CCU | 2007 VOL 6 | ISSUE 3

Colorectal Cancer™ UPDATE

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

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CME Certified

Colorectal Cancer Update
A Continuing Medical Education Audio Series

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 3 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Venook, Wexner, Willett and Hecht on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

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This program is supported by education grants from Genentech BioOncology, Roche Laboratories Inc and Sanofi-Aventis.

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UPCOMING EDUCATIONAL EVENTS

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Website: **www.asco.org**

Eastern Cooperative Oncology Group Meeting
June 8-10, 2007
Washington, DC
Website: **www.ecog.org**

CALGB Group Meeting
June 21-24, 2007
Baltimore, Maryland
Website: **www.calgb.org**

Ninth World Congress of Gastrointestinal Cancer
June 27-30, 2007
Barcelona, Spain
Website: **www.worldgicancer.com**

ECCO 14 — The European Cancer Conference
September 23-27, 2007
Barcelona, Spain
Website: **www.fecs.be**

70th Annual Colon and Rectal Surgery Conference
October 24-27, 2007
Minneapolis, Minnesota
Website: **www.colonrectalcourse.org**

INTERVIEW

Alan P Venook, MD

Dr Venook is Professor of Clinical Medicine and Associate Chief in the Division of Medical Oncology at the University of California, San Francisco in San Francisco, California.

Tracks 1-12

Select Excerpts from the Interview

Track 2

DR LOVE: What are your thoughts about using treatment holidays in metastatic disease?

DR VENOOK: I've always been a proponent of drug holidays without any basis for it — I just rely on common sense and try to do the best thing possible for my patients.

One of my patients is approximately four years into his metastatic disease. He initially responded to front-line FOLFOX/bevacizumab therapy and then developed neuropathy. We gave him six months off the treatment. During that time, his disease progressed a bit and the neuropathy was persistent. We switched to FOLFIRI and bevacizumab at the time of progression.

DR LOVE: So you stopped everything — is that what you normally do?

DR VENOOK: This was some years ago, and we stopped everything for that patient. Now my instinct is to continue the components of therapy without the oxaliplatin.

This patient was switched to FOLFIRI/bevacizumab and had another response, which then peaked. His neuropathy resolved, and his disease progressed.

We went back to FOLFOX and bevacizumab, and he responded again. He's four years out now on cetuximab and responding.

Track 6

DR LOVE: What are some of the current clinical trials that you anticipate will have the greatest impact on clinical practice over the next few years?

DR VENOOK: A study that has not yet opened but will be important to clinical practice patterns is the iBET trial (SWOG/NCCTG/NCIC iBET S0600). It will evaluate whether to continue bevacizumab for patients experiencing progression on first-line chemotherapy and bevacizumab.

Patients experiencing progression on FOLFOX/bevacizumab will be randomly assigned to either irinotecan/cetuximab or irinotecan/cetuximab and bevacizumab.

This trial will approach the biggest question I'm asked regularly: "Do you continue bevacizumab or don't you continue bevacizumab at the time of progression?"

DR LOVE: How do you approach that sort of situation outside of a protocol?

DR VENOOK: Generally, our instinct is to not continue bevacizumab, although I'll admit we often reintroduce it later on.

For a 30-year-old whose risk of stroke or myocardial infarction I believe to be sufficiently low, I might keep it going. For a 70-year-old with whom I suspect I've already tempted fate, I might stop. I don't have a one-size-fits-all answer.

DR LOVE: Do you factor in how the patient's tumor is responding to the therapy?

DR VENOOK: Yes, although it can cut either way. For a patient who shows a dramatic response but whose treatment is only palliative, you could argue to stop the bevacizumab because you've already obtained considerable value out of it.

The other way to look at it is, don't stop the bevacizumab because it may be contributing to the response. So it's a gray area. There's very little black and white about the decision.

Track 9

DR LOVE: What adjuvant studies are you currently enrolling patients on?

DR VENOOK: We enroll patients on ECOG-E5202, which I believe is an incredibly important study. Patients with Stage II disease are risk stratified based on the molecular features of their cancer (1.1).

Patients at low risk, who are expected to comprise about 60 percent of the patients, are observed. Patients at high risk — deletion on 18q, microsatellite stability — receive FOLFOX or FOLFOX/bevacizumab.

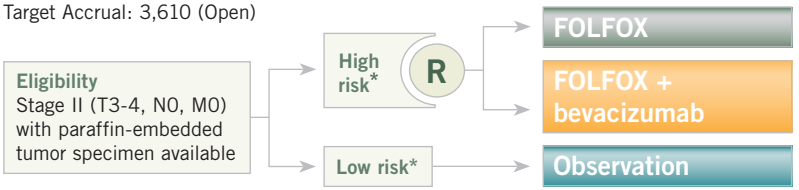
I believe that's such an absolutely important study to distinguish who doesn't need chemotherapy and to see whether the data hold up. It would be wonderful to save so many patients from exposure to chemotherapy.

We're also participating in the Intergroup study (CALGB-80203), evaluating FOLFOX or FOLFIRI with or without cetuximab (Venook 2006).

1.1

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, April 2007.

Track 12

DR LOVE: Would you discuss the evolving data on the use of capecitabine in combination with oxaliplatin in the adjuvant and metastatic settings?

DR VENOOK: In the adjuvant setting, we're not there yet. We do have data "in the hopper" — the AVANT trial. In the next year we hope to have information that might tell us it's safe, and at least equivalent, to substitute capecitabine for 5-FU.

Dr Cassidy conducted a study in the metastatic setting (NO16966) that is complex (Cassidy 2006). It was initially a CAPOX versus FOLFOX regimen. Then it was amended to be CAPOX with bevacizumab or placebo versus FOLFOX with bevacizumab or placebo.

The overall take-home message is that CAPOX does not appear to be inferior to FOLFOX in the advanced disease setting. I believe we can take that to the bank, except this was almost entirely a European trial.

The dose of capecitabine in this trial, 1 g/m^2 BID with oxaliplatin, is a larger dose than we use in the United States. A lot of data suggest, for not entirely certain reasons, that you can't dose patients in the United States at the same dose of capecitabine that you can use in Europe.

So with the caveat that you have to ensure that the dosing is okay, I believe CAPOX is not inferior to FOLFOX.

With the addition of bevacizumab, overall, patients did better. Progression-free survival was improved. However, it is curious that the incremental benefit of bevacizumab wasn't nearly as large as it has been with treatments in other colon cancer studies.

DR LOVE: What about the use of capecitabine alone in the adjuvant setting?

DR VENOOK: We use it occasionally. For a patient who isn't a candidate for FOLFOX — very elderly with comorbidities, neuropathy and the sort of red flags seen with oxaliplatin — we'll use capecitabine alone. ■

SELECT PUBLICATIONS

Cassidy J et al. **First efficacy and safety results from XELOX-1/NO16966, a randomised 2x2 factorial phase III trial of XELOX vs FOLFOX4 + bevacizumab or placebo in first-line metastatic colorectal cancer (MCRC).** *Proc ESMO* 2006;**Abstract LBA3**.

Chung KY, Kelsen D. **Adjuvant therapy for Stage II colorectal cancer: Who and with what?** *Curr Treat Options Gastroenterol* 2006;9(3):272-80. **Abstract**

Diep CB et al. **Genetic tumor markers with prognostic impact in Dukes' stages B and C colorectal cancer patients.** *J Clin Oncol* 2003;21(5):820-9. **Abstract**

Lang I et al. **Cetuximab with irinotecan in first-line treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer (mCRC). Preliminary safety results (CRYSTAL).** *Proc ASCO* 2006;**Abstract 3555**.

Locker GY et al. **ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer.** *J Clin Oncol* 2006;24(33):5313-27. **Abstract**

Sarli L et al. **Association between recurrence of sporadic colorectal cancer, high level of microsatellite instability, and loss of heterozygosity at chromosome 18q.** *Dis Colon Rectum* 2004;47(9):1467-82. **Abstract**

Van Cutsem E et al. **Cetuximab dose-escalation study in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): Pharmacokinetic and efficacy data of a randomized study.** Gastrointestinal Cancers Symposium 2007;**Abstract 237**.

Venook A et al. **Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results.** *Proc ASCO* 2006;**Abstract 3509**.

INTERVIEW

Steven D Wexner, MD

Dr Wexner is Chief of the Division of Colorectal Surgery at the Cleveland Clinic Florida in Weston, Florida.

Tracks 1-17

Select Excerpts from the Interview

Track 1

DR LOVE: Can you describe your initial evaluation of patients with rectal cancer?

DR WEXNER: First, I review the colonoscopy report from the gastroenterologist or the referring colorectal surgeon to ensure the patient has no synchronous lesions.

The next questions to ask are as follows: How close is the tumor to the sphincter? Will we be able to perform sphincter-saving surgery? What stage is the lesion?

The most important exam to start answering these questions is the "good old-fashioned" rectal exam. Anterior versus posterior positioning of the tumor can make a big difference in males because of the difficulty of getting under the prostate for distal dissection and in females because of the possibility of needing a posterior vaginectomy.

With posterior tumors, you have the luxury of a little more space to work with near the rectum. However, an advanced tumor could involve a posterior exenteration. So the first step is to observe the position of the tumor.

Another step in evaluating the patient is visualization of the lesion using either rigid proctosigmoidoscopy or, far more commonly, flexible sigmoidoscopy. For the most distal lesions, flexible sigmoidoscopy won't allow for an adequate visual analysis.

For a surgeon, it's better to evaluate the lesion by feel. For the higher lesions — midrectum and upper rectum — visualization with flexible sigmoidoscopy is possible.

Once the initial questions are answered, the next step in the algorithm is the ultrasound exam, which is performed immediately. Within an hour or two, the results are returned, and I know the tumor stage.

If the cancer is T3 and/or N1, the patient will be referred for chemotherapy and radiation therapy. If the tumor is T1 or T2, I have a different discussion with the patient.

Track 2

DR LOVE: How does neoadjuvant chemoradiation therapy impact the tumor and your ability to perform surgery?

DR WEXNER: The efficacy and safety of the chemotherapeutic agents and the method and modality of radiation therapy delivery have vastly improved over the last two decades.

We used to fear preoperative chemoradiation therapy because of the possibility of extreme skin damage, terrible radiation proctitis or making the tissue planes difficult to handle and increasing the morbidity of perineal wound healing.

Now we've gone from that extreme to the other extreme. In most cases I can only tell a patient underwent preoperative chemoradiation therapy by examining the site of the tumor, which is left with only a scar in one third of my patients.

Neoadjuvant chemoradiation therapy has dramatically improved, and it has made surgery easier to perform because large bulky tumors that seemingly used to become more fixed and more fibrotic with the treatment are now disappearing.

The tissue planes become a little edematous, but neoadjuvant treatment is facilitating dissection in most cases.

Track 3

DR LOVE: The standard for neoadjuvant therapy has been to administer continuous infusion 5-FU with radiation therapy. What have you observed in patients treated with capecitabine?

DR WEXNER: Clearly, not having a pump is advantageous from a quality-of-life standpoint (2.1), and the safety profile speaks for itself. The anecdotal reports are that patients are continuing to work and are not interrupting their schedules. ■

2.1

Preference for Oral or Intravenous Chemotherapy Regimens Among Patients with Advanced Colorectal Cancer: A Randomized Crossover Trial

	Oral capecitabine/ Mayo Cl*	Oral capecitabine/ de Gramont* (inpatient)	Oral capecitabine/ de Gramont* (outpatient)
Before treatment	N = 24	N = 43	N = 27
Prefer oral	19 (79)	36 (84)	18 (67)
Prefer intravenous	1 (4)	2 (5)	1 (4)
Undecided	4 (17)	5 (12)	7 (26)
After treatment	N = 17	N = 32	N = 25
Had a preference	14	30	22
Prefer oral	12 (86)	19 (63)	11 (50)
Prefer IV	2 (14)	11 (37)	11 (50)
No preference	3	2	3

* Patients were randomly assigned to one of three groups: capecitabine or the Mayo Clinic regimen, capecitabine or the inpatient de Gramont regimen or capecitabine or the outpatient de Gramont regimen. All patients received oral or IV treatment during the first treatment course and were crossed over to the opposite treatment during the second treatment course.

SOURCE: Twelves C et al. *Ann Oncol* 2006;17(2):239-45. **Abstract**

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Baxter NN et al. **Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: A population-based analysis.** *Int J Radiat Oncol Biol Phys* 2005a;61(2):426-31. **Abstract**

Baxter NN et al. **Lymph node evaluation in colorectal cancer patients: A population-based study.** *J Natl Cancer Inst* 2005b;97(3):219-25. **Abstract**

Bosset JF et al. **Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: Preliminary results — EORTC 22921.** *J Clin Oncol* 2005;23(24):5620-7. **Abstract**

Rodel C et al. **Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer.** *J Clin Oncol* 2005;23(34):8688-96. **Abstract**

Sauer R et al; German Rectal Cancer Study Group. **Preoperative versus postoperative chemoradiotherapy for rectal cancer.** *N Engl J Med* 2004;351(17):1731-40. **Abstract**

Twelves C et al. **A randomised cross-over trial comparing patient preference for oral capecitabine and 5-fluorouracil/leucovorin regimens in patients with advanced colorectal cancer.** *Ann Oncol* 2006;17(2):239-45. **Abstract**

INTERVIEW

Christopher Willett, MD

Dr Willett is Chairman of the Department of Radiation Oncology at Duke University Medical Center in Durham, North Carolina.

Tracks 1-8

Track 1	Bevacizumab as a potential radiation sensitizer in rectal cancer	Track 5	Capecitabine versus infusional 5-FU as neoadjuvant therapy in rectal cancer
Track 2	Clinical trial of bevacizumab alone and concurrent with chemoradiation therapy in rectal cancer	Track 6	Pathologic complete response with neoadjuvant combined chemoradiation and targeted therapies
Track 3	Direct evidence of antivascular effects of bevacizumab in rectal cancer	Track 7	Addition of oxaliplatin to neoadjuvant chemoradiation therapy for rectal cancer
Track 4	Clinical response to neoadjuvant chemoradiation with bevacizumab in rectal cancer	Track 8	American College of Surgeons trial of local excision in patients with T2 rectal cancer

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the background of your trial that evaluated bevacizumab as part of neoadjuvant treatment of rectal cancer?

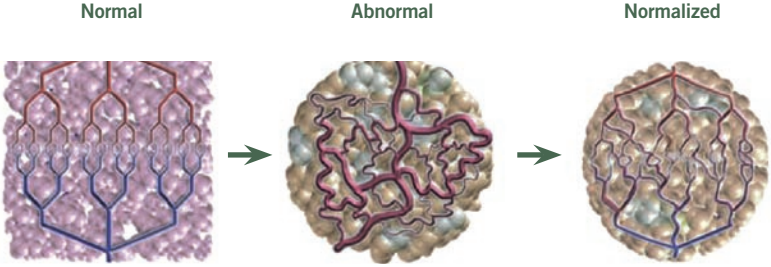
DR WILLETT: Dr Rakesh Jain had been interested in a hypothesis called "normalization" (Jain 2001; [3.1]), which he examined in preclinical models.

The hypothesis is that the tumor vasculature is highly inefficient and is associated with high levels of interstitial pressure and hypoxia. So if you administer anti-angiogenic agents — specifically agents targeting VEGF — these agents may work not only through direct blood vessel killing but also by improving the efficiency of the remaining tumor vasculature.

DR LOVE: What was known about bevacizumab and radiation sensitization?

DR WILLETT: The preclinical work (Lee 2000; Yuan 1996) in a variety of mouse models demonstrated that if bevacizumab was administered with radiation therapy, the amount of radiation needed to control the tumors was less than with radiation therapy alone.

3.1 **Effect of Anti-VEGF on Normalization of Tumor Vasculature**



Anti-VEGFR treatment prunes immature blood vessels and decreases the diameter of residual vessels. The tumor vasculature becomes less tortuous and more organized, with improved perivascular cells and basement membrane coverage.

SOURCE: Adapted by permission from Macmillan Publishers Ltd: *Nature Medicine* (Jain RK. **Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy.** *Nat Med* 2001;7(9):987-9), copyright 2001. No abstract available

Track 2

DR LOVE: How did you choose the study design for your trial of bevacizumab and chemoradiation therapy for patients with rectal cancer?

DR WILLETT: We wanted to observe the effect of bevacizumab as a single agent on rectal cancer before introducing radiation therapy and 5-FU.

According to the trial design (Willett 2004), patients received a single infusion of bevacizumab prior to the introduction of 5-FU and radiation therapy with concurrent bevacizumab. We were keenly interested in what would be happening at a relatively short period after the first bevacizumab infusion.

At day 12, typically, after the first bevacizumab infusion, evaluations (flexible sigmoidoscopies, biopsies, interstitial fluid pressure, functional imaging, serum/blood assays) were repeated in terms of the correlative studies.

So it provided an opportunity to observe a human malignancy in vivo after bevacizumab treatment, and it allowed an opportunity to see the resulting types of effects.

DR LOVE: How long did patients receive the chemoradiation therapy and bevacizumab?

DR WILLETT: The protocol design was as follows: An infusion of bevacizumab was administered on day one, and two weeks later a second infusion of bevacizumab was followed by the introduction of pelvic irradiation and continuous infusion 5-FU.

We administered a standard course of radiation therapy — 50.4 Gray over 5.5 weeks. A seven-day continuous infusion of 5-FU at 225 mg/m^2 was administered throughout the course of radiation therapy.

Bevacizumab was administered every other week for a total of four infusions of bevacizumab with 50 Gray of radiation and 5-FU during the course of external-beam radiation therapy. Surgery was performed seven to nine weeks after completion of the bevacizumab to allow for clearance of the drug, considering the half-life of bevacizumab.

Track 3

DR LOVE: Can you review the findings of your study?

DR WILLETT: The initial Phase I portion (Willett 2004) of the trial included six patients who received the first dose of bevacizumab in the trial, which was 5 mg/kg. At day 12, after the first infusion of bevacizumab, our first patient underwent a flexible sigmoidoscopy and appeared to show a response with the monotherapy alone.

We did not run into any dose-limiting toxicity. However, when we began to put the data together for the correlative studies, we noted some interesting findings (3.2).

One such finding was that the interstitial fluid pressure in these patients had dropped from baseline to day 12, a finding that perfectly matched the results that Dr Jain had observed in the xenograft models.

DR LOVE: You mentioned what happened to the first patient after two weeks — what about the other five patients?

DR WILLETT: Essentially, disease remained in the other five patients. Tumors seemed, in terms of response, about the same in size — no big changes. It is interesting that some of the tumors became perhaps a little more pale on gross visualization. We did see a drop in the tumor blood flow with perfusion CT scans.

According to the 18-fluorodeoxyglucose PET scans, essentially no difference had appeared in standardized uptake values between pretreatment and day 12. We also saw a drop in microvessel density between baseline and day 12, consistent with preclinical work.

You might ask whether a drop in tumor blood flow goes against the normalization hypothesis. Probably not — remember, the perfusion CT is a relatively gross measure. Even with a drop in blood flow, the level of tumor metabolic activity remained the same, which, in fact, suggested some element of normalization.

Track 4

DR LOVE: What were the clinical responses in the initial six patients at surgery?

DR WILLETT: In five of the six patients, we saw a flat ulcer in the surgical specimen with no exophytic or macroscopic disease. One patient had gross disease remaining. When these specimens were sectioned and examined histologically, we typically observed a nest of cells admixed into a deep fibrous tissue.

DR LOVE: In those five patients, if you had to make a guess, what fraction of the tumor do you think was destroyed?

DR WILLETT: That is a hard question. We used various grading scales to try to correlate the amount of residual disease with what one would have expected pretreatment. The clinical responses were excellent, with an ulcer remaining, and microscopic disease remained.

The next cohort of patients received bevacizumab at a higher dose level of 10 mg/kg. Five patients were assigned to that dose level. Two of the five patients who received the higher dose level showed complete pathological responses — that is, absolutely no malignant cells were left in the surgical specimens.

The other three patients also showed good responses, but again, microscopic disease remained. Note that these 11 patients were assessed by one pathologist, who "bread-loafed" the specimens individually, so the stringency of the pathological examination of these specimens was probably as tight as could be.

3.2

Antivascular Effects of Bevacizumab in Rectal Cancer

"...A single infusion of the VEGF-specific antibody bevacizumab decreases tumor perfusion, vascular volume, microvascular density, interstitial fluid pressure and the number of viable, circulating endothelial and progenitor cells, and increases the fraction of vessels with pericyte coverage in rectal carcinoma patients. These data indicate that VEGF blockade has a direct and rapid antivascular effect in human tumors."

SOURCE: Willett CG et al. *Nat Med* 2004;10(2):145-7. **Abstract**

Track 5

DR LOVE: What are your thoughts about the controversy regarding capecitabine versus continuous infusion 5-FU as neoadjuvant therapy for rectal cancer?

DR WILLETT: The need to address the question in a Phase III trial as neoadjuvant treatment for rectal carcinoma is clear. Many clinicians have adopted capecitabine as an alternative to infusional 5-FU regimens, and not only for rectal carcinoma.

The data from Phase I and II studies (Chau 2006; Glynne-Jones 2005) of capecitabine and radiation therapy (3.3) suggest that it is as beneficial as 5-FU infusions, with a slightly different toxicity profile. We have used it, but we also discuss the option carefully with the patient. ■

3.3

Objective Tumor Response by Imaging in a Phase II Study of Neoadjuvant CAPOX Followed by Synchronous Chemoradiation Therapy and Total Mesorectal Resection in Poor-Risk Rectal Cancer

Response	After neoadjuvant chemotherapy N = 68	After synchronous chemoradiation therapy N = 70
Objective response (95% CI)	88% (78% to 95%)	97% (90% to 100%)
Complete response	4%	20%
Partial response	84%	77%
Stable disease	12%	3%

SOURCE: Chau I et al. *J Clin Oncol* 2006;24(4):668-74. **Abstract**

SELECT PUBLICATIONS

Ryan DP et al. **Phase I/II study of preoperative oxaliplatin, fluorouracil, and external-beam radiation therapy in patients with locally advanced rectal cancer: Cancer and Leukemia Group B 89901.** *J Clin Oncol* 2006;24(16):2557-62. **Abstract**

Chau I et al. **Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer.** *J Clin Oncol* 2006;24(4):668-74. **Abstract**

Glynne-Jones R et al. **A phase I dose escalation study of continuous oral capecitabine in combination with oxaliplatin and pelvic radiation (XELOX-RT) in patients with locally advanced rectal cancer.** *Ann Oncol* 2006;17(1):50-6. **Abstract**

Glynne-Jones R et al. **Socrates phase II study results: Capecitabine (CAP) combined with oxaliplatin (OX) and preoperative radiation (RT) in patients (pts) with locally advanced rectal cancer (LARC).** *Proc ASCO* 2005;**Abstract 3527**.

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Rodel C et al. **Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer.** *J Clin Oncol* 2007;25(1):110-7. **Abstract**

Rodel C et al. **Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer.** *J Clin Oncol* 2003;21(16):3098-104. **Abstract**

Schmoll HJ et al. **Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: A planned safety analysis in 1,864 patients.** *J Clin Oncol* 2007;25(1):102-9. **Abstract**

Willett CG et al. **Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: Continued experience of a phase I trial in rectal cancer patients.** *J Clin Oncol* 2005;23(31):8136-9. No abstract available

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INTERVIEW

J Randolph Hecht, MD

Dr Hecht is Clinical Professor of Medicine and Director of the UCLA GI Oncology Program in the Division of Hematology/Oncology in the UCLA School of Medicine's Department of Medicine in Los Angeles, California.

Tracks 1-13

Track 1	Recent developments in the treatment of metastatic colorectal cancer
Track 2	Emerging clinical data with panitumumab
Track 3	Recent clinical trials of first-line therapy in metastatic colorectal cancer
Track 4	XELOX-1/NO16966: CAPOX or FOLFOX4 with or without bevacizumab as first-line therapy
Track 5	Investigations of chemotherapy holidays in the treatment of metastatic disease
Track 6	Doublet antibodies in the treatment of metastatic colorectal cancer
Track 7	Side effects and tolerability of the anti-EGFR antibody panitumumab
Track 8	Current role of panitumumab in the treatment of metastatic colorectal cancer
Track 9	Predictors of response to anti-EGFR antibodies
Track 10	Clinical trial strategies incorporating biologic agents in the adjuvant setting
Track 11	Use of chemotherapy with biologic agents to render hepatic metastases resectable
Track 12	Safety of bevacizumab and its role in the adjuvant setting
Track 13	Identification of targets for biologic agents and the individualization of therapy

Select Excerpts from the Interview

Track 4

DR LOVE: Can you discuss the results of "Trial 66," recently reported by Cassidy and Saltz (Cassidy 2007; Saltz 2007; [4.1])?

DR HECHT: Initially, that study compared CAPOX and FOLFOX, then bevacizumab was included and it became a two-by-two design. The investigators did reach their intended endpoint, demonstrating that CAPOX was not inferior to FOLFOX. In fact, the two arms were very similar.

In evaluating progression-free survival, they examined fluoropyrimidine/oxaliplatin-containing chemotherapy with or without bevacizumab, and a statistically significant improvement was observed, but it was not of the

expected magnitude. In fact, in an unplanned subgroup analysis, no PFS improvement was seen with FOLFOX, but it was evident when the CAPOX and FOLFOX arms were evaluated together. The hazard ratio was approximately 0.83. A fairly small improvement in median survival was seen.

So one of the questions that has arisen is, why are these results different than when FOLFOX with bevacizumab was evaluated in the second-line setting? Did the Europeans treat their patients differently? I'm anxious to see what additional data will be presented.

DR LOVE: In the IFL/bevacizumab study, when patients experienced toxicity from the chemotherapy, the chemotherapy was stopped and bevacizumab was continued until progression (Hurwitz 2004; [4.1]). In the 66 study, however, chemotherapy and bevacizumab were discontinued when patients developed toxicity, so patients ended up receiving less bevacizumab.

DR HECHT: That has been one of the interpretations of the data. The problem is, the data are the data. The question is, why are the data the data?

4.1

Progression-Free Survival and Response Rates in First-Line Trials of Metastatic Colorectal Cancer (CRC) Treated with Chemotherapy with or without Bevacizumab

Outcome variable	NO16966 (Saltz 2007) First-line CRC CT* vs CT* + bev	AVF2107 (Hurwitz 2004) First-line CRC CT† vs CT† + bev
PFS		
HR	0.83	0.58
p-value	0.0023	<0.0001
PFS (on treatment)		
HR	0.63	0.54
p-value	<0.0001	<0.0001
Response rate	49% vs 47%	35% vs 45%
p-value	0.99	0.004

CT = chemotherapy; bev = bevacizumab; PFS (on treatment) = progression-free survival; patients were censored at time of last scan showing nonprogressive disease if progressive disease or any-cause death occurred beyond 28 days after final dose of treatment.

* FOLFOX or CAPOX; † IFL

SOURCES: Saltz LB et al. Presentation. Gastrointestinal Cancers Symposium 2007;**Abstract 238**; Hurwitz H et al. *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Track 10

DR LOVE: Where are we right now with regard to colorectal cancer trials in the adjuvant setting evaluating bevacizumab?

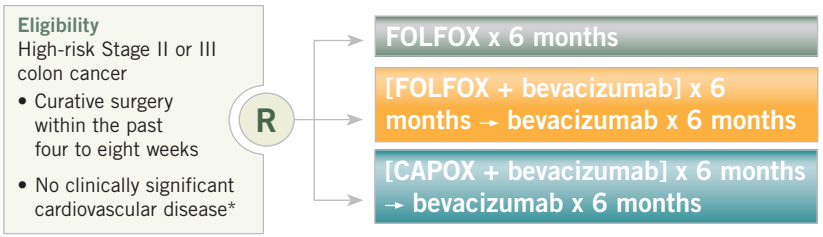
DR HECHT: Two trials are under way. One is the NSABP trial evaluating bevacizumab with a fluoropyrimidine and oxaliplatin for six months followed by six additional months of bevacizumab.

The other is the worldwide, three-arm AVANT trial (4.2), which compares FOLFOX as the standard, FOLFOX with bevacizumab or CAPOX with bevacizumab. That trial was closed for a few months because of a question regarding increased toxicity in one of the arms. However, it was felt that it was not sufficient to change the trial. Additional monitoring was incorporated, and it will be years before we receive adjuvant data. Other targeted therapies are being evaluated, such as antibodies, and I believe they will form the next wave of adjuvant trials. ■

4.2

AVANT Adjuvant Study: Phase III Randomized Trial Comparing FOLFOX to FOLFOX with Bevacizumab to CAPOX with Bevacizumab in Patients with Resected Colon Cancer

Target accrual: 3,450
Protocol IDs: UCLA-0412086-01, ROCHE-BO17920A, NCT00112918



* Cerebrovascular accident within the past six months; myocardial infarction within the past year; uncontrolled hypertension while on chronic medication; unstable angina; NYHA Class II-IV heart failure; serious cardiac arrhythmias that require medication. A cardiac monitoring plan is included in this study.

Study Contact

Joel Hecht, MD
Tel: 888-798-0719

SOURCE: NCI Physician Data Query, April 2007.

SELECT PUBLICATIONS

Cassidy J et al. **XELOX vs FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer (MCRC).** Gastrointestinal Cancers Symposium 2007;**Abstract 270**.

Hecht J et al. **Panitumumab antitumor activity in patients with metastatic colorectal cancer (mCRC) expressing low (1-9%) or negative (<1%) levels of epidermal growth factor receptor (EGFr).** *Proc ASCO* 2006;**Abstract 3547**.

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

Peeters M et al. **A phase 3, multicenter, randomized controlled trial of panitumumab plus best supportive care (BSC) versus BSC alone in patients with metastatic colorectal cancer.** Program and Abstracts of the 97th Annual Meeting of the American Association for Cancer Research 2006;**Abstract CP-1**.

Saltz LB et al. **Bevacizumab in combination with XELOX or FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC).** Presentation. Gastrointestinal Cancers Symposium 2007;**Abstract 238**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The results of the NO16966 study demonstrated that capecitabine/CAPOX was not inferior to _____ for treating advanced-stage colorectal cancer.**
   a. FOLFIRI
   b. FOLFOX
   c. Irinotecan/cetuximab

2. **Capecitabine is often administered at _____ doses in Europe than in the United States.**
   a. Higher
   b. Lower
   c. Equivalent

3. **CALGB-80405 will compare FOLFOX or _____ with bevacizumab and/or _____ as first-line therapy for colorectal cancer.**
   a. CAPOX, cetuximab
   b. FOLFIRI, cetuximab
   c. Neither a nor b

4. **The iBET trial will evaluate the continuation of bevacizumab at the time of disease progression.**
   a. True
   b. False

5. **The ECOG trial E5202 is evaluating oxaliplatin with 5-FU/LV with or without bevacizumab in patients with Stage III colon cancer.**
   a. True
   b. False

6. **Surgical procedures for rectal cancer have been facilitated by improvements in neoadjuvant chemoradiation therapy, which results in the shrinkage of large, bulky tumors.**
   a. True
   b. False

7. **The normalization hypothesis assumes that tumor vasculature is inefficient and hypoxic and is associated with _____ levels of interstitial pressure.**
   a. High
   b. Low

8. **NSABP-R-04 is evaluating the role of _____ as a part of neoadjuvant therapy for patients with rectal cancer.**
   a. Bevacizumab
   b. Oxaliplatin
   c. Both a and b
   d. None of the above

9. **XELOX-1/NO16966 ("Trial 66"), a Phase III study of first-line treatment of metastatic colorectal cancer, showed that progression-free survival significantly improved when bevacizumab was added to oxaliplatin-based therapy.**
   a. True
   b. False

10. **Patients in the Phase III AVANT adjuvant study are randomly assigned to _____.**
    a. FOLFOX
    b. FOLFOX and bevacizumab
    c. CAPOX and bevacizumab
    d. All of the above

11. **Exclusionary criteria for the AVANT trial include _____.**
    a. Myocardial infarction within the past year
    b. Unstable angina
    c. NYHA Class II-IV heart failure
    d. All of the above
    e. None of the above

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

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Colorectal Cancer Update — Issue 3, 2007

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GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment, 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
Alan P Venook, MD	5 4 3 2 1	5 4 3 2 1
Steven D Wexner, MD	5 4 3 2 1	5 4 3 2 1
Christopher Willett, MD	5 4 3 2 1	5 4 3 2 1
J Randolph Hecht, MD	5 4 3 2 1	5 4 3 2 1

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Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
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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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CCU307

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U P D A T E

This program is supported by education grants from
Genentech BioOncology, Roche Laboratories Inc and Sanofi-Aventis.

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Sponsored by Research To Practice.

Last review date: April 2007
Release date: April 2007
Expiration date: April 2008
Estimated time to complete: 3 hours