

Colorectal Cancer™

U P D A T E

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

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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

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment, and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriate patients about the availability of ongoing clinical trials.
- Evaluate the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients.
- Evaluate emerging research data on various neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer and explain the absolute risks and benefits of these regimens to patients.
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 1 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Hurwitz, Enzinger and Benson on the integration of emerging clinical research data into the management of colorectal cancer.

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UPCOMING EDUCATIONAL EVENTS

Society of Surgical Oncology
Cancer Symposium
March 23-26, 2006
San Diego, California
Event website: www.surgonc.org

American Association for Cancer Research
97th Annual Meeting
April 1-5, 2006
Washington, DC
Event website: www.aacr.org

NSABP Group Meeting
April 28-May 1, 2006
Denver, Colorado
Event website: www.nsabp.pitt.edu

2006 ASCO Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: www.asco.org

American College of Surgeons Oncology
Group (ACOSOG) Semiannual Meeting
June 22-24, 2006
Chicago, Illinois
Event website: www.acosog.org

ECOG Semiannual Meeting
June 23-25, 2006
Washington, DC
Event website: www.ecog.org

UICC World Cancer Congress 2006
July 8-12, 2006
Washington, DC
Event website: www.worldcancercongress.org

2nd Annual Oncology Congress
October 19-21, 2006
New York, New York
Event website: www.oncologycongress.com

48th Annual Meeting of the American Society
for Therapeutic Radiology and Oncology
November 5-9, 2006
Philadelphia, Pennsylvania
Event website: www.astro.org



EDITOR'S NOTE

Neil Love, MD

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Like all of our audio programs, this issue of *Colorectal Cancer Update* is stuffed like a kishka with scientific content. Herb Hurwitz updates us on the evolving and very encouraging short- and long-term safety data on the anti-VEGF agent bevacizumab; Peter Enzinger comprehensively reviews recent data on adjuvant chemotherapy, particularly trials of oxaliplatin regimens like FOLFOX and FLOX (I prefer lox) and studies of capecitabine, either alone or with oxaliplatin; and Al Benson discusses the background and design of ECOG trial 5202, a critical study evaluating FOLFOX alone or with bevacizumab in Stage II tumors that a central lab at MD Anderson designates as higher risk based on microsatellite instability and 18q deletions.

There is also a Cracker Jack[®]-like special prize included with this program, a report on an exciting patient education project we recently conducted on 150 people with colorectal cancer who reacted to an audio program outlining the risks and benefits of adjuvant chemotherapy.

As discussed on the last issue of this series, our findings provide a number of interesting insights about patient perspectives on this disease. To that end, the enclosed monograph includes a comprehensive look at the survey results and a CD with the 50-minute audio interview with John L Marshall, MD that formed the basis of the survey. Many of Dr Marshall's comments are also excerpted in the print report.

As this note is being composed, our CME group is preparing to travel to San Francisco for the third annual ASCO GI symposium, where we will present a poster outlining many of our major findings from this project. We look forward to onsite and "virtual" feedback regarding this initial foray into patient education and our plan to pilot a "boxed set" of six CDs in 2006 on a variety of patient education issues related to adjuvant systemic therapy for colon cancer.

Of all the fascinating nuggets to come out of this initiative, perhaps my favorite relates to ECOG trial 5202, which randomly assigns patients with higher-risk Stage II tumors to FOLFOX alone or with bevacizumab. Based on Dr Marshall's description of this study, 75 percent of the participants would be willing to enter the study if eligible (1.1, 1.2, 1.3).

Seventy-five percent is an impressive fraction and is far more than the estimated two to three percent of cancer patients nationally who enter clinical trials. Yet, perhaps we should not be too surprised by this finding. Trial 5202 offers participants not only a chance to move the field forward and protect the health of future generations but also the unique opportunity to have their tumor tissue analyzed by one of the best labs in the country. Based on those findings, participants can potentially receive a relatively nontoxic therapeutic agent (bevacizumab) that would not be available off protocol.

Seventy-five percent. Let's tap into this signal and get trials like 5202 and its siblings, NSABP-C-08 and AVANT, done — and done soon. We need more good stuff to talk about on our CME programs in the future, and nothing would be more interesting and encouraging than a trastuzumab-like step forward in adjuvant therapy for colon cancer. ■

— Neil Love, MD
NLove@ResearchToPractice.net
January 30, 2006

1.1 Have you participated in a colorectal cancer treatment research trial?



If no, have you ever been offered?



SOURCE: *Patient Perspectives on Colorectal Cancer 2006.*

1.2 Based on this discussion, if you were eligible to participate in ECOG trial 5202, would you be willing to participate?



SOURCE: *Patient Perspectives on Colorectal Cancer 2006.*

1.3 Would an audio discussion similar to the one you just heard presented by Dr Marshall have made it more likely that you would participate in a clinical trial?



SOURCE: *Patient Perspectives on Colorectal Cancer 2006.*



INTERVIEW

Herbert Hurwitz, MD

Dr Hurwitz is an Associate Professor of Medicine in the Division of Hematology/Oncology, Clinical Director of the Phase I Program and Co-leader of the GI Oncology Program at Duke University Medical Center in Durham, North Carolina.

Tracks 1-20

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Select Excerpts from the Interview

Track 2

► **DR LOVE:** Can you summarize the current available database on the safety of bevacizumab?

► **DR HURWITZ:** So far, the main side effect has been hypertension that, in general, is modest and easily manageable. It occurs in about a quarter of all patients, and perhaps one, two or three in 10 patients will need to start receiving blood pressure medication or will need an adjustment to a component of their blood pressure regimen. In general, all blood pressure medica-

tions used to date have been successful. The key issue is close monitoring of the patient.

As oncologists, we used to be able to forget about many general internal medicine issues because cancer mortality was the most important issue for our patients. Now that patients are able to stay on treatments for a year and longer in some cases, management of side effects will be important.

In particular, blood pressure should probably be measured at every clinic visit, and if a clear trend toward increased blood pressure appears, medication should be instituted. Best clinical judgment should be used in the selection and titration of any agent.

► **DR LOVE:** Is anything new in terms of what is known about the mechanism of developing hypertension?

► **DR HURWITZ:** The mechanism is not yet well understood. Preclinical models and some experience in the cardiovascular literature suggest that nitric oxide-mediated mechanisms are likely involved (Shen 1999).

Nitric oxide regulates many processes, including those related to vascular tone, renal hemodynamics and alterations of the renin-angiotensin system. In short, we don't yet know the mechanism of hypertension in these patients. More than likely, some component of all of these processes is involved.

At this time, we don't have enough mechanistic information to drive the selection of one antihypertensive medication over another. Currently, I suggest making this decision based on other reasons one drug may be preferred versus another — the way we do with all patients.

Tracks 4 and 6

► **DR LOVE:** Can you discuss the issues related to bowel perforation and bevacizumab? What have we learned over the last year or two?

► **DR HURWITZ:** The issues related to bowel perforation have many of the same general themes as the arteriovascular event risks. In general, these risks are low.

Several studies of bevacizumab — the large IFL study (Hurwitz 2004), the Phase II 5-FU/leucovorin study (Kabbinavar 2005) and the ECOG second-line FOLFOX with or without bevacizumab study (Giantonio 2005) — have reported a one to two percent risk of GI perforation.

A similar risk is apparent in the historic literature — anywhere between two to five percent of some type of bowel perforation, abscess or fistula formation with the use of chemotherapy alone.

The reasons for those findings are not well understood. These problems have not been observed as commonly in other tumor settings, aside from the ovarian cancer population. This may relate to the fact that GI-toxic regimens are used for colon cancer — more diarrhea and bowel inflammation and

inflammatory wound-healing responses, in general, may predispose these patients to perforation.

► **DR LOVE:** As bevacizumab data accumulate, have we learned anything more about the clinical presentation of these bowel perforations?

► **DR HURWITZ:** For the most part, the presentation of bowel perforation is what you would expect — essentially like an acute abdomen. The definition of bowel perforation, though, has often been very liberal to allow us to detect any event that might be even partially implicated.

As cancer doctors, we're quite used to dealing with the complications of regimens that affect bowel integrity. IFL, FOLFOX, and 5-FU alone all cause diarrhea, and if that gets out of hand, it can lead to an occasional serious or even life-threatening complication.

Patients who have bowel trouble and start to experience serious symptoms should be evaluated urgently, and standard management should be pursued.

Tracks 8-9

► **DR LOVE:** What do we know about patients who require emergent surgery while they're receiving bevacizumab?

► **DR HURWITZ:** The issue of surgery and bevacizumab needs to be broken down into two separate categories. One category includes patients who have major surgery and then receive bevacizumab.

Among patients who've waited at least a month prior to starting bevacizumab and who have healed sufficiently to be cleared by their surgeons, no increased risk of wound-healing complications is apparent. The converse setting, where patients are on bevacizumab and then go to surgery, is a bit more complicated.

The best data come from the IFL study (Hurwitz 2004). Most of the patients going to surgery did so for an urgent or emergent indication — usually major abdominal procedures.

Wound-healing complications ranged from minor to major wound dehiscence or major bruising at the site, and the wound-healing complication risk ranged from about four to 14 percent.

Most complications were manageable — rarely lethal. I would interpret that range in risk to mean that the rate does increase for emergent or urgent indications, such as drainage of an abscess or some other acute issue. That risk is acceptable, and the risk of wound-healing complications should not deter good surgical or interventional management when needed.

For highly elective surgery, one should respect the half-life of the drug, which is about 21 days. One should wait two to three half-lives of the drug — about 40 to 60 days — before elective surgery. This becomes a bit of a risk-benefit ratio, as we have not truly identified the best interval for timing elective

metastatic resection. I think the window for metastatic resections is probably about six weeks following cessation of treatment with bevacizumab.

► **DR LOVE:** With respect to hepatic resection or ablation, what do we know about the effect of bevacizumab on hepatic regeneration?

► **DR HURWITZ:** We don't know a lot about the effect of bevacizumab per se on hepatic regeneration. From clinical and preclinical information, we know that hepatic regeneration is angiogenesis-dependent.

We also know that the majority of hepatic regeneration occurs within a few weeks to a month or so after surgery. Some patients clearly take a little bit longer to regain both liver volume and function after major resection, particularly after a right hepatectomy.

In general, the patient should be well healed, should have normal liver function test results, and should be cleared by his or her surgeon before starting bevacizumab. I think a patient who's completely healed and who has normal liver function test results is a suitable candidate.

Allow two months, perhaps three months for some patients, to recuperate from such surgery — that time frame would be reasonable. For the smaller variations on hepatic resection, such as a left hepatectomy, shorter windows of time may be appropriate.

The administration of bevacizumab after radiofrequency ablation has not been well studied. It is a less invasive procedure, although it does have potential risks. A window of two to four weeks after radiofrequency ablation is probably adequate, provided the patient had no undue complications.

Track 16

► **DR LOVE:** Would you discuss the dosing of bevacizumab?

► **DR HURWITZ:** In the first-line setting, a dose of 5 mg/kg every two weeks, which is a dose intensity of 2.5 mg/kg per week, is the standard of care. Some ongoing studies, mostly of capecitabine-based regimens with oxaliplatin, are using three-week cycles of equivalent dose intensity. Those are 7.5 mg/kg every three weeks, which is essentially the same dosing, particularly given the long half-life of the drug. In the second-line setting, the dose is 10 mg/kg every two weeks.

An older study, the initial randomized Phase II trial (Kabbinavar 2003), evaluated placebo versus 5 mg/kg versus 10 mg/kg. In that study, the 5 mg/kg dose was a little bit better. A number of disclaimers relate to potential imbalances between the 5 and 10 mg groups. However, the 5 mg/kg dose looked good enough to pursue in a Phase III study, and that dose is clearly active. We know the safety profile of that drug in that setting.

Most patients have received bevacizumab in the first-line setting, so we see very few reasons to give bevacizumab in the second-line setting. One can

come up with a few scenarios, such as patients having been on a clinical trial without bevacizumab or some complication that caused postponing the treatment. If bevacizumab were truly to be used as a second-line agent, I would use a 10 mg/kg dose. In a hybrid scenario, such as a delayed first-line setting, I would use 5 mg/kg.

 **Track 17**

▶ **DR LOVE:** What about the combination of cetuximab and bevacizumab — where do you see that heading?

▶ **DR HURWITZ:** The issue of combining biologics is an interesting one. Right now, preclinical biology suggests synergy when targeting the EGF and VEGF axes. Interesting pilot data came from the BOND-2 trial, which looked at cetuximab with bevacizumab versus cetuximab/bevacizumab and irinotecan (Saltz 2005).

Both arms of that study appeared to do much better than the historical controls of the BOND-1 trial (Cunningham 2004), which evaluated cetuximab monotherapy or cetuximab with irinotecan (2.1). The response rates and time to progression were a lot higher than most of us expected.

For both theoretical and practical reasons, I think the combination is highly worthy of study. Two studies will address this question. The largest study will be a GI Intergroup study of one chemotherapy regimen picked by the investigator — either FOLFOX or FOLFIRI — with the addition of cetuximab, bevacizumab or both (CALGB-C80405). An industry-sponsored study will evaluate FOLFOX/bevacizumab with or without panitumumab, a monoclonal antibody that is essentially a biological cousin of cetuximab.

2.1 Efficacy Data from the BOND-2 Trial of Cetuximab/Bevacizumab with or without Irinotecan in Irinotecan-Refractory Colorectal Cancer Compared to Historical Controls

Efficacy parameter	Cetuximab/irinotecan + bevacizumab ¹ (n = 39)	Cetuximab/irinotecan ² (n = 218)	p-value
Response rate	38%	23%	0.03
Time to tumor progression	8.5 months	4 months	S*
Efficacy parameter	Cetuximab/bevacizumab ¹ (n = 35)	Cetuximab alone ² (n = 111)	p-value
Response rate	23%	11%	0.05
Time to tumor progression	6.9 months	1.5 months	S*

¹ BOND-2 trial
² BOND-1 trial
 * S = significant

SOURCE: Saltz LB et al. *Proc ASCO GI Cancers Symposium 2005*; [Abstract 169b](#).

Track 20

► **DR LOVE:** Previously, you mentioned the issue of capecitabine with bevacizumab. Is there any reason to believe this combination would be better or worse than bevacizumab with 5-FU?

► **DR HURWITZ:** My expectation is that the regimens would be comparable. Large Phase III studies have been conducted, primarily in Europe, including a FOLFOX versus CAPOX study with or without bevacizumab. This study has completed accrual, and the toxicity results will be available in the next year. Efficacy results will come shortly thereafter, but it may take a while for the survival endpoint data to appear.

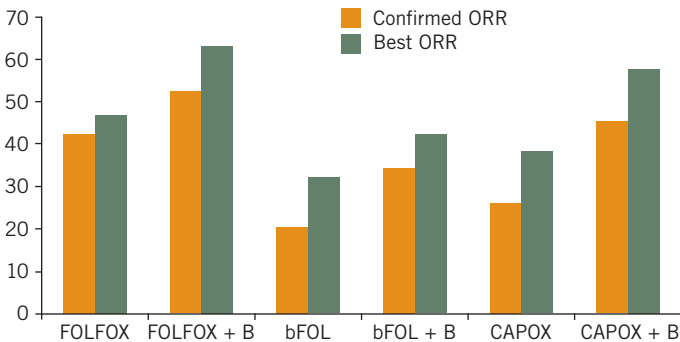
In general, capecitabine has tended to look similar to 5-FU, including the capecitabine/oxaliplatin versus infusional 5-FU/oxaliplatin data, without bevacizumab, reported at ASCO this past year (Arkenau 2005; Sastre 2005).

In addition, pilot data from our institution and the larger experience in the TREE-2 study suggest that efficacy should be comparable between capecitabine/oxaliplatin/bevacizumab and the FOLFOX regimen (2.2). That comparability, though, has not yet been validated. As far as clinical management goes, I would still consider an infusional 5-FU regimen with oxaliplatin or irinotecan — FOLFOX or FOLFIRI — as the standard platform on which to add bevacizumab.

For patients who are not candidates for pump therapy, the activity of capecitabine with oxaliplatin and bevacizumab is significant enough that it should be considered as a first-line option. The question of whether or not it's the best option will require the final results of this Phase III study. ■

2.2

Comparative Response Rates for TREE-1 and TREE-2



$p < 0.004$, from the pooled logistic regression analysis, likelihood ratio test
ORR = overall response rate; B = bevacizumab

SOURCE: Hochster HS et al. Poster. ASCO 2005; [Abstract 3515](#).

SELECT PUBLICATIONS

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- Cunningham D et al. **Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.** *N Engl J Med* 2004;351(4):337-45. [Abstract](#)
- Ellis LM. **Bevacizumab.** *Nat Rev Drug Discov* 2005;Suppl:8-9. [Abstract](#)
- Ellis LM et al. **Surgical resection after downsizing of colorectal liver metastasis in the era of bevacizumab.** *J Clin Oncol* 2005;23(22):4853-5. No abstract available
- Fernando N et al. **A phase II study of oxaliplatin, capecitabine and bevacizumab in the treatment of metastatic colorectal cancer.** *Proc ASCO* 2005;[Abstract 3556](#).
- Giantonio BJ et al. **High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** Presentation. ASCO GI 2005;[Abstract 169a](#).
- Hochster HS et al. **Bevacizumab (B) with oxaliplatin (O)-based chemotherapy in the first-line therapy of metastatic colorectal cancer (mCRC): Preliminary results of the randomized "TREE-2" trial.** *Proc ASCO GI Cancers Symposium* 2005;[Abstract 241](#).
- Hochster HS et al. **Safety and efficacy of bevacizumab (Bev) when added to oxaliplatin/ fluoropyrimidine (O/F) regimens as first-line treatment of metastatic colorectal cancer (mCRC): TREE 1 & 2 Studies.** *Proc ASCO* 2005;[Abstract 3515](#).
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- Kabbinavar FF et al. **Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: Results of a randomized phase II trial.** *J Clin Oncol* 2005;23(16):3697-705. [Abstract](#)
- Kabbinavar FF et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) to prolong progression-free survival in first-line colorectal cancer (CRC) in subjects who are not suitable candidates for first-line CPT-11.** *Proc ASCO* 2004;[Abstract 3516](#).
- 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](#)
- Saltz LB et al. **Interim report of randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** *Proc ASCO GI Cancers Symposium* 2005;[Abstract 169b](#).
- Sastre J et al. **Preliminary results of a randomized phase III trial of the TTD group comparing capecitabine and oxaliplatin (CapeOx) vs oxaliplatin and 5-fluorouracil in continuous infusion (5-FU CI) as first line treatment in advanced or metastatic colorectal cancer (CRC).** *Proc ASCO* 2005;[Abstract 3524](#).
- Scappaticci FA et al. **Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab.** *J Surg Oncol* 2005;91(3):173-80. [Abstract](#)
- Shen BQ et al. **Vascular endothelial growth factor governs endothelial nitric-oxide synthase expression via a KDR/Flk-1 receptor and a protein kinase C signaling pathway.** *J Biol Chem* 1999;274(46):33057-63. [Abstract](#)
- Welles L et al. **Preliminary results of a randomized study of the safety and tolerability of three oxaliplatin-based regimens as first-line treatment for advanced colorectal cancer (CRC) ("Tree" study).** *Proc ASCO* 2004;[Abstract 3537](#).



INTERVIEW

Peter C Enzinger, MD

Dr Enzinger is an Instructor in Medicine at Harvard Medical School and is Clinical Director of the Gastrointestinal Cancer Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

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Select Excerpts from the Interview

Track 2

► **DR LOVE:** Would you discuss the NSABP-C-07 and MOSAIC trials?

► **DR ENZINGER:** Unlike the MOSAIC study (de Gramont 2003; André 2004), the FLOX — or NSABP-C-07 — study (Wolmark 2005) specifically looked at a bolus regimen of 5-FU and leucovorin with or without oxaliplatin. In a sense, it was the traditional Roswell Park regimen with oxaliplatin added to every other treatment.

The accrual for the trial took a little bit longer than that of the MOSAIC study, and the results were reported at a later date. NSABP-C-07 investigators ultimately came to the conclusion that oxaliplatin adds a 4.9 percent absolute benefit when added to 5-FU and leucovorin therapy, almost the same absolute three-year benefit that was found in the MOSAIC study (3.1).

The question is whether we need to give infusional 5-FU or whether we can continue with bolus dosing of 5-FU. Ultimately, I think the infusional 5-FU schedules have lower overall toxicity, but the dose of oxaliplatin in the MOSAIC study was higher, so patients had a higher incidence of neuropathy.

In NSABP-C-07 (Wolmark 2005), a 10 percent difference in Grade III and Grade IV toxicities was evident between the Roswell Park regimen (FU/LV) and the same regimen plus oxaliplatin (FLOX). Seven percent of that difference is due to neuropathy. So the difference in overall toxicity is really only three percent.

The ultimate conclusion is that NSABP-C-07 is a confirmatory trial. It confirms the benefit of oxaliplatin, and it offers oncologists an alternative way of administering this agent in combination with 5-FU and leucovorin, which is reassuring.

I would like to see the overall survival advantage for both trials, and that will probably become evident as deaths increase. When we look at the number of patients who are dying and the patients who are having recurrences, we see that the number of patients with recurrences is increasing.

We're beginning to see a trend in that direction. My suspicion is that it's going to take some time before we actually see an overall survival advantage in either one of these trials.

3.1

Three-Year Disease-Free Survival (DFS) in NSABP-C-07 and MOSAIC

	Three-year DFS (oxaliplatin arm)	Benefit from oxaliplatin	Hazard ratio
NSABP-C-07	76.5%	4.9%	0.79
MOSAIC	78.2%	5.3%	0.77

SOURCES: Wolmark N et al. Presentation. ASCO 2005; [Abstract 3500](#); André T et al. *N Engl J Med* 2004;350(23):2343-51. [Abstract](#)

Track 5

► **DR LOVE:** In what situation would you discontinue oxaliplatin due to neurotoxicity? I hear people talk about discontinuation prior to the development of functional impairment. Is that your approach?

► **DR ENZINGER:** Yes, although I think the more interesting question is when to start attenuating the dose. Do you push the patient to functional impairment

using the full dose, or do you start attenuating early or drop the oxaliplatin as in the OPTIMOX trial (de Gramont 2004)?

There are many ways of doing this in metastatic disease, and I don't think there's one right or wrong way. With many other therapies available, giving treatment for a certain period of time and then switching to something else before these neuropathies arise may be the better approach.

Colleagues who treat lung and breast cancer utilize a set number of cycles, or they treat for a set period of time. It's really only with the GI malignancies, because our patients have such a poor prognosis, that we treat continuously. We probably should begin to consider adopting more of a breast or lung cancer type of approach. In part, I believe that patients will have a better quality of life using that kind of approach.

► **DR LOVE:** FOLFOX in the metastatic setting is very different from using it in the adjuvant setting. In the adjuvant setting, how many patients discontinue the drug? Generally, when is it stopped?

► **DR ENZINGER:** I almost always have to attenuate the oxaliplatin toward the end of the treatment. I need to attenuate oxaliplatin starting around the eighth or ninth treatment in 80 or 90 percent of all patients. I've had to drop oxaliplatin completely in 10 percent.

Track 6

► **DR LOVE:** When patients are about to start receiving FOLFOX for the first time and they ask you about the chances of having some type of residual neuropathy, how do you respond?

► **DR ENZINGER:** I tell them that we don't know whether or not this will occur. The data right now are out to 18 months. But I try to reassure the patient in the sense that the neuropathy — at least according to the MOSAIC study — is very mild. So I tell them that about 24 percent of patients have some residual neuropathy, but only 0.5 percent have debilitating neuropathy. I think those odds are pretty good.

Most patients have experienced some tingling or mild tingling, and that's what I tell my patients to expect. I don't believe that they're going to be left with any debilitating neuropathies. I think the risk for another adverse event is much higher than for long-term debilitating neuropathy.

Track 7

► **DR LOVE:** Another major trial that's had a big impact on clinical decision-making is the X-ACT study, which evaluated capecitabine versus 5-FU (Cassidy 2004; Twelves 2005a, 2005b). Can you summarize that study and discuss your interpretation of the findings?

► **DR ENZINGER:** The X-ACT study evaluated the FDA-approved dose of capecitabine, which is 2,500 mg/m² daily for 14 days straight every three weeks for six months. The standard treatment arm in that trial received the Mayo Clinic 5-FU regimen.

The study was powered to detect relatively small differences in survival and also to look at equivalence between the arms. The three-year results evaluated relapse-free survival, disease-free survival and overall survival.

At the three-year analysis, we saw that the regimen of capecitabine was at least equivalent to the Mayo Clinic 5-FU regimen (3.2). In fact, there was a statistically significant improvement in relapse-free survival, and disease-free survival was right on the edge of significant improvement.

I think overall survival will also show an improvement with further follow-up. We're seeing the same thing here that we're seeing in the metastatic disease setting — that capecitabine is probably slightly better than what we've observed with bolus 5-FU.

3.2 Efficacy of Adjuvant Treatment in Stage III Colon Cancer: The X-ACT Trial

	Number of events over a median of 3.8 years		HR (95% CI)	p-value E; S
	Capecitabine (n = 1,004)	5-FU/LV (n = 983)		
DFS	348	380	0.87 (0.75-1.00)	<0.001; 0.05
RFS	327	362	0.86 (0.74-0.99)	—; 0.04
OS	200	227	0.84 (0.69-1.01)	<0.001; 0.07

E = equivalence; S = superiority; DFS = disease-free survival; RFS = relapse-free survival; OS = overall survival

SOURCE: Twelves C et al. *N Engl J Med* 2005;352(26):2696-704. [Abstract](#)

 **Track 8**

► **DR LOVE:** How do you determine which patients are candidates for capecitabine in the adjuvant setting?

► **DR ENZINGER:** The goalpost for adjuvant treatment has been changed since X-ACT was initiated. Most doctors are now recommending FOLFOX, particularly for patients who are at higher risk for recurrence. So the question now is where capecitabine fits into this whole category.

We know capecitabine had a very nice toxicity profile in the head-to-head comparison with the Mayo Clinic regimen (Twelves 2005b). Toxicities across the board were less than those associated with the Mayo Clinic regimen, except for hand-foot syndrome, with which 17 percent of patients had severe Grade III to Grade IV toxicity.

But the reality is that this will occur during the first cycle. Then you attenuate treatment, and typically, patients will do fine for the rest of the adjuvant course.

Looking at the X-ACT data, a subgroup analysis suggests that patients with N1 disease did better than those with N2 disease, which makes sense to me and would actually fit in nicely with the FOLFOX paradigm.

In my mind, I would say that patients with N2 disease, the patients who have higher risk for recurrence, really should not even be given an option. Those patients should be pushed towards FOLFOX.

Patients who have a lower risk for recurrence, perhaps those with N1 disease, and patients who wish to avoid the neuropathies may actually be good candidates for capecitabine. So perhaps the patients with Stage IIIA disease would do well with capecitabine.

In my own practice, patients with high-risk Stage III disease receive FOLFOX. With low-risk patients, I have an intensive conversation about the risks and benefits of FOLFOX versus the Roswell Park 5-FU regimen versus capecitabine.

► **DR LOVE:** What are the situations in which you'd use the Roswell Park regimen instead of capecitabine?

► **DR ENZINGER:** In my opinion, the Roswell Park regimen is well suited for an elderly patient who needs the social support associated with coming to the office and seeing the nurses. Often, they enjoy the stimulation of coming for a visit.

Capecitabine is a therapy for a business professional, for somebody who believes that adjuvant therapy gets in their way and who wants to have the least number of interruptions possible.

Now we really haven't seen any direct comparisons between Roswell Park and capecitabine. Capecitabine has always been measured against the Mayo Clinic regimen, so I don't know how a toxicity analysis between these other two would work out.

I suspect that Roswell Park would be associated with more diarrhea, more hematologic toxicity and stomatitis, but the difference would be less than when compared with the Mayo Clinic regimen.

► **DR LOVE:** What about patients with Stage II disease?

► **DR ENZINGER:** I think patients with Stage II disease sometimes have a higher risk for recurrence than those with Stage III disease. A patient with Stage IIB colorectal cancer, in my opinion, may have a higher risk for recurrence than someone with Stage IIIA disease, and again, that's where I'd consider all three options.

I tend to push patients towards FOLFOX if they have tumors that have perforated.

Track 16

► **DR LOVE:** The design of randomized trials, both in the metastatic and the adjuvant setting, is becoming a lot more complicated because of all the new agents. What are some of the current research questions that you think are most interesting?

► **DR ENZINGER:** One of the most interesting questions in the adjuvant setting is the role of bevacizumab. It is now shown to be of significant benefit in the metastatic disease setting. Can we duplicate that in the adjuvant setting?

People have argued that we're destroying isolated cancer cells in the adjuvant setting, and isolated cancer cells don't need vasculature — they don't need to recruit oxygen. However, I believe our imaging capabilities are suboptimal.

We're able to detect cancer nodules that are approximately one centimeter in size — it's quite clear that we're not able to detect a cancer nodule less than 0.5 centimeters in size, even in the best-case scenarios. A one-centimeter nodule is significantly larger than the one- to two-millimeter nodule that is the size at which we think the angiogenic switch is being thrown.

If a patient has a tumor nodule between one and 10 millimeters, I believe that's where bevacizumab will probably have its greatest impact. Not only will it have an anti-angiogenic effect, but it'll also promote drug delivery into these fairly large conglomerates of tumor cells. We're talking about many millions of cells in these small tumor nodules.

In designing these trials, I would stratify and look at patients who have poor-risk Stage III disease — the patients who probably have residual tumor nodules, because I think bevacizumab may actually exert its greatest impact or activity in patients with macroscopic residual disease that we just can't see — not in microscopic residual disease.

Track 17

► **DR LOVE:** Can you discuss the upcoming Intergroup trial that will evaluate combined biologic therapy in metastatic disease?

► **DR ENZINGER:** In the upcoming Intergroup study, patients will be randomly assigned to standard chemotherapy (FOLFOX or FOLFIRI) with standard treatment (bevacizumab) or with experimental treatment that includes cetuximab or cetuximab with bevacizumab (3.3). Based on the data we've seen from the CBI trial (Saltz 2005), many of us expect the arm receiving both biologic agents to win.

The dilemma is that this will be very expensive therapy, but I think that it's going to be very interesting. I think many of us are already tempted to throw everything at these patients — particularly the patients who are at high risk. However, use of both biologics raises financial costs and also toxicity costs. ■

Randomized Phase III Study of Bevacizumab and/or Cetuximab Plus FOLFOX or FOLFIRI in Untreated Advanced Colorectal Cancer

Protocol IDs: CALGB-C80405, NCT00265850, SWOG-C80405
Target Accrual: 2,300 (Open)

Eligibility

No CNS metastases or carcinomatous meningitis
No prior treatment with VEGF or EGF receptors
More than 12 months since adjuvant 5-FU with or without oxaliplatin or irinotecan

R

FOLFOX or FOLFIRI + bevacizumab

FOLFOX or FOLFIRI + cetuximab

FOLFOX or FOLFIRI + bevacizumab + cetuximab

FOLFOX = 5-FU/leucovorin/oxaliplatin

FOLFIRI = 5-FU/leucovorin/irinotecan

SOURCE: NCI Physician Data Query, January 2006.

SELECT PUBLICATIONS

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INTERVIEW

Al B Benson III, MD

Dr Benson is a Professor of Medicine and Associate Director for Clinical Investigations at the Robert H Lurie Comprehensive Cancer Center at Northwestern University in Chicago, Illinois.

Tracks 1-8

- | | | | |
|----------------|---|----------------|---|
| Track 1 | Introduction by Dr Love | Track 5 | ECOG-E5202: Duration of bevacizumab therapy |
| Track 2 | Allelic loss of chromosome 18q and prognosis in colorectal cancer | Track 6 | ASCO treatment guidelines for Stage II disease |
| Track 3 | ECOG-E5202: FOLFOX with or without bevacizumab in molecularly identified high-risk Stage II disease | Track 7 | Current and potential future strategies to select patients for adjuvant therapy |
| Track 4 | ECOG-E5202: Eligibility criteria | Track 8 | Alternative methods of 5-FU administration |

Select Excerpts from the Interview

Track 2

► **DR LOVE:** Can you discuss the background to ECOG trial 5202 in patients with Stage II disease?

► **DR BENSON:** A great deal of emphasis has been placed on laboratory correlative work linked to outcome data from randomized clinical trials. Correlative laboratory studies can be designed in several ways, although the most typical evaluation to date is a retrospective analysis of patient tumor specimens obtained from patients in clinical trials for which outcome data are already available.

One area that has been evaluated extensively — mostly in the retrospective arena — is the phenomenon of 18q deletion, which has been associated with a much poorer prognosis. Under the direction of Stan Hamilton's laboratory, ECOG examined tumor blocks from the primary tumors of individuals who had entered one of two of the early Intergroup adjuvant trials, which were 5-FU based.

Unfortunately, because these are older trials, it was impossible to collect all of the tumor specimens we needed. However, we did have sufficient tumor specimens to conduct a retrospective analysis, which demonstrated that those

patients who retain the 18q allele have a far better survivorship than those who do not (Jen 1994).

We also looked at microsatellite instability (MSI) in this series of patients, and it appeared that patients with MSI and evidence of the TGF-beta mutation had a superior survivorship compared to those who did not (Watanabe 2001).

In the cooperative group setting, randomized trials for patients with Stage III disease who receive a 5-FU-based regimen report five-year survival rates near 65 percent. Among patients with 18q deletion — in other words, a poor-risk group — five-year survival was only 50 percent. This correlates with survival statistics for patients who had surgery alone. The implication is that the 5-FU-based regimen had no impact on outcome.

On the other hand, those so-called good-risk patients who retained 18q or had MSI with the TGF-beta mutation had a survival rate of 75 percent at five years. What we don't know in this population is whether this group would have done just as well with surgery alone or if the chemotherapy had some impact. We cannot answer those questions.

Tracks 4-5

► **DR LOVE:** How are the high- and low-risk patients identified in trial 5202?

► **DR BENSON:** The laboratory correlative data were felt to provide enough evidence to conduct a hypothesis-driven trial. The Intergroup elected to evaluate patients' primary tumor specimens for the 18q allele as well as for MSI. The specimens are collected as close to the time of surgery as possible.

When the result is known for the Stage II patients who are asked to participate in the trial, patients are assigned to either the high- or low-risk group. The low-risk group will include those individuals who retain 18q. Our projected survivorship for this group is nearly 90 percent. Of course, this trial will tell us if we're right or wrong in that assumption.

In the high-risk group, another suggestion based on retrospective data indicated that a 5-FU/leucovorin regimen would not be likely to have a major impact. Given the MOSAIC trial data implying that a worse prognostic group tends to receive a greater benefit from FOLFOX (André 2004), it was elected to incorporate FOLFOX into the randomization for the high-risk patients.

So the Intergroup strategy for both colon and rectal cancer is to randomly assign these patients between FOLFOX and FOLFOX with bevacizumab. This is what is being done for Stage II patients in the 5202 trial (4.1).

5202 is now active, and we encourage patients and physicians to participate since it is really the first large-scale prospective randomized trial to determine whether a molecular parameter in colon cancer can aid us in making treatment decisions. In addition, we will be storing tissue to evaluate other potential prognostic and predictive markers once we have outcome data available. ■

Phase III Randomized Study of Oxaliplatin, Leucovorin Calcium and Fluorouracil with or without Bevacizumab in Patients with Resected Stage II Colon Cancer

Protocol ID: ECOG-E5202
Target Accrual: 3,610 (Open)



* Patients are stratified according to disease stage (IIA versus IIB) and microsatellite stability (stable versus low-grade instability [MSI-L]). Patients at high risk for microsatellite instability (MSI) and loss of heterozygosity (LOH) at chromosome 18q are randomly assigned to one of two treatment arms (arms I and II), whereas patients at low risk for MSI and 18q LOH are assigned to arm III.

SOURCE: NCI Physician Data Query, May 2006.

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. Although the mechanism of bevacizumab-associated hypertension is not fully understood, preclinical models suggest that nitric oxide-mediated mechanisms may be involved.
 - a. True
 - b. False
2. Studies of bevacizumab in colon cancer patients demonstrate that the rate of bowel perforation ranges from _____.
 - a. 0 to 1 percent
 - b. 8 to 10 percent
 - c. 1 to 2 percent
 - d. 6 to 7 percent
3. In the first-line metastatic colorectal setting, the standard dose of bevacizumab for patients with colon cancer is _____.
 - a. 10 mg/kg every two weeks
 - b. 5 mg/kg every two weeks
 - c. 7.5 mg/kg every two weeks
 - d. None of the above
4. A comparison of results from the NSABP-C-07 and MOSAIC trials revealed a very similar absolute disease-free survival benefit of approximately _____ when oxaliplatin was added to 5-FU and leucovorin.
 - a. 3 percent
 - b. 5 percent
 - c. 8 percent
5. Following treatment with oxaliplatin, the probability of having debilitating residual neuropathy was _____ at 18 months according to data from the MOSAIC trial.
 - a. 5 percent
 - b. 0.5 percent
 - c. 3 percent
6. As adjuvant treatment of Stage III disease, the X-ACT trial found that the FDA-approved dose of capecitabine was at least equivalent to the Mayo Clinic regimen.
 - a. True
 - b. False
7. The status of chromosome 18q has strong prognostic value in patients with Stage II colorectal cancer.
 - a. True
 - b. False
8. Microsatellite instability (MSI) and TGF-beta mutation are associated with superior survival compared to survival among patients with MSI alone.
 - a. True
 - b. False
9. ECOG trial 5202 evaluates oxaliplatin plus 5-FU/LV with or without cetuximab in patients with Stage III colon cancer.
 - a. True
 - b. False
10. According to the ASCO guidelines, adjuvant chemotherapy should be discussed as an option in patients with Stage II colon cancer.
 - a. True
 - b. False
11. The CALGB-C80405 trial is a randomized Phase III trial evaluating FOLFOX or FOLFIRI plus bevacizumab versus _____ in patients with untreated advanced colorectal cancer.
 - a. FOLFOX or FOLFIRI plus cetuximab
 - b. FOLFOX or FOLFIRI plus bevacizumab and cetuximab
 - c. Both a and b
 - d. Neither a nor b

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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, and incorporate these data into management strategies in the local and advanced disease settings. 5 4 3 2 1 N/A
- Counsel appropriate patients about the availability of ongoing clinical trials. 5 4 3 2 1 N/A
- Evaluate the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients. 5 4 3 2 1 N/A
- Evaluate emerging research data on various neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer and explain the absolute risks and benefits of these regimens to patients. 5 4 3 2 1 N/A
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer. 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Herbert Hurwitz, MD	5 4 3 2 1	5 4 3 2 1
Peter C Enzinger, MD	5 4 3 2 1	5 4 3 2 1
Al B Benson III, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

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