Table of Contents

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 FOR THE 2004 *COLORECTAL CANCER UPDATE* SERIES

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 appropriately selected patients about the availability of ongoing clinical trials.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 2 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Goldberg, Grothey and Lenz on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

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

Richard M Goldberg, MD	Grants/Research Support: Pfizer Inc, Roche Laboratories Inc, Sanofi-Synthelabo Inc Consultant: Genentech BioOncology, Pfizer Inc, Roche Laboratories Inc, Sanofi-Synthelabo Inc Stock Shareholder: Bristol-Myers Squibb Company Honorarium: Eli Lilly & Company, Pfizer Inc, Roche Laboratories Inc, Sanofi-Synthelabo Inc
Axel Grothey, MD	Grants/Research Support: Aventis Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi-Synthelabo Inc, Consultant: Sanofi-Synthelabo Inc Honorarium: Aventis Pharmaceuticals Inc, Bristol-Myers Squibb Company, Roche Laboratories Inc, Sanofi-Synthelabo Inc
Heinz-Josef Lenz, MD, FACP	Consultant: Bristol-Myers Squibb Company, Chiron Corporation, Eli Lilly & Company, Genentech BioOncology, Pfizer Inc, Response Genetics Inc, Roche Laboratories Inc, Sanofi-Synthelabo Inc Honorarium: Aventis Pharmaceuticals Inc, Bristol-Myers Squibb Company, Chiron Corporation, Eli Lilly & Company, Genentech BioOncology, Pfizer Inc, Roche Laboratories Inc, Sanofi-Synthelabo Inc

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
5-FU, 5-fluourouracil	Various	Various
bevacizumab	Avastin™	Genentech BioOncology
capecitabine	Xeloda®	Roche Laboratories Inc
celecoxib	Celebrex®	Pfizer Inc
cetuximab	Erbitux™	ImClone Systems
cisplatin	Platinol®	Bristol-Myers Squibb Company
floxuridine	Various	Various
irinotecan	Camptosar®	Pfizer Inc
leucovorin calcium	Various	Various
oxaliplatin	Eloxatin®	Sanofi-Synthelabo Inc
UFT (tegafur+uracil)	Not FDA-approved	—

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Editor's Note

Rounds with the professors

As a senior student at the University of Pennsylvania School of Medicine, medical oncology was the last specialty I ever imagined entering. That notion rapidly changed when I met surgical oncologist Dr Robert Ravdin and medical oncologist Dr Sylvan Eisman. During my elective preceptorship with these caring and knowledgeable physicians, I was able to observe firsthand the art and science of medicine elevated to its highest level.

Making rounds with these doctors was particularly fascinating and taught me more than any textbook ever could. Years later, when I began conducting CME audio interviews, my penchant for case-based learning re-emerged and a favorite question became, "Can you discuss a patient from your practice whose clinical course illustrates your point?" This issue of *Colorectal Cancer Update* vividly demonstrates how interesting the responses can be.

Richard Goldberg follows up on a patient he first presented in this series two years ago — a young woman with liver-only metastases who responded very well to FOLFOX and then was sent for resection of the residual tumor. At the time of the first interview with Dr Goldberg, this woman was post-op, free of tumor and doing very well.

Unfortunately — as recounted in the current interview — a year after surgery, this woman developed tumor progression. Interestingly, the disease re-responded to the same FOLFOX therapy that Dr Goldberg originally initiated. As I listened to this case, I recalled similar stories in the late 1980s when adjuvant tamoxifen was used for one or two years in breast cancer patients. When some of these women developed tumor recurrence shortly after the discontinuation of their treatment, they experienced significant tumor responses to "tamoxifen rechallenge."

Dr Goldberg noted that he currently encourages patients to receive systemic therapy after hepatic resection, and both arms of a new NSABP randomized trial include postoperative systemic therapy with a combination of capecitabine and oxaliplatin.

Axel Grothey takes case presentation to yet another level in discussing a 34-year-old woman whose clinical course defies explanation. The patient presented at cesarean section with extensive intra-abdominal carcinomatosis and liver metastases from advanced colon cancer.

The patient also had a massive pulmonary embolus related to tumor compression of the inferior vena cava. Dr Grothey thought that chemotherapy would be futile in this gravely ill patient, but because of her young age, he opted to try an agent that at that

time (1996) had just become available to him — oxaliplatin, which was administered with 5-FU/leucovorin.

To the astonishment of the entire treating oncology team, the tumor virtually "melted away." Following surgical resection of the primary lesion, the patient remains totally well and cancer-free without any further antitumor therapy. Dr Grothey and I mused about how gratifying it would be if scenarios like this one became commonplace in oncology, and one wonders if extraordinary cases like this one might someday be studied for clues about new treatment approaches.

If one wants a glimpse into the future of cancer care, spending 90 minutes with Heinz-Josef Lenz will provide plenty of food for thought. When I asked Dr Lenz to select a patient from his practice who exemplified the future direction of oncology, he described a young woman with unresectable bilobar liver metastases.

This woman's therapy — FOLFOX and a COX-2 inhibitor — was chosen because of tissue profiling of treatment predictors. The patient had an excellent response and is now being considered for hepatic resection of the remaining tumor. While it is impossible to say how tissue predictive factors actually will play out in clinical practice, it is appealing to consider this type of case scenario for the future.

Clearly, data from randomized clinical trials must continue to shape our treatment guidelines, and the increased emphasis on evidence-based decision making has resulted in improved patient care. However, there will always be an important role for astute observations about individual cases, and nowhere is this more clearly demonstrated than in the clinical courses of the three patients treated by the professors featured in this issue.

—Neil Love, MD

Doctors with Cancer:

Research To Practice is launching a unique continuing medical education project and we seek your assistance. Our intention is to gather information via an anonymous survey of physicians with either a personal diagnosis of cancer or an immediate relative or spouse with a cancer diagnosis. The data will identify patient and family needs to be addressed in our CME programs. The survey may be completed by phone or email and a modest honorarium is available to a limited number of participants.

To launch this project, we are seeking physicians in either of the following situations:

1. A prostate cancer diagnosis
2. A diagnosis of any cancer for which chemotherapy has been administered

For more information please go to CliniciansWithCancer.com or email me (NLove@ResearchToPractice.net).

Thank you for your assistance.

Edited comments by Richard M Goldberg, MD

Adjuvant chemotherapy after resection of liver-only metastases

After a hepatic resection, I use chemotherapy as a standard in my practice, but I do it without sufficient data. A practicing oncologist must make many decisions without adequate data. I go by my instincts and try to draw conclusions from similar circumstances, either in the same disease or others.

In a small NCCTG trial (NCCTG-974651) of 44 patients with nonoptimally resectable liver-only metastases from colorectal cancer, 60 percent of the patients responded to FOLFOX (infusional 5-FU, leucovorin and oxaliplatin), and 17 were able to go on to surgery. Of those 17 patients, two had multiple small metastases throughout the liver that could not be resected. In one of the patients in whom the liver was resected, the tumor had a positive margin; the others had negative margins.

Unfortunately, in most of those patients the tumor recurred despite surgery. Of the patients who did not have a recurrence, all had received several cycles of chemotherapy after the resection. The median survival exceeded 30 months for the entire group, suggesting that surgery for patients whose tumors are resectable but not necessarily curable may still offer clinical benefit.

For patients with advanced disease, the N9741 trial established the superiority of FOLFOX over IFL (irinotecan, bolus 5-FU and leucovorin). In an analysis of that trial, 22 out of the 800 patients treated developed resectable disease. All of the patients who did not have tumor recurrence after resection had received some type of adjuvant chemotherapy.

Further investigation of the need for continuing chemotherapy after resection in these settings is necessary. The risk of recurrence, which exceeds 70 percent, depends on the number and distribution of lesions.

NSABP-C-09 adjuvant trial in patients with resected/ablated liver-only metastases

In patients with resected liver-only metastases, NCCTG conducted a pilot adjuvant trial (NCCTG-N9945) of oxaliplatin, capecitabine and a hepatic arterial infusion of FUDR (floxuridine). Based on that trial, NSABP-C-09 will randomly assign patients to oxaliplatin and capecitabine with or without a hepatic arterial

Dr Goldberg is a Professor, Chief of the Division of Hematology/Oncology and Associate Director of the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

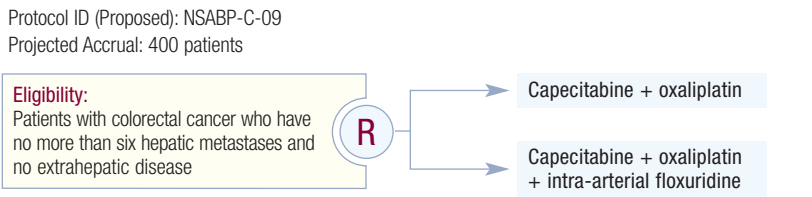
infusion of FUDR (Figure 1.1). The trial will determine whether a hepatic arterial infusion is necessary with a better chemotherapy regimen.

Capecitabine has a long half-life and mimics a 5-FU infusion. Although preliminary Phase II trial data suggests that capecitabine may be equivalent to 5-FU infusions, Phase III trial data do not yet exist. In patients with advanced disease, it's reasonable to substitute capecitabine for infusional 5-FU. In the adjuvant setting, I would prefer to see studies proving that 5-FU infusions and capecitabine are equivalent.

Theoretically, capecitabine may be advantageous because it is targeted 5-FU since higher levels of thymidine phosphorylase — the final activation step — are present in tumors compared to healthy tissue. Thymidine phophorylase levels may also be increased in the liver.

Figure 1.1

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



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

MOSAIC adjuvant trial

In patients with resected Stage II and Stage III disease, the MOSAIC adjuvant trial reported a 73 percent three-year disease-free survival for patients treated with 5-FU/leucovorin compared to a 78 percent three-year disease-free survival for patients treated with FOLFOX (Figure 1.2). Although patients with either Stage II or Stage III disease were included, patients with Stage III disease had a greater benefit.

Is three-year disease-free survival an adequate surrogate for five-year overall survival? My colleague Dan Sargent and I have submitted an abstract to the 2004 ASCO meeting showing that three-year disease-free survival is a very good surrogate and predictor of five-year overall survival. I believe the NCI has actually been willing to accept three-year disease-free survival as the primary endpoint for two new adjuvant trials on colon cancer in the United States — the NSABP and the Intergroup trials.

Figure 1.2

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

	FOLFOX	LV5FU2	Hazard ratio
Overall (n=1,123, 1,123)	77.8%	72.9%	0.77 [0.65-0.92], $p < 0.01$
Stage III (n=672, 675)	71.8%	65.5%	0.76 [0.62-0.92]
Stage II (n=451, 448)	86.6%	83.9%	0.82 [0.57-1.17]

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

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

Future Intergroup and NSABP adjuvant trials

An Intergroup adjuvant trial (N0147) led by NCCTG will compare six months of FOLFOX, six months of FOLFIRI, and three months of FOLFOX followed by three months of FOLFIRI (infusional 5-FU, leucovorin and irinotecan). We also intend to randomly assign patients to cetuximab or no other therapy.

The NSABP adjuvant trial will compare FOLFOX with or without bevacizumab. The Intergroup colorectal cancer task force, which I chair, felt it was important to evaluate both cetuximab and bevacizumab in parallel in the adjuvant setting.

Rationale for incorporating cetuximab into adjuvant colorectal cancer trials

Cetuximab targets the epidermal growth factor receptor (EGFR) — a cell surface receptor that is present in tumors of all sizes. Even if just a few cancer cells were present, such as in the adjuvant setting, at least 60 percent would have measurable EGFR on their surfaces. The clinical trial data with cetuximab is based on two studies — one conducted in the United States by Leonard Saltz and the other conducted in Europe by David Cunningham.

In all of the trials the patients had been previously treated with irinotecan, and most were refractory to it. Patients were treated with either cetuximab alone or in combination with irinotecan. The response rates were about 10 percent for cetuximab alone and 23 percent for cetuximab and irinotecan.

These data are consistent and indicate that cetuximab has activity that is augmented when combined with irinotecan. Additional research is needed since we don't know the response rates for cetuximab either alone or in combination with irinotecan and 5-FU as first-line therapy.

FOLFOX versus FOLFIRI in patients with metastatic colorectal cancer

When choosing between FOLFOX and FOLFIRI, I base my decision on my experience and the literature. Based on the Tournigand trial and other studies

presented at ASCO 2003, the activity for FOLFOX and FOLFIRI appear to be very similar. However, FOLFOX and FOLFIRI have some subtle toxicity differences. FOLFOX is associated with more neuropathy and neutropenia. FOLFIRI causes more nausea, diarrhea and alopecia. To some extent, the patients' comorbidities may factor into the decision.

Additionally, in patients with liver-only or lung-only disease, oxaliplatin-based regimens may be more effective in rendering them surgical candidates. We made that observation in an analysis of the CALGB-N9741 trial we submitted for the 2004 ASCO meeting. In my experience, the responses to oxaliplatin are sometimes more dramatic and rapid than the responses to irinotecan-based regimens. Patients who receive FOLFIRI or another irinotecan-based regimen may also become surgical candidates, but it seems more common with FOLFOX.

Incorporating capecitabine into the treatment of patients with colorectal cancer

While preliminary data suggest similar activity for capecitabine and infusional 5-FU, definitive data does not yet exist. I believe we will find that they are similar with perhaps different toxicity profiles. If capecitabine is utilized in a way to minimize toxicity, we'll probably see similar efficacy. How the changes in Medicare reimbursement factor into the delivery of 5-FU and capecitabine will be interesting to observe.

In the neoadjuvant setting for patients with rectal cancer, it may be useful to compare capecitabine plus radiation therapy to infusional 5-FU plus radiation therapy. Soft data exist to suggest that radiation therapy may induce thymidine phosphorylase and, hence, improve capecitabine's efficacy. Whether this is clinically meaningful will only be determined by clinical trials.

Select publications

Alberts SR et al. **Oxaliplatin (OXAL), 5-fluorouracil (5FU), and leucovorin (CF) for patients (pts) with liver only metastases (mets) from colorectal cancer (CRC): A North Central Cancer Treatment Group (NCCTG) phase II study.** *Proc ASCO* 2003;**Abstract 1053**.

Andre T et al. **FOLFOX7 compared to FOLFOX4. Preliminary results of the randomized optimox study.** *Proc ASCO* 2003;**Abstract 1016**.

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

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

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**

Saltz L et al. **Single agent IMC-C225 (Erbitux™) has activity in CPT-11-refractory colorectal cancer (CRC) that expresses the epidermal growth factor receptor (EGFR).** *Proc ASCO* 2002;**Abstract 504**.

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**

Edited comments by Axel Grothey, MD

Capecitabine versus 5-FU/leucovorin regimens

As first-line therapy, capecitabine and the Mayo Clinic regimen — bolus 5-FU/leucovorin — have comparable efficacy. However, they have different safety profiles. Capecitabine is associated with fewer potentially lethal complications, like neutropenic fever, and more hand-foot syndrome than bolus 5-FU regimens. Overall, the safety profile favors capecitabine over bolus 5-FU/leucovorin, which is an inferior 5-FU regimen. Whether capecitabine is comparable to infusional 5-FU regimens is not known.

Phase II trials of capecitabine/oxaliplatin (CAPOX)

The largest Phase II trial — an international trial conducted in Europe and Canada — enrolled 96 patients and evaluated a combination of capecitabine (1,000 mg/m^2 twice daily on days one through 14, followed by a one-week rest) and oxaliplatin (130 mg/m^2 every three weeks). This CAPOX regimen produced a 55 percent investigator-rated response rate, which is comparable to the response rates observed with FOLFOX-4, -6 or -7 (Figure 2.1). The time to progression and overall survival, likewise, were very similar to those observed with infusional regimens.

Figure 2.1

Phase II Trial of Capecitabine and Oxaliplatin (CAPOX) 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	16%	Neuropathic pain	6%
Diarrhea	16%	Neutropenia	7%
Nausea/vomiting	13%	Thrombocytopenia	4%
Asthenia	9%		

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

Dr Grothey is a Mayo Foundation Scholar at the Mayo Clinic College of Medicine in Rochester, Minnesota.

Another trial, conducted by our group in Germany, administered oxaliplatin on days one and eight. We had similar results with a greater than 50 percent response rate and a good toxicity and tolerability profile. The progression-free survival was more than seven months, and the overall survival is not yet available. Several other trials have also demonstrated that the CAPOX regimen is feasible and has about a 50 percent response rate and a more than seven-month progression-free survival.

Phase II randomized trial: Capecitabine/oxaliplatin (CAPOX) versus capecitabine/irinotecan (CAPIRI)

In a Phase II randomized trial comparing CAPOX to CAPIRI, we encountered early deaths in four out of the first 40 patients treated with CAPIRI. As a result, the irinotecan dose was reduced to 80 mg/m^2 on days one and eight. Overall, five out of the 79 patients treated with CAPIRI died within the first 60 days. Two deaths were related to pulmonary embolism — a complication observed with IFL (irinotecan, bolus 5-FU and leucovorin), two deaths were related to septic diarrhea (i.e., diarrhea, neutropenic fever and sepsis) and one death may have been cardiac related. Altogether, the 60-day all-cause mortality rate was 6.5 percent for CAPIRI, which is in the range that has been reported with IFL. The 60-day all cause mortality rate for CAPOX was 1.2 percent.

Ongoing Phase III trials comparing capecitabine and infusional 5-FU regimens

It's worthwhile to compare CAPOX and CAPIRI to their respective infusional regimens because capecitabine-containing regimens are so much more convenient for patients. Several trials on both sides of the Atlantic are currently comparing these regimens. Most of these trials have also added a biological agent. For example, SWOG-S0303 will compare CAPOX to FOLFOX-6 with or without bevacizumab in a two-by-two factorial design; EORTC-40015 will compare FOLFIRI to CAPIRI with or without celecoxib. Current challenges include the transition from infusional to oral 5-FU regimens and the incorporation of the new biologic agents (i.e., bevacizumab and cetuximab).

Selecting capecitabine versus infusional 5-FU regimens in a nonprotocol setting

In a nonprotocol setting, we have choices to offer patients and we can individualize treatment. Some patients do not want central venous lines, ports or pumps. Although Phase III trial data comparing capecitabine combination regimens and infusional 5-FU regimens are not available, if patients are informed about this lack of data and the results from the Phase II trials, then oral therapy can be discussed. I've used it and patients like it.

Phase III trial of IFL with or without bevacizumab

The bevacizumab trial results presented at ASCO 2003 were a great surprise. Bevacizumab was much more efficacious than I predicted; it will change our approach to patients with colorectal cancer. The problem with that trial was the

use of IFL — a regimen no longer used in clinical practice because of the Intergroup trial results presented by Rich Goldberg.

Bevacizumab plus IFL generated an impressive overall survival advantage of about five months when compared to IFL plus placebo. In my opinion, time to tumor progression is the best parameter to assess the first-line efficacy of a treatment, because subsequent treatments may influence overall survival. In the bevacizumab trial, the time to tumor progression for patients treated with bevacizumab plus IFL was a "two-digit number," the first ever such result reported in a Phase III trial. Looking at progression-free survival, the efficacy of bevacizumab in combination with chemotherapy was really impressive — a gain of four months. Additionally, the duration of response for the patients treated with bevacizumab plus IFL was 10.4 months, which was much longer than the duration of response for the patients treated with IFL plus placebo (Figure 2.2).

Figure 2.2

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 (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 (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**.

Initially designed as a three-arm trial, the third arm consisted of bolus 5-FU/leucovorin plus bevacizumab. When IFL plus bevacizumab was found to be a safe and feasible regimen, the third arm of the trial was closed to accrual so we have limited data about that regimen. Bolus 5-FU/leucovorin plus bevacizumab was better than IFL alone, in terms of response rate, progression-free survival and overall survival. The results for bolus 5-FU/leucovorin plus bevacizumab did not compare to the results for IFL plus bevacizumab, but bevacizumab added more than irinotecan to bolus 5-FU/leucovorin. This may also indicate that bevacizumab's efficacy is independent of the chemotherapy regimen used.

Bevacizumab plus capecitabine

In patients with heavily pretreated breast cancer, a trial has compared bevacizumab plus capecitabine to capecitabine alone. Although the trial was negative, the group of patients treated with bevacizumab plus capecitabine had a 10 percent increase in response rate — the same as seen in patients with colorectal cancer. However, this did not translate into a gain in survival or progression-free survival. In patients with colorectal cancer, a SWOG trial will compare CAPOX

with or without bevacizumab to FOLFOX with or without bevacizumab.

Use of bevacizumab as first-line therapy in patients with metastatic disease

My first impulse would be to use bevacizumab in combination with the best chemotherapy regimen — a FOLFOX regimen. However, very limited data exist for that combination. The second-line trial by ECOG, of FOLFOX-4 with or without bevacizumab, has completed accrual, but we don't have data yet. It might be a negative trial because the second-line setting may differ from the first-line setting, irrespective of the efficacy of FOLFOX plus bevacizumab. I would like to see results from clinical trials with FOLFOX plus bevacizumab in the first-line setting. If they turn out to be positive, then that will be the best first-line therapy.

With the currently available data, bevacizumab plus FOLFIRI would be the most likely first-line therapy. It may be safe to use bevacizumab with FOLFIRI. FOLFIRI is better than IFL because it causes less toxicity and greater efficacy. I can't see any reason bevacizumab plus FOLFIRI wouldn't be as good, if not better, than bevacizumab plus IFL.

Select publications

Cassidy J et al. Capecitabine Colorectal Cancer Study Group. **First-line oral capecitabine therapy in metastatic colorectal cancer: A favorable safety profile compared with intravenous 5-fluorouracil/leucovorin.** *Ann Oncol* 2002;13(4):566-75. **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 Suppl* 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**.

Hurwitz H et al. **Bevacizumab in combination with 5-fluorouracil and leucovorin: A promising regimen for first-line metastatic colorectal cancer.** *ASCO Gastrointestinal Cancers Symposium* 2004;**Abstract 286**.

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**.

Miller KD et al. **Phase III trial of capecitabine (Xeloda®) plus bevacizumab (Avastin™) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane.** *Breast Cancer Res Treat* 2002;76(Suppl 1);**Abstract 36**.

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

Scheithauer W et al; X-ACT Study Group. **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**

Van Cutsem E et al. Xeloda Colorectal Cancer Study Group. **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**

Edited comments by Heinz-Josef Lenz, MD, FACP

Genetic profiling to predict response to 5-FU/platinum combinations

Using genetic profiling, we have accumulated significant data allowing us to predict response to chemotherapy in gastrointestinal cancers. It's easier to predict nonresponse than response because it often takes only one pathway to be over- or underexpressed to render a drug ineffective, whereas all the genes need to be in place for it to be effective.

In the 5-FU pathway, we have identified three genes that can predict response (Figure 3.1). The target of 5-FU is the enzyme thymidylate synthase (TS), an essential enzyme for DNA synthesis. 5-FU is metabolized to FdUMP, which then binds in a suicidal manner to the TS protein. High levels of TS require high levels of 5-FU and some tumors have so much TS that we can't administer enough of the drug because the toxicities are too high.

Another enzyme in the 5-FU pathway, dipyrimidine dehydrogenase (DPD), is clinically important because loss of this enzyme activity, which occurs in about one in one million cases, leads to life-threatening toxicities. These are the patients who, after one dose of 5-FU, die because they cannot detoxify 5-FU. On the other hand, if DPD is highly active, 5-FU gets detoxified and cannot inhibit TS. High levels of either TS or DPD are associated with resistance to 5-FU; both have to be low for response to this therapy.

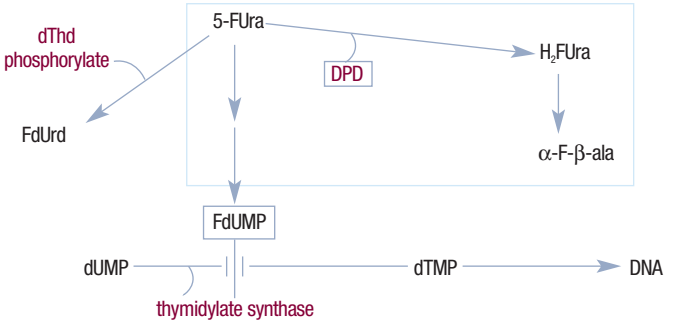
We have similar genes to predict outcome in the oxaliplatin and cisplatin pathways. Platinums are cytotoxic by setting inter- and intrastrand DNA adducts, but a cell can defend itself by excisional repair, actually cutting off these adducts. Gastric and colorectal tumors with high levels of repair capacity, reflected in high levels of ERCC-1, are therefore resistant to cisplatin and oxaliplatin chemotherapy.

By looking at these three enzymes we can determine which tumors may be more responsive to 5-FU/platinum combinations. In a prospective study of the 5-FU pathway, we found that after excluding the patients with high TS and DPD levels, the response rate was over 80 percent. As for ERCC-1, when we have low ERCC-1 and TS, the likelihood of response is approximately 60 to 70 percent. The problem is in the patients who do not fall into these categories; we do not know what treatments to use. We only know that 5-FU or a platinum would likely be unsuccessful.

Dr Lenz is an Associate Professor of Medicine and Preventative Medicine, Director of the Colorectal Center and Director of the GI Oncology Program at the USC/Norris Comprehensive Cancer Center in Los Angeles, California.

Figure 3.1

Metabolism and Mechanism of Action of 5-FU



SOURCES: Lenz HJ. Presentation, State of the Science Gastrointestinal Meeting, March 2001.

Genetic profiling to predict capecitabine efficacy and toxicity

Capecitabine functions in a manner similar to 5-FU, however, genetic activation is by thymidine phosphorylase (TP). When we added TP to the equation of TS and DPD, the predictive value went up to 100 percent. However, we expected high levels of TP would predict increased sensitivity to 5-FU and it's just the opposite; high levels actually result in resistance to 5-FU treatment and there's no biochemical explanation for it.

One hypothesis is that TP — also known as platelet-derived growth factor — plays a significant role in angiogenesis, and the role of angiogenesis overlays prediction of response to 5-FU. Many researchers believe the ratio of DPD and TP may be predictive for response to capecitabine, but we lack data from clinical trials to confirm this hypothesis.

Predictors of capecitabine-associated toxicities

The dose-limiting toxicities for capecitabine are mucositis and hand-foot syndrome. In our studies, the TS polymorphism predicted these toxicities. The cause of hand-foot syndrome is unknown, although there are theories that it may be caused by metabolites from the 5-FU, and particularly from the capecitabine pathway, and there are speculations that DPD plays an important role.

COX2 inhibition interferes with the prostaglandin pathway, so celecoxib has been combined with 5-FU to decrease the potential for diarrhea. What's exciting is the potential effect on survival by COX2 inhibition. Data comparing capecitabine with or without celecoxib showed a survival benefit for the combination in patients with metastatic colon cancer.

Potential biological mechanisms for oxaliplatin-associated neurotoxicity

We have preliminary preclinical data identifying patients at high risk for neurotoxicity, a dose-limiting toxicity for oxaliplatin, which we are trying to verify in prospective trials. The etiology of neurotoxicity appears to be related to the repair capacity in the neuron and the channels of sodium and calcium that potentially regulate the interaction between oxaliplatin and the nerve.

Based on this, when treating patients with oxaliplatin, I offer them prophylactic magnesium and calcium. Approximately half of my patients accept it and the other half wait to see if they develop symptoms. I do not recommend any glutathiones to decrease neurotoxicity because glutathiones are a critical element in the pathway of platinum resistance.

SWOG-S0304: Neoadjuvant trial using molecular markers to select chemotherapeutic regimens for patients with rectal cancer

SWOG-S0304 was the first clinical trial ever to use TS, DPD and ERCC-1 to determine which chemotherapy regimen patients will receive (Figure 3.2). It is a neoadjuvant trial for patients with locally advanced, borderline resectable rectal cancer.

Initially they will receive chemotherapy, based on their genetic profile, followed by chemoradiation with capecitabine. If they respond they may then undergo surgical resection. We want to know if these three genes can actually increase the likelihood of response to therapy.

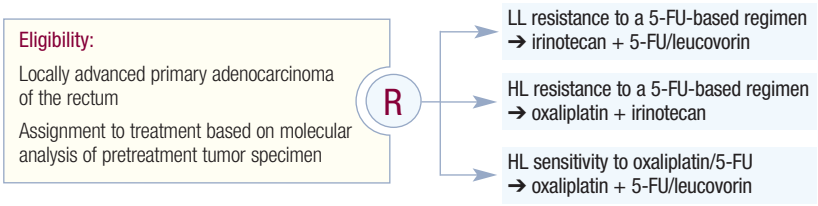
We felt the safety profile of capecitabine demonstrated in numerous Phase II trials made it a good choice for the chemoradiation portion of this study. However, I believe randomized trials need to be conducted before capecitabine can replace standard therapy. My colleagues in Europe have the opposite opinion — based on the same trials, they have already replaced infusional therapy with capecitabine.

If this trial is successful, the next step will be a prospective clinical study testing the value of TS, DPD and ERCC-1 in predicting response to 5-FU and oxaliplatin. Patients with higher likelihood of response to 5-FU and oxaliplatin will be randomly assigned to FOLFOX and other patients will be randomly assigned to oxaliplatin plus ironotecan versus FOLFIRI. This design would allow us to compare the nonselected versus selected patient population and evaluate how patients with an unfavorable genetic profile respond to treatment.

Figure 3.2

Phase II Study of Targeted Induction Chemotherapy Followed by Chemo-radiotherapy in Patients with Locally Advanced Adenocarcinoma of the Rectum

Target Accrual: 10-65 (Approved – not yet active)
Protocol ID: SWOG-S0304



LL = low likelihood; HL = high likelihood

Approximately 2 weeks after the completion of induction chemotherapy, patients with stable disease or better receive capecitabine plus radiation for five weeks

After chemoradiotherapy, patients may undergo attempted surgical resection at the discretion of the treating physician.

Study Contact:

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SOURCE: NCI Physician Data Query, March 2004.

Select publications

Ando M et al. **Genetic polymorphisms in the phenobarbital-responsive enhancer module of the UDP-Glucuronosyltransferase (UGT) 1A1 gene and irinotecan toxicity in Japanese patients.** *Proc ASCO* 2003;**Abstract 496**.

Arch-Ferrer JE et al. **Genetic expression of thymidylate synthase, dihydropyrimidine dehydrogenase and thymidine phosphorylase and its clinical correlation in gastric adenocarcinoma.** *Proc ASCO* 2003;**Abstract 1101**.

Iqbal S, Lenz HJ. **Targeted therapy and pharmacogenomic programs.** *Cancer* 2003;97(8 Suppl):2076-82. **Abstract**

Lenz HJ et al. **A multivariate analysis of genetic markers for clinical response to 5-FU/oxaliplatin chemotherapy in advanced colorectal cancer.** *Proc ASCO* 2002;**Abstract 513**.

Lenz HJ. **Pharmacogenomics in colorectal cancer.** *Semin Oncol* 2003;30(4 Suppl 15):47-53. **Abstract**

Marsh S, McLeod HL. **Cancer pharmacogenetics.** *Br J Cancer* 2004;90(1):8-11. **Abstract**

Park DJ et al. **Tailoring chemotherapy in advanced colorectal cancer.** *Curr Opin Pharmacol* 2003;3(4):378-85. **Abstract**

Wasserman E et al. **Severe CPT-11 toxicity in patients with Gilbert's syndrome: Two case reports.** *Ann Oncol* 1997;8(10):1049-51. **Abstract**

Watters JW, McLeod HL. **Cancer pharmacogenomics: Current and future applications.** *Biochim Biophys Acta* 2003;1603(2):99-111. **Abstract**

Post-test: *Colorectal Cancer Update*, Issue 2, 2004

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The NSABP-C-09 adjuvant trial will randomly assign patients to which of the following treatments:**
   a. Oxaliplatin and capecitabine
   b. Oxaliplatin and capecitabine with or without a hepatic arterial infusion of FUDR
   c. Oxaliplatin and 5-FU and a hepatic arterial infusion of FUDR
   d. Both a and b
   e. Both b and c

2. **The MOSAIC adjuvant trial reported a significant difference in three-year disease-free survival and five-year overall survival in patients treated with FOLFOX.**
   a. True
   b. False

3. **The Intergroup adjuvant trial (N0147) will compare which of the following chemotherapy regimens:**
   a. Six months of FOLFOX
   b. Six months of FOLFIRI
   c. Three months of FOLFOX followed by three months of FOLFIRI
   d. All of the above
   e. None of the above

4. **Cetuximab targets:**
   a Epidermal growth factor receptor
   b. Vascular endothelial growth factor
   c. Thymidine phosphorylase
   d. All of the above
   e. None of the above

5. **In patients with metastatic colorectal cancer, Phase III trial data suggest that capecitabine and oxaliplatin (CAPOX) is superior to FOLFOX.**
   a. True
   b. False

6. **A Phase II randomized trial comparing capecitabine and oxaliplatin (CAPOX) to capecitabine and irinotecan (CAPIRI) demonstrated a higher 60-day all-cause mortality rate for CAPIRI.**
   a. True
   b. False

7. **Which of the following regimens was not one of the initial three treatment arms in the Phase III bevacizumab trial presented at ASCO 2003 by Dr Hurwitz?**
   a. FOLFOX plus bevacizumab
   b. IFL plus bevacizumab
   c. Bolus 5-FU/leucovorin plus bevacizumab
   d. All of the above
   e. None of the above

8. **As first-line therapy in patients with metastatic colorectal cancer, IFL plus bevacizumab resulted in a five-month improvement in overall survival compared to IFL plus placebo.**
   a. True
   b. False

9. **The enzymes thymidylate synthase (TS) and dipyrimidine dehydrogenase (DPD) can be used to predict response to 5-FU therapy.**
   a. True
   b. False

10. **Genetic profiling in colorectal cancer is currently more successful in predicting nonresponse than response to chemotherapy.**
    a. True
    b. False

11. **A critical issue for bevacizumab is that a marker for response to treatment has not yet been identified.**
    a. True
    b. False

12. **In the SWOG-S0304 trial of targeted induction chemotherapy followed by chemoradiation, patients will be assigned to one of three chemotherapy arms based on:**
    a. Pure randomization
    b. Genetic profile and the predicted response to specific cyctotoxic agents
    c. Investigator's discretion
    d. All of the above
    e. None of the above

Post-test Answer Key: 1d, 2b, 3d, 4a, 5b, 6a, 7a, 8a, 9a, 10a, 11a, 12b

Evaluation Form: *Colorectal Cancer Update*, Issue 2, 2004

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

Please answer the following questions by circling the appropriate rating:

5 = *Outstanding*	4 = *Good*	3 = *Satisfactory*	2 = *Fair*	1 = *Poor*	NA= *not applicable to this issue of CCU*

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 NA
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy. . . . . 5 4 3 2 1 NA
- Develop and explain a management strategy for patients with metastatic colorectal cancer. . . . . 5 4 3 2 1 NA
- Describe ongoing clinical trials in colorectal cancer and counsel patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 NA

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Richard M Goldberg, MD	5 4 3 2 1	5 4 3 2 1
Axel Grothey, MD	5 4 3 2 1	5 4 3 2 1
Heinz-Josef Lenz, MD, FACP	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 2, 2004

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If yes, please describe any change(s) you plan to make in your practice as a result of this activity.

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What other topics would you like to see addressed in future educational programs?

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

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