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Colorectal Cancer™ UPDATE

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

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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 1 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Wolff, Berlin and Lenz on the integration of emerging clinical research data into the management of colorectal cancer.

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UPCOMING EDUCATIONAL EVENTS

NCCN 12th Annual Conference: Clinical Practice Guidelines and Quality Cancer Care
March 14-18, 2007
Hollywood, Florida
Event website: **www.nccn.org**

Society of Surgical Oncology Cancer Symposium
March 15-18, 2007
Washington, DC
Event website: **www.surgonc.org**

Preoperative Therapy in Invasive Breast Cancer: Reviewing the State of the Science and Exploring New Research Directions
March 26-27, 2007
Bethesda, Maryland
Event website: **http://ctep.cancer.gov/bcmeeting**

American Association for Cancer Research Annual Meeting
April 14-18, 2007
Los Angeles, California
Event website: **www.aacr.org**

NCCTG Semi-Annual Meeting
April 16-19, 2007
Rochester, Minnesota
Event website: **http://ncctg.mayo.edu**

NSABP Semi-Annual Meeting
April 27-30, 2007
Jacksonville, Florida
Event website: **www.nsabp.org**

SWOG Semi-Annual Meeting
May 2-6, 2007
Chicago, Illinois
Event website: **www.swog.org**

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

INTERVIEW

Robert A Wolff, MD

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

Tracks 1-19

Select Excerpts from the Interview

Tracks 2-7

DR LOVE: Can you present a case from your practice that exemplifies the key issues involved with neoadjuvant therapy of rectal cancer?

DR WOLFF: I recently evaluated a 57-year-old woman who experienced one or two episodes of rectal bleeding, which didn't set off any alarms. Then she had some changes in her bowel habits with more bleeding that prompted her to see her physician.

A digital rectal examination revealed a mass, and flexible sigmoidoscopy revealed a mid to low rectal tumor, about five centimeters from the anal verge. She had T3N1 disease.

DR LOVE: What treatment options did you discuss with her?

DR WOLFF: We talked about the rationale for preoperative therapy, such as improved chances of sphincter preservation. If we tell a patient that we recommend preoperative therapy and that we have a protocol with a novel molecular agent — bevacizumab — which has efficacy in advanced disease (Hurwitz 2004) and may have potent radiosensitizing effects (Willett 2005, 2004), the study is usually of great interest to patients in whom the risks associated with bevacizumab (myocardial infarction and stroke) are quite low.

We are currently conducting a Phase II neoadjuvant trial of capecitabine (administered daily Monday through Friday) and bevacizumab (in weeks one, three and five) with standard doses of radiation therapy (1.1). We have found this to be a well-tolerated regimen, and we haven't seen toxicity above what we've seen with capecitabine and radiation therapy.

DR LOVE: What is the timing between bevacizumab and surgery?

DR WOLFF: We wait at least six weeks between. Patients with rectal cancer receive chemoradiation therapy followed by six weeks of rest and then a reevaluation by the surgeon with a proctoscopy.

DR LOVE: What did this patient elect to do?

DR WOLFF: She went on the trial. She experienced what I consider an easy course of therapy. She had Grade II perianal erythema and some mild moist desquamation, but she didn't have severe skin reactions.

She experienced nice downstaging. Her pathologic stage at surgery was T2N0. She did not show a complete response, but she was down to microscopic disease, which makes us feel good about her overall prognosis.

Track 8

DR LOVE: What postoperative recommendation did you provide to this patient?

DR WOLFF: I offer patients FOLFOX or CAPOX because I view capecitabine and infusional 5-FU as essentially equivalent. She opted to take CAPOX because she had previously received capecitabine.

1.1

Phase II Trial of Neoadjuvant Capecitabine, Bevacizumab and Radiation Therapy in Patients with Locally Advanced Rectal Cancer

Protocol IDs: 2003-0832, NCT00113230
Target Accrual: 50 (Open)

Eligibility

- T3/T4 rectal cancer
- No distant metastases
- ECOG performance status 0 or 1

→ **Bevacizumab + capecitabine + radiation therapy → surgery**

[**Bevacizumab** q2wk x 3] + [(**capecitabine** BID + **radiation therapy**) 5 days/week x 5 weeks] → surgery

Study Contact

MD Anderson Cancer Center at The University of Texas
Christopher Crane, MD
Tel: 713-563-2300, Ext 3-2300

SOURCES: NCI Physician Data Query, November 2006; MD Anderson Cancer Center Website (**http://utm-ext01a.mdacc.tmc.edu/dept/prot/clinicaltrialswp.nsf/index/2003-0832**), January 2007.

Track 12

DR LOVE: The NSABP is conducting the R-04 trial, which is evaluating capecitabine versus 5-FU with or without oxaliplatin. What are your thoughts about oxaliplatin in this situation?

DR WOLFF: Oxaliplatin is a little more user friendly with radiation therapy than irinotecan. We are currently conducting a study for patients with anal cancer evaluating CAPOX combined with radiation therapy (1.2). We are excited about the results that we are seeing. Every tumor has shown a complete response, and these responses have been durable. The numbers are small, but we believe it is a viable strategy.

Tracks 13-14

DR LOVE: Can you discuss your therapeutic approach to older patients with colon cancer?

DR WOLFF: I recently saw a 78-year-old woman who had a resected T3N2M0 colon tumor and six positive lymph nodes. She'd had a prior stroke and was functional, but she needed some assistance from her husband.

We wanted to use adjuvant therapy but weren't comfortable with the idea of oxaliplatin. We elected to use single-agent capecitabine as adjuvant therapy. She had a somewhat tough time with some diarrhea, even receiving reduced doses, but ended up receiving four months of therapy. She is three years out and doing fine now with no evidence of disease.

DR LOVE: What were your thoughts on Rich Goldberg's presentation at ASCO 2006 about the tolerance to chemotherapy in older patients (Sargent 2006)?

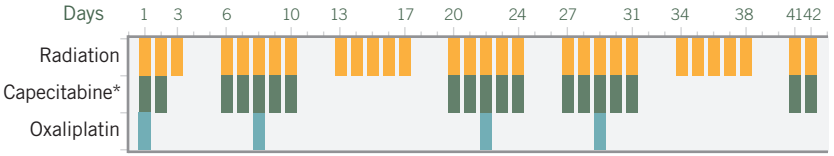
1.2

Phase II Study of Capecitabine, Oxaliplatin and Radiation Therapy in Patients with Stage II-IIIB Squamous Cell Carcinoma of the Anal Canal

Protocol IDs: MDA-2003-0874, NCT00093379
Target Accrual: 71 (Open)

Regimen → **CAPOX + radiation therapy**

Treatment schedule



* Patients with T3-T4 lesions also receive oral capecitabine twice daily and undergo radiation therapy once daily on days 43 and 44.

Eligibility

- Stage II-IIIB (TX1-4, NX, M0) anal cancer
- ECOG performance status 0 or 1

Study Contacts

MD Anderson Cancer Center at The University of Texas

Cathy Eng, MD
Tel: 713-792-2828; 800-392-1611

Christopher Crane, MD
Tel: 713-563-2340; 800-392-1611

SOURCE: NCI Physician Data Query, January 2007.

DR WOLFF: This is an important research question to ask. From my view, it's not so much about age, because I believe the overall take-home message is the elderly can tolerate this therapy (Sargent 2006).

I recently treated a woman who is 72 years old with CAPOX. She came to me because she had a strong aversion to a two-day infusional pump as part of her treatment.

Tracks 15-17

DR WOLFF: Another patient who is relevant to your question about the elderly is a 75-year-old man who presented with colon cancer and a single focus of metastatic disease in the periphery of the right lobe of the liver. His primary tumor had been resected. He was in overall good health with some hypertension.

His lesion may have been amenable to ablation, which is not typically our preference if we have the option to resect. Given the choice between ablation and resection, the data are trending toward resection as always more appropriate.

So he received two or three months of FOLFOX to try to make the tumor resectable and experienced some nice tumor reduction. He underwent surgery to remove the hepatic lesion, and it took a little longer than average to recover.

Tracks 18-19

DR LOVE: Do you think the use of chemotherapy with bevacizumab and cetuximab is rational off protocol in pre-op situations where you are going for cure?

DR WOLFF: In select cases it may be. I believe there will be a subset of patients for whom the biologic doublet, regardless of the chemotherapy backbone, will provide more bang for your buck. However, I would not be in favor of using the combination for all patients.

I usually have a fairly sequential way of going through drugs. If patients start with FOLFOX/bevacizumab, then they usually receive either FOLFIRI/bevacizumab or irinotecan as a single agent and then irinotecan and cetuximab.

I tell many of my patients that what they're trying to accomplish is not a race — it's a marathon. You want to stretch out the clock. If you just plow through your cytotoxics and molecular therapies and put them all into "the soup" at once, I don't know what you're going to have left.

DR LOVE: In your algorithm, where will panitumumab fit in?

DR WOLFF: Panitumumab will probably be used with regimens like FOLFIRI on an every two-week schedule. It will be more convenient than receiving weekly cetuximab. Furthermore, physicians will be excited by the fact that allergic reactions aren't common with panitumumab. ■

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De Gramont A et al. **Targeted agents for adjuvant therapy of colon cancer.** *Semin Oncol* 2006;33(Suppl 11):42-5. **Abstract**

Hochster HS. **Bevacizumab in combination with chemotherapy: First-line treatment of patients with metastatic colorectal cancer.** *Semin Oncol* 2006;33(5 Suppl 10):8-14. **Abstract**

Hoff PM. **Bevacizumab in older patients and patients with poorer performance status.** *Semin Oncol* 2006;33(5 Suppl 10):19-25. **Abstract**

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

Sargent DJ et al. **A pooled safety and efficacy analysis of the FOLFOX4 regimen (bimonthly oxaliplatin plus fluorouracil/leucovorin) in elderly compared to younger patients with colorectal cancer.** *Proc ASCO* 2006;**Abstract 3517**.

Vincenzi B et al. **The new era in the treatment of advanced colorectal cancer patients: The role of monoclonal antibodies.** *Expert Opin Emerg Drugs* 2006;11(4):665-83. **Abstract**

Willett CG et al. **Combined vascular endothelial growth factor-targeted therapy and radiotherapy for rectal cancer: Theory and clinical practice.** *Semin Oncol* 2006;33(5 Suppl 10):35-40. **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

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

INTERVIEW

Jordan D Berlin, MD

Dr Berlin is Clinical Director of GI Oncology and Associate Professor of Medicine at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee.

Tracks 1-23

Select Excerpts from the Interview

Track 3

DR LOVE: Can you review what has been seen in clinical trials with panitumumab?

DR BERLIN: This agent has been tested in metastatic disease in a randomized trial versus best supportive care (Peeters 2006) and as first-line therapy in combination with irinotecan-containing regimens (Hecht 2006).

Progression-free survival was well over 10 months, which corresponds with what we have seen thus far with the newer bevacizumab-containing regimens.

The PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) trial, which has completed accrual, is evaluating panitumumab with either FOLFIRI or FOLFOX plus bevacizumab (2.1). Those data, at least for toxicity, should be available soon.

The current availability of panitumumab is based on data from the Phase III trial in which patients were randomly assigned to panitumumab or best supportive care in the third-line setting (Peeters 2006; [2.2]).

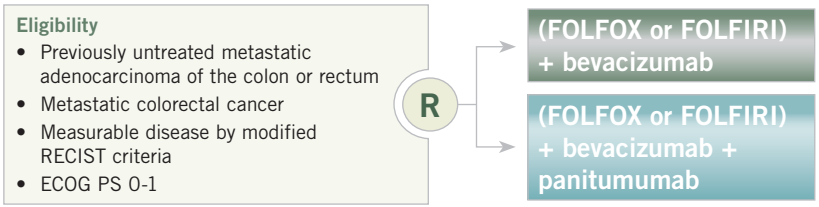
Crossover was allowed, meaning that patients initially assigned to best supportive care were able to go on to panitumumab as soon as their doctors considered that their disease had progressed. That may have played a role in the results, but the bottom line was that the panitumumab group had a better progression-free survival than the best supportive care group.

No survival difference appeared, but a large majority of the patients on the best supportive care arm actually received panitumumab, so we assume that this played a role in the lack of survival benefit.

2.1

Phase III Randomized Trial of Chemotherapy and Bevacizumab with or without Panitumumab as First-Line Treatment of Metastatic Colorectal Cancer: The Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) Study

Protocol IDs: 200402-49, NCT00115765
Target accrual: Approximately 1,000 (Closed)



SOURCES: NCI Physician Data Query, January 2007; Amgen Press Release, April 26, 2005.

Tracks 4-6

DR LOVE: What is your clinical algorithm for the treatment of metastatic colon cancer?

DR BERLIN: We start with bevacizumab in combination with either FOLFIRI or FOLFOX first line. Because of the clinical trials we have participated in, we tend to start more often with FOLFIRI than with FOLFOX. We then switch to the other regimen in the second line — if we start with FOLFIRI, we switch to FOLFOX.

2.2

Multicenter Phase III Trial of Best Supportive Care (BSC) with or without Panitumumab in Metastatic Colorectal Cancer

Accrual: 463 (Closed)

Eligibility
Metastatic colorectal cancer, ECOG 0-2, radiologic documentation of progression after fluoropyrimidine, irinotecan and oxaliplatin, EGFR staining ≥ 1% of tumor cells

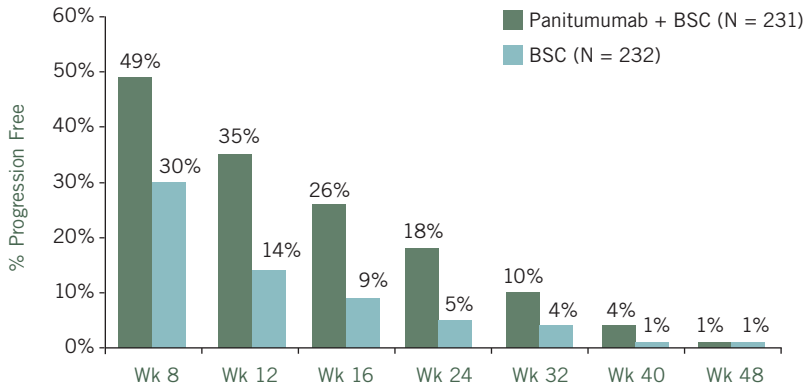
R

- Panitumumab + BSC
- BSC → PD → optional panitumumab crossover study

PD = progressive disease

- Primary endpoint: Progression-free survival
- Secondary endpoints: Overall survival, best overall objective response, duration of and time to response

Progression-Free Survival Rates at Prespecified Time Points



SOURCE: With permission. Peeters M et al. Presentation. AACR 2006;**Abstract CP-1**.

We do not continue bevacizumab beyond the first-line setting, and we use irinotecan with cetuximab as third-line therapy. However, that may change to irinotecan in combination with panitumumab.

DR LOVE: What are your thoughts on the issue of every two-week scheduling of panitumumab and infusion reactions?

DR BERLIN: Every two-week scheduling reduces cost to some extent because you're not paying the infusion cost every week. We also are interested in every two-week scheduling to minimize infusion reactions because we are in an area where the cetuximab-associated infusion reaction is more common.

DR LOVE: Rich Goldberg from North Carolina has also talked about the high incidence of cetuximab-associated infusion reaction. Do you believe there is a regional relationship to infusion reactions?

DR BERLIN: We believe it's real. We do not believe it's a statistical fluke, because of the volume of patients we've treated and the volume of patients treated elsewhere. In addition, we have a physician who transferred from New Orleans, who had worked with cetuximab in head and neck cancer for over a year, had never seen an infusion reaction and has yet to administer cetuximab without an infusion reaction at Vanderbilt. We are running around a 15 percent Grade III or Grade IV infusion reaction rate.

DR LOVE: What other geographic areas are seeing a high incidence of cetuximab-associated infusion reactions?

DR BERLIN: The regions that report high rates of infusion reactions with cetuximab appear to be some areas of North Carolina, South Carolina and Tennessee. It is not seen as much in the higher elevations of these regions. Whether it's the higher elevation or the specific location is not clear, but it is not seen as much there. We are currently working on a paper on this subject that includes patients from Vanderbilt, the University of North Carolina and the Sarah Cannon Cancer Center, which is a large network of cancer centers.

DR LOVE: Could this phenomenon be related to the pharmacogenetics of the people in certain areas, or is it environmental?

DR BERLIN: In modern day America it is more likely related to environment, because our patients don't come from just one area. They are originally from different areas — they are not just people who are native to Tennessee. We see a variety of patients from all over the world.

DR LOVE: What exactly do we know about the incidence of infusion reactions with panitumumab?

DR BERLIN: I have yet to hear about a patient who has had an infusion reaction with panitumumab. The infusion reaction rate is less than one percent, and the patients who experience a panitumumab-associated infusion reaction are generally able to receive the drug a second time with premedication.

Track 7

DR LOVE: Can you comment on the combination of an EGFR antibody and bevacizumab?

DR BERLIN: At this point, we don't know if that's truly beneficial. A couple of years ago when Dr Saltz presented data on the BOND-2 trial, he showed that the combination of cetuximab and bevacizumab looked better than cetuximab alone from the BOND-1 trial, and the combination of irinotecan/cetuximab/bevacizumab looked better than irinotecan/cetuximab alone (Saltz 2005).

Of course, comparing trial to trial is problematic. BOND-2 was a small, Phase II trial. So we don't know if the differences are real, but they provide a good rationale for what has been called "horizontal targeting," or targeting two separate pathways.

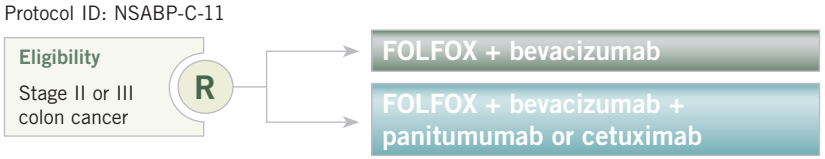
The PACCE trial (2.1) and the Intergroup trial (C80405) investigated whether double-antibody therapy in the first-line setting is better. The Intergroup trial is evaluating chemotherapy (FOLFIRI or FOLFOX) with cetuximab or bevacizumab or both.

DR LOVE: The NSABP is considering adding an EGFR inhibitor to FOLFOX/bevacizumab for their next adjuvant trial (2.3). What do you think about that strategy?

DR BERLIN: I believe that is a reasonable leap, and I am much in favor of it. I don't know which EGFR inhibitor the NSABP will settle on, but I know that they will use one of the antibodies in combination with FOLFOX/bevacizumab versus FOLFOX/bevacizumab alone.

2.3

Proposed Phase III Randomized Study of FOLFOX and Bevacizumab with or without Panitumumab or Cetuximab in Patients with Resected Stage II or III Colon Cancer



SOURCE: NSABP group meeting, April 2006.

Track 14

DR LOVE: What is your approach to using bevacizumab in patients with prior arterial events?

DR BERLIN: Patients who were 65 years of age and older with a prior event had more than a 17 percent risk of a second event while on bevacizumab — quite a substantial risk (2.4). However, we have a number of 65-year-old patients who have had a previous MI and are receiving bevacizumab. We have warned them about the potential for arterial events, but it's hard not to recommend a drug with a survival benefit this good.

Track 16

DR LOVE: How do you approach treatment of hypertension associated with bevacizumab in a patient with metastatic disease?

DR BERLIN: We tend to use the beta blockers or the ACE inhibitors. We treat patients on bevacizumab more aggressively for hypertension because of the potential for reversible posterior leukoencephalopathy syndrome (RPLS), which can be mistaken for a stroke or a TIA. The syndrome can include confusion, symptoms of a stroke, seizures or even coma or death. RPLS

happens rarely, but almost always in conjunction with at least some level of hypertension, and treating the hypertension usually leads to reversibility. ■

2.4 **Incidence of Arterial Thromboembolic Events (ATEs) in a Pooled Analysis of Five Randomized Trials of Chemotherapy with or without Bevacizumab**

	Bevacizumab/chemotherapy	Chemotherapy alone
All patients	37/963 (3.8%)	13/782 (1.7%)
Age ≥ 65 years	24/339 (7.1%)	7/279 (2.5%)
History of ATEs	14/89 (15.7%)	2/59 (3.4%)
Age ≥ 65 years and history of ATEs	12/67 (17.9%)	1/46 (2.2%)

SOURCE: Skillings JR et al. *Proc ASCO* 2005;**Abstract 3019**.

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Hecht J et al. **ABX-EGF monotherapy in patients (pts) with metastatic colorectal cancer (mCRC): An updated analysis.** *Proc ASCO* 2004;**Abstract 3511**.

Hedrick E et al. **Safety of bevacizumab plus chemotherapy as first-line treatment of patients with metastatic colorectal cancer: Updated results from a large observational registry in the US (BRiTE).** *Proc ASCO* 2006;**Abstract 3536**.

Lenz HJ. **Anti-EGFR mechanism of action: Antitumor effect and underlying cause of adverse events.** *Oncology (Williston Park)* 2006;20(5 Suppl 2):5-13. **Abstract**

Melichar B et al. **Successful management of infusion reaction accompanying the start of cetuximab therapy.** *Support Care Cancer* 2006;[Epub ahead of print]. **Abstract**

Patel DD, Goldberg RM. **Cetuximab-associated infusion reactions: Pathology and management.** *Oncology (Williston Park)* 2006;20(11):1373-82. **Abstract**

Peeters M et al. **A Phase 3, multicenter, randomized controlled trial (RCT) of panitumumab plus best supportive care (BSC) vs BSC alone in patients (pts) with metastatic colorectal cancer (mCRC).** *Proc AACR* 2006;**Abstract CP-1**.

Saif MW, Cohenuram M. **Role of panitumumab in the management of metastatic colorectal cancer.** *Clin Colorectal Cancer* 2006;6(2):118-24. **Abstract**

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

Skillings JR et al. **Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy.** *Proc ASCO* 2005;**Abstract 3019**.

Wainberg Z, Hecht JR. **A phase III randomized, open-label, controlled trial of chemotherapy and bevacizumab with or without panitumumab in the first-line treatment of patients with metastatic colorectal cancer.** *Clin Colorectal Cancer* 2006;5(5):363-7.
No abstract available

INTERVIEW

Heinz-Josef Lenz, MD

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

Tracks 1-16

Select Excerpts from the Interview

Track 3

DR LOVE: Can you discuss what we know about the mechanism of action of cetuximab and panitumumab?

DR LENZ: These are two monoclonal antibodies that both inhibit the epidermal growth factor receptor (EGFR). The EGFR is a critical mainstay of tumor development, tumor progression, metastasis and invasion.

When you examine the data for either one of these two agents, you see efficacy in the third- and fourth-line settings. This provides clues that the EGFR is untouched by classical chemotherapy — there are no mechanisms of cross resistance — and shows how important this receptor is in the process of tumor progression.

We want to understand which patients might benefit most from these therapies. The first goal is to evaluate the mechanism of resistance of cetuximab. We went back to the literature and found data from animal models showing that when tumors overexpress vascular endothelial growth factor (VEGF), cetuximab does not work.

In our clinical trial at the University of Southern California, 40 patients were treated with cetuximab, again in the third- and fourth-line settings. When we measured VEGF in the tumor, that's exactly what we found: Tumors with high levels of VEGF do not respond to cetuximab (Vallböhmer 2005).

DR LOVE: Is the VEGF receptor found on the tumor cells?

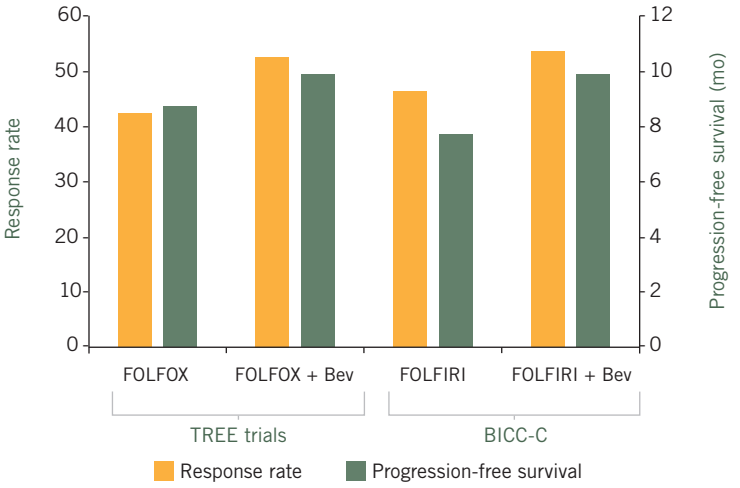
DR LENZ: Yes. The VEGF receptor is expressed not only on the endothelial cells but also significantly on tumor cells (Fan 2005). It is interesting because with anti-VEGF treatment you have an anti-angiogenic effect as well as an antitumor effect.

Track 8

DR LOVE: In general, how do you approach first-line therapy in metastatic colon cancer?

3.1

Comparison of Response Rates and Progression-Free Survival in Trials that Evaluated FOLFOX or FOLFIRI with and without Bevacizumab for First-Line Treatment of Metastatic Colon Cancer: TREE and BICC-C Trials



SOURCES: Grothey A. Presentation. Best of ASCO 2006, Beverly Hills; Hochster HS et al. Presentation. ASCO 2006;**Abstract 3510**; Fuchs C et al. ASCO 2006;**Abstract 3506**.

DR LENZ: I usually use either a backbone of FOLFOX or FOLFIRI, usually combined with bevacizumab. We know some patients will benefit more from FOLFIRI and others will benefit more from FOLFOX, and that will also be true for bevacizumab and cetuximab (3.1). We know that bevacizumab has little activity as monotherapy. It needs chemotherapy to be effective cytotoxically.

Track 14

DR LOVE: What did you think about the presentation done at ASCO 2006 evaluating the side effects of fluoropyrimidine monotherapy based on geography (3.2)?

DR LENZ: Dan Haller presented these data, and he comprehensively evaluated the frequency of side effects of 5-FU or capecitabine in the United States and the rest of the world (Haller 2006).

An ongoing discrepancy exists between the toxicities reported in Europe and the United States, and we know there are significant differences in 5-FU toxicity among different ethnic populations. Asians, African-Americans and Caucasians experience different levels of toxicity. That is explained by the genetic make-up of the patient — not the tumor.

The biggest difference between Europe and the United States is the supplementation of food with folates, which has a significant benefit for cardiovascular and neurological development and so on. In Europe, folate supplementation is not common. We also know that Americans are much more eager to supplement their diet with vitamins, including folic acid.

We believe one of the major explanations for the differences in fluoropyrimidine toxicities may be the supplement of folate in our food and the intake of vitamin supplements. The more supplementation of folate, the higher the toxicity.

3.2

Regional Differences in Tolerability of Fluoropyrimidines

Adjusted relative risk (95% CI) for US vs non-US patients

	First-line MCRC	Adjuvant colon cancer
Grade III/IV AEs	1.75 (1.34-2.29)	1.48 (1.10-1.99)
Grade III/IV GI AEs	1.74 (1.27-2.37)	1.68 (1.23-2.30)
Grade III/IV neutropenia	1.46 (0.98-2.18)	1.44 (0.90-2.30)

CI = confidence interval
MCRC = metastatic colorectal cancer
AE = adverse event
GI= gastrointestinal

SOURCE: With permission. Haller DG et al. *Proc ASCO* 2006;**Abstract 3514**.

We also believe another reason may be some difference of genetic background, because our populations have changed and the genetic pool is not as homogeneous as when the immigrants came over from Europe.

However, I don't believe that's the only explanation. I believe there is a lifestyle factor in that equation. From my point of view, the most reasonable explanation for the differences in toxicities by region is a combination of genetic background and folate supplementation, and that's exactly what Dan Haller concluded. ■

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Van Cutsem E. **Challenges in the use of epidermal growth factor receptor inhibitors in colorectal cancer.** *Oncologist* 2006;11(9):1010-7. **Abstract**

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **MD Anderson is conducting a Phase II neoadjuvant trial of capecitabine and _____ in combination with radiation therapy for patients with rectal cancer.**
   a. Cetuximab
   b. Bevacizumab
   c. Panitumumab
   d. All of the above
   e. None of the above

2. **NSABP-C-08 evaluated FOLFOX with or without _____ in patients with Stage II or III colon cancer.**
   a. Cetuximab
   b. Panitumumab
   c. Bevacizumab

3. **The NSABP is considering an adjuvant clinical trial evaluating FOLFOX/ bevacizumab with or without an EGFR inhibitor.**
   a. True
   b. False

4. **Which of the following might increase the risk of developing an arterial thromboembolic event while being treated with bevacizumab?**
   a. Age of 65 years or older
   b. Concomitant treatment with aspirin
   c. History of a prior arterial thromboembolic event
   d. All of the above
   e. Both a and c

5. **Reversible posterior leukoencephalopathy syndrome (RPLS) is a rare syndrome that may be mistaken for a stroke or TIA and is associated with hypertension during treatment with bevacizumab.**
   a. True
   b. False

6. **A presentation by Richard Goldberg at ASCO 2006 demonstrated that elderly patients enrolled in clinical trials tolerated FOLFOX as well as younger patients.**
   a. True
   b. False

7. **Which of the following is a fully human antibody that targets the epidermal growth factor receptor (EGFR)?**
   a. Cetuximab
   b. Panitumumab
   c. Both a and b
   d. None of the above

8. **Among patients with previously treated metastatic colorectal cancer, _____ with best supportive care was associated with improved progression-free survival compared to best supportive care alone.**
   a. Panitumumab
   b. Bevacizumab
   c. Cetuximab
   d. All of the above

9. **The PACCE trial is evaluating chemotherapy and bevacizumab with or without _____ in the metastatic setting.**
   a. Cetuximab
   b. Panitumumab
   c. Both a and b
   d. None of the above

Post-test answer key: 1b, 2c, 3a, 4e, 5a, 6a, 7b, 8a, 9b

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Robert A Wolff, MD	5 4 3 2 1	5 4 3 2 1
Jordan D Berlin, MD	5 4 3 2 1	5 4 3 2 1
Heinz-Josef Lenz, 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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EVALUATION FORM

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.....

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.....

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

.....

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.....

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Colorectal Cancer™

U P D A T E

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