The MOSAIC adjuvant trial was a well-designed and well-conducted, multinational study comparing FOLFOX4 to the DeGramont regimen. The primary endpoint was three-year, disease-free survival.

In planning the study, the investigators calculated the expected disease-free survival to be 73 percent in the control group and 79 percent in the experimental arm — a 25 percent reduction in the risk of recurrence. Amazingly, the actual three-year, disease-free survival was 73 percent and 78 percent, respectively.

The reduction was not statistically significant for patients with Stage II disease, but there were fewer events in those patients, and it may still be too early to develop firm conclusions about that subset.

NSABP adjuvant trial C-08 in Stage II and III colon cancer

NSABP-C-08 is essentially a three-by-two factorial design. Patients with Stage II and III colon cancer will be randomized to bolus 5-FU/leucovorin and oxaliplatin 85 mg (FLOX) or FOLFOX6 or capecitabine/oxaliplatin (CAPOX). In each arm, patients are further randomized to bevacizumab or not.

The C-08 trial will also involve very interesting correlative science studies on the tumor. It's not possible to utilize fresh tissue in adjuvant studies, but the NSABP has devised a way to perform gene arrays using paraffin-embedded blocks.

This will be a powerful research tool, because the sample can be processed normally, patients can be entered into the study postoperatively, and it won't interfere with surgical practice.

Utilization of irinotecan combinations versus oxaliplatin combinations

There are several considerations in deciding whether to utilize an irinotecan-containing regimen or an oxaliplatin-containing regimen as first-line therapy for metastatic disease. The recent NCCTG-N9741 data presented by Rich Goldberg, comparing FOLFOX, IFL and IROX, is compelling. Although there are issues with the study in regard to the use of infusional versus bolus 5-FU and crossover regimens, FOLFOX was clearly superior to IFL. Another consideration is the data presented by Tournigand at ASCO a couple of years ago, which suggested using either regimen up front — as long as they were infusional — and ultimately resulted in equivalent survival.

Clinically, my decision is based upon individual preferences and values, such as concerns about hair loss, neuropathy, etcetera, but most of my patients will receive both regimens. I tend to utilize oxaliplatin-containing regimens prior to irinotecan.

Improved survival with IFL/bevacizumab versus IFL alone in patients with metastatic colorectal cancer

Although we've been discussing angiogenesis for as long as Judah Folkman has been working in the area — about 30 years — we have not had clear evidence that antiangiogenics were effective in controlling cancer.

Data from a randomized Phase II trial, recently reported in the *Journal of Clinical Oncology*, demonstrated a benefit when bevacizumab was combined with IFL compared to IFL alone. At ASCO this year, results of a Phase III study in patients with metastatic colorectal cancer demonstrated IFL/bevacizumab improved median survival by five months when compared to IFL alone. The magnitude of this improvement should not be discounted; the increase in median survival used to justify the substitution of IFL for 5-FU/LV was only 1.5 months.

An important issue being addressed by several cooperative group trials is whether the addition of bevacizumab to other chemotherapy regimens will result in similar improvements seen when added to IFL. It's a reasonable assumption that it will be as effective, and cooperative groups are launching additional trials incorporating bevacizumab.

Management of patients with asymptomatic, advanced colorectal cancer

Only two studies have addressed the management of patients with asymptomatic colon cancer. The Nordic study, done a number of years ago, suggested that early chemotherapy was preferred for asymptomatic patients; however, that study had limitations. Another trial was conducted by a Canadian group and the Australian GI Trialists' Group. Patients with asymptomatic advanced colorectal cancer were randomized to immediate chemotherapy or

delay of chemotherapy until they were symptomatic. This study is being prepared for publication, and it demonstrated no apparent benefit in starting chemotherapy before onset of symptoms.

It's important to recognize that these results are based on 5-FU/leucovorin regimens. Would the results be different with the newer agents, such as oxaliplatin and irinotecan? I suspect we will never know the answer because those trials will never be performed. In clinical practice, the issue is decided by patient and physician preference. I tell patients either choice is a reasonable alternative. I would prefer to treat them earlier, but there are certainly opportunities to delay treatment based on lifestyle decisions.

Select publications

Neoadjuvant therapy for the treatment of rectal cancer

Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: A randomized trial. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. *J Clin Oncol* 1992;10(6):904-11.

DeGramont 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.**

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.

Maindrault F et al. **Time to disease control (TDC) to evaluate the impact on survival of three chemotherapy lines in metastatic colorectal cancer (MRC) based on 5-fluorouracil, oxaliplatin and irinotecan (GERCOR).** *Proc ASCO* 2001;**Abstract 581.**

Bevacizumab in the treatment of colorectal cancer

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.**

Bergsland EK et al. **Bevacizumab (BV) + chemotherapy (CT) may improve survival in metastatic colorectal cancer (MCRC) subjects with unfavorable prognostic indicators.** *Proc ASCO* 2001;**Abstract 2247.**

Berlin JD. **Targeting vascular endothelial growth factor in colorectal cancer.** *Oncology (Huntingt)* 2002;16(8 Suppl 7):13-5. **Abstract**

Fernando NH, Hurwitz HI. **Inhibition of vascular endothelial growth factor in the treatment of colorectal cancer.** *Semin Oncol* 2003;30(3 Suppl 6):39-50. **Abstract**

Giantonio BJ et al. **Incorporating angiogenesis inhibition with bevacizumab (anti-VEGF) into frontline chemotherapy with irinotecan (CPT-11), fluorouracil and leucovorin (FU/LV) for advanced colorectal cancer (advCRC): A toxicity analysis of ECOG study E2200.** *Proc ASCO* 2002;**Abstract 503.**

Gray R et al. **The safety of adding angiogenesis inhibition into treatment for colorectal, breast, and lung cancer: The Eastern Cooperative Oncology Group's (ECOG) experience with bevacizumab (anti-VEGF).** *Proc ASCO* 2003;**Abstract 825.**

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**

Yehuda Patt, MD

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Edited comments by Dr Patt

Case Study: A 52-year-old patient presenting with a primary sigmoid lesion and synchronous bilateral liver metastases

Initial presentation

- Large, nearly obstructive tumor in the sigmoid colon with bleeding and anemia
- CT scan revealed 10 bilobar, multifocal liver lesions and an enlarged spleen
- CEA: 800 ng/mg
- History of alcohol use and stigmata of cirrhosis on physical exam

Local treatment with anterior colon resection

- Developed wound dehiscence and infection
- Night fevers, 101°F and pain requiring morphine sulfate 60 mg BID
- Hepatomegaly 7- to 10-cm below the right costal margin; no ascites, no pedal edema
- Liver function tests normal; albumin 2.8 mg/dL
- Significant weight loss

Systemic therapy after recovery from the infection: Oxaliplatin and capecitabine

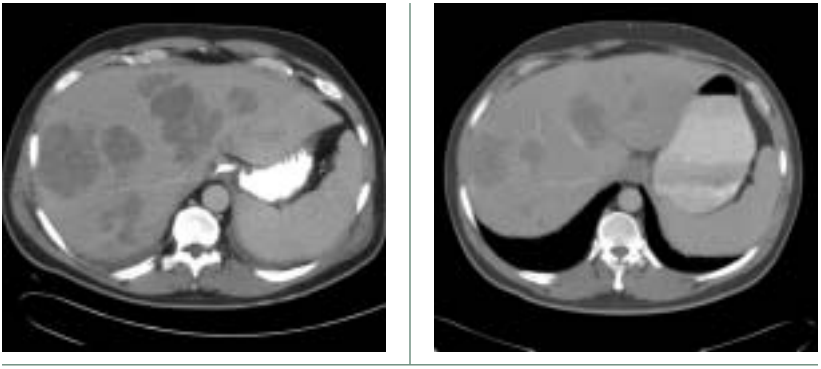
- Partial response of all liver metastases, with clearing of two segments of the left lobe
- CEA: 60 ng/mg
- Pain completely ameliorated by the fourth cycle
- Liver no longer palpable on physical exam
- Fever resolved
- Albumin 3.7 mg/dL
- Returned to work, good appetite (gained 30 lbs) and exercising

Management of the liver metastases

The metastases in the left lobe are receding dramatically. In the past, I would never have fathomed the possibility of subjecting a patient like this to a surgical intervention in the liver, but if he continues to respond, it's not impossible; the left lobe of the liver could be spared.

If this patient's disease involved only one lobe and he continued to respond like this, then in another two or three cycles, we would have resected the lobe that was previously involved with tumor. In this patient there is still tumor in the left lobe of the liver, so this will be a debulking procedure unless we achieve a further dramatic response.

CT scan of the liver: Pretreatment and after two cycles of capecitabine/oxaliplatin (XELOX)



Management of patients with potentially resectable liver metastases

We are conducting a trial with neoadjuvant capecitabine/oxaliplatin in patients with resectable liver disease. Most patients with more than one metastatic lesion, or those with lesions requiring at least a lobectomy, would go on this protocol for neoadjuvant therapy. In contrast, patients treated at Memorial Sloan-Kettering would have their tumor resected first, then they would have a pump put into the hepatic artery to be treated with a combination of hepatic-arterial chemotherapy and systemic therapy.

The advantage to using neoadjuvant capecitabine/oxaliplatin is that we have an *in vivo* test of drug sensitivity so we'll know whether the patient's tumor is actually sensitive to the chemotherapy, and it doesn't need to be given blindly or postoperatively. If the patient's disease does not respond to the neoadjuvant treatment but is still resectable — because the treatment is only for three cycles — then we do not administer the same treatment postoperatively. On the other hand, if the patient has explosive disease and within three cycles of treatment the disease is metastatic to other sites, one would not want to resect that

patient's tumor because that would be an exercise in futility. This is our approach in patients with clearly resectable liver metastases.

Phase II capecitabine/irinotecan (CAPIRI) trial

We just completed a multi-institutional trial evaluating irinotecan administered on day one every 21 days plus daily capecitabine for 14 days and seven days of rest. We treated 50 patients and witnessed some dramatic responses — disease that was nonresectable became resectable. We had a confirmed response rate of 45 percent.

We had the option of administering irinotecan on day one and day eight, but it became evident from European data that giving irinotecan on the first day was more tolerable. In fact, the toxicity pattern that we observed was different. Diarrhea occurred in approximately 20 percent of patients and there was some neutropenia, but not the massive complications seen in association with the Saltz regimen.

Phase II Trial of Capecitabine plus Irinotecan for Chemotherapy-Naïve Patients with Metastatic Colorectal Cancer Closed Protocol

Actual Accrual: 50 patients

Eligibility: Previously untreated patients with metastatic colorectal cancer

Treatment: Irinotecan 250 mg/m^2 intravenously on day 1* plus capecitabine 1,000 mg/m^2 orally twice daily for 14 days

*Treatment repeats every 21 days.

Phase II Capecitabine/Irinotecan (CAPIRI) Trial (n=50): Incidence of Common Grade 3/4 Adverse Events

Diarrhea	20%
Neutropenia	18%
Nausea/vomiting	10%
Dehydration	10%
Hand-foot syndrome	8%

DERIVED FROM: Patt YZ et al. **Capecitabine plus irinotecan for chemotherapy-naïve patients with metastatic colorectal cancer (MCRC): US multicenter phase II trial.** *Proc ASCO* 2003;**Abstract 1130.**

Capecitabine is preferable to 5-FU infusions for several reasons. Data from Europe demonstrated that continuous 5-FU infusions are probably better than bolus 5-FU. Rich Goldberg has shown that the continuous 48-hour infusion was better than the Mayo Clinic regimen, but the 48-hour infusion is essentially an extended bolus, not the continuous infusion that was recommended by Lokich.

With capecitabine, not only can you achieve continuous 5-FU serum concentrations, but there is also the enzymatic advantage of increased

thymidine phosphorylase concentrations in the tumor, which increases tumor specificity.

Additionally, if I were a patient, I would definitely prefer taking pills rather than having a pump. There is a good pharmacokinetic rationale for capecitabine, and it is also associated with fewer complications than a catheter in the subclavian vein, such as a decreased risk of infectious complications.

Use of irinotecan and oxaliplatin in clinical practice

According to European data comparing the FOLFOX (oxaliplatin plus 5-FU/leucovorin) regimen to the FOLFIRI (irinotecan/5-FU/leucovorin) regimen as first-line therapy with crossover on progression to the other regimen, patients who were initially started on FOLFOX had a greater chance of their disease becoming resectable. With FOLFOX, the quality of the response was better and the response rate was approximately 10 percent higher. Therefore, it makes good sense to use oxaliplatin up front. The question then becomes: How do we combine all the drugs we have today?

A pilot study, published by Falcone in the *Journal of Clinical Oncology*, evaluated the combination of oxaliplatin, irinotecan, infusional 5-FU and leucovorin in patients with metastatic colorectal cancer. That trial reported a 12 percent complete response rate — five out of 42 patients had disease that completely responded. The partial response rate was 59.5 percent (25 out of 42 patients), and the objective response rate (complete plus partial response) was 71.4 percent.

More importantly, complete resection of residual tumor was possible in 11 patients (26 percent), progression-free survival was 10.4 months and median survival was 26.5 months. Toxicities included: Grade 3 diarrhea in 21 percent of the patients, Grade 3/4 neutropenia in 86 percent of the patients or 16 percent of the cycles, and Grade 4 febrile neutropenia in 14 percent of the patients.

Even though they observed a good response rate, the question is: How do we combine everything we have today? Should everything be thrown in together? Should we use these drugs sequentially? We are now in an era requiring new trials to evaluate the three drugs either concomitantly or sequentially.

I recommend conducting Phase II trials before proceeding to Phase III studies. I don't even think that it would be rational to compare capecitabine/oxaliplatin to capecitabine/irinotecan in a Phase III trial, because all of the patients will be crossed over when they fail. We could never achieve a survival endpoint because all of the patients will be exposed to all of the agents.

Capecitabine in other gastrointestinal tumors

In a retrospective trial, we evaluated capecitabine monotherapy in patients with hepatobiliary cancers — hepatoma, cholangiocarcinoma and gallbladder carcinoma. Among patients with hepatoma, the response rate was about 15 percent — but there were only about 30 patients. Only eight patients had

gallbladder carcinoma, of whom two had a complete response and two had a partial response. Sixteen patients had cholangiocarcinoma, of whom two responded.

We published a paper in the *Journal of Clinical Oncology* evaluating a combination of continuous infusion 5-FU and recombinant interferon-alpha in the management of hepatocellular carcinoma. Fifty-six percent (24/43) of the patients had liver cirrhosis. In the hepatoma patients, the response rate was only 15 percent but the median survival was 15 months. Based on that study, we decided to evaluate a combination of capecitabine and interferon.

We are launching a new protocol with the combination of capecitabine and Pegasys® (peginterferon-alpha-2a). The combination of capecitabine and interferon-alpha-2b resulted in a median survival of 15 months. This rate of survival in patients with hepatoma — even though the response rate is not high — is quite impressive. There is a very high rate of disease stability. It is a treatment that can be tolerated by patients with hepatoma, as opposed to cisplatin and anthracyclines, which are extremely dangerous in patients with severe liver cirrhosis.

We will also be assessing capecitabine in combination with oxaliplatin in other GI tumors. Previous trials have evaluated GTX — Gemzar® (gemcitabine), Taxotere® (docetaxel) and Xeloda® (capecitabine) — in patients with pancreatic cancer. I foresee benefits from agents like capecitabine, oxaliplatin and irinotecan possibly in combination with gemcitabine in various GI malignancies.

Select publications

Publications discussed by Dr Patt

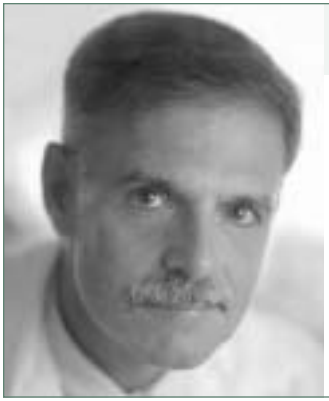
Douillard JY et al. **Metastatic colorectal cancer: Integrating irinotecan into combination and sequential chemotherapy.** *Ann Oncol* 2003;14(Suppl 2): ii7-ii12. **Abstract**

Falcone A et al. **Biweekly chemotherapy with oxaliplatin, irinotecan, infusional fluorouracil, and leucovorin: A pilot study in patients with metastatic colorectal cancer.** *J Clin Oncol* 2002;20:4006-14. **Abstract**

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.**

Patt YZ et al. **Capecitabine plus irinotecan for chemotherapy-naïve patients with metastatic colorectal cancer (MCRC): US multicenter phase II trial.** *Proc ASCO* 2003;**Abstract 1130.**

Patt YZ et al. **Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon alfa-2b for treatment of hepatocellular carcinoma.** *J Clin Oncol* 2003;21:421-7. **Abstract**



Lawrence D Wagman, MD, FACS

Chair, Division of Surgery,
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City of Hope National Medical Center

Edited comments by Dr Wagman

Rationale for NSABP-C-09: Hepatic artery infusion of floxuridine

Clinical studies have been conducted in the last 15 years evaluating hepatic artery infusion of floxuridine, either as an adjuvant or as a treatment for nonresectable colorectal cancer that has metastasized to the liver. Compared to the systemic agents that were available earlier, it's a more potent therapy. In nonresectable disease, there are higher response rates using hepatic arterial infusions of floxuridine.

A recent Phase III single-institution randomized trial by Nancy Kemeny at Memorial Sloan-Kettering added systemic 5-FU/leucovorin to floxuridine hepatic artery infusions that were administered after complete resection of hepatic metastases. There was a statistically significant improvement in the disease-free survival for the patients treated with both intrahepatic and systemic therapy. That trial generated renewed interest in floxuridine hepatic artery infusions.

NSABP-C-09: Phase III randomized trial comparing oxaliplatin/capecitabine with or without hepatic artery infusion of floxuridine

The NSABP-C-09 trial currently in development will assess the value of adding a hepatic artery infusion of floxuridine to systemic capecitabine and oxaliplatin following resection, ablation, or both, of liver metastases. Patients with colorectal cancer who have no more than six hepatic metastases and no extrahepatic disease will be randomized to either pump placement or no pump placement. The treatment arms are nearly parallel, except for the addition of the hepatic artery infusion.

The trial allows either cryoablation or radiofrequency ablation of the hepatic metastases. Standardization of the ablation is critical and will be accomplished

primarily by intraoperative identification of the lesions on ultrasound, which is equivalent and sometimes slightly better than intraoperative palpation of the liver by the surgeon. An ultrasound of the lesions will be taken at the time of needle (radiofrequency ablation) or probe (cryoablation) placement to document the placement and then after the completion of the ablation. We will review the first three cases for all the sites participating in the trial.

Input from the medical oncologists on the protocol-development team assisted in making the decision to use postoperative oxaliplatin and capecitabine. Reports of toxicities with irinotecan led us to be more interested in oxaliplatin as one of the two primary agents in the protocol. Oxaliplatin has now taken a very important position in our trials.

Capecitabine is particularly interesting because it's an oral agent. It relieves the complexity of delivery but is still administered over an extended period of time. Because capecitabine is absorbed in the gut, it goes to the liver via the portal circulation. In that sense, we're achieving both a portal infusion and an arterial infusion. Although we've never proven that or evaluated drug levels, it's a very interesting concept. Another attractive feature of capecitabine is its preferential up-take by cancer cells. In Phase II trials, oxaliplatin and capecitabine together have activity that exceeds 5-FU/leucovorin.

Phase III Trial Comparing Intravenous Oxaliplatin and Oral Capecitabine and Hepatic Arterial Infusion of Floxuridine to Intravenous Oxaliplatin and Oral Capecitabine in Patients with Resected or Ablated Metastases to the Liver from Colorectal Cancer Proposed Protocol

Protocol ID: NSABP-C-09

Projected Accrual: 400 patients

Eligibility: Patients with colorectal cancer who have no more than 6 hepatic metastases and no extrahepatic disease

ARM 1: Capecitabine + oxaliplatin

ARM 2: Capecitabine + oxaliplatin + intra-arterial floxuridine

SOURCE: NSABP Annual Group Meeting, Orlando, Florida, June 26-29, 2003

Quality-of-life issues associated with hepatic artery infusion of floxuridine

NSABP-C-09 will also have a quality-of-life analysis to help us decide which of the therapies is better in terms of the patient's psychological and physical response to having a pump. We've completed a pilot quality-of-life study at the City of Hope in patients with pumps. Patients are very aware of the presence of the pump, and there's more pain when they are rolling over in bed. Psychologically, though, some of the patients describe an increased sense of protection because they have an additional therapy, whereas other patients sense they are getting more therapy, which puts more pressure on them.

The side effects from hepatic artery infusion definitely affect how patients feel. Patients who develop a rise in their liver function test levels and an elevated bilirubin level may start to notice the obvious manifestations — jaundice and more fatigue. The symptoms may be minimal; therefore, it is important for oncologists to do the blood work on schedule. After two weeks of an infusion, patients can feel 100 percent, but they may actually be developing abnormalities in their liver function that require either a dosage reduction or holding the drug.

Management of patients with colorectal cancer with liver-only metastases

Our first choice for these types of patients — who are willing to enroll and meet the eligibility criteria — is the North Central Cancer Treatment Group Phase II trial evaluating the treatment arm of the proposed NSABP-C-09 trial. Those patients will have their liver metastases resected or ablated. Then, they will receive a hepatic artery infusion of floxuridine and systemic oxaliplatin and capecitabine. If patients don't want to enroll in that trial, we offer them similar therapy off protocol.

We also offer these patients participation in a trial we have been conducting at the City of Hope for a number of years. Instead of a hepatic artery infusion, we use a portal vein infusion of floxuridine. We use portal vein infusions only in patients with completely resected disease.

Phase II Study of Hepatic Arterial Infusion with Floxuridine and Dexamethasone Followed by Systemic Therapy with Oxaliplatin and Capecitabine in Patients with Surgically Resected Liver Metastases from Primary Colorectal Carcinoma. Open Protocol

Protocol IDs: NCCTG-N9945, NSABP-CI-66

Projected Accrual: 15-75 patients

Eligibility: Patients with colorectal cancer who have hepatic metastases and no extrahepatic disease. Patients must have had prior surgical resection of the colorectal cancer and hepatic metastases.

Therapy: (Intra-arterial floxuridine + dexamethasone) → oxaliplatin + capecitabine

Treatment repeats every six weeks for four courses in the absence of disease recurrence or unacceptable toxicity. After completion of the fourth course, patients receive oxaliplatin and capecitabine every three weeks for two courses in the absence of disease recurrence or unacceptable toxicity.

Study Contacts:

North Central Cancer Treatment Group
Steven R Alberts, MD, Protocol Chair
Tel: 507-284-4918

National Surgical Adjuvant Breast and Bowel Project
Roy E Smith, MD, Protocol Chair
Tel: 412-330-4600

SOURCE: NCI Physician Data Query, July 2003.

Portal vein infusions

We're probably the only ones who have studied portal vein infusions in the adjuvant setting. It was studied in patients with nonresectable disease and

found to be ineffective. Portal vein infusions have no value in that setting because a metastasis that is one-half to one centimeter has primarily hepatic artery perfusion. On the other hand, the blood supply to very small metastases is a mixture from the hepatic artery and the portal vein.

Although we have never done a prospective randomized trial comparing infusions in the hepatic artery to infusions in the portal vein, our experience indicates that the outcomes with portal vein infusions are very similar to those with hepatic artery infusions. Additionally, the toxicity with the portal vein infusion is much lower. Chemical hepatitis is essentially nonexistent with portal vein infusions. There is no biliary sclerosis or long-term complications such as stenosis of the bile ducts that is associated with hepatic artery infusions. The mechanical complications and infection rates with both methods of administration are the same.

Select publications

Hepatic artery infusion of floxuridine in colorectal cancer

Barnett KT, Malafa MP. **Complications of hepatic artery infusion: A review of 4580 reported cases.** *Int J Gastrointest Cancer* 2001;30(3):147-60. **Abstract**

Dawson LA et al. **Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies.** *J Clin Oncol* 2000;18(11):2210-8. **Abstract**

Dizon DS, Kemeny NE. **Intrahepatic arterial infusion of chemotherapy: Clinical results.** *Semin Oncol* 2002;29(2):126-35. **Abstract**

Ensminger WD. **Intrahepatic arterial infusion of chemotherapy: Pharmacologic principles.** *Semin Oncol* 2002;29(2):119-25. **Abstract**

Kemeny M. **Hepatic artery infusion of chemotherapy as a treatment for hepatic metastases from colorectal cancer.** *Cancer J* 2002;8(Suppl 1):82-8. **Abstract**

Kemeny MM et al. **Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: Surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy—an intergroup study.** *J Clin Oncol* 2002;20(6):1499-505. **Abstract**

Kemeny N et al. **Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer.** *N Engl J Med* 1999;341(27):2039-48. **Abstract**

Lorenz M, Muller HH. **Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma.** *J Clin Oncol* 2000;18(2):243-54. **Abstract**

Scaife CL et al. **Feasibility of adjuvant hepatic arterial infusion of chemotherapy after radiofrequency ablation with or without resection in patients with hepatic metastases from colorectal cancer.** *Ann Surg Oncol* 2003;10(4):348-54. **Abstract**

Zanon C et al. **Combined regional and systemic chemotherapy by a mini-invasive approach for the treatment of colorectal liver metastases.** *Am J Clin Oncol* 2001;24(4):354-9. **Abstract**

Post-test: Colorectal Cancer Update, Issue 3, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. NSABP-C-08, a three-by-two factorial adjuvant study for Stages II/III colon cancer, includes which of the following arms:
   a. Weekly bolus 5-FU/leucovorin/oxaliplatin, plus or minus bevacizumab
   b. Two-weekly infusional 5-FU/leucovorin/oxaliplatin, plus or minus bevacizumab
   c. Capecitabine/oxaliplatin, plus or minus bevacizumab
   d. All of the above

2. As demonstrated in the MOSAIC trial, oxaliplatin-associated Grade III neurotoxicity is not reversible in the majority of cases.
   a. True
   b. False

3. In patients with colorectal cancer and potentially resectable liver metastases, neoadjuvant chemotherapy may serve as an *in vivo* test of drug sensitivity.
   a. True
   b. False

4. The proposed NSABP-R-04 trial randomizes patients to preoperative infusional 5-FU and radiotherapy versus:
   a. Preoperative capecitabine and radiotherapy
   b. Preoperative oxaliplatin and radiotherapy
   c. Postoperative infusional 5-FU and radiotherapy
   d. Postoperative oxaliplatin and radiotherapy

5. The proposed NSABP-R-04 trial will have a second randomization to erythropoietin or no erythropoietin.
   a. True
   b. False

6. In a Phase III trial of bolus irinotecan plus 5-fluorouracil/leucovorin with or without bevacizumab as first-line therapy in patients with metastatic colorectal cancer, the bevacizumab combination prolonged survival.
   a. True
   b. False

7. In the planned NSABP-C-09 trial, the hepatic metastases can be removed by:
   a. Surgical resection
   b. Cryoablation
   c. Radiofrequency ablation
   d. Any of the above

8. A Phase III trial demonstrated that the addition of systemic 5-FU/leucovorin to a floxuridine hepatic artery infusion, administered after complete resection of hepatic metastases, improved disease-free survival.
   a. True
   b. False

9. In a Phase II trial, capecitabine/irinotecan had a 45 percent response rate in patients with metastatic colorectal cancer.
   a. True
   b. False

10. In the MOSAIC adjuvant trial, FOLFOX4 resulted in a 24 percent relative reduction in recurrence compared to infusional 5-FU/LV in patients with Stage III colorectal cancer.
    a. True
    b. False

11. A recent trial evaluating the use of early versus delayed chemotherapy in asymptomatic patients with advanced colon cancer demonstrated an advantage for immediate therapy.
    a. True
    b. False

Post-test Answer Key: 1d, 2b, 3a, 4a, 5a, 6a, 7d, 8a, 9a, 10a, 11b

Evaluation Form: Colorectal Cancer Update, Issue 3, 2003

NL Communications Inc 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 3

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

- Counsel patients with metastatic colorectal cancer about the use of oxaliplatin- or irinotecan-containing chemotherapy regimens 5 4 3 2 1
- Discuss the advantages of neoadjuvant chemotherapy in patients with colorectal cancer who have resectable liver metastases 5 4 3 2 1
- Evaluate the potential future role for bevacizumab in the treatment of colorectal cancer in the metastatic and adjuvant setting 5 4 3 2 1
- Describe the rationale and design of the planned NSABP trial of preoperative capecitabine for primary rectal cancer 5 4 3 2 1
- Describe the planned NSABP-C-09 trial in order to counsel patients about eligibility for participation 5 4 3 2 1
- Consider the implications of the MOSAIC trial for incorporation of oxaliplatin-containing regimens as adjuvant therapy for colorectal cancer 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Norman Wolmark, MD	5 4 3 2 1	5 4 3 2 1
John Zalcberg, MB, BS, PhD, FRACP	5 4 3 2 1	5 4 3 2 1
Yehuda Patt, MD	5 4 3 2 1	5 4 3 2 1
Lawrence D Wagman, MD, FACS	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 3, 2003

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_____

_____

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

_____

_____

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☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ BS ☐ Other _____

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