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Colorectal Cancer™ UPDATE

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

EDITOR

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INTERVIEWS

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Charles S Fuchs, MD, MPH
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CME Certified

Colorectal Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Colorectal cancer (CRC) is among the most common cancer types diagnosed in the United States, and its clinical management is continuously evolving. Published results from ongoing trials lead to the emergence of new therapeutic agents and regimens, novel biomarkers influencing 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 scientific developments and expert perspectives, this CME activity assists medical oncologists with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Assess the evidence-based role of chemotherapy and/or biologic agents as radiation sensitizers in the management of locally advanced rectal cancer.
- Counsel patients with Stage II colon cancer about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers.
- Educate elderly patients (older than age 70) with colon cancer about the benefits and risks of adjuvant chemotherapy.
- Develop up-to-date clinical management strategies for metastatic CRC, incorporating chemotherapy and anti-VEGF and anti-EGFR antibodies.
- Formulate a treatment plan for patients with synchronous primary CRC and liver-only metastases.
- Identify novel agents under active investigation for the treatment of CRC.
- Counsel appropriately selected patients with CRC about participation in ongoing clinical trials.

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TABLE OF CONTENTS

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INTERVIEW

Alan P Venook, MD

Dr Venook is Professor of Clinical Medicine at the University of California, San Francisco in San Francisco, California.

Tracks 1-15

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you comment on the results from the NSABP-C-08 adjuvant trial evaluating FOLFOX with or without bevacizumab?

DR VENOOK: This Phase III trial included patients with Stage II or Stage III colon cancer, and the ultimate endpoint was three-year disease-free survival. After one year of treatment, the curves were clearly separate, with 40 percent

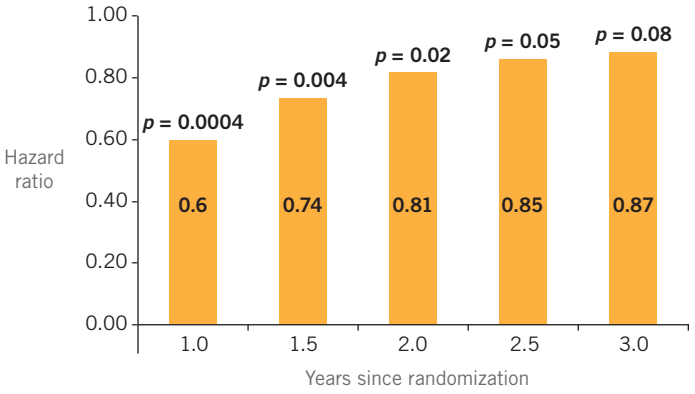
fewer recurrences on the bevacizumab arm. However, by the end of three years, the converging survival curves turned out not to favor either arm (Wolmark 2009; [1.1]). These data amplify what may be different about a drug such as bevacizumab in that it may delay recurrence or suppress disease as opposed to eradicating disease.

DR LOVE: If the primary endpoint had been disease-free survival at two years, would the study have been positive?

DR VENOOK: Yes, and that's disconcerting because another ASCO abstract suggested that two-year disease-free survival is an adequate surrogate endpoint (Sargent 2009). Dr Wolmark concluded that the next step is to consider lengthening the duration of bevacizumab. However, in a well-stated critique, Lee Ellis argued against that by noting that C-08 was a negative study and bevacizumab did not cure patients in this setting.

1.1

NSABP-C-08: Hazard Ratio for Disease-Free Survival According to Time Since Randomization



SOURCE: Wolmark N et al. *Proc ASCO* 2009;**Abstract LBA4**.

DR LOVE: The "cytostatic" type effect seen in C-08 is reminiscent of data in the metastatic setting, from the BRiTE registry (Grothey 2008; [1.2]), demonstrating that patients with progression on chemotherapy/bevacizumab had longer survival when bevacizumab was continued on disease progression. Do situations exist outside of a protocol setting in which you would consider continuing bevacizumab and changing chemotherapy upon disease progression?

DR VENOOK: Circumstances do exist in which I would continue bevacizumab, though they are not evidence based. In patients with extremely aggressive, high-volume disease who are quite ill and respond well to chemotherapy/bevacizumab, I would be wary about discontinuing bevacizumab on disease progression. I believe most clinicians have seen patients whose disease appears to explode when bevacizumab is stopped.

1.2

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%

"These data are the first report of a survival benefit associated with continuation of bevacizumab beyond PD in patients who received bevacizumab-containing first-line therapy. In BRiTE, the use of BBP, which was observed in 44% of patients who experienced PD, is one possible explanation for the longer-than-expected median OS observed in the study population, and it suggests that traditionally defined tumor progression may not indicate a loss of clinical benefit from bevacizumab.

These results support the hypothesis that continued suppression of the VEGF pathway may be important to maximize the clinical benefit from bevacizumab in mCRC. Ongoing phase III clinical trials, such as SWOG S0600, will help to additionally delineate the optimal duration of bevacizumab therapy in this setting."

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

Tracks 3-4

DR LOVE: Would you discuss the data presented at ASCO on the Onco*type* DX assay for patients with Stage II colon cancer?

DR VENOOK: This is a fabulous technological advance but with less clinical importance thus far. Thirteen genes were identified through rigorous analysis of prior NSABP studies for this RT-PCR assay.

Kerr reported on the data from the QUASAR study, which were used to validate the gene signature and establish whether it was prognostic with regard to relapse and/or predictive of benefit from chemotherapy. The QUASAR study was conducted in the United Kingdom, and it consisted of patients with Stage II colon cancer.

The treatments were not uniform, but fundamentally both a no-treatment group and a fluoropyrimidine-treatment group were included.

The data presented by Dr Kerr validated that this genomic signature does in fact have independent prognostic value for Stage II colon cancer (Kerr 2009). The assay establishes a Recurrence Score® that provides a range of recurrence risk between 12 and 22 percent (1.3). However, unlike the Onco*type* DX assay for breast cancer, the data did not show the colon cancer assay to be predictive of chemotherapy benefit.

DR LOVE: If the test were available now, would it have a clinical role?

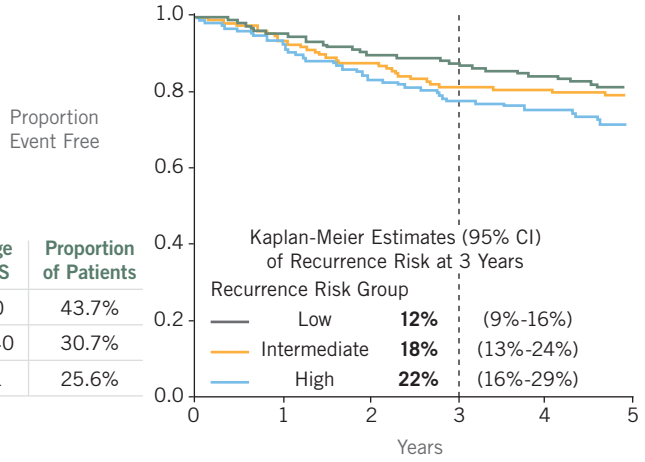
DR VENOOK: I have no doubt that this assay moves us a step forward. It's independent of microsatellite instability and tumor stage, so the finding is real.

For patients who are perfectly good candidates for therapy but whose tumors lack distinguishing high-risk features, such as lymphovascular invasion, I see it as a tiebreaker. In my experience, most patients with Stage II colon cancer either want or don't want treatment philosophically, and I don't know how much difference this test will make. ■

1.3

QUASAR/Oncotype DX Results: Recurrence Risk in Prespecified Recurrence Risk Groups (n = 711)

Recurrence Risk Group	Range of RS	Proportion of Patients
Low	<30	43.7%
Intermediate	30-40	30.7%
High	≥41	25.6%



SOURCE: With permission from Kerr D et al. *Proc ASCO* 2009;**Abstract 4000**.

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Kerr D et al. **A quantitative multigene RT-PCR assay for prediction of recurrence in stage II colon cancer: Selection of the genes in four large studies and results of the independent, prospectively designed QUASAR validation study.** *Proc ASCO* 2009;**Abstract 4000**.

Sargent DJ et al. **Use of two-year disease-free survival (DFS) as a primary endpoint in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: New data from 12,676 patients from MOSAIC, X-ACT, PETACC-3, NSABP C-06 and C-07, and C89803.** *Proc ASCO* 2009;**Abstract 4011**.

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INTERVIEW

Charles S Fuchs, MD, MPH

Dr Fuchs is Director of the Center for Gastrointestinal Cancer at Dana-Farber/Harvard Cancer Center and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-15

Select Excerpts from the Interview

Track 1

DR LOVE: Would you summarize the study you published on the relationship between insulin levels and the recurrence of CRC?

DR FUCHS: In an earlier adjuvant study with approximately 3,700 patients, we found that patients with noninsulin-dependent diabetes and high-risk Stage II or Stage III colon cancer had higher mortality rates (Meyerhardt 2003). This may not be surprising because of noncancer-related deaths, but in fact they had a much higher rate of colon cancer recurrence, leading to the speculation that insulin may be a negative driver of disease.

These data led to the study in which we measured C-peptide — a marker of long-term insulin secretion — and insulin-like growth factor binding protein 1 (IGFBP-1), which inversely correlates with insulin levels (Wolpin 2009; [2.1]). We found that patients with higher levels of C-peptide — and thus higher levels of insulin — had a higher risk of colon cancer-related mortality. In addition, patients with low IGFBP-1 — and thus high levels of insulin — had higher cancer mortality rates, supporting the notion that insulin could be a driver of recurrence.

2.1

Prospective Observational Study Evaluating the Association between Mortality and Prediagnosis Circulating C-Peptide and Insulin-Like Growth Factor Binding Protein 1 (IGFBP-1)

"Among patients with surgically resected colorectal cancer, high prediagnosis plasma levels of C-peptide were associated with an approximate doubling of the risk for death, whereas elevated levels of IGFBP-1 were associated with an approximate 50% reduction in mortality....

Although this study does not provide definitive evidence for causality, alterations in circulating insulin and related hormones are a plausible mechanism by which excess energy balance may adversely affect survival after curative resection of colorectal cancer."

SOURCE: Wolpin BM et al. *J Clin Oncol* 2009;27(2):176-85.

Track 4

DR LOVE: What were your thoughts about the data presented at ASCO and then published in the *JCO* on the outcome of the primary tumor in patients treated for synchronous Stage IV CRC who did not undergo resection?

DR FUCHS: This was a terrific observational series. In the 1990s, the majority of patients who presented with a synchronous primary tumor and metastatic disease, even if asymptomatic, underwent a colectomy prior to systemic therapy.

With the introduction of irinotecan and oxaliplatin, physicians began questioning whether it was necessary to remove asymptomatic primary tumors because they had better therapies to manage both the primary tumors and the metastases.

Using a prospective institutional database from Memorial Sloan-Kettering, Poultsides and colleagues identified 233 patients receiving treatment between

2000 and 2006 for synchronous metastatic colorectal cancer and an unresected asymptomatic primary tumor who had received an oxaliplatin- or irinotecan-based regimen. Approximately half of these patients also received bevacizumab, and none of them underwent colectomy as initial therapy.

Ultimately, 93 percent of the patients never required surgical palliation of their primary tumors, leading the investigators to conclude that prophylactic resection was not necessary for these patients (Poultsides 2009; [2.2]). Only seven percent of the patients required an emergent surgical intervention, and the use of bevacizumab did not increase the intervention rate. Frankly, that makes sense because the perforations associated with bevacizumab don't occur at the site of the primary tumor — they occur elsewhere.

The fact is that when we send these patients for a hemicolectomy, the recovery period delays systemic therapy. That may not be a major issue, but it derails the logical first step, which is to treat with chemotherapy.

2.2

Outcome of Primary Tumors in Patients with Synchronous Stage IV Colorectal Cancer Receiving Combination Chemotherapy with or without Bevacizumab in the Absence of Primary Surgical Resection

	Time from initiation of chemotherapy to intervention		Survival after intervention
	N (%)	Median	Median
Operative intervention	16 (7%)	7 mo	6 mo
Nonoperative intervention	10 (4%)	12 mo	8 mo
Curative resection	47 (20%)	8 mo	44 mo
Preemptive resection	8 (3%)	9 mo	15 mo

Median survival from initiation of chemotherapy for the 152 patients who never required an intervention was 13 months.

SOURCE: Poultsides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Track 12

DR LOVE: Would you review the design of the ECOG-E5202 trial?

DR FUCHS: This study is stratifying patients with Stage II colon cancer by two molecular features: microsatellite instability (MSI), which confers a better prognosis, and loss of heterozygosity (LOH) at chromosome 18q, which we believe confers a worse prognosis. In the trial, patients with MSI-high disease are considered to be at low risk, and they receive no active therapy. Patients at higher risk — those with disease that is microsatellite stable and 18q LOH — are randomly assigned to receive FOLFOX with or without bevacizumab (2.3).

DR LOVE: What do we know about these two markers?

DR FUCHS: The data have consistently shown that MSI predicts for better outcome, and I believe that can be useful. Of note, at least two studies have suggested that patients with tumors exhibiting high-frequency MSI do not benefit from fluorouracil-based adjuvant chemotherapy, including a large pooled analysis by Dan Sargent (Sargent 2008). But the jury is still out on this issue.

We are not certain about the role of 18q LOH. In an earlier ECOG analysis of Stage II and Stage III colon cancer, patients with Stage III disease who had 18q LOH experienced worse outcomes (Watanabe 2001). However, in the same data set, 18q was not predictive in the Stage II cohort. More recently, a series of larger efforts failed to confirm the earlier ECOG data.

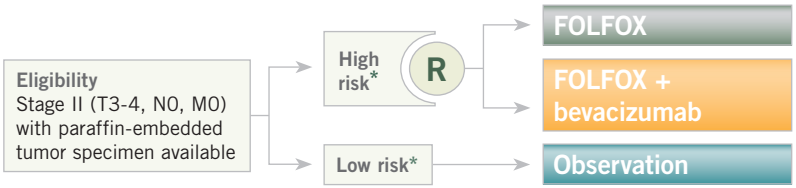
In the PETACC-3 study, comparing FOLFIRI to FU/leucovorin for patients with Stage III colon cancer, 18q LOH was not predictive.

I don't want to say that the test is not worthwhile, because our colleagues at ECOG will say that if one uses their method, it's a useful test. So we'll have to wait to see what E5202 shows. ■

2.3

FOLFOX with or without Bevacizumab for Patients with Resected Stage II Colon Cancer at High Risk for Recurrence

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



* Patients who are at high risk based on microsatellite instability (MSI) and loss of heterozygosity (LOH) at chromosome 18q are randomly assigned to one of two treatment arms. Patients who are at low risk based on MSI and 18q LOH are assigned to observation.

SOURCE: NCI Physician Data Query, December 2009.

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Wolpin BM et al. **Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer.** *J Clin Oncol* 2009;27(2):176-85.

INTERVIEW

Richard M Goldberg, MD

Dr Goldberg is Professor and Chief in the Division of Hematology/Oncology and Associate Director of the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Tracks 1-17

Select Excerpts from the Interview

Track 5

DR LOVE: Would you comment on the two presentations at ASCO 2009 evaluating oxaliplatin-containing neoadjuvant chemoradiation therapy for patients with rectal cancer?

DR GOLDBERG: Good initial Phase II data had emerged, including a CALGB

study with Dave Ryan as principal investigator, which reported complete remission rates in the mid-20 percent range after preoperative 5-FU/oxaliplatin and radiation therapy (Ryan 2006). You'd expect those rates to be between 10 and 15 percent with 5-FU alone.

In these two large randomized studies, however, no advantage was observed in complete remission rate, pathologically negative specimens or nodal status (Aschele 2009; Gerard 2009; [3.1]). We were disappointed by the results. I see a number of patients for second opinions whose physicians have already adopted the strategy of adding oxaliplatin to 5-FU as a radiation sensitizer.

I believe that these data are strong enough that such an approach should not be considered outside the context of a clinical trial. The NSABP-R-04 study is evaluating preoperative chemoradiation therapy with or without oxaliplatin, so we'll have another big data set to help confirm or refute these findings.

DR LOVE: What is known about biologics for rectal cancer, particularly in terms of neoadjuvant chemoradiation therapy?

DR GOLDBERG: Interesting data published by Chris Willett evaluated bevacizumab (Willett 2004, 2009). The authors studied interstitial fluid pressures after administration of single-agent bevacizumab and found that the fluid pressures decreased, presumably indicating that you obtain better tumor

3.1

Preoperative Chemoradiation Therapy with or without Weekly Oxaliplatin (Oxa) for Patients with Locally Advanced Rectal Cancer

	STAR-01[1]		Prodige 2-ACCORD 12/0405[2]	
	5-FU/RT	5-FU/Oxa/RT	CAPE45	CAPOX50
Efficacy				
Primary endpoint*	16%	16%	14%	19%
	$p = 0.94$		$p = 0.11$	
Adverse events				
Any Grade III/IV event	8%	24%	11%	25%
	$p < 0.0001$		$p < 0.0001$	
Diarrhea (Grade III/IV)	4%	15%	3%	13%
	$p < 0.0001$		$p < 0.0001$	
Neuropathy†	0.5%	36%	0.4%	5%
	$p < 0.0001$		$p < 0.002$	

CAPE45 = radiation therapy (45 Gy x 5 wk) and capecitabine (800 mg/m^2 BID/day); CAPOX50 = radiation therapy (50 Gy x 5 wk), capecitabine (800 mg/m^2 BID/day [except weekends]), and oxaliplatin (50 mg/m^2 weekly)

* Pathologic complete response[1]; complete sterilization of operative specimen/no visible tumor cells[2]; † Neurosensory (Grade II/III)[1]; peripheral neuropathy (Grade II)[2]

SOURCES: [1] Aschele C et al. *Proc ASCO* 2009;**Abstract CRA4008**; [2] Gerard JP et al. *Proc ASCO* 2009;**Abstract LBA4007**.

profusion and therefore better distribution of chemotherapy with the addition of bevacizumab to 5-FU.

We've seen only Phase I and some Phase II data with bevacizumab in that setting. I would not recommend it as an off-study approach. We also have interesting data that cetuximab is an effective radiation sensitizer in head and neck cancer (Bonner 2006) and questioning whether that approach can be applied to rectal cancer. Those studies are in progress, but I'm not aware of any data yet.

Tracks 9-10, 14

Case discussion

A 39-year-old woman presents with right-sided, obstructive, K-ras wild-type colon cancer and extensive hepatic metastases

DR GOLDBERG: We enrolled this patient on CALGB-80405, and she was randomly assigned to receive FOLFOX and bevacizumab. The design of that study is in evolution, but at that time the trial evaluated FOLFOX/bevacizumab, FOLFOX/cetuximab or the combination. This was before we were aware of the implications of a K-ras mutation.

Currently, the study only includes patients with K-ras wild-type colon cancer, and patients are randomly assigned to either FOLFOX/bevacizumab or FOLFOX/cetuximab because we now have data indicating that double-antibody modulation does not seem to be helpful and may actually be harmful to patients.

Of note, within five days of starting treatment, this patient was admitted to the hospital with severe right upper quadrant pain. We thought she had a perforation because she had recently undergone surgery. It turns out that she had such a dramatic response to treatment that she developed liver capsule irritation and experienced pain due to a necrotic tumor. Her disease simply melted away.

After 14 months of therapy, her CEA level returned to normal and she was perfectly functional. She began to experience mild oxaliplatin-related neuropathy, so we reduced the dose and she remains on oxaliplatin. She hasn't experienced any problems whatsoever with the bevacizumab.

Eventually, as happens with most patients in her circumstances, her CEA level increased 10-fold to approximately 50 ng/mL. So I was suspicious that her disease was escaping control. A CT scan revealed progressive disease in the liver. She said, "I understand my disease is progressing, but from a quality-of-life perspective, I want to get rid of the cancer in my colon." So she underwent a resection of the primary tumor, and after she recovered, we administered panitumumab and irinotecan.

DR LOVE: What are you thinking in terms of the next systemic therapy you might administer?

DR GOLDBERG: That's a tough question. For a patient who has responded to FOLFOX/bevacizumab in the past, the question is whether there is a chance that she could become responsive to these agents again. Aimery de Gramont evaluated patients on the OPTIMOX trial, and the longer the interval between initial treatment with oxaliplatin and re-treatment, the more likely patients were to respond (de Gramont 2009; [3.2]).

I have re-treated a few patients with FOLFOX whose disease had previously progressed on it two or three years before, and I have seen responses in those circumstances. ■

3.2

Oxaliplatin Sensitivity in Patients with Advanced Colorectal Cancer Previously Treated with Oxaliplatin-Based Therapy: Analysis of OPTIMOX1 and OPTIMOX2

	FOLFOX reintroduction response rate (%)					Median survival (months)	
Interval	N	CR + PR	SD	PD	NE	PFS from reintroduction	Survival from reintroduction
<6 months	116	15	30	52	3	3.0	8.9
6-12 months	148	24	39	24	13	5.0	16.7
>12 months	66	35	36	11	18	7.1	22.2
						$p < 0.0001$	$p < 0.0001$

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; PFS = progression-free survival

SOURCE: De Gramont A et al. *Proc ASCO* 2009;**Abstract 4024**.

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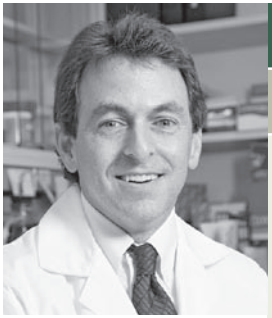

INTERVIEW

Lee M Ellis, MD

Dr Ellis is Professor of Surgery and Cancer Biology, Chair Ad Interim in the Department of Cancer Biology and William C Liedtke Jr Chair in Cancer Research at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-6

Track 1 Analysis of the NSABP-C-08 study results

Track 2 Biologic insights from NSABP-C-08

Track 3 Mechanism of action of cediranib and the HORIZON trials for patients with mCRC

Track 4 Targeting the V600E B-raf mutation in colon cancer and other solid tumors

Track 5 Preoperative chemobiologic therapy for patients with hepatic metastases

Track 6 Avoiding surgery for patients with asymptomatic primary colon cancer and metastatic disease

Select Excerpts from the Interview

Track 3

DR LOVE: Would you discuss the novel agent cediranib and its evaluation in the HORIZON trials for patients with metastatic disease?

DR ELLIS: Cediranib is a potent drug and is a much more selective inhibitor of the VEGF receptor tyrosine kinase receptors VEGFR-1, VEGFR-2 and VEGFR-3 than other agents. The three current trials for patients with CRC are called the HORIZON trials. HORIZON II and HORIZON III are both in the front-line setting and have completed accrual.

The HORIZON III trial is being conducted in the United States and is evaluating FOLFOX and cediranib versus FOLFOX and bevacizumab. HORIZON II is being conducted in Europe and other countries where bevacizumab may not be currently approved and is therefore evaluating FOLFOX with or without cediranib.

DR LOVE: What is known about the safety profile of cediranib versus bevacizumab?

DR ELLIS: An intermediate evaluation for safety was made, and the 20-mg dose of cediranib was found to be safe (Cunningham 2008). Cediranib can

cause hypertension, and discussion has taken place as to whether hypertension is a surrogate marker for cediranib benefit. Then the question arises, if you administer an antihypertensive, do you reverse any benefit that you obtain by escalating the dose to hypertension?

Of note, a preclinical study was published in *Clinical Cancer Research* a couple of years ago by Steve Wedge in which rats were treated with cediranib until they achieved hypertension. Antihypertensives were then administered and did not have any effect on cediranib efficacy in the rat model (Curwen 2008).

Track 5

DR LOVE: What are your thoughts on the issue of resection of hepatic-only metastases from CRC and the controversy that's arisen, particularly about the issue of preoperative versus postoperative therapy?

DR ELLIS: This subject remains controversial. I have two patients who recently presented with locally advanced sigmoid colon cancer and liver metastases — one will receive neoadjuvant chemotherapy, and the other will not. So even within my practice, nuances such as a patient's age or tumor location guide my treatment approach.

I don't believe that any hard data suggest that neoadjuvant chemotherapy is of benefit, but I want to recognize Bernard Nordlinger's European study, which reported that chemotherapy — both in the neoadjuvant and adjuvant settings — provided a nine percent improvement in disease-free survival compared to no chemotherapy (Nordlinger 2008; [4.1]). However, we are unable to sort out whether the benefit came from the neoadjuvant or the adjuvant chemotherapy.

4.1

EORTC-40983: Perioperative FOLFOX4 for Patients with Potentially Resectable Colorectal Cancer Hepatic Metastases

	FOLFOX4 → surgery → FOLFOX4	Surgery alone	HR (95.66% CI)	*p*-value
Three-year progression-free survival				
All patients randomly assigned (n = 182, 182)	35.4%	28.1%	0.79 (0.62-1.02)	0.058
All patients who underwent resection (n = 151, 152)	42.4%	33.2%	0.73 (0.55-0.97)	0.025
Reversible postoperative complications (n = 159, 170)	25%	16%	—	0.04
Postoperative death (n = 159, 170)	1%	1%	—	—

HR = hazard ratio; CI = confidence interval

SOURCE: Nordlinger B et al. *Lancet* 2008;371(9617):1007-16.

Another concern in the past was that people were afraid that neoadjuvant chemotherapy would cause liver damage and make it more difficult for the patient to recover from surgery. A number of studies have since been published reporting that if long-term neoadjuvant chemotherapy is not administered, the patients seem to fare well (Kesmodel 2008; [4.2]; Reddy 2008). The perioperative mortality is not greatly increased, and this is also shown in Nordlinger's study (Nordlinger 2008).

At academic centers, we are all aware of the potency of bevacizumab, and most of us tend to "drag our feet" somewhat in sending patients to the operating room. We use a minimum of six weeks, but I wait eight weeks before I take a patient who has received bevacizumab into the operating room. ■

4.2

Preoperative Bevacizumab (BV) and Postoperative Complication Rates among Patients Undergoing Hepatic Surgery for Colorectal Cancer (CRC) Liver Metastases

"[I]n this study, the addition of BV to neoadjuvant cytotoxic CTX in patients who have CRC liver metastases was not associated with an increase in postoperative complications. In addition, there was no association between postoperative complications and the time interval from BV discontinuation to surgery, although all patients underwent surgery at least 30 days after the last BV dose. These data suggest that BV may be administered in combination with neoadjuvant CTX before resection of CRC liver metastases without increasing postoperative morbidity.

Although the optimal timing of surgery in patients who receive BV requires additional investigation, in this study there was no statistically significant increase in complication rates in patients who received BV within 31 to 60 days (n = 40) of surgery. Therefore, on the basis of these results, we still recommend waiting at least 6 weeks from discontinuation of BV to surgery."

SOURCE: Kesmodel SB et al. *J Clin Oncol* 2008;26(32):5254–60.

SELECT PUBLICATIONS

Cunningham D et al. **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**.

Curwen JO et al. **Inhibition of vascular endothelial growth factor-a signaling induces hypertension: Examining the effect of cediranib (Recentin; AZD2171) treatment on blood pressure in rat and the use of concomitant antihypertensive therapy.** *Clin Cancer Res* 2008;14(10):3124–31.

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.

Nordlinger B et al. **Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial.** *Lancet* 2008;371(9617):1007–16.

Reddy SK et al. **Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases.** *J Am Coll Surg* 2008;206(1):96–106.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the QUASAR validation study, the Onco*type* DX colon cancer assay was able to _____ in patients with Stage II colon cancer.**
   a. Define a Recurrence Score as predictor of recurrence risk
   b. Predict benefit from 5-FU as adjuvant therapy
   c. Both a and b
   d. None of the above
2. **Patients with Stage II colon cancer and a high-risk Recurrence Score have approximately a _____ risk of relapse based on the Onco*type* DX colon cancer assay.**
   a. 12 percent
   b. 22 percent
   c. 50 percent
3. **A retrospective analysis of patients with synchronous Stage IV colorectal cancer (CRC) receiving combination chemotherapy without surgery as initial treatment reported that more than 90 percent of the patients never required surgical treatment or intervention for their primary CRC.**
   a. True
   b. False
4. **In ECOG-E5202, patients with resected Stage II colon cancer who are at low risk of recurrence based on microsatellite instability and loss of heterozygosity at chromosome 18 are observed without further treatment.**
   a. True
   b. False
5. **In ECOG-E5202, patients with resected Stage II colon cancer who are at high risk of recurrence based on microsatellite instability and loss of heterozygosity at chromosome 18 are randomly assigned to which of the following treatments?**
   a. FOLFOX with or without bevacizumab
   b. FOLFOX with or without cetuximab
6. **The STAR-01 trial, evaluating preoperative fluorouracil-based chemoradiation therapy with or without oxaliplatin for patients with locally advanced rectal cancer, reported a statistically significant benefit in pathologic complete response rate for the oxaliplatin-containing arm versus the chemoradiation therapy-only arm.**
   a. True
   b. False
7. **The NSABP-C-08 trial, comparing FOLFOX to FOLFOX and bevacizumab for patients with Stage II or Stage III CRC, reported a statistically significant advantage with the combination with regard to the primary endpoint of three-year disease-free survival.**
   a. True
   b. False
8. **In the HORIZON III trial, FOLFOX/cediranib is being compared to _____ as first-line therapy for metastatic CRC.**
   a. Cediranib alone
   b. FOLFOX/bevacizumab
   c. FOLFOX/cetuximab
9. **In EORTC-40983, perioperative chemotherapy was associated with _____ than surgical resection alone for patients with resectable liver metastases.**
   a. Longer progression-free survival
   b. More postoperative complications
   c. Higher postoperative mortality
   d. Both a and b
10. **In a study evaluating neoadjuvant chemotherapy with or without bevacizumab, Kesmodel and colleagues observed no increase in postoperative complications among the patients who discontinued bevacizumab at least _____ days before surgical resection of CRC liver metastases.**
    a. 10
    b. 30
    c. 40
    d. 60

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Colorectal Cancer Update — Issue 3, 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

How would you characterize your level of knowledge on the following topics?

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

	BEFORE	AFTER
Findings from the QUASAR validation study of a quantitative multigene RT-PCR assay for the assessment of recurrence risk in Stage II colon cancer	4 3 2 1	4 3 2 1
Pooled analysis of the benefits of adjuvant chemotherapy for elderly patients (older than age 70) with colon cancer	4 3 2 1	4 3 2 1
Perspectives on the results of NSABP-C-08: Adjuvant FOLFOX with or without bevacizumab	4 3 2 1	4 3 2 1
Study results of oxaliplatin-containing neoadjuvant chemoradiation therapy for rectal cancer	4 3 2 1	4 3 2 1
Memorial Sloan-Kettering Cancer Center study of outcomes for patients with asymptomatic primary colon cancer and metastases treated with systemic therapy alone	4 3 2 1	4 3 2 1
Rationale and eligibility for the ECOG-E5202 trial evaluating FOLFOX with or without bevacizumab for high-risk, resected Stage II colon cancer	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

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

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

- Assess the evidence-based role of chemotherapy and/or biologic agents as radiation sensitizers in the management of locally advanced rectal cancer. . . 4 3 2 1 N/M N/A
- Counsel patients with Stage II colon cancer about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers.. . . . . 4 3 2 1 N/M N/A
- Educate elderly patients (older than age 70) with colon cancer about the benefits and risks of adjuvant chemotherapy. . . . . 4 3 2 1 N/M N/A
- Develop up-to-date clinical management strategies for metastatic CRC, incorporating chemotherapy and anti-VEGF and anti-EGFR antibodies . . . . . 4 3 2 1 N/M N/A
- Formulate a treatment plan for patients with synchronous primary CRC and liver-only metastases. . . . . 4 3 2 1 N/M N/A
- Identify novel agents under active investigation for the treatment of CRC. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with CRC about participation in ongoing clinical trials.. . . . . 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

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

.....

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

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

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

PART TWO — Please tell us about the faculty and editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Alan P Venook, MD	4 3 2 1	4 3 2 1
Charles S Fuchs, MD, MPH	4 3 2 1	4 3 2 1
Richard M Goldberg, MD	4 3 2 1	4 3 2 1
Lee M Ellis, 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 faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

Name: ..... Specialty: .....

Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other .....

Medical License/ME Number: ..... Last 4 Digits of SSN (required): .....

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City, State, Zip: .....

Telephone: ..... Fax: .....

Email: .....

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.

CCU309

Colorectal Cancer™ UPDATE

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Colorectal Cancer™

U P D A T E

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