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Colorectal Cancer™ UPDATE

Conversations with Oncology Research Leaders
Bridging the Gap between Research and Patient Care

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HOW TO USE THIS MONOGRAPH

This CME activity 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 located 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:

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment.
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy.
- Develop and explain a management strategy for patients with metastatic colorectal cancer.
- Describe ongoing clinical trials in colorectal cancer and counsel patients about the availability of ongoing clinical trials.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 4 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Wolff, Gold, Fisher and Douillard on the integration of emerging clinical research data into the management of colorectal cancer.

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Jean-Yves Douillard, MD, PhD	Consultant: Aventis Pharmaceuticals Inc, Bristol-Myers Squibb Company Honorarium: AstraZeneca Pharmaceuticals LP, Roche Laboratories Inc, Sanofi-Synthelabo Inc

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bevacizumab	Avastin™	Genentech BioOncology
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
fluorouracil (5-FU)	Various	Various
irinotecan	Camptosar®	Pfizer Inc
leucovorin calcium	Various	Various
midazolam HCL	Versed®	Roche Laboratories Inc
oxaliplatin	Eloxatin®	Sanofi-Synthelabo Inc
paclitaxel	Taxol®	Bristol-Myers Squibb Company

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Editor's Note

Polyp boy

The last thing I heard before slipping into a Versed®-induced stupor was my gastroenterologist graciously inviting me to watch the TV monitor as his colonoscope went window-shopping past my intestinal mucosa.

Minutes, hours or days later, I stumbled into consciousness again to see GI Joe holding snapshots of a handful of barely visible white mounds. "Benign-appearing polyps," he said, brightly. "I took them out and you'll be fine." My daughter Jennifer, the COO of our burgeoning CME enterprise, snickered, "I feel a CCU editor's note coming on here." Yeah, me too.

Gradually over the next few hours, the enormity of the moment dawned on me. I wasn't a man whose doctor ordered a "routine" PSA as part of incidental blood work and now had to decide whether to have his prostate removed because two percent of one core biopsy had Gleason 6 in it. I wasn't a woman who had religiously gone for her yearly mammograms only to be diagnosed with a 1.2-centimeter infiltrating tumor that would require chemotherapy. I was a person who just had a bunch of potentially premalignant lesions snipped off painlessly. Not that there's anything wrong with waiting 10 more years and maybe having my sigmoid removed and a course of adjuvant chemo, but this sure seemed a whole lot easier.

Aside from being very thought provoking, this experience led me to again consider the role of the medical oncologist in the cancer control process. As a result, I've created the following not-so-simple but brief CME pre-test. The answers are, of course, open for discussion:

Should every medical oncologist be actively involved in education and advocacy related to colorectal cancer prevention, screening and diagnosis?

A. No
B. Yes

Answer A: No

Justification: This is a pragmatic and serious question — not a platitude or non sequitur. Our time is precious. The potential for clinical revenue is diminishing. Urologists are out there pushing PSAs, radiologists and surgeons pretty much have breast screening under control and the GI guys are talking about colonoscopy. Let's focus our attention on what we do best — providing research-based, compassionate care to people with cancer.

Answer B: Yes

Justification: We are the only docs who see the bottom line and can put this in perspective. Many or most patients with metastatic breast or prostate cancer had screening done but will still die of the disease. When was the last time you saw someone die of colorectal cancer who had followed screening guidelines for a while? It does happen, of course, but how often?

How many more patients are out there like the one discussed by Dr George Fisher in this program — a young postpartum woman who was diagnosed with T3 rectal cancer and liver metastases after months of symptomatic treatment for "hemorrhoids"? Additional related issues for oncologists to consider are clinical trials of chemoprevention and lifestyle and dietary alterations. The known biology of colonic carcinogenesis and the potential for chemoprevention of colorectal cancer are at least as promising as with any solid tumor.

My role is not to provide the answers but to stoke the debate. Meanwhile I will treasure the snapshots of that gang of tiny baby rascals who someday might have made my life miserable but now are stuck in formalin.

— Neil Love, MD
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Select Publications

Asano TK, McLeod RS. **Nonsteroidal anti-inflammatory drugs and aspirin for the prevention of colorectal adenomas and cancer: A systematic review.** *Dis Colon Rectum* 2004;47(5):665-73. **Abstract**

Bast RC Jr et al. **2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: Clinical practice guidelines of the American Society of Clinical Oncology.** *J Clin Oncol* 2001;19(6):1865-78. **Abstract**

Key TJ et al. **Diet, nutrition and the prevention of cancer.** *Public Health Nutr* 2004;7(1A):187-200. **Abstract**

Lieberman DA, Atkin W. **Review article: Balancing the ideal versus the practical — considerations of colorectal cancer prevention and screening.** *Aliment Pharmacol Ther* 2004;19(Suppl 1)71-6. **Abstract**

Lindblom A et al. **Colorectal cancer as a complex disease: Defining at-risk subjects in the general population — a preventive strategy.** *Expert Rev Anticancer Ther* 2004;4(3):377-85. **Abstract**

O'Malley AS et al. **Patient and provider barriers to colorectal cancer screening in the primary care safety-net.** *Prev Med* 2004;39(1):56-63. **Abstract**

Rozen P. **Cancer of the gastrointestinal tract: Early detection or early prevention?** *Eur J Cancer Prev* 2004;13(1):71-5. **Abstract**

Seeff LC et al. **Patterns and predictors of colorectal cancer test use in the adult U.S. population.** *Cancer* 2004;100(10):2093-103. **Abstract**

Smith RA et al. **American Cancer Society guidelines for the early detection of cancer, 2004.** *CA Cancer J Clin* 2004;54(1):41-52. **Abstract**

U.S. Preventive Services Task Force. **Screening for colorectal cancer: Recommendation and rationale.** *Ann Intern Med* 2002;137(2):129-31. **Abstract**

Winawer S et al. **Colorectal cancer screening and surveillance: Clinical guidelines and rationale — update based on new evidence.** *Gastroenterology* 2003;124(2):544-60. **Abstract**

Young GP et al. **Choice of fecal occult blood tests for colorectal cancer screening: Recommendations based on performance characteristics in population studies: A WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report.** *Am J Gastroenterol* 2002;97(10):2499-507. **Abstract**

Continuous infusion 5-FU versus capecitabine in rectal cancer

In the adjuvant setting, when infusional 5-FU rather than bolus 5-FU is combined with radiation therapy, disease-free and overall survival are improved. Infusional 5-FU is a better radiosensitizing agent. The advantage of infusional 5-FU with radiation therapy is probably more of a systemic rather than a local control benefit.

An Intergroup trial published in the *New England Journal of Medicine* demonstrated a trend toward better local control using infusional 5-FU compared to bolus 5-FU. That study is proof of the principle that infusional 5-FU is a superior treatment modality when combined with radiation therapy.

Capecitabine is an interesting alternative to infusional 5-FU for several reasons. With infusional 5-FU, catheter-related problems can develop, such as thrombosis and infection. Additionally, patients are required to carry an ambulatory pump. When the pump is on for a couple of weeks it's no big deal, but generally by the fifth week of radiation therapy, patients are tired of it. Capecitabine is a nicer route of administration.

Additionally, capecitabine is a prodrug, and it has to be converted to 5-FU at the intracellular level. One of the enzymes responsible for that conversion is thymidine phosphorylase (TP), which is expressed in higher concentrations in the rectal mucosa.

At the biological level, that may mean that the rectum, the rectal mucosa and the tumor cells have a higher intracellular concentration of 5-FU, leading to both an active cytotoxic benefit and more radiosensitization. We have therefore been interested in evaluating capecitabine as a radiosensitizer compared to infusional 5-FU.

In the future, we will combine capecitabine with bevacizumab. That trial is not yet open, but we will pursue not only conventional cytotoxic agents with radiation but also utilize biologic agents such as bevacizumab for this group of patients.

Dr Wolff is an Associate Professor of Medicine and Deputy Chairman for Clinical Affairs at the University of Texas MD Anderson Cancer Center's Department of Gastrointestinal Medical Oncology in Houston, Texas.

When we evaluated capecitabine plus irinotecan (CAPIRI), we limited accrual to patients with metastatic rectal cancer. They were a challenging group not only because they have metastatic disease but also because of concern about local control issues. We prefer to spare these patients surgery, but we obviously have to worry about obstructive symptoms, pelvic symptoms and the like. Many of our trials — particularly of novel chemoradiation programs — are limited to patients with metastatic rectal cancer as opposed to resectable disease.

Dose and schedule of capecitabine utilized with preoperative radiation therapy

For preoperative radiation therapy, we've used capecitabine — mostly on protocol — in a seven-day continuous treatment using approximately 1,650 mg/m^2 per day throughout the course of radiation therapy at 50.4 Gray.

It is confusing that in some of our preoperative protocols, the radiotherapy was changed. People are beginning to evaluate concomitant boost radiation therapy, particularly toward the end of radiation therapy. The San Antonio group reported on concomitant boost radiation therapy for rectal cancer with twice daily radiation on the first and last few days of radiation therapy. We've evaluated boost radiation therapy only during the last few days.

The other way you can administer capecitabine is five days in a row with the weekends off. In my experience, that is a little easier because it carries less risk of hand-foot syndrome and less perianal skin irritation and diarrhea. I don't think those schedules result in substantial differences. In terms of efficacy, I doubt if a direct comparison between a seven-day and five-day schedule of capecitabine would result in a meaningful difference in pathological CR rates, tolerance, etcetera.

Potential explanations for the negative results of CALGB-C89803

I was surprised that this adjuvant study comparing IFL (irinotecan, bolus 5-FU and leucovorin) versus 5-FU/leucovorin was negative (1.1). One potential explanation is synergy — a concept that is bandied about a lot among oncologists. I don't think there's any question that the combination of 5-FU and oxaliplatin is truly synergistic. Most clinicians and laboratory-based physicians argue that 5-FU/leucovorin and irinotecan — at least with 5-FU/leucovorin as a bolus — is only additive. That is the simplest explanation why IFL didn't really gain much ground in the adjuvant setting. Clones that are resistant to 5-FU/leucovorin may be somewhat effected by irinotecan but the data indicate the effect is not significant.

If you pick the right patient population or if you use infusional 5-FU with irinotecan, which may have more of a positive interaction, would you get the same result? I don't know. Infusional 5-FU and irinotecan or capecitabine and irinotecan may actually be good combinations, but I'm not certain how much that will be pursued. Cooperative groups will need to decide whether or not to investigate combination chemotherapy with irinotecan because we already have a very nice combination in FOLFOX4 that has demonstrated superiority.

1.1 Adjuvant IFL versus 5-FU/LV (FL) in Patients with Stage III Colon Cancer

	IFL	5-FU/LV	*p*-value
Grade III/IV diarrhea	31%	35%	0.11
Grade III/IV neutropenia	42%	5%	<0.00001
Febrile neutropenia	4%	1%	0.0005
Grade III/IV nausea	12%	11%	0.46
Deaths during treatment	2.8%	1.0%	0.008

"1264 pts were randomized between April, 1999 and April, 2001. Median follow up is 2.6 years, and 67% of total expected deaths and 85% of total expected failures have occurred. Median OS and failure-free survival (FFS) have not yet been reached. IFL shows no improvement over FL in terms of either OS (p=0.88) or FFS (p=0.84) …

"In stage III colon cancer, IFL, as compared to FL, is associated with a greater degree of neutropenia, neutropenic fever, and death on treatment, with no associated clinical benefit. Weekly bolus IFL should not be used in the management of stage III colon cancer."

SOURCE: Saltz LB et al. **Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin alone (FL) in Stage III colon cancer (Intergroup trial CALGB C89803).** *Proc ASCO* 2004;**Abstract 3500**.

Another potential explanation for the negative outcome is that patients were not able to receive enough treatment with IFL due to toxicity. A few more treatment-related deaths occurred in the IFL arm of that study, but it doesn't appear that the toxicity issues were enough to discontinue therapy for those patients.

Phase II trial of 5-FU/leucovorin with or without bevacizumab

In a Phase II trial evaluating 5-FU/leucovorin with or without bevacizumab in patients previously treated for metastatic disease, bevacizumab resulted in higher response rates, improved time to progression and a trend toward improved survival. This trial actually launched the Phase III trial that was presented last year at ASCO, which demonstrated an advantage to adding bevacizumab to IFL. Those results were striking and were a tremendous boost to the morale of many medical oncologists. In preliminary analyses, it appears that 5-FU/leucovorin and bevacizumab are at least as good as 5-FU/leucovorin and irinotecan. It's fascinating that substituting a biological agent for a third chemotherapeutic drug can produce similar efficacy.

Select Publications

O'Connell MJ et al. **Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery.** *N Engl J Med* 1994;331(8):502-7. **Abstract**

Saltz LB et al. **Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin alone (FL) in Stage III colon cancer (Intergroup trial CALGB C89803).** *Proc ASCO* 2004;**Abstract 3500**.

Philip J Gold, MD

EDITED COMMENTS

SWOG-S0303: Phase III randomized trial comparing FOLFOX6 to CAPOX with or without bevacizumab

We do not yet have head-to-head comparisons between capecitabine and infusional 5-FU when administered in combination with irinotecan or oxaliplatin. Those studies are all in development or just opening.

Our next effort will be SWOG-S0303 (2.1), a very large Intergroup trial that will randomly assign patients to FOLFOX6 (infusional 5-FU, leucovorin and oxaliplatin) or CAPOX (capecitabine and oxaliplatin). A second randomization will then assign the patients to bevacizumab or placebo.

2.1 Phase III Study of Fluorouracil/Leucovorin and Oxaliplatin versus Capecitabine and Oxaliplatin with or without Bevacizumab

Protocol ID: SWOG-S0303
Target Accrual: 2,200 (Open)

Eligibility:
Locally advanced, recurrent or metastatic colorectal cancer not curable by surgery or amenable to radiotherapy with curative intent

R

- Continuous 5-FU over 46-48 hours + leucovorin + oxaliplatin → R → Bevacizumab / Placebo
- Capecitabine + oxaliplatin → R → Bevacizumab / Placebo

Study Contacts:
Southwest Oncology Group
Charles Blanke, MD, Study Coordinator Tel: 503-494-1556
Heinz-Josef Lenz, MD, Study Coordinator Tel: 323-865-3955; 800-872-2273

SOURCE: NCI Physician Data Query, June 2004.

That trial will answer two questions: (1) Can capecitabine substitute for infusional 5-FU as first-line therapy in patients with metastatic colorectal cancer, and (2) What does the addition of a novel biologic agent contribute?

Rationale for the study design of SWOG-S0303

Based on preliminary data from N9741, FOLFOX (infusional 5-FU, leucovorin

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and oxaliplatin) was selected as the standard arm — although it was modified to FOLFOX6, which eliminates the day-two visit. In Europe, FOLFOX6 has been shown to be superior to FOLFOX4. Because of the drive to incorporate capecitabine-containing regimens, CAPOX became the other chemotherapy arm.

As reported at ASCO 2003, the addition of bevacizumab to IFL improved outcomes compared to IFL alone. The response rates, median survival times and times to progression for FOLFOX4 and IFL plus bevacizumab are superimposable.

We're curious as to whether adding bevacizumab to an oxaliplatin-containing regimen will provide improvement similar to that seen when bevacizumab was added to IFL. ECOG-3200 is evaluating bevacizumab plus an oxaliplatin-containing regimen as second-line therapy.

If that trial demonstrates an advantage for the addition of bevacizumab, it is my hunch that all patients enrolled in SWOG-S0303 will receive bevacizumab, and the second randomization will be eliminated.

Capecitabine versus infusional 5-FU

Capecitabine may be more beneficial than infusional 5-FU, particularly if we can identify patients with high levels of intratumoral thymidine phosphorylase (TP) — the rate-limiting step for the activation of capecitabine. Patients with high levels of TP and lower levels of thymidylate synthase may have a higher probability of responding to capecitabine.

Compared to bolus 5-FU, capecitabine has a higher response rate and less toxicity, but equivalent survival. However, we don't yet have a head-to-head comparison between infusional 5-FU and capecitabine. Based on trials conducted mainly in Europe, my hunch is that they will be virtually identical.

For FOLFOX4 or FOLFOX6, the pooled response rate is about 45 percent, the time to progression is approximately eight months and the median survival is approximately 19 months. According to pooled data — admittedly not a scientific method — similar results are reported for CAPOX and CAPIRI. While we await results from large Phase III comparative trials, the Phase II data suggest a similar level of activity for capecitabine-containing regimens compared to infusional 5-FU-containing regimens.

Potential utility of capecitabine-containing regimens for patients with metastatic disease

With capecitabine-containing regimens, we can remove the central line and eliminate the discomfort and potential complications it causes in patients receiving infusional 5-FU. Capecitabine is more convenient for patients, extremely well-tolerated and less expensive. We treated many patients with CAPIRI as a study protocol, and we were so pleased with the toxicity and efficacy results that it has become an off-study option.

SWOG-S0030: Phase II trial of capecitabine in elderly patients

A Phase II trial being conducted by SWOG (SWOG-S0030) will evaluate single-agent capecitabine in patients who are 70 years of age or older. It is a new trial that will accrue approximately 60 elderly patients. If I do not believe an elderly patient will tolerate oxaliplatin or irinotecan, I use single-agent capecitabine as a nonprotocol therapy.

Phase III trial of bevacizumab plus IFL

This was the most positive Phase III colon cancer trial for metastatic disease ever reported, and the first validation that an antiangiogenic agent, bevacizumab, may be effective in treating human cancer. In terms of efficacy, three numbers impressed me: the improvement in the response rate, time to progression and survival.

We enrolled about eight patients in that trial and encountered minimal additive toxicity from the bevacizumab. Hypertension is probably the most likely toxicity, but the incidence of significant hypertension was very modest. Six cases of GI perforation were reported, of which almost all were related to an underlying inflammatory state — peptic ulcer disease or diverticular disease. Epistaxis is another toxicity associated with bevacizumab; however, it usually stops spontaneously, and we did not encounter a problem in our limited number of patients.

Select Publications

Cassidy J et al. **XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer.** *J Clin Oncol* 2004;22(11):2084-91. **Abstract**

Goldberg RM et al. **A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer.** *J Clin Oncol* 2004;22(1):23-30. **Abstract**

Grothey A et al. **Capecitabine plus irinotecan (CAPIRI) vs capecitabine plus oxaliplatin (CAPOX) as first-line therapy of advanced colorectal cancer (ACRC): Updated results of a randomized phase II trial.** *Eur J Cancer* 2003;1(5 Suppl):90;**Abstract 295**.

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**.

Hoff PM et al. **Phase II study of capecitabine in patients with fluorouracil-resistant metastatic colorectal carcinoma.** *J Clin Oncol* 2004;22(11):2078-83. **Abstract**

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Kim JS et al. **Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer.** *Int J Radiat Oncol Biol Phys* 2002;54(2):403-8. **Abstract**

Patt YZ et al. **Capecitabine plus irinotecan: A highly active first-line treatment for metastatic colorectal cancer (MCRC).** *ASCO Gastrointestinal Cancers Symposium* 2004;**Abstract 228**.

Shields AF et al. **Treatment of advanced colorectal carcinoma with oxaliplatin and capecitabine: A phase II trial.** *Cancer* 2004;100(3):531-7. **Abstract**

Capecitabine plus radiation therapy for the treatment of rectal cancer

Four Phase I studies and one relatively small Phase II trial have compared different capecitabine dosing schedules in combination with radiation. These were not always rectal cancer studies, but all of them showed that this combination was reasonably safe to administer.

The utilized schedules varied from every day to Monday through Friday to two weeks on, one week off. For convenience, we chose a Monday through Friday schedule to match our continuous Monday through Friday infusion regimen.

That way, patients received capecitabine every day they received radiation therapy. We used 1,000 mg/m^2 twice daily, which was remarkably well-tolerated for the four or five weeks of radiation.

A small Phase II trial showed a pathologic complete response rate comparable to what we have seen with continuous infusion 5-FU. I cannot compare apples and oranges, but at least it is in the same ballpark, and capecitabine is a lot easier to administer. I think this is really a convenience issue. I don't believe the thymidine phosphorylase upregulation data. I think it makes a nice pharmacologic argument as to why capecitabine should be superior, but I would not be disappointed if that data were all wrong. It would be exciting, however, if that data were true because the best way of taking advantage of that would be with radiation.

Utilization of capecitabine versus infusional 5-FU

I am not a big fan of bolus 5-FU. In fact, I am not sure there is any role for it in patients with metastatic disease. I believe capecitabine will be nearly as good as infusional 5-FU, but I don't know that it needs to be identical. I suspect that it will be similar enough and convenient enough to be widely used. I think the biggest obstacles are financial ones — people with copays or substantial out-of-pocket expenses for oral drugs and oncologists who feel threatened that they will lose revenue without bolus 5-FU. However, capecitabine is clearly an easier treatment. I have heard many people voice concerns about noncompliance, but I don't think

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those issues are pertinent. No population is more compliant than cancer patients. And frankly, if I give patients pills and tell them that they are good for their cancer, and they do not take those pills, I'll respect that.

Response of the primary versus metastatic lesion to FOLFOX

It's difficult to measure the actual size of primary lesions with CT assessment. When we measure them in terms of symptoms, I believe primary tumors tend to respond better than distant metastatic sites. Because flow through the lumen is a function of the radius cubed, minimal shrinkage or a minor response may result in major symptom improvement. I think, symptomatically, FOLFOX is actually a good therapy. We have known for years that neoadjuvant chemotherapy for obstructive esophageal lesions provides relief of dysphagia in approximately 80 percent of patients; however, we see response rates of only 30, 40 or 50 percent. I think when you're looking at symptoms of a primary lesion, you get good relief, but the actual response rate is hard to measure, so I can't tell you that they respond exactly the same way.

Impact of the MOSAIC adjuvant trial on clinical practice

The MOSAIC trial (3.1) is really shifting the sands of adjuvant therapy for colorectal cancer, particularly in light of the negative CALGB study, which showed that irinotecan and 5-FU combined were not better than 5-FU alone. The questions that remain are: How much better is adjuvant FOLFOX? Is the toxicity worth any incremental improvement? And will that incremental improvement hold up in terms of overall survival?

Certainly the toxicity seems tolerable. In the MOSAIC trial, about 18 percent of the participants had Grade III neuropathy during or shortly after the study. At one-year follow-up, that decreased to one percent. Grade III neuropathy is no fun, but patients have been living with cisplatin neurotoxicity for years. I think adjuvant FOLFOX is finding believers, not only in academic circles but also in the community. In particular, it's being used for young patients with high-risk Stage III disease.

3.1 MOSAIC Trial: Estimated Three-Year Disease-Free Survival for Adjuvant Chemotherapy

	FOLFOX	LV5FU2	Hazard ratio
Overall (n=1,123, 1,123)	78.2%	72.9%	0.77 [0.65-0.91], $p = 0.002$
Stage III (n=672, 675)	72.2%	65.3%	0.76 [0.62-0.92]
Stage II (n=451, 448)	87.0%	84.3%	0.80 [0.56-1.15]

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

SOURCE: Andre T et al; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. **Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.** *N Engl J Med* 2004;350(23):2343-51. **Abstract**

Phase III trial results of bevacizumab in combination with bolus IFL

When irinotecan was approved in combination with bolus 5-FU/leucovorin (IFL) based on a 2.2-month median survival advantage compared to bolus 5-FU/leucovorin, it was definitely an incremental advance. However, I thought it was a bit over the top for the FDA to make its unprecedented statement that this regimen was the standard of care. The data for bevacizumab in combination with bolus IFL data blew that away with an approximately 4.8-month improvement in median survival, a higher response rate and no increase in toxicity. The bevacizumab plus IFL trial was very well executed and had all the right endpoints.

Proposed NSABP trial: Adjuvant FOLFOX with or without bevacizumab

The original trial randomly assigned patients to FLOX, FOLFOX or CAPOX, with a second randomization to bevacizumab or placebo. That trial design was going to require approximately 5,500 patients, and it was decided to ask only the bevacizumab question, which may be the more important question.

This gets back to the philosophical question of which data are necessary to change clinical practice. In the ovarian cancer community, carboplatin in combination with paclitaxel was adopted long before GOG decided to conduct a Phase III trial. With only good reproducible Phase II studies, a switch to carboplatin in combination with paclitaxel occurred for the treatment of patients with ovarian cancer. It's a bit disingenuous of the intellectual community to say, "You can't use capecitabine in combination with oxaliplatin but must use what's been shown to be the standard of care." If the standard of care is FOLFOX4, then why are they using FOLFOX6 and modified FOLFOX6? Those are just shades of gray.

Select Publications

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**.

Dunst J et al. **Phase-II-study off preoperative chemoradiation with capecitabine in rectal cancer.** *Proc ASCO* 2004;**Abstract 3559**.

Glynne-Jones R et al. **A phase I study of preoperative radiation and capecitabine in combination with oxaliplatin in locally advanced rectal cancer.** *Proc ASCO* 2003;**Abstract 1174**.

Hickish T et al. **FOLFOX4 as adjuvant treatment for stage II colon cancer (CC): Subpopulation data from the MOSAIC trial.** *Proc ASCO* 2004;**Abstract 3619**.

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**.

Kocakova I et al. **Combined therapy of locally advanced rectal adenocarcinoma with capecitabine and concurrent radiotherapy.** *Proc ASCO* 2003;**Abstract 1295**.

Lin EH et al. **A phase II study of capecitabine and radiotherapy plus concomitant boost in patients (pts) with locally advanced rectal cancer (LARC): Preliminary safety analysis.** *Proc ASCO* 2003;**Abstract 1152**.

Role of infusional 5-FU, bolus 5-FU and capecitabine

We are convinced that infusional 5-FU is more efficacious and better tolerated than bolus 5-FU. Physicians in the United States are slowly moving toward infusional 5-FU. With the FDA's approval of oxaliplatin and the FOLFOX regimen, United States physicians will use infusional 5-FU more, but they're still concerned about lines and pumps.

Based on the results we now have from Phase II and Phase III trials, I'm convinced capecitabine will eventually be able to replace 5-FU. For the combination regimens of capecitabine with oxaliplatin or irinotecan, we have to wait for ongoing trials to mature. In France we are conducting a trial comparing XELOX (capecitabine and oxaliplatin) to FOLFOX. The preliminary results from Europe (4.1) demonstrate a 45 to 50 percent response rate for XELOX, which is similar to the response rate for FOLFOX. If the randomized trial were to show noninferiority, we would eliminate infusional 5-FU in favor of the oral fluoropyrimidine.

4.1 Phase II Trial of Capecitabine and Oxaliplatin (XELOX) as First-Line Therapy in Patients (n=96) with Metastatic Colorectal Cancer

Response rate			
Investigator	55%	Median overall survival	19.5 mo
Independent review	45%	Median progression-free survival	7.6 mo
Grade III/IV toxicity			
Sensory neuropathy	17%	Neuropathic pain	6%
Diarrhea	16%	Neutropenia	7%
Nausea/vomiting	13%	Thrombocytopenia	4%
Asthenia	9%		

SOURCES: Cassidy J et al. **XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer.** *J Clin Oncol* 2004;22(11):2084-91. **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**.

Dr Douillard is a Professor and Head of the Department of Medical Oncology at the Centre R Gauducheau in Saint Herblain, France.

Trial evaluating IFL plus bevacizumab

The results from the trial evaluating IFL plus bevacizumab were a big surprise (4.2). It was a well-conducted study with a large number of patients, and hopefully the results will be confirmed by other trials. I believe those data are accurate, and I believe they offer a major contribution. I regret that bevacizumab was combined with IFL and not FOLFIRI (infusional 5-FU, leucovorin and irinotecan). If bevacizumab combined with FOLFIRI were to improve the survival the same percentage as when combined with IFL, median survival might be 25 to 26 months.

4.2 Efficacy Results from Phase III Trial of Bevacizumab (BV) in Combination with Bolus Irinotecan, 5-Fluorouracil and Leucovorin (IFL) as First-Line Therapy in Patients with Metastatic Colorectal Cancer

	IFL/placebo (n=412)	IFL/BV (n=403)	*p*-value
Median survival (mo)	15.6	20.3	0.00003
Progression-free survival (mo)	6.24	10.6	<0.00001
Objective response rate (CR + PR)	35%	45%	0.0029
Duration of response (mo)	7.1	10.4	0.0014

SOURCE: Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Implications of the MOSAIC adjuvant trial results

The MOSAIC adjuvant trial data demonstrate that combination therapy (infusional 5-FU, leucovorin and oxaliplatin) improves results compared to a single agent, which we knew was true in metastatic disease.

The trial enrolled patients with Stage II and III disease, but I would have preferred separate trials for patients with Stage II and Stage III disease. Clearly, combination therapy improved the three-year disease-free survival with a 23 percent reduction in the risk of relapse.

Generally, a disease-free survival advantage equates to an advantage in five-year survival, but I would still like to see the five-year survival data. Even though oxaliplatin is not approved as adjuvant therapy in France, I offer combination therapy with FOLFOX to young patients with a high risk of recurrence who are not enrolled in a clinical trial.

Next year we should have results from a study being conducted in France that compares FOLFIRI to single-agent 5-FU in patients at high risk with more than four positive lymph nodes. If that trial turns out to be positive, two trials will have shown that combination therapy does better than single-agent 5-FU, and we should move to combination adjuvant therapy.

Select Publications

Andre T et al; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. **Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.** *N Engl J Med* 2004;350(23):2343-51. **Abstract**

Arkenau HT et al. **Phase III trial of infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first line treatment in advanced colorectal carcinoma (ACRC): Results of an interim safety analysis.** *Proc ASCO* 2004;**Abstract 3546**.

Cassidy J et al. **Improved safety of capecitabine versus bolus 5-fluorouracil/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT phase III study).** *ASCO Gastrointestinal Cancers Symposium* 2004;**Abstract 219**.

Cassidy J et al. **XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer.** *J Clin Oncol* 2004;22(11):2084-91. **Abstract**

Gray RG et al. **QUASAR: A randomized study of adjuvant chemotherapy (CT) vs observation including 3238 colorectal cancer patients.** *Proc ASCO* 2004;**Abstract 3501**.

Grothey A et al. **Capecitabine/irinotecan (CapIri) and capecitabine/oxaliplatin (CapOx) are active second-line protocols in patients with advanced colorectal cancer (ACRC) after failure of first-line combination therapy: Results of a randomized phase II study.** *Proc ASCO* 2004;**Abstract 3534**.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Lopez-Gomez L et al. **XELOX (capecitabine and oxaliplatin) as 1st line treatment for elderly patients (pts) with advanced/metastatic colorectal cancer (MCRC).** *Proc ASCO* 2004;**Abstract 3688**.

Lopez-Vivanco G et al. **Combination of oxaliplatin and capecitabine (CAPOX) in first and second-line treatment for metastatic colorectal carcinoma (MCRC).** *Proc ASCO* 2004;**Abstract 3701**.

Ppeiffer P et al. **Phase II study of short-time infusion of oxaliplatin in combination with capecitabine (XELOX30) in patients with progressive colorectal cancer after irinotecan and 5-fluorouracil (FU) treatment.** *Proc ASCO* 2004;**Abstract 3562**.

Scheithauer W et al. **Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: Safety results of a randomized, phase III trial.** *Ann Oncol* 2003;14(12):1735-43. **Abstract**

Tournigand C et al. **FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study.** *J Clin Oncol* 2004;22(2):229-37. **Abstract**

Twelves C et al. **XELOX (capecitabine plus oxaliplatin), a safe and active first-line regimen for elderly patients with metastatic colorectal cancer (MCRC): Post-hoc analysis of a large phase II study.** *Proc ASCO* 2004;**Abstract 3555**.

Van Cutsem E et al. **Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study.** *J Clin Oncol* 2001;19(21):4097-106. **Abstract**

Van Cutsem E et al. **Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: Integrated efficacy data and novel analyses from two large, randomised, phase III trials.** *Br J Cancer* 2004;90(6):1190-7. **Abstract**

Post-test: *Colorectal Cancer Update* — Issue 4, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In an Intergroup trial published in the *New England Journal of Medicine*, comparing bolus 5-FU and radiation therapy to infusional 5-FU and radiation therapy in rectal cancer, infusional 5-FU resulted in:**
   a. A trend toward improved local control
   b. Decreased distant metastases
   c. All of the above

2. **Phase II trial results demonstrate a 45 to 50 percent response rate for XELOX (capecitabine and oxaliplatin) as first-line therapy in patients with metastatic colorectal cancer.**
   a. True
   b. False

3. **The X-ACT trial is evaluating the efficacy of capecitabine as _____.**
   a. First-line therapy for metastatic disease
   b. Second-line therapy for metastatic disease
   c. Adjuvant therapy
   d. All of the above
   e. None of the above

4. **The MOSAIC adjuvant trial demonstrated an improvement in the three-year disease-free survival for patients treated with infusional 5-FU, leucovorin and oxaliplatin.**
   a. True
   b. False

5. **In the pivotal trial evaluating the efficacy of bevacizumab, it was combined with which regimen?**
   a. FOLFOX
   b. FOLFIRI
   c. IFL
   d. All of the above
   e. None of the above

6. **SWOG-S0303 will randomly assign patients with metastatic colorectal cancer to:**
   a. FOLFOX6 or CAPOX
   b. FOLFOX6 or IFL
   c. Bevacizumab or placebo
   d. Both a and b
   e. Both a and c

7. **Phase III randomized trials have documented the efficacy of bevacizumab when administered in combination with an oxaliplatin-containing regimen.**
   a. True
   b. False

8. **Which of the following side effects have been reported with bevacizumab?**
   a. Hypertension
   b. GI perforation
   c. Epistaxis
   d. All of the above
   e. None of the above

9. **In the adjuvant CALGB trial C89803 reported by Dr Saltz, IFL resulted in a statistically significant improvement in failure-free and overall survival compared to 5-FU/LV in patients with Stage III colon cancer.**
   a. True
   b. False

10. **SWOG-S0030 is a Phase II trial in patients 70 years of age or older with metastatic disease, which will evaluate:**
    a. Single-agent oxaliplatin
    b. Single-agent irinotecan
    c. Single-agent capecitabine
    d. Oxaliplatin plus bevacizumab

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

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Colorectal Cancer Update — Issue 4, 2004

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GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *CCU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment. . . . . 5 4 3 2 1 N/A
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for patients with metastatic colorectal cancer. . . . . 5 4 3 2 1 N/A
- Describe ongoing clinical trials in colorectal cancer and counsel patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Robert A Wolff, MD	5 4 3 2 1	5 4 3 2 1
Philip J Gold, MD	5 4 3 2 1	5 4 3 2 1
George A Fisher, MD, PhD	5 4 3 2 1	5 4 3 2 1
Jean-Yves Douillard, MD, PhD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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Stimulated my intellectual curiosity 5 4 3 2 1
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