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Colorectal Cancer™ UPDATE

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 appropriately selected patients about the availability of ongoing clinical trials.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including the use of oxaliplatin- and capecitabine-containing regimens, and explain the absolute risks and benefits of adjuvant chemotherapy 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 4 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Ellis, Philip, Diasio and Giantonio 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

Research To Practice designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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 **blue underlined text**.

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In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Ellis — Grants/Research Support and Consultant: ImClone Systems; Honorarium: Amgen Inc, Genentech BioOncology, Novartis Pharmaceuticals. **Dr Philip —** Grants/Research Support and Speakers Bureau: Genentech BioOncology, Pfizer Inc, Roche Laboratories Inc; Consultant: Bristol-Myers Squibb Company. **Dr Diasio —** Grants/Research Support: Roche Laboratories Inc, Sanofi-Aventis; Consultant, Honorarium and Speakers Bureau: Bristol-Myers Squibb Company, Genentech BioOncology, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis. **Dr Giantonio —** Speakers Bureau: Genentech BioOncology.

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UPCOMING EDUCATIONAL EVENTS

International Society of Gastrointestinal Oncology
2nd Annual Conference
July 14-16, 2005
Arlington, Virginia
Event website: **www.isgio.org**

2005 ASCO/AACR Workshop —
Methods in Clinical Cancer Research
July 30-August 5, 2005
Vail, Colorado
Event website: **www.vailworkshop.org**

47th Annual Meeting of American Society for
Therapeutic Radiology and Oncology
October 16-20, 2005
Denver, Colorado
Event website: **www.astro.org**

Colorectal Cancer: Molecular Pathways
and Therapies
October 19-23, 2005
Dana Point, California
Event website: **www.aacr.org/page3506.aspx**

AACR-NCI-EORTC International Conference:
Molecular Targets and Cancer Therapeutics
November 14-18, 2005
Philadelphia, Pennsylvania
Event website: **www.aacr.org/page3525.aspx**

2006 Gastrointestinal Cancers Symposium
January 26-28, 2006
San Francisco, California
Event website: **www.asco.org/meetings**

Editor's Note

Four aces

The first ace was dealt just after Thanksgiving when the NCI issued a press release indicating that ECOG trial E3200 demonstrated a survival advantage for the addition of bevacizumab to FOLFOX as second-line therapy for advanced colorectal cancer. The many oncologists who, over the course of 18 months, had already begun to adopt this regimen as first-line therapy collectively exhaled in quiet relief. In a subsequent interview for our lung cancer series, Eric Rowinsky boldly predicted that in five years, "VEGF inhibitors will be used across the board with all chemotherapy regimens."

A few months later, another ace slid across the table. It was March 13, and the NCI — about to enter the *Guinness Book of World Records* for the most clinical trial press releases in a year — told us that another ECOG study (E4599) demonstrated a survival advantage for the addition of bevacizumab to chemotherapy — this time in non-small cell lung cancer.

Alan Sandler, the principal investigator of E4599, was previously interviewed for our lung cancer series, and at that time, like an expectant father who has no idea of his baby's due date, Alan was waiting for the ECOG data monitoring committee to tell him when and whether this research concept would deliver.

A couple of months later, and just a few days after the NCI press release, I again interviewed Alan. The smile on his face had grown considerably since our last meeting. No wonder. It's been a long while since a study in this patient population resulted in a survival advantage. Based on these results, it may be that platinum-taxane-bev triplets will become the standard of care as first-line therapy for non-small cell lung cancer in the near future.

(From top left clockwise) Bruce Giantonio, Principal Investigator (PI) of ECOG-E3200 (interviewed in this issue of *Colorectal Cancer Update*); Alan Sandler, PI of ECOG-E4599 (*Lung Cancer Update* 3, 2005); Kathy Miller, PI of ECOG-E2100 (*Breast Cancer Update* 9, 2004), Edith Perez; PI of NCCTG-N9831 (*Breast Cancer Update* 4, 2005)

The third ace came just weeks later when the busy workers at the NCI press release factory jettisoned another bombshell: A third ECOG study (may the Force be with you, Jedi Sledge) met its primary endpoint by demonstrating a progression-free survival advantage for the addition of — you guessed it — bevacizumab to paclitaxel as first-line therapy for metastatic breast cancer. Strangely enough, just a few days earlier I was in Indianapolis recording an interview with Kathy Miller, the principal investigator of ECOG trial E2100, for our oncology nursing audio series. Here is a snippet of our conversation:

DR LOVE: You're the third car in the bevacizumab race. I just interviewed Alan Sandler about the bevacizumab lung trial a couple of weeks ago, so you're next and I say that it's going to happen.

DR MILLER: I am hoping so, but it's probably no surprise that the PI of the trial firmly believes it will be positive. Hopefully, this will not be yet another reminder that I can firmly believe something and be proven wrong.

DR LOVE: What's the latest in terms of when you think the data might be available?

DR MILLER: As the PI, I review all of the events, both good and bad, and to avoid any potential bias, all I'm allowed to know is that the study will be reviewed by the ECOG Data Monitoring Committee (DMC) at their next meeting, which is five days from today.

DR LOVE: Five days from now!

DR MILLER: Yes, and that is all I am allowed to know. After reviewing the data, they will give their recommendation as they always do.

DR LOVE: Is this a planned review?

DR MILLER: Yes, and their recommendation could be to continue to follow the patients as per protocol, or to release the data — either because of clearly positive or clearly negative results.

DR LOVE: Theoretically, have enough events occurred so that if the trial is positive, we would know it?

DR MILLER: I am not allowed to know that. The ECOG operations and statistical folks are appropriately fanatical about avoiding any potential for bias. This is the first efficacy review. The other reviews have been only on the toxicity data, and they have always indicated no toxicity concerns and that the trial should continue.

DR LOVE: I see a late-breaking ASCO thing in your future.

DR MILLER: Deadlines are not favorable for that this year.

DR LOVE: Forget deadlines.

DR MILLER: I'm holding out hope for the San Antonio meeting later this year, Neil, because if the DMC at this meeting suggests that the results should be made public, then we'll have that data in time for that deadline. I must say that I am truly sick of people calling and saying, "When? When?" and I'm sure that the ECOG statisticians are equally tired of my calling

and emailing them. But it's likely that within a week or two after that DMC meeting, I'll hear whether the results tell us something other than to continue on and keep waiting.

Kathy's wait ended soon after that and, deadlines aside, she did in fact present these data in Orlando to the multitudes at ASCO. In the interview, she discussed a pilot trial evaluating bevacizumab in the adjuvant breast cancer setting, and clearly the momentum to study this question will now increase considerably.

Finally, on April 26, after fervently committing to take the day off for my birthday, I succumbed to temptation and checked my email. Sure enough, the fourth and most spectacular ace had just been dealt, and Edith Perez's "heads up" in an interview just published in *Breast Cancer Update* had come to pass. In what is destined to be one of the sentinel moments in clinical cancer research, the NCI press release gremlins let us know that the combined analysis of the NSABP and Intergroup adjuvant trastuzumab breast cancer trials demonstrated a whopping 52 percent reduction in relapse rate for patients receiving trastuzumab. Edward Romond presented this at ASCO soon after Kathy's presentation.

Notwithstanding the Monday morning quarterbacking that this monumental data set will generate, because of the tens of thousands of patients with HER2-positive disease who were not offered off-protocol trastuzumab, this study will be viewed by some as the "end of the beginning" of the war on cancer. Or is it the beginning of the end? This unprecedented quartet of clinical trial results will undoubtedly be discussed endlessly at CME meetings and tumor boards internationally, and the impact on the daily management of patients with these three most common solid tumors will be immediate and dramatic.

In this program, Bruce Giantonio reviews the first of the four studies, ECOG-E3200, and Lee Ellis, Philip Philip and Bob Diasio weigh in on what these data and other recent trial results mean for clinical practice and future research. Cancer patients and their oncologists needed a morale boost after what has seemed to be glacier-like progress in this devastating disease. With these four spectacular aces in hand, it's time to put down some serious money on prospects for the future.

— Neil Love, MD
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NCI press releases

Bevacizumab Combined with Oxaliplatin-Based Chemotherapy Prolongs Survival for Previously Treated Patients with Advanced Colorectal Cancer: **www.nci.nih.gov/newscenter/pressreleases/BevacizumabOxaliplatin**

Bevacizumab Combined with Chemotherapy Prolongs Survival for Some Patients with Advanced Lung Cancer: **www.nci.nih.gov/newscenter/pressreleases/AvastinLung**

Bevacizumab Combined with Chemotherapy Improves Progression-Free Survival for Patients with Advanced Breast Cancer: **www.nci.nih.gov/newscenter/pressreleases/AvastinBreast**

Herceptin® Combined with Chemotherapy Improves Disease-Free Survival for Patients with Early-Stage Breast Cancer: **www.nci.nih.gov/newscenter/pressreleases/HerceptinCombination2005**

Potential mechanism of action of anti-VEGF therapy

Now that bevacizumab is approved as front-line therapy for colorectal cancer in combination with intravenous 5-FU, ongoing laboratory experiments are attempting to determine its mechanism of action. Most believe it is anti-angiogenic; however, recent papers from Harvard and Massachusetts General Hospital have shown that anti-VEGF therapy can normalize the tumor vasculature.

Normal vasculature is efficient, whereas abnormal tumor vasculature is inefficient. Rakesh Jain demonstrated that approximately five days after anti-VEGF therapy was administered to a mouse, abnormal tumor vasculature became more normalized (Winkler 2004). From a laboratory perspective, I believe a biphasic response occurs with anti-VEGF therapy. Initially, it may help the delivery of chemotherapy, and in the long term it may be truly anti-angiogenic.

Jain has hypothesized that an early window of opportunity exists for enhancing the uptake of chemotherapy or oxygen for radiation therapy. One of the advantages of bevacizumab is that it has a long half-life. After administering one dose of bevacizumab, the half-life is approximately 20 days, so if bevacizumab is combined with intravenous 5-FU, FOLFOX, FOLFIRI or other agents, we're likely to hit that window of opportunity, resulting in true enhancement of the effects of chemotherapy.

Bevacizumab in combination therapy

At ASCO 2004, it was reported that bevacizumab improved the efficacy of 5-FU/leucovorin in patients with first-line metastatic colorectal cancer who were not ideal candidates to receive irinotecan (Kabbinavar 2004, 2005a, 2005b). The study did not reach its primary endpoint in overall survival because too few patients were enrolled; however, approximately a four-month improvement in overall and progression-free survival was seen, which was statistically significant and similar to that seen in other trials.

Giantonio presented data demonstrating that bevacizumab improved the efficacy of FOLFOX (Giantonio 2005a, 2005b). Clinical trials have also shown

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that anti-VEGF therapy — bevacizumab being the most studied — also improves the effects of IFL (Hurwitz 2004). We assume it would also improve the efficacy of FOLFIRI. Since we aren't sure of the mechanism of action of anti-VEGF therapy, we don't know whether bevacizumab would be better with one agent versus another.

One interesting study reported at the ASCO GI meeting this year is BOND-2, which is a randomized Phase II trial of cetuximab/bevacizumab/irinotecan versus cetuximab/bevacizumab in irinotecan-refractory colorectal cancer (Saltz 2005a, 2005b). It will be interesting to see whether bevacizumab can improve the effects of cetuximab — two biologic agents — without any chemotherapy in the second-line setting.

Combination of anti-VEGF therapy with chemotherapy to enhance the effects of radiation therapy in the neoadjuvant rectal cancer setting

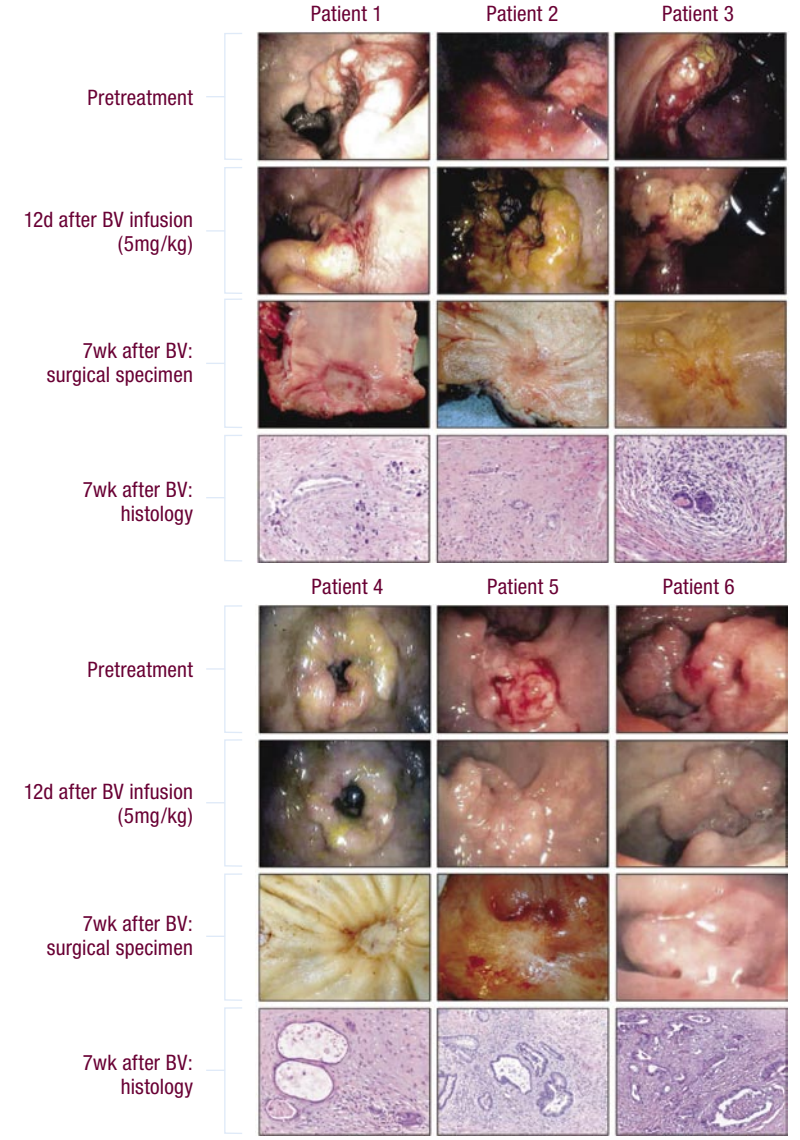
To most patients, sphincter preservation is extremely important. Many patients will accept a therapy with a higher risk of recurrence in order to maintain sphincter function and avoid a colostomy. In residency, I learned that life with a colostomy is greatly overrated. Patients will travel far and consult with numerous surgeons in order to find one who will try to save their sphincter. Unfortunately, if a tumor clearly involves the sphincter, little can be done to save the sphincter mechanism.

For these reasons, the advent of neoadjuvant chemoradiation therapy followed by sphincter preservation surgery is critically important. In a clinical trial conducted by Willett at Massachusetts General Hospital, bevacizumab was used with 5-FU to enhance the effects of radiation therapy preoperatively (Willett 2004a). In 2004, Willett published in *Nature Medicine* photos of the responses that were obtained with this novel regimen (1.1, 1.2; pages 8-9). All six patients had a near-complete response, and there was just a little ulcer remaining where the tumor was before.

The concept of adding bevacizumab is being expanded upon by Willett and other institutions, such as MD Anderson and Sloan-Kettering. At ASCO in 2004, Willett presented follow-up data with approximately 11 patients, and they all appear to have a better gross clinical response than we would expect with only microscopic patches of tumor cells remaining (Willett 2004b).

The overall analysis hasn't been done, and this is a very small number of patients. However, we should follow this in the future and see if with a larger number of patients we continue to observe this excellent pathologic response to the combination of anti-VEGF therapy, chemotherapy and radiation therapy.

1.1 Tumor Response to Preoperative Bevacizumab Alone Followed by Bevacizumab, 5-FU and Radiation Therapy

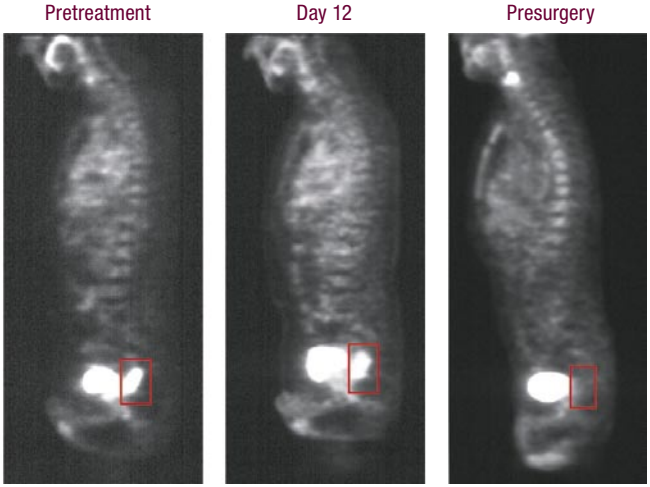


BV = bevacizumab

Endoscopic and pathologic evaluation of rectal tumors before treatment, 12 days after bevacizumab alone and 6 to 7 weeks after completion of bevacizumab concurrent with 5-FU and radiation therapy. Surgical specimens showed Grade II tumor regression in patients 1 through 5 and Grade III in patient 6, by Mandard criteria.

SOURCE: Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004a;10(2):145-7. **Abstract**

1.2 Tumor Response to Preoperative Bevacizumab Alone Followed by Bevacizumab, 5-FU and Radiation Therapy



Tumor FDG uptake before treatment (pretreatment), 12 days after bevacizumab alone and six to seven weeks after completion of bevacizumab concurrent with 5-FU and radiation therapy (presurgery). Sagittal projections of FDG-PET scans for patient 1 are shown. Tumor is outlined in box, posterior to bladder.

SOURCE: Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004a;10(2):145-7. **Abstract**

Laparoscopically assisted versus open colectomy

Laparoscopic surgery is safe when performed by an experienced surgeon. From a patient's perspective, it is critical to use a surgeon who has been trained in this technique or has performed at least 50 cases. Many of us in academic centers don't typically see patients with early-stage tumors, and for that reason have fewer patients undergoing laparoscopically assisted colectomy than in community practices.

Laparoscopically assisted colectomy has taught us that we can remove the colon through a smaller incision, and we believe patients recover better with smaller incisions. When performing an open colectomy, we now make smaller incisions and use retractors more efficiently. However, a study published in the *New England Journal of Medicine*, which randomly assigned patients to laparoscopically assisted versus open colectomy, reported a surprising variability in the length of incisions in both groups, ranging from two or three centimeters, respectively, to 35 centimeters (Clinical Outcomes of Surgical Therapy Study Group 2004).

While I believe the open technique is safer, I respect the opinions of the physicians who are experts in laparoscopic surgery. Laparoscopically assisted colectomy is preferable in some cases, such as in an elderly patient with a poor performance status who has a small tumor in the sigmoid colon or right colon. The laparoscopic surgery requires more time in the operating room, but an experienced surgeon can perform these cases relatively quickly.

I am more comfortable with the open technique because it allows me to palpate around the abdomen. We can do a laparoscopic ultrasound of the liver and run the bowel, but to me, nothing compares to that tactile sensation. Sometimes I can feel a lymph node at the base of the mesentery that can't be seen, or I feel things on the liver that I may not see with a laparoscope. Tactile sensation is important to get a good feel for the location of the tumor, the lymph nodes and anything else that may be going on in the abdomen.

Select publications

Alekshun T, Garrett C. **Targeted therapies in the treatment of colorectal cancers.** *Cancer Control* 2005;12(2):105-10. **Abstract**

Clinical Outcomes of Surgical Therapy Study Group. **A comparison of laparoscopically assisted and open colectomy for colon cancer.** *N Engl J Med* 2004;350(20):2050-9. **Abstract**

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.** *Proc ASCO GI Cancers Symposium* 2005a;**Abstract 169a**.

Giantonio BJ et al. **High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO* 2005b;**Abstract 2**.

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

Hurwitz HI et al. **Bevacizumab in combination with Fluorouracil and leucovorin: An active regimen for first-line metastatic colorectal cancer.** *J Clin Oncol* 2005;23(15):3502-8. **Abstract**

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 FF et al. **Combined analysis of efficacy: The addition of Bevacizumab to Fluorouracil/Leucovorin Improves Survival for Patients With Metastatic Colorectal Cancer.** *J Clin Oncol* 2005;23(16):3706-12. **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* 2005a;**Abstract 169b**.

Saltz LB et al. **Randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** *Proc ASCO* 2005b;**Abstract 3508**.

Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004a;10(2):145-7. **Abstract**

Willett CG et al. **Phase I study of neoadjuvant bevacizumab, 5-fluorouracil, and radiation therapy followed by surgery for patients with primary rectal cancer.** *Proc ASCO* 2004b;**Abstract 3589**.

Winkler F et al. **Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: Role of oxygenation, angiopoietin-1, and matrix metalloproteinases.** *Cancer Cell* 2004;6(6):553-63. **Abstract**

Philip A Philip, MD, PhD

EDITED COMMENTS

Role of adjuvant capecitabine: Implications of the X-ACT trial

The X-ACT adjuvant trial confirmed what was already known about capecitabine — it is as good as or even better than 5-FU/leucovorin (Cassidy 2004, 2005; Twelves 2005). The X-ACT adjuvant trial also informed us that we should be using capecitabine as an active chemotherapy agent. However, it's not an oral agent that we can administer to a patient and then forget about. The adjuvant dose we start is 2.5 g/m^2 per day (days one to 14 of a 21-day cycle), not 2 g/m^2 per day as we use for metastatic disease.

In situations in which a single-agent fluoropyrimidine is being used or contemplated, capecitabine should be used. I don't believe at this time that, if given the option, a patient will opt for intravenous treatment unless an issue arises regarding who will pay for the capecitabine. Capecitabine should be the drug of choice for patients who will receive a single-agent fluoropyrimidine, because it's easier to administer and doesn't interfere much with the patient's daily routine. It has side effects, and we have to pay attention to them. But overall, it's a treatment that patients will prefer.

In which patients should we use single-agent therapy? In patients with Stage III disease, the data on adjuvant FOLFOX have completely transformed my practice (Andre 2004). I use FOLFOX in patients with Stage III disease, except in those who refuse the combination, cannot take a neurotoxic drug or are too old for such a combination. Those patients who don't receive adjuvant FOLFOX receive single-agent capecitabine. The next question becomes: Can we combine capecitabine with oxaliplatin? Adjuvant CAPOX is still experimental, and it should be used as part of a clinical trial. We still have to wait for the head-to-head comparison with FOLFOX.

For patients with Stage II disease, it becomes more interesting. You may still want to use adjuvant FOLFOX, although in the original European trial, less benefit was seen in patients with Stage II disease (Andre 2004). In general, our nonprotocol approach in patients with Stage II disease is to use single-agent

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capecitabine. We're increasingly administering adjuvant chemotherapy in patients with Stage II disease, and capecitabine is our drug of choice.

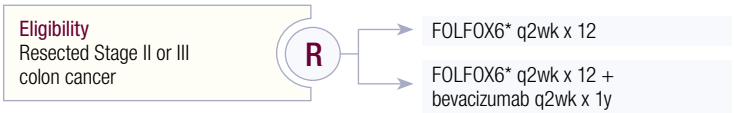
NSABP-C-08: Phase III randomized trial of adjuvant FOLFOX with or without bevacizumab in patients with resected Stage II or III colon cancer

The specific question being asked by NSABP-C-08 (2.1) relates to the use of bevacizumab. The duration of therapy with bevacizumab is also of interest in this study because it continues after adjuvant chemotherapy for another six months. The rationale for that remains to be seen, because we don't know whether we should use it for six months, 12 months or 24 months. Does adjuvant bevacizumab have a benefit beyond that associated with adjuvant chemotherapy? Does bevacizumab alone have any activity?

We also have to evaluate the toxicity associated with this regimen because of what we've seen with bevacizumab. NSABP-C-08 is a good trial because the best use of bevacizumab might be early in the natural history of the disease. This may be the way to go, but one of the concerns with the regimen is, obviously, toxicity. We'll need to see what happens.

2.1 Phase III Randomized Study of Adjuvant FOLFOX with or without Bevacizumab in Patients with Resected Stage II or III Colon Cancer

Protocol ID: NSABP-C-08
Target Accrual: 2,632 (Open)



* Modified FOLFOX6

Study Contact:
Carmen Allegra, MD
Email: callegra@nmcr.com
National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Data Query, May 2005.

NSABP-R-04: Phase III randomized trial in patients with rectal cancer of neoadjuvant chemoradiation therapy with capecitabine versus intravenous 5-FU/leucovorin with or without oxaliplatin

I have mixed thoughts with respect to the first randomization in NSABP-R-04 because I already use capecitabine with radiation therapy. We started using this at our institution several years ago when there weren't any protocols available. We reviewed and published our experience confirming the safety of this approach (Vaishampayan 2002); therefore, we have been using capecitabine routinely in these patients off protocol.

I am interested in the second randomization in the trial using oxaliplatin. I have started using that in combination with radiation therapy in some, but not all, patients. For example, I have used oxaliplatin in healthier patients with a better performance status and in patients with whom I have special concerns about not being able to preserve the sphincter, where I want to obtain a maximum pathologic response.

Clinical approach to the management of patients with metastatic disease

At our institution, we evaluated the combination of capecitabine and oxaliplatin (CAPOX). At this time, our front-line nonprotocol treatment approach includes bevacizumab and CAPOX. Granted, no Phase III trial data are available comparing CAPOX to FOLFOX.

However, in the metastatic disease setting, taking into account the convenience for patients of receiving an oral agent instead of continuous infusion 5-FU, we feel that CAPOX would be better than FOLFOX. I probably would not make the same comment for adjuvant therapy. But in the metastatic disease setting, my approach would be bevacizumab plus CAPOX.

For patients with disease that has progressed on an oxaliplatin-based treatment, we move to an irinotecan-based therapy. The question becomes: Do we use irinotecan as a single agent or in combination with a fluoropyrimidine (eg, capecitabine or 5-FU/leucovorin)? The third- or fourth-line options would be any of the above with or without cetuximab.

Select publications

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

Cassidy J et al. **Analysis of post-study chemotherapy in patients (pts) enrolled in the X-ACT phase III trial of capecitabine (X) vs bolus 5-FU/LV as adjuvant therapy for Dukes' C colon cancer: No differences in treatment arms that could influence survival outcome.** *Proc ASCO* 2005;**Abstract 3586**.

Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** *Proc ASCO* 2004;**Abstract 3509**.

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.** *Proc ASCO GI Cancers Symposium* 2005;**Abstract 169a**.

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

Twelves C et al. **Updated efficacy findings from the X-ACT phase III trial of capecitabine (X) vs bolus 5-FU/LV as adjuvant therapy for patients (pts) with Dukes' C colon cancer.** *Proc ASCO* 2005;**Abstract 3521**.

Vaishampayan UN et al. **A single-institution experience with concurrent capecitabine and radiation therapy in gastrointestinal malignancies.** *Int J Radiat Oncol Biol Phys* 2002;53(3):675-9. **Abstract**

Clinical trials of adjuvant therapy for colorectal cancer

The MOSAIC trial

The MOSAIC trial (de Gramont 2003) randomly assigned Stage II and III patients to the FOLFOX4 regimen with oxaliplatin as opposed to the typical infusional 5-FU/leucovorin regimen used in France.

This multinational study demonstrated almost a 25 percent reduction in the rate of metastasis in patients with Stage III disease who received the FOLFOX regimen.

We now have longer follow-up data from the MOSAIC trial (Andre 2004; de Gramont 2005; [3.1]). While the data for Stage II disease are still not statistically significant, the data in patients with Stage III are even better, and we're beginning to approach the parameters to evaluate overall survival data. A definite improvement with FOLFOX was shown in the MOSAIC trial, and based on these data, the FDA approved this regimen as adjuvant therapy in Stage III disease.

The X-ACT trial

The other adjuvant study we should note is the X-ACT trial, which compared capecitabine 1,250 mg/m^2 bid versus the Mayo Clinic 5-FU/leucovorin regimen in patients with resected Dukes' C colon cancer. This is an intriguing study because it addresses the clinical issue of using oral 5-FU for patients who are in relatively good health, have a good performance status and who oftentimes can continue to work. For them, the option of using an oral agent rather than intravenous therapy is very attractive.

Overall survival cannot be evaluated at this point, but disease-free survival was superior for patients on the capecitabine arm (Cassidy 2004; [3.2]). The *p*-value was approximately 0.05, bordering significance, as did the hazard ratio with the confidence intervals approaching the 1.00 mark but not crossing it. That's important because it suggests that this is a statistically significant effect.

Dr Diasio is a Professor of Medicine (Hematology/Oncology) and Pharmacology/Toxicology and Genetics, Associate Director for Basic Sciences at UAB Comprehensive Cancer Center, Chairman of the Department of Pharmacology and Toxicology and the Newman H Waters Professor and Director, Division of Clinical Pharmacology at the University of Alabama Birmingham, in Birmingham, Alabama.

3.1 MOSAIC Adjuvant Trial: Disease-Free and Overall Survival at Four Years

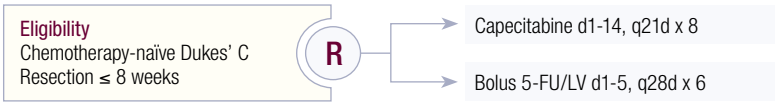
Endpoint	FOLFOX4 (n = 1,123)	5-FU/LV (n = 1,123)	HR (95% CI)	*p*-value
DFS (%)				
All	76.4	69.8	0.77 (0.65-0.90)	<0.001
Stage III	69.7	61.0	0.75 (0.62-0.89)	
Stage II	85.1	81.3	0.82 (0.60-1.13)	
OS (%)				
All	84.9	82.8	0.91 (0.75-1.11)	

HR = hazard ratio; CI = confidence interval; DFS = disease-free survival; OS = overall survival

SOURCE: de Gramont A et al. **Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: Efficacy results with a median follow-up of 4 years.** Presentation. ASCO 2005;**Abstract 3501**.

3.2 X-ACT Study: Randomized Phase III Adjuvant Trial Comparing Capecitabine to Bolus 5-FU/Leucovorin in Patients with Dukes' C Colon Cancer

Protocol IDs: X-ACT, ROCHE-M66001, NCT00009737
Accrual: 1,987 (Closed)



Efficacy data	Capecitabine (n = 1,004)	5-FU/LV (n = 983)	HR (95% CI)	*p*-value
Primary endpoint				
3-year DFS	64.2%	60.6%	0.87 (0.75-1.00)	0.0528
Secondary endpoint				
3-year RFS	65.5%	61.9%	0.86 (0.74-0.99)	0.0407
3-year OS	81.3%	77.6%	0.84 (0.69-1.01)	0.0706

LV = leucovorin; HR = hazard ratio; CI = confidence interval; DFS = disease-free survival; RFS = relapse-free survival; OS = overall survival

SOURCES: Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** *Proc ASCO* 2004;**Abstract 3509**; NCI Physician Data Query, May 2005.

ASCO paper on adjuvant therapy in Stage II disease

Typically, patients with no evidence of lymph node involvement, no matter how deeply the tumor appears to extend, do not receive chemotherapy for Stage II disease. However, increasing data suggest that some patients with penetration of the intestinal wall, who would not have been treated in the past, may benefit from chemotherapy.

The ASCO committee published an aggressive position paper stating that perhaps these patients should be offered adjuvant therapy (Benson 2004). While we don't

have any convincing objective data to validate the use of adjuvant therapy in Stage II disease, subsets within that population may benefit. The ultimate proof of the benefit in such patients will come from ongoing adjuvant studies.

One reason it may be difficult to demonstrate a benefit from adjuvant therapy in Stage II disease is that fewer events occur. However, the MOSAIC trial and some of the earlier Intergroup studies have suggested certain patients can benefit from chemotherapy.

I believe we're at the point now that with consideration of the tumor's histologic characterization, the localization, whether it's in the right or left side of the colon, the occurrence of methylation, microsatellite instability, TS, p53 and various other new markers being identified that we may be able to identify subsets that will benefit from adjuvant therapy.

Capecitabine/oxaliplatin in the adjuvant setting

The MOSAIC trial was reported in 2003 and led to the FDA approval of FOLFOX4 for adjuvant therapy in Stage III disease. The X-ACT trial data were reported in 2004, and we expect capecitabine will be approved in this setting also. At this time, FOLFOX appears to be superior, and that might limit the overall use of capecitabine.

However, down the road, with the availability of oxaliplatin in the practice setting, practitioners may begin to do what they did in advanced disease — use CAPOX. The CAPOX regimen is very appealing to a number of oncologists and patients, but we have no data on that combination in the adjuvant setting.

Adjuvant therapy in the nonprotocol setting

While some clinicians are still using 5-FU/leucovorin in the adjuvant setting, now that FOLFOX has been approved, I believe we'll see a change in treatment patterns in the adjuvant setting just as we've seen in advanced disease. Whether adjuvant 5-FU/leucovorin without oxaliplatin is justifiable depends on the individual patient.

For example, for an elderly patient unable to take oxaliplatin, 5-FU/leucovorin could be considered. That's also a situation in which capecitabine might have a role, based on the X-ACT study, which provides strong evidence that capecitabine is better than 5-FU/leucovorin in the adjuvant setting.

However, I believe that for the majority of patients who have reasonable performance status and are in excellent health, it's preferable to use adjuvant FOLFOX. Capecitabine as adjuvant therapy for patients with Stage II disease is appealing because it's an oral agent, and given the ASCO position paper on treating Stage II disease, I foresee increased use of this. We just don't have the clinical data at this point.

Select publications

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

Benson AB III et al. **American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer.** *J Clin Oncol* 2004;22(16):3408-19. **Abstract**

Cassidy J et al. **Analysis of post-study chemotherapy in patients (pts) enrolled in the X-ACT phase III trial of capecitabine (X) vs bolus 5-FU/LV as adjuvant therapy for Dukes' C colon cancer: No differences in treatment arms that could influence survival outcome.** *Proc ASCO* 2005;**Abstract 3586**.

Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** *Proc ASCO* 2004;**Abstract 3509**.

Chau I et al. **A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer.** *Ann Oncol* 2005;16(4):549-57. **Abstract**

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

de Gramont A et al. **Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: Efficacy results with a median follow-up of 4 years.** *Proc ASCO* 2005;**Abstract 3501**.

Diaz-Rubio Garcia E et al. **A panel discussion of controversies and challenges in the adjuvant treatment of colon cancer.** *Clin Transl Oncol* 2005;7(1):3-11. **Abstract**

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.** *Proc ASCO GI Cancers Symposium* 2005;**Abstract 169a**.

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

Hobday TJ. **An overview of approaches to adjuvant therapy for colorectal cancer in the United States.** *Clin Colorectal Cancer* 2005;5(Suppl 1):11-8. **Abstract**

O'Connell MJ et al. **Durable improvement in disease-free survival (DFS) and overall survival (OS) for stage II or III colon cancer treated with leucovorin-modulated fluorouracil (FL): 10-year follow-up of National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol C-03.** *Proc ASCO* 2005;**Abstract 3511**.

Poplin EA et al. **Phase III Southwest Oncology Group 9415/Intergroup 0153 randomized trial of fluorouracil, leucovorin, and levamisole versus fluorouracil continuous infusion and levamisole for adjuvant treatment of stage III and high-risk stage II colon cancer.** *J Clin Oncol* 2005;23(9):1819-25. **Abstract**

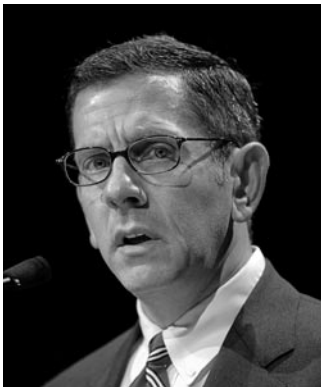
Sargent DJ, Adjuvant Colon Cancer Endpoints (ACCENT) Group. **Endpoints for Colon Adjuvant Clinical Trials (CACT): Recommendations based on individual patient data (IPD) from 20898 patients (pts) and 18 randomized trials.** *Proc ASCO* 2005;**Abstract 3512**.

Schmoll HJ et al. **Early safety findings from a phase III trial of capecitabine plus oxaliplatin (XELOX) vs bolus 5-FU/LV as adjuvant therapy for patients (pts) with stage III colon cancer.** *Proc ASCO* 2005;**Abstract 3523**.

Twelves C et al. **Updated efficacy findings from the X-ACT phase III trial of capecitabine (X) vs bolus 5-FU/LV as adjuvant therapy for patients (pts) with Dukes' C colon cancer.** *Proc ASCO* 2005;**Abstract 3521**.

van Cutsem E et al. **Oral capecitabine: Bridging the Atlantic divide in colon cancer treatment.** *Semin Oncol* 2005;32(1):43-51. **Abstract**

ECOG-E3200: FOLFOX4 with bevacizumab versus FOLFOX4 versus bevacizumab in patients with previously treated advanced colorectal cancer



Safety

We did not observe any unexpected toxicities with the use of bevacizumab. One of the key things to keep in mind about ECOG-E3200 is that we used a higher dose of bevacizumab (10 mg/kg every two weeks) than has been reported in any of the colorectal cancer studies, except for that first trial by Dr Kabbinavar (Kabbinavar 2003). ECOG-E3200 demonstrated statistically significant increases in nausea, vomiting and neuropathy in the bevacizumab arm (Giantonio 2005b), which were probably due to these patients staying on treatment longer because of the addition of bevacizumab.

I don't believe bevacizumab is enhancing these side effects; rather, it's just allowing the patients to stay on treatment longer. We observed about a 15 percent incidence of Grade III neuropathy in the patients treated with FOLFOX4 and bevacizumab compared to nine percent in the patients treated with FOLFOX4 alone (Giantonio 2005b).

We observed bowel perforations in ECOG-E3200 similar to what was reported by Dr Hurwitz (Hurwitz 2004). We saw three cases in the patients treated with FOLFOX4 plus bevacizumab, three cases in the patients treated with bevacizumab alone and no cases in the patients treated with FOLFOX4 alone. Four of our six cases of perforation occurred within the first cycle of therapy, which is different from Dr Hurwitz's experience. In his IFL plus bevacizumab study, there was no association with time on treatment and the development of the perforation.

Efficacy

In October 2004, an interim analysis was conducted and presented to the ECOG Data Monitoring Committee. Based on their review, they recommended the release of the study data. At the Data Monitoring Committee's meeting, a statistically significant (p = 0.0024) improvement in median overall survival

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— the primary endpoint of the trial — was reported. The patients who received FOLFOX4 plus bevacizumab had a median overall survival of 12.5 months compared to 10.7 months for those treated with FOLFOX4 alone. The hazard ratio was 0.74; patients treated with bevacizumab in combination with FOLFOX had a 26 percent reduction in the risk of death (Giantonio 2005a; [4.1, 4.2]).*

It was recognized that these data were important because FOLFOX has evolved as front-line therapy for patients with metastatic colorectal cancer in the United States. Even though ECOG-E3200 is a study of second-line therapy, it makes many of us more comfortable in extrapolating these data to the front-line setting.

4.1 ECOG-E3200: Efficacy and Toxicity Results of High-Dose Bevacizumab Combined with FOLFOX4 versus FOLFOX4 at 28-Month Follow-Up

Efficacy data	FOLFOX4 + bevacizumab (n = 289)	FOLFOX4 (n = 290)	HR	*p*-value
Overall response Complete response Stable disease	21.8% 1.9% 51.7%	9.2% 0.7% 45.0%		$p < 0.0001$
Median overall survival (months)	12.9	10.8	0.76	0.0018
Median PFS (months)	7.2	4.8	0.64	$p < 0.0001$

HR = hazard ratio

	FOLFOX4 + bevacizumab (n = 287)		FOLFOX4 (n = 284)		
Toxicity data	Grade III	Grade IV	Grade III	Grade IV	*p*-value
Hypertension	5%	1%	2%	<1%	0.018
Bleeding	3%	<1%	<1%	0%	0.011
Neuropathy	16%	<1%	9%	<1%	0.016
Venous thrombosis	9%	1%	3%	4%	0.46
Cardiac ischemia	1%	2%	0%	1%	
Cerebrovascular ischemia	1%	0%	0%	0%	0.62*

* Cardiac and cerebrovascular ischemia combined

SOURCE: Giantonio BJ et al. **High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** Presentation. ASCO 2005b;**Abstract 2**.

** Data discussed in the interview reflect data presented at ASCO GI 2005. Updated data presented at ASCO 2005 are shown in 4.1.*

Clinical implications of ECOG-E3200

I think ECOG-E3200 adds very strongly to the existing data that bevacizumab in combination with FOLFOX, as first-line therapy, should further improve median overall survival. Given what we can accomplish with chemotherapy alone using FOLFOX and FOLFIRI, as demonstrated by Dr Tournigand (Tournigand 2004), conceivably, we can anticipate starting to move the median overall survival to two or more years. That is remarkable when just four years ago the median overall survival was about 12 months for the control arm of 5-FU/leucovorin in the IFL study (Saltz 2000).

In patients with metastatic disease, I generally start with FOLFOX plus bevacizumab. When they progress, I switch to FOLFIRI, and based on their insurance, I keep them on bevacizumab. When using FOLFIRI plus bevacizumab, I had been using a dose of 5 mg/kg; however, based on the results from ECOG-E3200, I'll probably try to increase the dose to 10 mg/kg if I can obtain approval from the patient's insurance company.

In terms of the management of some of the concerning side effects, particularly bowel perforation, I think it shouldn't deter clinicians from using bevacizumab. All these perforations presented with abdominal pain. I think we just have to be a bit more vigilant in our evaluation. With prompt intervention, the bowel perforation can be effectively managed.

4.2 Conclusions from ECOG Study E3200

"In conclusion, bevacizumab given at 10 mg/kg in combination with FOLFOX4 improves overall survival, progression-free survival and response for previously treated patients with advanced colorectal cancer.

"Bevacizumab and FOLFOX4 is well tolerated. Hypertension, bleeding and vomiting are associated with the combination. Bowel perforation occurred infrequently but only in bevacizumab-treated patients. An increase in sensory neuropathy may be related to time on treatment.

"Bevacizumab appears to be inactive when used as a single agent in the previously treated population."

SOURCE: Giantonio BJ et al. **High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** Presentation. ASCO 2005b;**Abstract 2**.

Regimens of bevacizumab in combination with oxaliplatin or irinotecan

The magnitude of benefit for FOLFOX4 with bevacizumab in ECOG-E3200 was about two months (Giantonio 2005a, 2005b), and the magnitude of benefit for IFL with bevacizumab, as reported by Dr Hurwitz, was a little more than four

months (Hurwitz 2004). The important difference was that IFL was being used as first-line therapy.

A randomized Phase III study being conducted in Europe will ask a survival question for the addition of bevacizumab to FOLFOX in the first-line setting. If the magnitude of benefit is the same, I think that will add to the data set indicating that it is important for bevacizumab to be administered with chemotherapy.

One of the intriguing hypotheses, at least in colorectal cancer, is that the benefit seen with the addition of bevacizumab may be independent of the specific chemotherapy used. A number of mechanisms have been proposed to help explain the benefit associated with bevacizumab. One is that there may be improved chemotherapy delivery into the tumor, resulting in a higher tumor kill. There's some merit to that, and emerging clinical data support it.

Dr Willett has looked at the changes in microvascular density and interstitial pressures in tumors from patients who have received bevacizumab. The patients underwent colonoscopy to have the measurements performed on the tumor, received a single dose of bevacizumab and 12 days later had a second colonoscopy to have those measurements repeated (Willett 2004a, 2004b).

In his study, we saw both a reduction in microvascular density and an improvement in interstitial pressures, which enhances the flow through the tumor and potentially allows greater drug delivery into the tumor.

Select publications

Giantonio BJ. **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 Cancers Symposium 2005a;**Abstract 169a**.

Giantonio BJ et al. **High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO* 2005b;**Abstract 2**.

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

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

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

Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004a;10(2):145-7. **Abstract**

Willett CG et al. **Phase I study of neoadjuvant bevacizumab, 5-fluorouracil, and radiation therapy followed by surgery for patients with primary rectal cancer.** *Proc ASCO* 2004b;**Abstract 3589**.

Post-test:

Colorectal Cancer Update — Issue 4, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In a Phase I clinical trial, combining bevacizumab with 5-FU enhanced the effects of preoperative radiation therapy.
   a. True
   b. False

2. A study published in the *New England Journal of Medicine*, which randomly assigned patients to laparoscopically assisted versus open colectomy, reported that the length of incisions in both groups ranged from three centimeters to 35 centimeters.
   a. True
   b. False

3. The X-ACT adjuvant trial confirmed that the benefits of _____ are comparable to or greater than 5-FU/leucovorin.
   a. FOLFOX
   b. FOLFIRI
   c. Capecitabine
   d. Both a and b
   e. None of the above

4. NSABP-C-08 will compare adjuvant _____ with or without bevacizumab.
   a. FOLFOX
   b. FOLFIRI
   c. Capecitabine
   d. Both a and b
   e. None of the above

5. A recently published ASCO position paper stated that adjuvant chemotherapy is currently contraindicated for all patients with Stage II disease.
   a. True
   b. False

6. Based on a three-year disease-free survival benefit demonstrated in the MOSAIC trial, FOLFOX is now frequently used as an adjuvant therapy option for patients with Stage III colorectal cancer.
   a. True
   b. False

7. The FDA approved which dose of bevacizumab every two weeks to be used first line with any intravenous 5-FU-containing regimen in patients with advanced colon cancer?
   a. 5 mg/m^2
   b. 7.5 mg/m^2
   c. 10 mg/m^2

8. ECOG-E3200 demonstrated that patients treated with bevacizumab plus FOLFOX4 had a better overall median survival than patients treated with _____.
   a. Bevacizumab plus IFL
   b. FOLFOX4 alone
   c. Cetuximab plus FOLFOX4
   d. Cetuximab plus IFL

9. ECOG-E3200 evaluated which dose of bevacizumab?
   a. 2.5 mg/kg
   b. 5 mg/kg
   c. 10 mg/kg
   d. 15 mg/kg

10. NSABP trial R-04 will evaluate neoadjuvant chemoradiation therapy with capecitabine versus intravenous 5-FU/leucovorin with or without _____ in patients with rectal cancer.
    a. Irinotecan
    b. Bevacizumab
    c. Oxaliplatin
    d. Celecoxib

11. In ECOG-E3200, which of the following Grade III/IV adverse events occurred more frequently in patients who received FOLFOX4 plus bevacizumab?
    a. Hypertension
    b. Bleeding
    c. Neuropathy
    d. a and b
    e. a, b and c

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

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To what extent does this issue of *CCU* address the following 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 appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including the use of oxaliplatin- and capecitabine-containing regimens, and explain the absolute risks and benefits of adjuvant chemotherapy 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
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Philip A Philip, MD, PhD	5 4 3 2 1	5 4 3 2 1
Robert B Diasio, MD	5 4 3 2 1	5 4 3 2 1
Bruce J Giantonio, 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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