CCU | 2009 VOL 8 | ISSUE 1

Colorectal Cancer™ UPDATE

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

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INTERVIEWS

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Colorectal Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Colorectal cancer is among the most common types of cancer in the United States, and management strategies are continuously evolving. Published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents, novel biomarkers affecting treatment selection and alterations to existing management algorithms. 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 with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Recall the ongoing clinical trials evaluating the addition of biologic agents to conventional adjuvant chemotherapy as treatment for Stage II and Stage III colon cancer.
- Utilize biomarkers to predict response or resistance to chemotherapy and/or biologic agents in patients with colorectal cancer (CRC).
- Develop up-to-date clinical management strategies for metastatic CRC, incorporating chemotherapy, VEGF inhibitors and EGFR inhibitors.
- Assess the application of recently reported and ongoing clinical trials evaluating tyrosine kinase inhibitors or the combination of EGFR and VEGF inhibition for patients with CRC.
- Counsel patients about the potential risk of oxaliplatin-induced neurotoxicity and the preventive measures that may offset its occurrence.
- Formulate a treatment plan for patients with synchronous or metachronous liver-only CRC metastases.
- Assess appropriate patients with CRC for eligibility in ongoing clinical trials.

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This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology and Sanofi-Aventis.

Last review date: February 2009; Release date: February 2009; Expiration date: February 2010

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INTERVIEW

Paulo M Hoff, MD

Dr Hoff is Clinical Director at the University of São Paulo's Instituto do Câncer do Estado de São Paulo (ICESP) and Executive Director at the Hospital Sírio-Libanês in São Paulo, Brazil.

Tracks 1-12

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the tyrosine kinase inhibitors (TKIs) that are being investigated in the treatment of colorectal cancer?

DR HOFF: Two TKIs are currently being evaluated in Phase III trials in colorectal cancer. A large international trial is evaluating FOLFIRI with or without sunitinib — which blocks VEGF and PDGF receptors — as first-line therapy for metastatic disease (A6181122). Because the trial includes one arm without a biologic agent, it's primarily being conducted outside of the United States, where that approach is more acceptable.

The other TKI under investigation, cediranib, blocks VEGFR-1, VEGFR-2, VEGFR-3 and c-Kit. Data from HORIZON I, a Phase II randomized trial

evaluating second-line therapy with FOLFOX/bevacizumab versus FOLFOX/cediranib at 20 milligrams per day versus FOLFOX/cediranib at 30 milligrams per day, were reported at ASCO 2008 (Cunningham 2008).

Although no statistical difference in progression-free survival was evident among the three arms, the data suggest that cediranib has clinical activity in the same range as bevacizumab. The response rate was numerically better for FOLFOX/bevacizumab but was not statistically different (Cunningham 2008; [1.1]).

Two Phase III trials are currently evaluating cediranib in the first-line setting. One, being conducted outside of the United States, originally evaluated two different doses of cediranib. After the HORIZON I data became available, the trial was modified to evaluate FOLFOX with placebo or cediranib at 20 milligrams per day. This trial has recently completed accrual of 1,050 patients.

The other trial, HORIZON III, is being conducted in the United States and compares FOLFOX/bevacizumab to FOLFOX/cediranib at 20 milligrams per day. This trial has a target accrual of 1,600 patients, which should be completed within the next few months. We may have efficacy data from both of these trials by late 2009 or early 2010.

1.1

HORIZON I: A Phase II Randomized Study Comparing FOLFOX/Cediranib to FOLFOX/Bevacizumab as Second-Line Therapy for Patients with Metastatic Colorectal Cancer

	FOLFOX + cediranib 20 mg (n = 70)	FOLFOX + cediranib 30 mg (n = 73)	FOLFOX + bevacizumab 10 mg* (n = 66)
Median progression-free survival	5.8 months[1]	7.2 months[2]	7.8 months
Partial response rate	18%	19%	27%

* More favorable prognosis

[1] Hazard ratio of FOLFOX/cediranib 20 mg:FOLFOX/bevacizumab = 1.28 (*p*-value = 0.29)

[2] Hazard ratio of FOLFOX/cediranib 30 mg:FOLFOX/bevacizumab = 1.17 (*p*-value = 0.79)

Grade III/IV adverse events occurring in at least 10 percent of patients

	FOLFOX + cediranib 20 mg (n = 70)	FOLFOX + cediranib 30 mg (n = 73)	FOLFOX + bevacizumab 10 mg/kg (n = 66)
Diarrhea	14%	19%	17%
Fatigue	13%	10%	14%
Hypertension	10%	22%	12%
Neutropenia	31%	34%	27%
Thrombocytopenia	4%	10%	0%
Asthenia	9%	12%	3%

SOURCE: Cunningham D et al, on behalf of the HORIZON I study group. *Proc ASCO* 2008;**Abstract 4028**.

Track 2

DR LOVE: How do the side effects of cediranib compare to those of bevacizumab?

DR HOFF: The toxicity profiles from two arms of the HORIZON I trial, FOLFOX/bevacizumab and FOLFOX/cediranib at 20 milligrams per day, are similar. However, some differences are evident.

Numerically at least, patients taking cediranib experience somewhat more asthenia (Cunningham 2008; [1.1]). In my practice, patients mention more dysphonia and hoarseness with cediranib, although this has not been a major problem. The other side effects we see with cediranib are those you would expect from an anti-VEGF agent, such as hypertension.

We believe this is a class effect. How the hypertension associated with bevacizumab compares to that induced by cediranib will be better answered by the larger HORIZON III trial with 1,600 patients.

Tracks 3-5, 7

DR LOVE: Would you discuss the design of the AVANT trial and when you expect the data will be available?

DR HOFF: The AVANT study was designed to explore the use of adjuvant bevacizumab in patients with Stage III or high-risk Stage II colon cancer. Patients were randomly assigned to receive FOLFOX, FOLFOX/bevacizumab or CAPOX/bevacizumab. We accrued 3,450 patients, and we don't expect results until perhaps 2010 or early 2011.

DR LOVE: What were your thoughts about the toxicity data presented at ASCO 2008 on the NSABP-C-08 trial?

DR HOFF: No substantial increase in toxicity was observed with the addition of bevacizumab to adjuvant FOLFOX. I found it particularly interesting that the rate of thrombocytopenia decreased among the patients who received bevacizumab (Allegra 2008; [1.2]).

DR LOVE: Why do you think they did not see a significant increase in bowel perforations with bevacizumab in NSABP-C-08 (Allegra 2008; [1.2]) when it has been reported in the advanced-disease studies?

DR HOFF: A couple of explanations are possible. One is that patients in the adjuvant trial were healthier than those with advanced disease. In the adjuvant setting, patients have less of a chance of having carcinomatosis, which could play a role in bowel perforation.

Also, we cannot discard the possibility of numbers. One would not expect a large number of perforations in a trial the size of NSABP-C-08, with only a few more than 1,000 patients receiving bevacizumab.

DR LOVE: They also did not report a significant increase in arterial events.

DR HOFF: The trials are avoiding patients with a history of arterial events. Also, patients treated for cancer who are presumed free of disease tend to take good care of themselves in terms of diet and exercise. We must remember, however, that these data are preliminary. They are encouraging and may turn out to be true, but I believe it's early for us to disregard the possibility of arterial events or bowel perforations in this population.

DR LOVE: Would you consider using bevacizumab in the adjuvant setting in your practice?

DR HOFF: I believe it would be premature to use it to treat micrometastatic disease off study. At this point, no role exists in the adjuvant setting for these molecular-targeted agents — bevacizumab, cetuximab, panitumumab or any agents currently in the investigational phase. We should not forget the lesson we learned from irinotecan: We all expected it to be effective in the adjuvant setting, but it was not. ■

1.2

Initial Safety Report of NSABP-C-08: Adjuvant FOLFOX6 with or without Bevacizumab (Bev) in Stage I to Stage III Colorectal Cancer

Endpoint	FOLFOX6 (n = 1,356)	FOLFOX6 + bev (n = 1,354)	*p*-value
GI perforation	0.15%	0.3%	ns
Hemorrhage	1.9%	1.9%	ns
Cardiac ischemia	0.76%	1.51%	ns
CNS ischemia	0.38%	0.45%	ns
Peripheral arterial ischemia	0.23%	0%	ns
Thrombocytopenia (Grade III+)	3.4%	1.4%	<0.001
Allergic reaction (Grade III+)	4.7%	3.1%	0.03
Hypertension (Grade III+)	1.8%	12%	<0.0001
Any pain (Grade III+)	6.3%	11.1%	<0.0001
Proteinuria (Grade III+)	0.8%	2.7%	<0.001
Wound complications (Grade III+)	0.3%	1.7%	<0.001
18-month mortality	1.33%	1.35%	1.0

SOURCE: Allegra CJ et al. *Proc ASCO* 2008;**Abstract 4006**.

SELECT PUBLICATIONS

Allegra CJ et al. **Initial safety report of NSABP C-08, a randomized phase III study of modified 5-fluorouracil (5-FU)/leucovorin (LCV) and oxaliplatin (OX) (mFOLFOX6) with or without bevacizumab (bev) in the adjuvant treatment of patients with stage II/III colon cancer.** *Proc ASCO* 2008;**Abstract 4006**.

Cunningham D et al, on behalf of the HORIZON I study group. **A phase II, double-blind, randomized multicenter study of cediranib with FOLFOX versus bevacizumab with FOLFOX in patients with previously treated metastatic colorectal cancer (mCRC): Final PFS results.** *Proc ASCO* 2008;**Abstract 4028**.

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 USC/Norris Comprehensive Cancer Center in Los Angeles, California.

Tracks 1-16

Track 1 Case discussion: A 36-year-old woman with a synchronous primary colon cancer and unresectable, bilobar hepatic metastases

Track 2 ERCC1 and thymidylate synthase as predictors of response to chemotherapy

Track 3 Potential relationship between K-ras status and bevacizumab sensitivity

Track 4 Enhanced efficacy of partnering anti-VEGF therapy with oxaliplatin for patients who have experienced disease progression after irinotecan-based therapy

Track 5 Conversion of hepatic metastases from unresectable to resectable with FOLFIRI and bevacizumab/cetuximab in CALGB-C80405

Track 6 Defining parameters for resectable colorectal liver metastases

Track 7 Surgical approach for patients with synchronous primary colon and hepatic metastases

Track 8 BOND-2: Cetuximab/bevacizumab with or without irinotecan in irinotecan-refractory mCRC

Track 9 Toxicity and efficacy in PACCE (chemotherapy/bevacizumab with panitumumab) and CAIRO-2 (chemotherapy/bevacizumab with cetuximab)

Track 10 Case follow-up: Repeat perioperative FOLFIRI/bevacizumab/cetuximab for a recurrent hepatic metastasis followed by resection

Track 11 Incidence of high levels of ERCC1 in CRC and response to FOLFIRI

Track 12 Biologic rationale for potential cure from resection of CRC hepatic metastases

Track 13 Translating the paradigm of resection for CRC metastases to the treatment of breast cancer

Track 14 Role of preoperative therapy to elucidate tumor biology in patients with hepatic-only metastases

Track 15 Colon cancer stem cells and mechanisms of chemoresistance and tumor recurrence

Track 16 Use of molecular signatures to tailor individualized treatment for patients with CRC

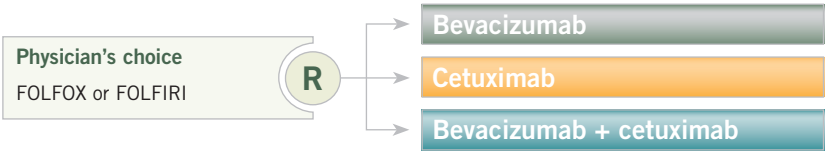
Case Presentation

A 36-year-old woman presented with primary K-ras wild-type colon cancer and unresectable bilobar hepatic metastases. The primary tumor was resected, and she was randomly assigned to FOLFIRI/cetuximab/bevacizumab as part of CALGB trial 80405 (2.1). After eight months, her liver metastases were deemed resectable. She underwent hepatic resection and radiofrequency ablation, followed by three months of additional FOLFIRI/bevacizumab/cetuximab. One year later, scans revealed a 2-cm hepatic lesion. She restarted FOLFIRI/cetuximab/bevacizumab, and the tumor was resected after it decreased to one centimeter. After surgery, she restarted the same systemic therapy.

2.1

CALGB-C80405: Chemotherapy and Biologic Agents Alone or in Combination in the Treatment of Metastatic Colorectal Cancer

Target accrual: 2,300



Select Eligibility Criteria

- Untreated metastatic disease
- More than 12 months since adjuvant 5-FU with or without oxaliplatin or irinotecan
- K-ras wild-type gene
- No CNS metastases
- No prior anti-VEGF or anti-EGF treatment

SOURCE: NCI Physician Data Query, January 2009.

Select Excerpts from the Interview

Track 2

DR LOVE: Let's discuss this case. In CALGB-C80405, the clinician can select either FOLFOX or FOLFIRI. Why did you choose FOLFIRI?

DR LENZ: The choice between FOLFOX and FOLFIRI as first-line therapy for metastatic colorectal cancer is controversial. I believe that in the community these combinations are interchangeable in terms of efficacy and toxicity.

During the past few years, we have established a molecular signature that predicts response. With certain genes, FOLFOX does not work and FOLFIRI has a higher chance of providing benefit. We tested the patient for two genes that predict for sensitivity to 5-FU and oxaliplatin — thymidylate synthase (TS) and excision repair cross-complementation group 1 (ERCC1). The latter has been tested prospectively and validated in non-small cell lung cancer (Bepler 2008).

Patients with colorectal cancer and high levels of ERCC1 are unlikely to benefit from platinum-based chemotherapy (Uchida 2008) and may benefit more from irinotecan (Vallböhmer 2006). In this patient, the TS and ERCC1 were so high that I knew oxaliplatin was unlikely to be of any benefit. In the United States, most oncologists would have chosen FOLFOX/bevacizumab, which is the most used combination regimen. We chose FOLFIRI, however, because this patient had high levels of TS and ERCC1.

Tracks 8-9

DR LOVE: This patient is receiving double antibody therapy, which has become controversial. As one of the investigators in the BOND-2 trial, what's your view of this strategy?

DR LENZ: In BOND-2, patients with refractory colorectal cancer were randomly assigned to irinotecan/cetuximab/bevacizumab versus cetuximab/bevacizumab. In these patients with refractory disease, both monoclonal antibodies demonstrated significant efficacy, which was enhanced by the addition of irinotecan (Saltz 2007).

This clinical trial is striking not only because of significant efficacy in patients with highly refractory disease but also because of low toxicity. No overlapping or additional toxicities were encountered (Saltz 2007). I was surprised when the initial data were reported from the first-line trials, PACCE and CAIRO-2.

In the PACCE trial, the investigator had a choice between FOLFOX and FOLFIRI. Patients were then randomly assigned to bevacizumab versus bevacizumab/panitumumab (Hecht 2008a, 2008b). CAIRO-2 evaluated CAPOX/bevacizumab with or without cetuximab (Punt 2008).

Among the patients receiving both monoclonal antibodies, the trials demonstrated similar patterns of increased toxicity and a decrease in efficacy, as measured by response rate and progression-free survival (Hecht 2008a; Punt 2008). One explanation for these results is that K-ras sorts out patients who benefit from cetuximab or panitumumab, and the particular chemotherapeutic agent may also play a significant role. But K-ras alone will not explain the differences in toxicity and efficacy.

As we have seen in other clinical trials, particularly those with oxaliplatin-based combinations with bevacizumab, some patients may be harmed by increasing resistance to certain chemotherapies when cetuximab is combined with bevacizumab. ■

SELECT PUBLICATIONS

Bepler G et al. **Molecular analysis-based treatment strategies for non-small cell lung cancer.** *Cancer Control* 2008;15(2):130-9. **Abstract**

Hecht JR et al. **An updated analysis of safety and efficacy of oxaliplatin (Ox)/bevacizumab (bev) +/- panitumumab (pmab) for first-line treatment (tx) of metastatic colorectal cancer (mCRC) from a randomized, controlled trial (PACCE).** Gastrointestinal Cancers Symposium 2008a;**Abstract 273**.

Hecht JR et al. **Interim results from PACCE: Irinotecan (Iri)/bevacizumab (bev) ± panitumumab (pmab) as first-line treatment (tx) for metastatic colorectal cancer (mCRC).** Gastrointestinal Cancers Symposium 2008b;**Abstract 279**.

Punt CJ et al. **Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG).** *Proc ASCO* 2008;**LBA4011**.

Saltz LB et al. **Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: The BOND-2 study.** *J Clin Oncol* 2007;25(29):4557-61. **Abstract**

Uchida K et al. **Thymidylate synthase, dihydropyrimidine dehydrogenase, ERCC1, and thymidine phosphorylase gene expression in primary and metastatic gastrointestinal adenocarcinoma tissue in patients treated on a phase I trial of oxaliplatin and capecitabine.** *BMC Cancer* 2008;8(1):386. **Abstract**

Vallböhmer D et al. **Molecular determinants of irinotecan efficacy.** *Int J Cancer* 2006;119(10):2435-42. **Abstract**

INTERVIEW

Howard S Hochster, MD

Dr Hochster is Professor of Medicine and Clinical Pharmacology at the NYU Cancer Institute in New York, New York.

Tracks 1-10

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the CONcePT trial?

DR HOCHSTER: Our goal was to conduct the first randomized, placebo-controlled study of calcium/magnesium for the prevention of oxaliplatin-induced neurotoxicity. A second goal was to improve the time to treatment failure (Hochster 2008; [3.1]).

We knew about the scheduling issue with oxaliplatin from Dr de Gramont's OPTIMOX1 study, which used a high dose of oxaliplatin for six cycles and then discontinued it until the patient's disease progressed (Tournigand 2006). In the CONcePT study, we used a conventional dose of oxaliplatin but administered it in four-month blocks (intermittent oxaliplatin). Patients received four months of FOLFOX with bevacizumab, four months of 5-FU with bevacizumab and then automatically restarted oxaliplatin at the eighth month (Hochster 2008; [3.1]).

Accrual to the trial was slow, and most doctors did not believe we needed a randomized study of calcium/magnesium because they all knew it worked. So we amended the protocol after 140 patients had enrolled and allowed everyone to receive calcium/magnesium. After that amendment, the trial involved only the randomization to either intermittent or continuous oxaliplatin (Hochster 2008).

After 180 patients enrolled, the Independent Data Monitoring Committee (IDMC) reviewed the data. It appeared that fewer responses occurred in the group who had been receiving calcium/magnesium. At that point, the IDMC stopped the trial and didn't allow anyone to receive calcium/magnesium.

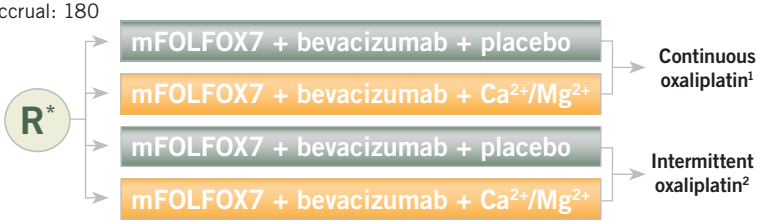
In the meantime, we submitted all of the scans to an independent radiology review committee. As we presented at the 2008 Gastrointestinal Cancers Symposium, the response rate was equivalent or slightly better for the patients receiving calcium/magnesium, with an odds ratio of 1.3 (Hochster 2008; [3.2]).

Furthermore, we reported that the hazard ratio for time to treatment failure was approximately 0.6 in favor of intermittent oxaliplatin. Instead of about four months with continuous oxaliplatin, the median time to treatment failure — the primary endpoint — was about six months for the group who received intermittent oxaliplatin.

The difference in median progression-free survival was even longer — seven versus 12 months. With a truncated study of only 140 patients, the difference was large enough to indicate a real effect on time to treatment failure and progression-free survival (Grothey 2008; [3.3]).

3.1 **CONcePT: Combined Oxaliplatin Neurotoxicity Prevention Trial**

Protocol ID: NCT00129870
Accrual: 180



* No randomization to placebo after protocol amendment

[1] FOLFOX7 + bevacizumab until treatment failure
[2] Alternating between FOLFOX7 + bevacizumab x 8 and 5-FU/LV + bevacizumab x 8

Ca^{2+}/Mg^{2+} = 1 g calcium gluconate and 1 g magnesium sulfate over 30 minutes pre- and postoxaliplatin

Eligibility

- Metastatic measurable colorectal cancer
- No prior therapy for metastatic disease
- No peripheral neuropathy > Grade I
- No uncontrolled hypertension
- No significant history of bleeding within six months

SOURCE: Hochster HS et al. Gastrointestinal Cancers Symposium 2008;**Abstract 280**.

3.2 **CONcePT: Effect of Calcium/Magnesium (Ca/Mg) on Overall Response Rate (ORR) Among Evaluable Patients Receiving FOLFOX with Bevacizumab**

	Continuous oxaliplatin		Intermittent oxaliplatin	
	Placebo (n = 28)	Ca/Mg (n = 31)	Placebo (n = 31)	Ca/Mg (n = 28)
ORR	21%	36%	45%	43%

Ca/Mg relative to placebo: Odds ratio = 1.29 (95% CI: 0.57-2.98); $p = 0.565$

SOURCE: Hochster HS et al. Gastrointestinal Cancers Symposium 2008;**Abstract 280**.

3.3 **CONcePT: Time to Treatment Failure (TTF) and Progression-Free Survival (PFS) for Intermittent versus Continuous Oxaliplatin**

	Continuous oxaliplatin (n = 68)	Intermittent oxaliplatin (n = 71)	Hazard ratio (95% CI)	*p*-value
Median TTF	4.2 months	5.6 months	0.58 (0.41-0.83)	0.0025
Median PFS	7.3 months	12 months	0.53 (0.29-0.99)	0.048

CI = confidence interval

SOURCE: Grothey A et al. *Proc ASCO* 2008;**Abstract 4010**.

Tracks 4-5

DR LOVE: What's your conclusion?

DR HOCHSTER: I believe the data are clear that calcium/magnesium does not interfere with the activity of FOLFOX and that its use does reduce cumulative and acute neurotoxicity. So I believe it's safe to use. Those who found calcium/magnesium helpful before should not be concerned about readopting it as a standard approach.

DR LOVE: Do you use calcium/magnesium preventively in your practice?

DR HOCHSTER: I do. I have gone back to using it all the time. I had stopped for about eight to 10 months while we were assessing the data from the CONcePT study.

DR LOVE: Do you use it routinely for every patient in the adjuvant and metastatic settings?

DR HOCHSTER: In the metastatic setting, we have the response data. If somebody wants to be a stickler, they might say that we don't know that an effect is evident in the adjuvant setting. So it could be more risky to use it in the adjuvant setting, but I do not see how that's a possibility.

DR LOVE: What about the use of intermittent oxaliplatin as evaluated in CONcePT?

DR HOCHSTER: I believe to obtain the maximum benefit from oxaliplatin it is important to take a break and then use it again. In CONcePT, we used four months on, four months off and four months on again. Patients demonstrated a 12-month median time to disease progression, which is what we thought would happen when we added bevacizumab (Grothey 2008; [3.3]). This is a way to derive more benefit from oxaliplatin.

Track 10

DR LOVE: Would you discuss the selection of therapy for a patient for whom you would like to downstage unresectable liver metastases?

DR HOCHSTER: We don't have particularly helpful data indicating whether FOLFOX or FOLFIRI is the preferable regimen in this setting — I believe either can be effective. The real issue today might be the use of bevacizumab or cetuximab. Tumor shrinkage with bevacizumab may not be as much as we'd like.

In the large NO16966 study, the response rate was the same for FOLFOX with or without bevacizumab (Saltz 2008). However, in the CRYSTAL trial — a first-line study of FOLFIRI with or without cetuximab — patients with wild-type K-ras benefited and their response rate was augmented with the addition of cetuximab (Van Cutsem 2008).

So the real question is, should we be using cetuximab as our first-line antibody if we're trying to shrink K-ras wild-type liver metastases preoperatively? ■

SELECT PUBLICATIONS

Grothey A et al. **Intermittent oxaliplatin (oxali) administration and time-to-treatment-failure (TTF) in metastatic colorectal cancer (mCRC): Final results of the phase III CONcePT trial.** *Proc ASCO* 2008;**Abstract 4010**.

Hochster HS et al. **Effect of intravenous (IV) calcium and magnesium (Ca/Mg) versus placebo on response to FOLFOX + bevacizumab (BEV) in the CONcePT trial.** Gastrointestinal Cancers Symposium 2008;**Abstract 280**.

Kesmodel SB et al. **Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases.** *J Clin Oncol* 2008;26(32):5254-60. **Abstract**

Saltz LB et al. **Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study.** *J Clin Oncol* 2008;26(12):2013-9. **Abstract**

Tournigand C et al. **OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer — A GERCOR study.** *J Clin Oncol* 2006;24(3):394-400. **Abstract**

Van Cutsem E et al. **KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience.** *Proc ASCO* 2008;**Abstract 2**.

INTERVIEW

Herbert I Hurwitz, MD

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

Tracks 1-10

Track 1	Potential role of dual antibodies in combination with chemotherapy in the treatment of mCRC	Track 6	Risk factors for chemotherapy/bevacizumab-associated cardiovascular complications
Track 2	Potential impact of K-ras status on efficacy of FOLFOX versus FOLFIRI in mCRC	Track 7	Correlation between bevacizumab-associated hypertension and antitumor efficacy
Track 3	Defining resectability in patients with hepatic-only metastases	Track 8	Perspective on improved outcome with the use of bevacizumab beyond first disease progression in the BRiTE registry
Track 4	Selection of a chemotherapy regimen for downstaging potentially resectable hepatic metastases	Track 9	Clinical approach to treatment holidays for patients with mCRC
Track 5	Pre- and postoperative timing for administration of bevacizumab and wound healing	Track 10	Insulin-like growth factor axis and colorectal cancer

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: What are your thoughts about the choice of systemic therapy to downstage K-ras wild-type unresectable liver-only metastases?

DR HURWITZ: Based on the BRiTE registry in the United States and the First BEAT trial in Europe, approximately 10 percent of patients treated with FOLFOX/bevacizumab undergo surgery with curative intent and 80 percent or more of those have an R0 resection (ie, no disease left; [Cassidy 2008]). With FOLFIRI/cetuximab, the downstaging rate is in the five to 10 percent range and the R0 rate is 60 to 70 percent.

All this means is that active first-line chemotherapy will downstage disease in some patients. I do not believe the available data allow us to make any inferences related to which chemotherapy regimen is better. Clinicians should simply choose what they consider to be their most active or preferred chemotherapy regimen.

DR LOVE: What is your preferred regimen in this situation?

DR HURWITZ: Barring contraindications, I prefer FOLFOX or CAPOX with bevacizumab. Bevacizumab is currently supported by more data suggesting benefit, including a survival benefit. For a patient with a good performance status who is not a candidate for a VEGF inhibitor, such as one with a history of cardiac symptoms, cetuximab in the first-line setting may make sense.

Although wound complications are an issue with bevacizumab, the risk is small. Most hepatic surgeons want patients to be off of chemotherapy for at least one month before surgery to let the liver recover from any treatment-related side effects and to improve the patient's performance status. The time off of bevacizumab should probably be consistent with its half-life, and the goal is approximately six to eight weeks. With that time frame, a significant increase in surgical risk is not evident.

Postoperatively, I don't believe any undue risk ensues in resuming chemotherapy or bevacizumab once the patient is well healed, which is usually eight weeks after a liver resection. The initial safety report from NSABP-C-08, evaluating adjuvant FOLFOX with bevacizumab, demonstrated a one to two percent increase in wound complications associated with bevacizumab (Allegra 2008; [1.2, page 6]). That rate was largely a result of hernia formation, which in the context of a potentially curative resection should be manageable.

Track 8

DR LOVE: Would you comment on the BRiTE registry data evaluating the use of bevacizumab beyond first disease progression?

DR HURWITZ: The BRiTE registry was established to follow patients who received first-line therapy with bevacizumab in order to define rare toxicities, such as cardiovascular issues and wound healing (Grothey 2008; [4.1]). We can't estimate the actual rate of these problems or identify contributing factors without evaluating thousands of patients.

The registry also gathered some outcomes data and found that patients who continued to receive bevacizumab past first disease progression fared better than those who did not (Grothey 2008; [4.2]; Ellis 2008; [4.3]). I believe this finding is consistent with two phenomena. One is that patients with more indolent disease experience progression more slowly and fare better if you continue their treatment. The other is that additional bevacizumab after initial disease progression is beneficial. It might be that bevacizumab is working best in the patients who have more indolent disease.

The BRiTE registry data also emphasize that what we call disease progression in a clinical trial may be defined differently in clinical practice. In practice, if a patient's disease has a relatively slow progression during the course of two years, although the measurements may technically meet RECIST criteria for progression, the clinician may judge the rate of progression to be slow enough to say that the patient is benefiting from therapy and that clinician may choose to continue one part of the regimen while adjusting other elements.

4.1 BRiTE Registry: Incidence of Bevacizumab-Targeted Adverse Events According to Treatment Received After Disease Progression

	No treatment after disease progression (n = 253)	Treatment without bevacizumab after disease progression (n = 531)	Treatment with bevacizumab after disease progression (n = 642)
New or worsened hypertension requiring medication	19.0%	19.2%	24.6%
Arterial thromboembolic event	2.0%	1.3%	1.2%
Grade III/IV bleeding event	2.4%	2.1%	1.9%
GI perforation	2.4%	1.5%	1.6%

SOURCE: Grothey A et al. *J Clin Oncol* 2008;26(33):5326-34. **Abstract**

4.2 BRiTE Registry: Survival According to Treatment Received After Disease Progression

	No treatment after disease progression (n = 253)	Treatment without bevacizumab after disease progression (n = 531)	Treatment with bevacizumab after disease progression (n = 642)
Median overall survival	12.6 months	19.9 months	31.8 months
Median survival beyond disease progression	3.6 months	9.5 months	19.2 months
One-year survival rate	52.5%	77.3%	87.7%

SOURCE: Grothey A et al. *J Clin Oncol* 2008;26(33):5326-34. **Abstract**

4.3 Beyond BRiTE: New Questions for Treatment After Progression on Bevacizumab

"The BRiTE study, among others, raises interesting questions. For example, what should we use in second-line therapy for metastatic CRC in patients who have experienced progression on a bevacizumab-containing regimen? For the sake of discussion, let us assume that a patient has experienced progression on infusional fluorouracil, leucovorin, and oxaliplatin plus bevacizumab (approximately 60% to 70% of patients in the United States will receive a similar first-line regimen). On the basis of National Comprehensive Cancer Network guidelines, it would be reasonable to consider an irinotecan-based regimen ± cetuximab for such a patient.

However, since these guidelines were developed, we have learned that patients with tumors with mutated *KRAS* are unlikely to benefit from anti-EGFR MoAB therapy. If this holds true, then cetuximab (or panitumumab) should not be considered for patients whose tumors express mutated *KRAS*. This limits our options in second- and third-line therapy yet provides an opportunity to study other biologics in this setting."

SOURCE: Ellis LM, Haller DG. *J Clin Oncol* 2008;26(33):5313-5. No abstract available

Track 9

DR LOVE: How do you approach the continuation of bevacizumab and the use of treatment holidays in metastatic disease?

DR HURWITZ: I expect the best answer to how long to administer bevacizumab will come from prospective studies that randomly assign patients to continuation or noncontinuation. The separate question of how to navigate treatment holidays is an excellent one now that patients are likely to receive first-line therapy for nine to 12 months and, if they're faring particularly well, even longer.

We often need to manage the side effects of some or all of the drugs. Both oxaliplatin and irinotecan can be difficult drugs to continue past four to six months. Oxaliplatin causes neuropathy and cumulative asthenia, and patients can experience asthenia and diarrhea with irinotecan.

Therefore, we almost certainly have to navigate a holiday or what I call a "working holiday," which involves the continuation of the parts of the regimen that are still tolerable. So FOLFOX/bevacizumab becomes 5-FU/bevacizumab and FOLFIRI/bevacizumab becomes 5-FU/bevacizumab.

I believe the best data for the use of bevacizumab suggest that it works better with some chemotherapy, so I have a bias toward maintaining 5-FU. If they can't do that, I believe clinicians should use their best judgment about how to make the next gradation of a holiday. Few data exist for bevacizumab as monotherapy, and I tend to offer my patients a complete break. Whether you continue with no treatment, bevacizumab or 5-FU/bevacizumab, you're still observing the patient. If his or her CEA rises or a tumor size increases on CAT scans, then you can adjust and add more therapy or move on to your next treatment. ■

SELECT PUBLICATIONS

Allegra CJ et al. **Initial safety report of NSABP C-08, a randomized phase III study of modified 5-fluorouracil (5-FU)/leucovorin (LCV) and oxaliplatin (OX) (mFOLFOX6) with or without bevacizumab (bev) in the adjuvant treatment of patients with stage II/III colon cancer.** *Proc ASCO* 2008;**Abstract 4006**.

Cassidy J et al. **Surgery with curative intent in patients (pts) treated with first-line chemotherapy (CT) + bevacizumab (BEV) for metastatic colorectal cancer (mCRC): First BEAT and NO16966.** *Proc ASCO* 2008;**Abstract 4022**.

Ellis LM, Haller DG. **Bevacizumab beyond progression: Does this make sense?** *J Clin Oncol* 2008;26(33):5313-5. No abstract available

Grothey A et al. **Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: Results from a large observational cohort study (BRiTE).** *J Clin Oncol* 2008;26(33):5326-34. **Abstract**

Hochster HS et al. **Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: Results of the TREE Study.** *J Clin Oncol* 2008;26(21):3523-9. **Abstract**

Hurwitz HI et al. **The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-ras mutation status: Analysis of a phase III study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer.** *Oncologist* 2009;14(1):22-8. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a Phase II randomized trial, FOLFOX/cediranib was compared to _____ as second-line therapy for metastatic colorectal cancer.**
   a. Cediranib alone
   b. FOLFOX/bevacizumab
   c. FOLFIRI/bevacizumab
2. **In the AVANT trial, patients are randomly assigned to receive FOLFOX or _____.**
   a. FOLFOX/bevacizumab
   b. CAPOX/bevacizumab
   c. Both a and b
3. **Patients with metastatic colorectal cancer and high gene expression levels of ERCC1 may be less likely to benefit from _____.**
   a. Capecitabine
   b. Irinotecan
   c. Oxaliplatin
4. **BOND-2 evaluated which of the following regimens for patients with irinotecan-refractory metastatic colorectal cancer?**
   a. FOLFOX
   b. Cetuximab/bevacizumab
   c. Cetuximab/bevacizumab/irinotecan
   d. Both b and c
   e. All of the above
5. **Which of the following trials evaluated the combination of chemotherapy with EGFR and VEGF inhibition as first-line therapy for patients with metastatic colorectal cancer?**
   a. PACCE
   b. BOND-2
   c. CAIRO-2
   d. Both a and c
   e. All of the above
6. **Which of the following trials evaluated the use of calcium/magnesium to prevent oxaliplatin-induced neuropathy?**
   a. CRYSTAL
   b. CONcePT
   c. OPTIMOX1
   d. All of the above
   e. None of the above
7. **In the metastatic setting, the use of calcium/magnesium to prevent oxaliplatin-induced neuropathy does not appear to decrease the response rate for FOLFOX/bevacizumab.**
   a. True
   b. False
8. **The use of intermittent oxaliplatin compared to continuous oxaliplatin improved the median _____ for patients with metastatic disease who also received bevacizumab.**
   a. Time to treatment failure
   b. Progression-free survival
   c. Both a and b
   d. None of the above
9. **Patients with _____ K-ras do not benefit from treatment with a cetuximab-containing regimen.**
   a. Mutant
   b. Wild-type
   c. Both a and b
   d. None of the above
10. **Data from the BRiTE registry support the hypothesis that continued use of bevacizumab beyond disease progression improves overall survival.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Colorectal Cancer Update — Issue 1, 2009

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- **HORIZON II and III studies of the TKI cediranib in metastatic CRC (mCRC)** 4 3 2 1
- **Initial safety report of NSABP-C-08: Adjuvant FOLFOX6 with or without bevacizumab** . . 4 3 2 1
- **CRYSTAL: K-ras status and efficacy of first-line FOLFIRI with or without cetuximab in mCRC** . . 4 3 2 1
- **ERCC1 and thymidylate synthase as predictors of clinical outcomes for patients treated with oxaliplatin versus irinotecan** 4 3 2 1
- **CONcePT: Randomized trial of calcium/magnesium and intermittent oxaliplatin in mCRC** . . . 4 3 2 1
- **BRiTE registry: Outcomes with the use of bevacizumab beyond first disease progression** 4 3 2 1
- **Defining the parameters for resectable CRC liver metastases and selection and timing of systemic therapy** 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- **HORIZON II and III studies of the TKI cediranib in metastatic CRC (mCRC)** 4 3 2 1
- **Initial safety report of NSABP-C-08: Adjuvant FOLFOX6 with or without bevacizumab** . . 4 3 2 1
- **CRYSTAL: K-ras status and efficacy of first-line FOLFIRI with or without cetuximab in mCRC** . . 4 3 2 1
- **ERCC1 and thymidylate synthase as predictors of clinical outcomes for patients treated with oxaliplatin versus irinotecan** 4 3 2 1
- **CONcePT: Randomized trial of calcium/magnesium and intermittent oxaliplatin in mCRC** . . . 4 3 2 1
- **BRiTE registry: Outcomes with the use of bevacizumab beyond first disease progression** 4 3 2 1
- **Defining the parameters for resectable CRC liver metastases and selection and timing of systemic therapy** 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: . . . . . .

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If no, please explain: . . . . . .

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4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will be able to:

- Recall the ongoing clinical trials evaluating the addition of biologic agents to conventional adjuvant chemotherapy as treatment for Stage II and Stage III colon cancer. . . . . 4 3 2 1 N/M N/A
- Utilize biomarkers to predict response or resistance to chemotherapy and/or biologic agents in patients with colorectal cancer (CRC). . . . . 4 3 2 1 N/M N/A
- Develop up-to-date clinical management strategies for metastatic CRC, incorporating chemotherapy, VEGF inhibitors and EGFR inhibitors. . . . . 4 3 2 1 N/M N/A
- Assess the application of recently reported and ongoing clinical trials evaluating tyrosine kinase inhibitors or the combination of EGFR and VEGF inhibition for patients with CRC. . . . . 4 3 2 1 N/M N/A
- Counsel patients about the potential risk of oxaliplatin-induced neurotoxicity and the preventive measures that may offset its occurrence. . . . . 4 3 2 1 N/M N/A
- Formulate a treatment plan for patients with synchronous or metachronous liver-only CRC metastases. . . . . 4 3 2 1 N/M N/A
- Assess appropriate patients with CRC for eligibility in ongoing clinical trials. . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

. . . . . .

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

.....

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☐ Yes, I am willing to participate in a follow-up survey. ☐ No, I am not willing to participate in a follow-up survey.

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Paulo M Hoff, MD	4 3 2 1	4 3 2 1
Heinz-Josef Lenz, MD	4 3 2 1	4 3 2 1
Howard S Hochster, MD	4 3 2 1	4 3 2 1
Herbert I Hurwitz, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

.....

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Colorectal Cancer™

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This program is supported by educational grants from
AstraZeneca Pharmaceuticals LP, Genentech BioOncology and Sanofi-Aventis.

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Last review date: February 2009
Release date: February 2009
Expiration date: February 2010
Estimated time to complete: 3 hours