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Colorectal Cancer™ UPDATE

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

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INTERVIEWS

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CME Certified

Colorectal Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Colorectal cancer is among the most common types of cancer 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

- Evaluate the emerging role of chemotherapy and/or biologic agents as radiation sensitizers in the management of locally advanced rectal cancer.
- Identify patients with Stage II colon cancer who have a high risk of recurrence based on microsatellite instability and loss of heterozygosity at chromosome 18q.
- Counsel appropriately selected patients about participation in ongoing clinical trials evaluating the addition of biologic agents to conventional chemotherapy.
- Use biomarkers to predict response or resistance to systemic treatments for patients with colorectal cancer (CRC).
- Develop up-to-date clinical management strategies for metastatic CRC, incorporating chemotherapy, anti-VEGF and anti-EGFR antibodies.
- Advise patients about the potential risks and benefits associated with the use of maintenance therapy for metastatic CRC.
- Formulate a treatment plan for patients with synchronous or metachronous primary CRC and liver-only metastases.
- Apply the results of recent clinical trials when recommending adjuvant imatinib for patients with operable gastrointestinal stromal tumors (GIST).

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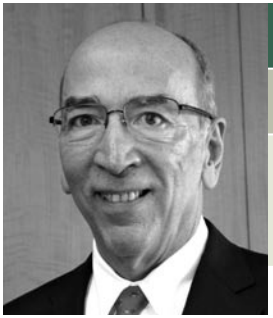


INTERVIEW

Daniel G Haller, MD

Dr Haller is Professor of Medicine at the Abramson Cancer Center at the University of Pennsylvania in Philadelphia, Pennsylvania.

Tracks 1-18

Select Excerpts from the Interview

Track 4

DR LOVE: Do you currently use oxaliplatin as neoadjuvant therapy for rectal cancer outside of a clinical trial?

DR HALLER: We offer neoadjuvant oxaliplatin as an option to patients after discussing the standard treatment and the NSABP-R-04 trial, which is evaluating preoperative chemoradiation therapy with or without oxaliplatin for these patients. We have a lot of experience with neoadjuvant oxaliplatin because I served as the chair of the ECOG-E1297 trial.

That Phase I study evaluated neoadjuvant radiation therapy with biweekly oxaliplatin and infusional 5-FU followed by surgery and adjuvant fluorouracil/leucovorin for patients with locally advanced rectal cancer. The regimen was well tolerated, and the rates of major pathologic response were promising (Rosenthal 2008).

In addition, many Phase II trials have suggested higher pathologic complete response rates with oxaliplatin (1.1). This makes sense because platinum agents are radiation sensitizers.

1.1 Selected Phase II Trials Incorporating Oxaliplatin as Part of Preoperative Chemoradiation Therapy for Locally Advanced/Unresectable Rectal Cancer

Trial	Preoperative regimen	N	Path CR
Aschele 2005	Oxaliplatin/fluorouracil[1]/radiation therapy	25	28%
Carraro 2002	Oxaliplatin/fluorouracil[2]/leucovorin/radiation therapy	22	25%
Fakih 2008*	Oxaliplatin/capecitabine/radiation therapy	25	24%
Koeberle 2008	Oxaliplatin/capecitabine/radiation therapy	60	23%
Rödel 2007	Oxaliplatin/capecitabine/radiation therapy	104	16%
Ryan 2006	Oxaliplatin/fluorouracil[1]/radiation therapy	32	25%

Path CR = pathologic complete response

[1] Continuous infusion 5-fluorouracil; [2] Bolus 5-fluorouracil; * Included Stage II/III rectal cancer

SOURCES: Aschele C et al. *Ann Oncol* 2005;16(7):1140-6. **Abstract**; Carraro S et al. *Int J Radiat Oncol Biol Phys* 2002;54(2):397-402. **Abstract**; Fakih MG et al. *Int J Radiat Oncol Biol Phys* 2008;72(3):650-7. **Abstract**; Koeberle D et al. *Br J Cancer* 2008;98(7):1204-9. **Abstract**; Rödel C et al. *J Clin Oncol* 2007;25(1):110-7. **Abstract**; Ryan DP et al. *J Clin Oncol* 2006;24(16):2557-62. **Abstract**

Tracks 5-6

DR LOVE: What is the status of your study, UPCC 09204, evaluating cetuximab and radiation therapy for rectal cancer?

DR HALLER: Our study has been on hold since ASCO 2008, partially because of the evolving data on K-ras. We are in the process of rewriting the trial so that only patients with wild-type K-ras receive the antibody.

We are aware of the radiosensitization data with cetuximab, but in the trials with chemotherapy and anti-EGFR agents, the patients with mutated K-ras have lower response rates and shorter progression-free survival rates. We were concerned that without data to fully support combining anti-EGFR agents with radiation therapy, we might be harming patients.

DR LOVE: What do we know about the relationship between B-raf and the efficacy of anti-EGFR antibodies?

DR HALLER: B-raf mutations are downstream from K-ras. The seminal paper on B-raf mutations was recently published, and the investigators reported that if a patient's tumor had wild-type K-ras and also had mutated B-raf, the cancer did not respond to panitumumab or cetuximab (Di Nicolantonio 2008; [1.2]).

The Mayo Clinic and MD Anderson are now including B-raf in their panel along with K-ras on a routine basis, and they are starting to integrate this information into practice.

Tracks 8-9

DR LOVE: For which patients would you consider front-line chemotherapy with cetuximab?

DR HALLER: If we evaluate only the patient's K-ras status, 60 percent will have K-ras wild type, and they have the highest likelihood of benefiting from an anti-EGFR antibody. The clearest message from the CRYSTAL trial — which evaluated up-front FOLFIRI with or without cetuximab — was that patients with K-ras wild-type tumors showed an improvement in response rate with cetuximab compared to those with mutant K-ras tumors (Van Cutsem 2009).

Therefore, for patients with K-ras wild-type tumors who are experiencing disease-related symptoms or for patients in whom we want to downstage metastatic disease for a liver resection, chemotherapy with cetuximab would be a reasonable choice.

DR LOVE: Does it matter whether you use FOLFOX or FOLFIRI with cetuximab?

1.2 Effect of K-ras and B-raf Mutation Status on Response to Panitumumab or Cetuximab in Patients with Metastatic Colorectal Cancer (N = 113)

	K-ras mutation status		B-raf mutation with K-ras wild-type tumors	
	Mutant K-ras 34/113 (30%)	Wild-type K-ras 79/113 (70%)	Mutant B-raf 11/79 (14%)	Wild-type B-raf 68/79 (86%)
Response rate	6%	28%	0%	32%

"KRAS and BRAF mutations correlate with lack of response to treatment with monoclonal antibodies targeting epidermal growth factor receptor. The number of responders and nonresponders (stable disease [SD] + progressive disease [PD]) is indicated according to KRAS or BRAF mutational status."

SOURCE: Di Nicolantonio F et al. *J Clin Oncol* 2008;26(35):5705-12. **Abstract**

DR HALLER: Although it was a smaller trial, Bokemeyer's OPUS trial of front-line FOLFOX with or without cetuximab showed essentially the same overall response rate when cetuximab was added, as seen in the CRYSTAL trial of FOLFIRI (Bokemeyer 2009). So the chemotherapy backbone is irrelevant — rather, it's the K-ras mutational status and the anti-EGFR agent that matter.

DR LOVE: How do cetuximab and bevacizumab indirectly compare, when combined with chemotherapy for first-line treatment of metastatic disease?

DR HALLER: CALGB-C80405 is addressing that question (3.1, page 12). The comparison is FOLFOX or FOLFIRI — dealer's choice — with bevacizumab versus cetuximab versus both antibodies, and it was modified after ASCO 2008 to address K-ras wild-type disease only.

DR LOVE: What are your thoughts about the third arm, which combines the two antibodies?

DR HALLER: The third arm has become difficult with the publication of the PACCE data (Hecht 2008; [1.3]). However, with the assurance that the Data Safety Monitoring Board is watching the study carefully, I can accept it.

Bevacizumab does not tend to improve response rate when you combine it with an active backbone. Len Saltz published trial data evaluating FOLFOX or XELOX with or without bevacizumab as first-line therapy for metastatic colorectal cancer, and no difference was seen in response rate when bevacizumab was added (Saltz 2008).

With bevacizumab, response is not the detectable endpoint — rather, it's progression-free survival. Cetuximab and bevacizumab have different attributes that lead to the selection of one versus the other, depending on the status of the patient.

I believe that it will be difficult for CALGB-C80405 to be positive for its primary endpoint, which is overall survival, because patients who don't receive bevacizumab or cetuximab up front may receive it in the second line, and therefore it will be a washout.

1.3

PACCE: A Phase IIIB Trial of Chemotherapy, Bevacizumab and Panitumumab Compared to Chemotherapy and Bevacizumab Alone for mCRC

"In the PACCE trial, the combination of panitumumab with bevacizumab and chemotherapy resulted in a decrease in PFS and in excess serious toxicity, particularly diarrhea, infections, and pulmonary embolism in patients with mCRC. Results were largely consistent between the oxaliplatin and irinotecan cohorts.

Administration of chemotherapy and dual EGFR/VEGF inhibition should be conducted only in a research setting, using selected populations and/or novel administration schedules or combinations. Molecular markers in this setting should expand beyond the *KRAS* biomarker."

SOURCE: Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80. **Abstract**

DR LOVE: How do these two strategies compare with regard to toxicities?

DR HALLER: The toxicity differences between these agents are significant. With cetuximab, patients experience visible effects on the skin and potentially higher rates of toxicities such as infections that are secondary to the skin problems. We don't have formal psychosocial testing, but patients seem to be more uncomfortable on the anti-EGFR antibodies.

With bevacizumab, the symptoms are generally not palpable to the patient unless they are allowed to get out of hand. We see more hypertension and potentially some decrease in wound healing with this agent.

At the end of the day, if the results of the CALGB-C80405 trial are as I have suggested, bevacizumab may be the preferred agent for an asymptomatic patient, whereas a patient with a lot of tumor-related symptoms who needs a response may be willing to endure more toxicity for a higher response rate. ■

SELECT PUBLICATIONS

Bokemeyer C et al. **Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer.** *J Clin Oncol* 2009;27(5):663-71. **Abstract**

Cunningham D et al. **Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.** *N Engl J Med* 2004;351(4):337-45. **Abstract**

Di Nicolantonio F et al. **Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer.** *J Clin Oncol* 2008;26(35):5705-12. **Abstract**

Hecht JR et al. **A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer.** *J Clin Oncol* 2009;27(5):672-80. **Abstract**

Jimeno A et al. **KRAS mutations and sensitivity to epidermal growth factor receptor inhibitors in colorectal cancer: Practical application of patient selection.** *J Clin Oncol* 2009;27(7):1130-6. **Abstract**

Lièvre A et al. **KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab.** *J Clin Oncol* 2008;26(3):374-9. **Abstract**

Rosenthal DI et al. **Phase I study of preoperative radiation therapy with concurrent infusional 5-fluorouracil and oxaliplatin followed by surgery and postoperative 5-fluorouracil plus leucovorin for T3/T4 rectal adenocarcinoma: ECOG E1297.** *Int J Radiat Oncol Biol Phys* 2008;72(1):108-13. **Abstract**

Rougier P et al. **Addition of cetuximab to FOLFIRI in first-line metastatic colorectal cancer (mCRC): Updated survival data and influence of KRAS status on outcome in the CRYSTAL study.** Gastrointestinal Cancers Symposium 2009;**Abstract 443**.

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**

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**

Tol J et al. **Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer.** *N Engl J Med* 2009;360(6):563-72. **Abstract**

Van Cutsem E et al. **Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.** *N Engl J Med* 2009;360(14):1408-17. **Abstract**

INTERVIEW

Axel Grothey, MD

Dr Grothey is Professor of Oncology in the Department of Medical Oncology at the Mayo Clinic in Rochester, Minnesota.

Tracks 1-14

Track 1 **Case discussion:** A woman in her early fifties with mCRC who was treated with FOLFOX/bevacizumab followed by maintenance 5-FU/bevacizumab for several years

Track 2 Re-treatment with FOLFOX/bevacizumab for mCRC after disease progression

Track 3 Value of the continuation of biologic agents as maintenance therapy

Track 4 BRiTE registry: Bevacizumab beyond first progression

Track 5 iBET (SWOG-S0060): Irinotecan-based chemotherapy and cetuximab with or without bevacizumab after disease progression on an oxaliplatin- and bevacizumab-containing regimen

Track 6 **Case discussion:** A 16-year-old young woman with highly symptomatic, de novo metastatic rectal cancer to the lung and diffuse lymphadenopathy who had a near complete response to FOLFOX/bevacizumab

Track 7 Use of cetuximab for a patient with progressive K-ras wild-type metastatic rectal cancer who was intolerant to FOLFIRI

Track 8 Perspective on the treatment of an adolescent with metastatic rectal cancer

Track 9 Balancing continuation of therapy and quality of life for patients with long-term responses to treatment for metastatic disease

Track 10 **Case discussion:** An 80-year-old man with synchronous primary colon cancer and potentially surgically resectable liver metastases

Track 11 Estimating competing causes of mortality in elderly patients

Track 12 Risk factors for chemotherapy-associated hepatotoxicity in patients with resectable mCRC

Track 13 Risk of arterial thromboembolic events associated with bevacizumab in the elderly

Track 14 Treatment selection for recurrent mCRC in an elderly patient

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: Would you discuss your paper that was recently published in the *JCO* on the BRiTE registry data demonstrating an apparent advantage to continuation of bevacizumab on disease progression?

DR GROTHEY: Considering the magnitude of benefit reported by this registry (2.1), I believe it raises awareness that we need to test this practice prospectively. The implications of this effect are huge because bevacizumab and VEGF inhibition probably work in a number of different tumor types — breast cancer, lung cancer, colon cancer and potentially other tumors. If this principle of continuation of biologic therapy is sound, then we need to test it further.

DR LOVE: This concept is being tested in the iBET study.

DR GROTHEY: The iBET study had to be modified to account for the fact that data on K-ras became available. We're dealing with a phenomenon that current clinical trials must take into account: Colorectal cancer is at least two different diseases, probably more. Our trials must be modified accordingly.

We are now stratifying all patients by K-ras status — wild-type versus mutant. The iBET trial hasn't been reopened yet. When it has, it will address the issue of whether continuation of bevacizumab is better than reintroduction of cetuximab as second-line therapy for patients with wild-type K-ras.

Patients with K-ras wild-type tumors whose disease has progressed on FOLFOX, CAPOX or OPTIMOX with bevacizumab will be randomly assigned to either of two arms — irinotecan-based therapy with cetuximab or bevacizumab (2.2).

K-ras mutant tumors are somewhat of an orphan disease right now. To some extent we know that chemotherapy with bevacizumab is effective for patients with K-ras mutant tumors, but we're using K-ras mutant status as a platform for drug development.

A German AIO-initiated trial that has expanded throughout Europe is also evaluating whether bevacizumab should be continued beyond disease progression. They have a sample size of about 1,000 patients. I believe that trial may answer this question because they have a pragmatic approach.

Patients are allowed to cross over from FOLFOX to FOLFIRI or from FOLFIRI to FOLFOX, with or without bevacizumab (2.3). ■

2.1

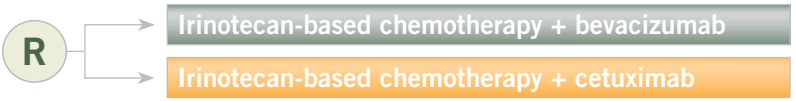
BRiTE Registry: Survival According to Treatment Received After Disease Progression

	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**

2.2 iBET (Amended Protocol): A Phase III Study of Irinotecan-Based Therapy with Cetuximab or Bevacizumab for Patients with Metastatic Colon Cancer and K-ras Wild-Type Tumor Expression After Disease Progression on Bevacizumab-Containing First-Line Therapy

Protocol IDs: SWOG-S0600, NCT00499369
Target accrual: 1,260 (Temporarily closed)



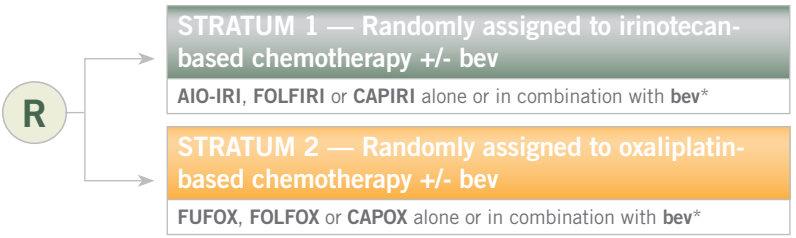
Eligibility

- Confirmed metastatic disease with disease progression after first-line therapy with bevacizumab and CAPOX, FOLFOX or OPTIMOX
- No prior irinotecan or cetuximab
- No uncontrolled hypertension (ie, SBP > 150 mmHg or DBP > 90 mmHg)

SOURCES: Axel Grothey, Personal Communication, January 2009; NCI Physician Data Query, April 2009.

2.3 European Study of Bevacizumab (Bev) and Crossover Fluoropyrimidine-Based Chemotherapy for Patients with Metastatic Colorectal Cancer (mCRC) Progressing on First-Line Chemotherapy with Bev

Protocol ID: NCT00700102 Target Accrual: 820 (Open)



Eligibility

- mCRC and disease progression
- Previous treatment with first-line chemotherapy and bev
- No first-line progression-free survival < 4 months
- No clinically significant cardiovascular disease within 1 year of randomization
- No CNS metastases

* 5 mg/kg IV on days 1 and 14 of each four-week cycle or 7.5 mg/kg on days 1 and 22 of each six-week cycle

SOURCE: www.clinicaltrials.gov. Accessed April 2009.

SELECT PUBLICATION

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**

INTERVIEW

Charles D Blanke, MD

Dr Blanke is Systemic Therapy Provincial Program Leader at the BC Cancer Agency and Head of the Division of Medical Oncology at the University of British Columbia in Vancouver, British Columbia.

Tracks 1-9

Track 1 Combining anti-EGFR antibodies and anti-VEGF antibodies

Track 2 First-line therapy for patients with mCRC and wild-type K-ras

Track 3 Ongoing clinical research strategies to optimize the use of biologic agents in CRC

Track 4 Novel agents under investigation in CRC

Track 5 **Case discussion:** A 50-year-old woman with CRC and four positive lymph nodes who had multiple complications from surgery and adjuvant therapy

Track 6 Adjuvant therapy for Stage II colon cancer

Track 7 Microsatellite instability and genomic analyses in CRC

Track 8 **Case discussion:** A 65-year-old man with resected node-positive rectal cancer, concomitant COPD and possible non-small cell lung cancer

Track 9 Improvements in overall survival for patients with mCRC

WEB TRACKS

1 ACOSOG-Z9001: A Phase III randomized trial of adjuvant imatinib versus placebo for resected, localized, primary gastrointestinal stromal tumor (GIST)

2 RTOG-0312: A Phase II trial of neoadjuvant/adjuvant imatinib for operable GIST

3 Dose of imatinib for patients with metastatic GIST and exon 9 mutations

4 Correlation of imatinib plasma levels with clinical benefit in metastatic GIST

5 Incidence and mortality trends in GIST

Select Excerpts from the Interview

Track 1

DR LOVE: What are your thoughts about the dual-antibody approach for metastatic colorectal cancer outside of a clinical trial?

DR BLANKE: We have bevacizumab, an anti-VEGF antibody, that works well, and we have antibodies that target the EGF receptor, such as panitumumab and cetuximab, which are also effective. Although earlier data suggested that dual-antibody therapy would significantly improve progression-free survival (Saltz 2007), a number of trials now suggest that this strategy is not benefi-

cial or, in certain patient populations, may even be harmful (Hecht 2009; Tol 2009). Based on these data, I certainly would not combine the two antibodies outside of a clinical trial.

DR LOVE: How are the ongoing trials that have a dual-antibody arm addressing this issue?

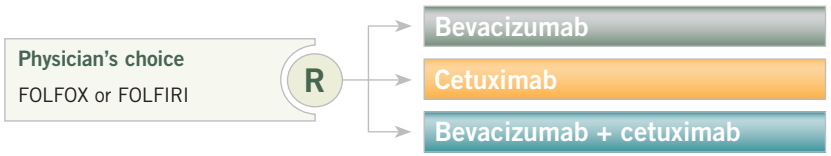
DR BLANKE: At least two North American Intergroup trials had dual-antibody arms. Highly contentious discussions arose regarding both of these trials, and the resulting decisions were different. In the second-line SWOG-S0600 trial — evaluating irinotecan-based chemotherapy and cetuximab with or without bevacizumab — the investigators decided to close the arms containing combined anti-VEGF and anti-EGFR antibodies.

However, in the CALGB-C80405 front-line trial — evaluating FOLFOX or FOLFIRI, physician's choice, with bevacizumab versus cetuximab versus both antibodies — we decided to continue the trial (3.1). Intense discussion took place regarding the elimination of that dual-antibody arm, but I was concerned that if we did that, we would never know the answer to the dual-antibody question.

3.1

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

Target accrual: 2,300 (Open)



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

Study Contacts

CALGB
Alan Venook, MD
Tel: 415-353-7065

SWOG
Charles D Blanke, MD
Tel: 604-877-6098 ext 2738

SOURCE: NCI Physician Data Query, March 2009.

Track 2

DR LOVE: What is your usual first-line approach for patients with K-ras wild-type tumors?

DR BLANKE: We know in theory and in practice that current chemotherapy regimens offer essentially the same benefit. A number of randomized trials

demonstrate that the FOLFOX-like regimens and the FOLFIRI-like regimens are equivalent in this regard.

Therefore, I base my chemotherapy decisions on the regimen's toxicities. If oxaliplatin-associated neuropathy would pose a serious concern for a patient because of hobbies or profession, then I choose FOLFIRI. However, if I'm more concerned about diarrhea or, less likely, alopecia, I tend to use FOLFOX, as 80 percent of American physicians do.

Deciding which biologic agent to use is more challenging, and this applies mainly to patients with K-ras wild-type tumors. I believe the best data are for administering bevacizumab. That remains the standard practice and that's my approach.

However, investigators differ. Some trials have shown an increase in response rate when bevacizumab is added to chemotherapy, but others have not. On the other hand, most of us believe that the response rate is higher if we add an EGFR inhibitor, such as cetuximab. So while I use bevacizumab with chemotherapy 90 percent of the time, I tend to use the anti-EGFR antibody up front in the small population of patients whose tumors might be surgically resectable if I can downsize them, even in the advanced-disease or metastatic settings.

Track 3

DR LOVE: What current clinical research questions are you most interested in having answered?

DR BLANKE: I believe the paramount question is, which biologic agent is best for the treatment of metastatic disease? That will be answered by the CALGB-C80405 trial.

Additionally, I'd like to know whether bevacizumab should be continued beyond disease progression. Some theoretical reasons suggest that it's a great idea, while others suggest it's a useless strategy. We hope ongoing European trials will answer this question. Retrospective data from the BRiTE study show that continuing bevacizumab is associated with prolonged overall survival, but that's a registry and not a clinical trial (Grothey 2008).

Track 6

DR LOVE: What are your thoughts about adjuvant therapy for Stage II disease?

DR BLANKE: Across the board, for the average patient with Stage II colon cancer, adjuvant therapy is beneficial — based on data from the large trials — but I believe the benefit is approximately three percent. It may be five percent, it may be two percent, but it's probably three percent. In my experience, most oncologists don't feel that's sufficient to treat these patients. However, as in the breast cancer population, I believe most of our patients feel it's worth it.

DR LOVE: What would you use to treat a patient with Stage II disease?

DR BLANKE: For a patient with Stage II colon cancer at normal risk, I believe some form of 5-FU or capecitabine is the treatment of choice. I recommend capecitabine for these patients. I don't feel adding oxaliplatin is justified in that particular population, based on the de Gramont data (de Gramont 2007; [3.2]). ■

3.2

MOSAIC Adjuvant Trial Comparing FOLFOX4 to 5-FU/Leucovorin (LV): Five-Year Disease-Free Survival Update

	FOLFOX4	5-FU/LV	Difference	Hazard ratio	*p*-value
ITT (overall population)	73.3%	67.4%	+5.9%	0.80	0.003
Stage III	66.4%	58.9%	+7.5%	0.78	0.005
Stage II	83.7%	79.9%	+3.8%	0.84	0.258
High-risk Stage II (n = 576)	82.1%	74.9%	+7.2%	0.74	—
Low-risk Stage II (n = 323)	86.3%	89.1%	-2.8%	1.22	—

ITT = intent to treat

SOURCE: De Gramont A et al. *Proc ASCO* 2007;**Abstract 4007**.

SELECT PUBLICATIONS

Blanke CD. **Dual-antibody therapy in advanced colorectal cancer: Gather ye rosebuds while ye may.** *J Clin Oncol* 2009;27(5):655-8. **Abstract**

De Gramont A et al. **Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years.** *Proc ASCO* 2007;**Abstract 4007**.

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):5313-5. **Abstract**

Hecht JR et al. **A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer.** *J Clin Oncol* 2009;27(5):672-80. **Abstract**

Mayer RJ. **Targeted therapy for advanced colorectal cancer — More is not always better.** *N Engl J Med* 2009;360(6):623-5. No abstract available

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**

Skougaard K et al. **Bevacizumab in combination with cetuximab and irinotecan (BCI) after failure of cetuximab and irinotecan (CI) in patients with metastatic colorectal cancer (mCRC).** Gastrointestinal Cancers Symposium 2009;**Abstract 482**.

Spigel DR et al. **Phase II trial of modified FOLFOX6, bevacizumab, and cetuximab in first-line metastatic colorectal cancer treatment.** Gastrointestinal Cancers Symposium 2009;**Abstract 490**.

Tol J et al. **Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer.** *N Engl J Med* 2009;360(6):563-72. **Abstract**

INTERVIEW

Al B Benson III, MD

Dr Benson is Professor of Medicine and Associate Director for Clinical Investigations at the Robert H Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois.

Tracks 1-10

Track 1	**Case discussion:** A 43-year-old man with low-risk, right-sided Stage II CRC who had a family history of colon cancer
Track 2	ECOG-E5202: FOLFOX with or without bevacizumab for resected Stage II colon cancer at high risk for recurrence based on molecular markers
Track 3	Preliminary safety data from NSABP-C-08: Adjuvant FOLFOX with or without bevacizumab
Track 4	Supporting data for the observation arm in ECOG-E5202
Track 5	Genomic profiles as prognostic and predictive factors for CRC
Track 6	**Case discussion:** A 62-year-old woman who received adjuvant FOLFOX approximately one year ago for Stage IIIC colon cancer presents with K-ras wild-type liver metastases
Track 7	Preoperative therapy for patients with liver-only CRC metastases
Track 8	Postoperative therapy for patients with resected liver-only CRC metastases
Track 9	Factors influencing the use of preoperative therapy for patients with liver-only CRC metastases
Track 10	Yttrium-90 microspheres for CRC liver metastases

Select Excerpts from the Interview

Track 2

DR LOVE: Would you review the ECOG-E5202 adjuvant trial (4.1), for which you are the principal investigator?

DR BENSON: It is a large study for patients with Stage II colon cancer. It will be the largest of its kind to collect tumor samples and the first of its kind to use molecular markers to define a treatment strategy.

The markers used in this project are microsatellite instability and 18q loss of heterozygosity. These markers were chosen because a number of retrospective analyses strongly suggest that these are important prognostic markers for patients with colon cancer.

Patients with microsatellite instability and those who retain 18q are considered to have a low risk of recurrence. If our hypothesis is correct, those individuals would have a projected survivorship of nearly 90 percent. So the low-risk

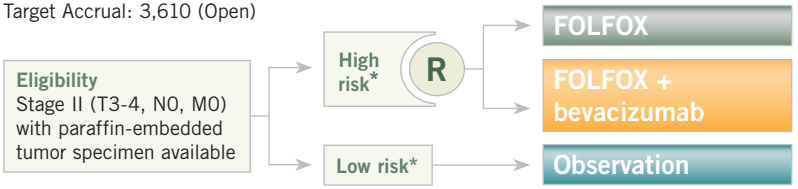
group is observed. The group with high-risk disease — for the most part, the individuals with microsatellite-stable tumors and 18q loss of heterozygosity — are randomly assigned to receive FOLFOX or FOLFOX with bevacizumab. This strategy is identical to the one employed in NSABP-C-08, which included patients with Stage II or Stage III colon cancer, although selection was not on the basis of marker determination.

Because we are collecting such a large sample of tumors, this study will open the door for many other analyses, including molecular markers. We will also incorporate pathologic features in a multivariate analysis.

4.1

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 are stratified according to disease stage (IIA versus IIB) and microsatellite stability (stability versus low-grade instability). 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, April 2009.

Track 3

DR LOVE: NSABP has already presented safety data from their adjuvant bevacizumab trial (Allegra 2008; [4.2]). With 1,600 patients, do you have any safety data yet?

DR BENSON: We have been evaluating the safety data continuously. Thus far in our toxicity assessment, we have not seen any surprises. I believe that is consistent with the NSABP's observations for FOLFOX/bevacizumab (Allegra 2008; [4.2]).

DR LOVE: The safety data from NSABP-C-08 seemed encouraging, at least in terms of bowel perforations and arterial thrombotic events.

DR BENSON: Fortunately, those events are relatively uncommon. It is reassuring, particularly for a postoperative patient population. As most patients in the adjuvant setting are treated between 28 and 60 days after surgery, potential concerns involve wound healing and changes in the anastomosis. However, we haven't seen anything unusual thus far.

4.2

Initial Safety Report of NSABP-C-08: Adjuvant FOLFOX6 with or without Bevacizumab (Bev) in Stage II 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

NS = not significant

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

Track 8

DR LOVE: Would you comment on the use of preoperative versus postoperative therapy for patients with resectable liver metastases?

DR BENSON: We don't have definitive evidence as to which strategy is best. One approach is a "sandwich strategy," by which you administer part of the chemotherapy before surgery and part after surgery. Most patients experience the best response within the first two to three months of therapy, so a longer duration is not necessary for patients with resectable metastases.

I believe that patients whose disease shows evidence of response to neoadjuvant chemotherapy appear to have a chemosensitive tumor, and a strategy of administering additional chemotherapy after that would be important.

It's a more difficult decision for a patient who seemed to have no benefit from chemotherapy or experienced a little tumor growth but whose disease was still resectable. You would postulate that chemotherapy didn't offer a substantial benefit. So how do you proceed postoperatively? Do you add a biologic agent? Do you change your chemotherapy platform? Those questions are unanswered. ■

SELECT PUBLICATION

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**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a study by Di Nicolantonio and colleagues, what proportion of patients with K-ras wild-type tumors and B-raf mutations experienced response to cetuximab or panitumumab in metastatic colorectal cancer?**
   a. 0 percent
   b. 32 percent
   c. 68 percent
   d. 100 percent

2. **In a subgroup analysis of the CRYSTAL trial, patients whose tumors had _____ K-ras did not benefit from the addition of cetuximab to first-line chemotherapy.**
   a. Wild-type
   b. Mutant
   c. Either a or b
   d. None of the above

3. **In CALGB-C80405, which evaluates chemotherapy in combination with antibody therapy for previously untreated metastatic colorectal cancer, the chemotherapy regimen used is _____.**
   a. FOLFOX
   b. FOLFIRI
   c. FOLFOX or FOLFIRI, at the discretion of the physician

4. **Due to controversies regarding the risks and benefits of dual-antibody therapy, the CALGB-C80405 trial, which included an arm in which patients would receive both bevacizumab and cetuximab for metastatic colorectal cancer, was permanently closed.**
   a. True
   b. False

5. **Data from the BRiTE registry support the hypothesis that continued use of bevacizumab beyond disease progression improves overall survival.**
   a. True
   b. False

6. **The iBET trial was temporarily closed and the protocol was amended to integrate K-ras tumor status.**
   a. True
   b. False

7. **In a European study of crossover fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer, patients are allowed to cross over from FOLFOX to FOLFIRI or from FOLFIRI to FOLFOX, with or without _____.**
   a. Bevacizumab
   b. Cetuximab
   c. Oxaliplatin

8. **Six-year follow-up data from the MOSAIC adjuvant trial demonstrated that overall survival was significantly improved for patients with Stage II colon cancer who received adjuvant FOLFOX compared to those who received 5-FU/leucovorin.**
   a. True
   b. False

9. **In ECOG-E5202, patients with resected Stage II colon cancer 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

10. **In ECOG-E5202, patients with resected Stage II colon cancer 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
    b. FOLFOX with bevacizumab
    c. FOLFOX with cetuximab
    d. Either a or b
    e. All of the above

11. **The incidence of which of the following adverse events was significantly increased with the addition of bevacizumab to adjuvant FOLFOX in the initial safety data from NSABP-C-08?**
    a. GI perforation
    b. Hemorrhage
    c. Cardiac ischemia
    d. CNS ischemia
    e. None of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Colorectal Cancer Update — Issue 2, 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

- **ACOSOG trial evaluating laparoscopic versus open surgery for rectal cancer** 4 3 2 1
- **CALGB-80405 evaluating chemotherapy in combination with bevacizumab and/or cetuximab as first-line therapy for metastatic colorectal cancer (mCRC)** 4 3 2 1
- **Efficacy of cetuximab for mCRC based on K-ras status** 4 3 2 1
- **NCCTG-N0147 evaluating adjuvant FOLFOX with or without cetuximab for Stage III colon cancer** 4 3 2 1
- **BRiTE registry: Outcomes with the use of bevacizumab beyond first disease progression** 4 3 2 1
- **ECOG-E5202 evaluating FOLFOX with or without bevacizumab for resected Stage II colon cancer with a high risk of recurrence** 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

- **ACOSOG trial evaluating laparoscopic versus open surgery for rectal cancer** 4 3 2 1
- **CALGB-80405 evaluating chemotherapy in combination with bevacizumab and/or cetuximab as first-line therapy for metastatic colorectal cancer (mCRC)** 4 3 2 1
- **Efficacy of cetuximab for mCRC based on K-ras status** 4 3 2 1
- **NCCTG-N0147 evaluating adjuvant FOLFOX with or without cetuximab for Stage III colon cancer** 4 3 2 1
- **BRiTE registry: Outcomes with the use of bevacizumab beyond first disease progression** 4 3 2 1
- **ECOG-E5202 evaluating FOLFOX with or without bevacizumab for resected Stage II colon cancer with a high risk of recurrence** 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 LEARNER statements by circling the appropriate selection:

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:

- Evaluate the emerging 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
- Identify patients with Stage II colon cancer who have a high risk of recurrence based on microsatellite instability and loss of heterozygosity at chromosome 18q. ..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about participation in ongoing clinical trials evaluating the addition of biologic agents to conventional chemotherapy. ..... 4 3 2 1 N/M N/A
- Use biomarkers to predict response or resistance to systemic treatments for 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, anti-VEGF and anti-EGFR antibodies. ..... 4 3 2 1 N/M N/A
- Advise patients about the potential risks and benefits associated with the use of maintenance therapy for metastatic CRC. ..... 4 3 2 1 N/M N/A
- Formulate a treatment plan for patients with synchronous or metachronous primary CRC and liver-only metastases. ..... 4 3 2 1 N/M N/A
- Apply the results of recent clinical trials when recommending adjuvant imatinib for patients with operable gastrointestinal stromal tumors (GIST). ..... 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 editor and faculty for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Daniel G Haller, MD	4 3 2 1	4 3 2 1
Axel Grothey, MD	4 3 2 1	4 3 2 1
Charles D Blanke, MD	4 3 2 1	4 3 2 1
Al B Benson III, 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™

U P D A T E

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