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A CME On-Demand Webcast

The Art of Individualized Treatment in the Management of Colorectal Cancer

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Syllabus

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Sincerely,

Robert S. Stern
President
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Faculty Biographies

Chair

Richard M. Goldberg, MD
Professor of Medicine
Chief, Division of Hematology and Oncology
University of North Carolina School of Medicine
Chapel Hill, North Carolina

Richard M. Goldberg, MD, is professor and chief of the Division of Hematology/Oncology and associate director for Clinical Research at the UNC Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill, North Carolina. He is also the physician-in-chief of the North Carolina Cancer Hospital.

Dr. Goldberg completed his medical training at the Upstate Medical Center in Syracuse, New York, in 1979. Following his training in internal medicine, he spent two years as a fellow in medical oncology at the Vincent T. Lombardi Cancer Research Center, Washington, DC. In 1984, he became an associate in medical oncology at the Geisinger Medical Center and Clinic in Danville, Pennsylvania, and was appointed vice chairman of the Departments of Medicine there in 1992. From 1994–2003, he was professor of oncology at the Mayo Clinic in Rochester, Minnesota, and chaired the Mayo Gastrointestinal Cancer Research Program. In 2004, he was appointed the chair of the Gastrointestinal Cancer Committee for the Cancer and Acute Leukemia Group B (CALGB).

Dr. Goldberg is a member of the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), and the American Joint Commission on Cancer (AJCC) Colorectal Task Force. He has been an invited reviewer for many leading medical and oncology journals, and has served on the editorial boards of the National Cancer Institute's *Physician Data Query* program, the *Journal of Clinical Oncology*, *Clinical Colorectal Cancer*, and *Oncology*. He has coauthored more than 200 publications.

Faculty
Jeffrey Meyerhardt, MD, MPH
Assistant Professor of Medicine
Department of Medical Oncology
Harvard Medical School
Dana-Farber Cancer Institute
Boston, Massachusetts

Jeffrey Meyerhardt, MD, MPH, is associate physician in the Department of Medical Oncology at Dana-Farber Cancer Institute in Boston, Massachusetts. He is also a member of the Gastrointestinal Cancer Center and assistant professor of medicine at Harvard Medical School, also in Boston.

Dr. Meyerhardt conducts outcomes research in patients with gastrointestinal cancer, particularly the relationship between diet and lifestyle in patients with colorectal cancer. In addition, he has served as lead investigator and co-investigator of multiple clinical trials for patients with gastrointestinal cancers.

A member of the Cancer and Acute Leukemia Group B (CALGB) GI Committee, CALGB Prevention Subcommittee, and the American Society of Clinical Oncology (ASCO) Scientific Review Committee, Dr. Meyerhardt also teaches epidemiology to first-year medical students. He received his undergraduate degree from Haverford College in Pennsylvania, his medical degree from Yale School of Medicine, New Haven, Connecticut, and his masters of public health from Harvard School of Public Health in Boston.

Faculty
Alan P. Venook, MD
Professor of Clinical Medicine
Department of Medicine
University of California, San Francisco
San Francisco, California

Alan P. Venook, MD, is professor of clinical medicine at the University of California, San Francisco (UCSF), where he leads the Gastrointestinal Oncology Clinical Program.

A nationally recognized expert in colorectal and liver cancers, Dr. Venook received his BA degree from Rutgers University, New Brunswick, New Jersey, in 1976 and graduated from the UCSF School of Medicine in 1980. He spent two years in the Public Health Service following internship and completed his training in internal medicine at the University of California, Davis, as well as his hematology and oncology training at UCSF. He has been a member of the UCSF faculty since 1988.

The focus of Dr. Venook's research is developing and refining methods of treating tumors in the liver with directed approaches, including infusional chemotherapy or biologic agents. He is also an expert in the management of cancer patients with liver disease.

Program Information

PROGRAM OVERVIEW

- Case Study of a 62-Year-Old Woman with Colorectal Cancer (CRC)
- Molecular Oncogenesis of CRC
- Primary Treatment with Adjuvant Chemotherapy
- Nonpharmacologic Strategies to Improve Outcomes in Nonmetastatic CRC
- Clinical Challenges of Comorbid Conditions
- Targeted Biologic Therapies in Metastatic CRC (Mechanisms, Efficacy, and Safety)
- Second-Line Therapies for Metastatic CRC
- Investigational Targeted Therapy Regimens
- Genetic Markers and Response to Biologic Therapies for CRC

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CME INSTRUCTIONS

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Program Information

Target Audience

This CME activity is directed to medical oncologists, gastroenterologists, and other healthcare professionals who provide care to patients with colorectal cancer.

Activity Goal

The goal of this CME activity is to present the current and emerging first- and second-line treatments for stage III and metastatic colorectal cancer, with a focus on targeted therapies. The emphasis is on individualizing treatment, taking into consideration comorbid conditions, lifestyle, and disease-related factors. Potential outcomes will be illustrated through a case study.

Learning Objectives

- Evaluate the molecular basis of colorectal oncogenesis and relevant therapeutic targets to implement optimal colorectal cancer (CRC) treatment intervention.
- Utilize an understanding of the available CRC treatment options to improve patient selection, dosing, and response to therapy.
- Utilizing an understanding of the side effect and drug-drug interaction profiles of CRC treatment options, select the most appropriate treatment for improved patient outcomes.
- Customize the management of CRC to optimize CRC patient outcomes.

CME INFORMATION: PHYSICIANS

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Richard M. Goldberg, MD, has received grant/research support from Pfizer Inc; and is a consultant for ALMAC Group Ltd, Amgen Inc, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Genentech, Inc, Genomic Health, Inc, ImClone Systems Inc, sanofi-aventis, Taiho Pharmaceutical Company Ltd, and Yakult.

Jeffrey Meyerhardt, MD, MPH, is on the speakers bureau for Genentech, Inc and Pfizer Inc.

Alan P. Venook, MD, has received grant/research support from Genentech, Inc, Novartis Pharmaceuticals Corporation, and Pfizer Inc.

Peer Reviewer has received grant/research support from AstraZeneca; and has received speaker honoraria from the New York Academy of Sciences (NYAS).

Projects In Knowledge's staff members have no significant relationships to disclose.

This activity will include a discussion of complex treatment regimens, some of which contain drugs that may not be FDA approved or that have off-label indications for use in patients with colorectal cancer.

Conflicts of interest are thoroughly vetted by the Executive Committee of Projects In Knowledge. All conflicts are resolved prior to the beginning of the activity by the Trust In Knowledge peer review process.

The opinions expressed in this activity are those of the faculty and do not necessarily reflect those of Projects In Knowledge.

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Introduction

Colorectal cancer is the fourth most common cancer in the United States. Incidence and mortality rates have declined over the past 20 years, possibly due to more widespread screening, improved methods of detection, and more successful treatments. Nonetheless, the American Cancer Society estimates that 49,960 deaths from colorectal cancers will occur in 2008, accounting for 9% of all cancer deaths.

More than 90% of colorectal cancer cases are diagnosed in people who are aged 50 years and older. Other risk factors besides age include a family history of the disease, a personal history of polyps or chronic irritable bowel disease, and diabetes. Obesity, lack of exercise, eating a Western diet (ie, high intake of meat, fat, refined grains, and dessert), heavy alcohol consumption, and smoking are also associated with increased risk. Acquired gene mutations may also promote colorectal cancer. For example, these may include *APC* mutations, *P53* mutations, *K-ras* mutations, COX-2 overexpression, p27 loss, and DCC loss.

Treatment of Nonmetastatic Stage III Disease

Surgery is the primary treatment for nonmetastatic stage III colorectal cancer. However, numerous studies have shown that adjuvant chemotherapy significantly improves survival rates over surgery alone.

Greene and colleagues found that 5-year survival rates for patients with stage IIIA colon cancer were 52% with surgery alone compared with 71% for surgery plus adjuvant chemotherapy. For patients with stage IIIB colon cancers, 5-year survival was 37% with surgery alone versus 51% for surgery with chemotherapy. For patients with stage IIIC colon cancer, 5-year survival was 21% for surgery alone and 32% for surgery plus adjuvant chemotherapy.

Another study randomized 1987 patients with resected stage III disease to receive either bolus 5-fluorouracil (5-FU)/leucovorin (LV) (the Mayo Clinic regimen) or capecitabine for 24 weeks. Five-year disease-free and overall survival were not statistically significantly different for patients in the 5-FU/LV group compared with the capecitabine group, indicating that oral capecitabine is an effective alternative to 5-FU/LV as an adjuvant treatment for stage III colon cancer.

In the MOSAIC study, 2246 patients with fully resected stage II or III colorectal cancer were randomly assigned to receive 5-FU/LV or FOLFOX4 (5-FU/LV plus oxaliplatin). Treatment with FOLFOX4 was associated with a 73% 5-year disease-free survival rate compared with 67% with 5-FU/LV.

No data are yet available regarding the efficacy of the targeted biologic treatments bevacizumab, cetuximab, and panitumumab as adjuvant therapy for colorectal cancer. Two trials investigating adjuvant use of bevacizumab in patients with stage II and III colorectal cancer have completed accrual and results are pending, and other trials of adjuvant bevacizumab or cetuximab are accruing subjects.

Various comorbid conditions can have an impact on the efficacy of chemotherapy for colorectal cancer. For example, patients with diabetes mellitus who have developed diabetes-related nerve damage may be more likely to develop chemotherapy-induced neuropathy during treatment for colorectal cancer. Obesity prior to a diagnosis of colorectal cancer is associated with poorer disease-specific survival. In addition, studies by Meyerhardt and colleagues have shown that colon cancer patients who exercise less may be at greater risk of recurrence, while patients who are heavy consumers of a Western diet may have poorer rates of disease-free survival. Individualized management of colorectal cancer therefore must take into account the patient's overall health, comorbid conditions, and lifestyle choices, and should include appropriate counseling.

Treatment for Metastatic Colorectal Cancer

Research has also examined the comparative efficacy of various chemotherapy regimens on patients with metastatic colorectal cancer. Goldberg and colleagues found that the FOLFOX regimen improved response rate, time to progression, and overall survival compared with either irinotecan/5-FU/LV (IFL) or irinotecan/oxaliplatin (IROX). Compared with the other two regimens, FOLFOX had a higher incidence of grade 3/4 neutropenia and grade 3/4 paresthesias, but a lower incidence of grade 3/4 diarrhea. Several studies comparing oxaliplatin-based regimens (eg, FOLFOX) with irinotecan-based regimens (eg, FOLFIRI, IFL) all found the efficacy of the two regimens to be similar, although differences in toxicity profiles were noted.

Targeted Biologic Therapies

Targeted monoclonal antibodies represent some of the newest developments in colorectal cancer treatment. These include bevacizumab, which targets vascular endothelial growth factor (VEGF), and two epidermal growth factor receptor (EGFR) inhibitors, cetuximab and panitumumab. VEGF strongly stimulates proliferation of new blood vessels to the tumor, which may promote tumor growth and metastasis. It has been suggested that anti-VEGF treatment causes regression of existing microvessels, normalizes the structure and function of the remaining vasculature, and inhibits neovascularization. EGFR is a transmembrane receptor of the tyrosine kinase growth factor receptor family. It is expressed in normal epithelial tissues but also in various cancers including colorectal cancer. Activation by binding of EGF or transforming growth factor-alpha (TGF-α) produces various intracellular signals that promote tumor growth and metastasis. EGFR inhibitors bind to the receptors, competitively blocking binding of EGF and TGF-α and thereby inhibiting tumor cell growth and division.

Targeted Therapies in First-line Treatment of Metastatic Colorectal Cancer

Bevacizumab has shown efficacy as part of first-line therapy for metastatic colorectal cancer. Hurwitz and colleagues compared the efficacy of bevacizumab added to IFL versus IFL alone as a first-line treatment of patients with metastatic colorectal cancer. The combined treatment significantly extended progression-free survival and overall survival rates over IFL alone. Saltz and colleagues found that the addition of bevacizumab to either of two oxaliplatin-based chemotherapy regimens, FOLFOX4 and XELOX, significantly improved progression-free survival. A third study by Fuchs and colleagues showed that adding bevacizumab to FOLFIRI or modified bolus IFL (mIFL) improved progression-free survival over the chemotherapy regimens alone. Toxicity values again varied.

Bevacizumab is associated with an increased risk of thromboembolic events, bleeding, gastrointestinal perforations, and surgical wound-healing complications. Bevacizumab should not be administered to patients who have had an arterial thromboembolic event in the prior six months, uncontrolled cardiovascular disease, bleeding or coagulation disorders, or other risk factors for bleeding, and should be used judiciously in patients with untreated brain metastases. Bevacizumab should also be avoided in patients with a recent history of gastrointestinal perforation, abdominal fistulas, or intra-abdominal abscesses. Administration of bevacizumab should be withheld for four to six weeks after major surgery or invasive gastrointestinal procedures, and should be stopped at least six weeks prior to elective surgical procedures.

Cetuximab has also shown benefit as part of first-line treatment in metastatic colorectal cancer. The CRYSTAL trial found a significantly increased response rate and 1-year progression-free survival rate when cetuximab was combined with FOLFIRI. EGFR inhibitors, such as cetuximab and panitumumab, commonly induce skin reactions, including an acne-like rash, postinflammatory effects, dry skin, fissures, and paronychia. Skin toxicity may be a predictor of response to EGFR inhibitors.

It is unclear whether combining targeted therapies further improves outcomes in the first-line treatment setting. Panitumumab did not improve progression-free survival when added to bevacizumab plus either FOLFOX or FOLFIRI in the first-line treatment setting. A clinical trial

testing FOLFOX or FOLFIRI plus cetuximab in combination with bevacizumab is currently recruiting participants.

Targeted Therapies for Second-line Treatment of Metastatic Colorectal Cancer

Several studies have examined targeted therapies as second-line treatment of colorectal cancer after disease progression following first-line therapy.

The BRiTe study examined the question of whether there was any gain in survival if first-line bevacizumab treatment is continued beyond first progression. Patients who continued to receive bevacizumab after progression achieved an overall survival of 19.2 months compared with 9.5 months among patients who received second-line treatment without bevacizumab and 3.6 months for patients who received no second-line treatment.

In the BOND trial, patients who progressed on irinotecan-based therapy were treated either with irinotecan plus cetuximab or cetuximab alone. Median time to progression was significantly greater in the combination therapy group (4.1 versus 1.5 months), while the median survival time for the combination therapy group was 8.6 months compared with 6.9 months in the monotherapy group. However, the combination regimen was associated with more grade 3/4 diarrhea.

In the panitumumab registration trial, Van Cutsem and colleagues found that median progression-free survival was significantly improved for patients with chemorefractory colorectal cancer who received panitumumab combined with best supportive care compared with those who received best supportive care alone.

Researchers have also investigated combined monoclonal antibody therapies as second-line treatment for patients with metastatic colorectal cancer. The BOND-2 study gave patients with irinotecan-refractory colon cancer combined treatments with cetuximab and bevacizumab together with irinotecan, a treatment that achieved improved time to progression over treatment with cetuximab and bevacizumab alone. Toxicities encountered with the combined regimen were comparable to those that could be expected from the same agents when administered individually, the researchers said, but they added that a 28% incidence of grade 3/4 diarrhea in a previously treated population was "noteworthy." An ongoing phase III trial intends to study irinotecan/FOLFIRI and cetuximab together with bevacizumab as a second-line therapy for patients with metastatic colorectal cancer compared with irinotecan/FOLFIRI and cetuximab alone.

Predicting Response to Targeted Therapies

Recent research has shown that colorectal cancer patients with *K-ras* mutations in their tumors are resistant to treatment with EGFR monoclonal antibodies. Lievre and colleagues found an association between cetuximab resistance and the *K-ras* mutation in two studies involving a total of 119 advanced colorectal cancer patients. A third study by Khambata-Ford and colleagues affirmed that association and also found that patients whose tumors demonstrate high expression levels of anti-EGFR ligands epiregulin and amphiregulin are more likely to have antitumor activity resulting from cetuximab therapy. Amado and colleagues found that patients with tumors harboring *K-ras* mutations displayed a similar resistance to monotherapy with panitumumab. The sum of the data suggests that only patients with intact *K-ras* genes in their tumors have a chance of benefiting from this class of drugs.

Conclusions

The role of targeted therapies is evolving in colorectal cancer. Targeted therapies have been demonstrated to be of benefit in patients with advanced disease, and recent data suggest that analysis of the *K-ras* gene in tumors may enable physicians to determine if EGFR antibodies are of potential value or should be avoided.

Targeted therapies have been tested but have not yet been shown to improve outcomes in earlier-stage patients; however, those data should be available over the next few years. The combination of targeted therapies is also under investigation.

Suggested Readings

Amado RG, Wolf M, Peeters M, et al. Wild-type *KRAS* is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26:1626-1634.

Colucci G, Gebbia V, Paoletti O, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol*. 2005;23:4866-4875.

Cunningham D, Humbet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351:337-345.

Fuchs C, Marshall J, Mitchell E, et al. Updated results of BICC-C study comparing first-line irinotecan/fluoropymidine combinations with or without celecoxib in mCRC: updated efficacy data. Abstract 4027. Presented at: 43rd annual meeting of the American Society of Clinical Oncology; June 1-5, 2007; Chicago, IL.

Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*. 2007;20:1539-1544.

Goldberg RM, Morton RF, Sargent DJ, et al. N9741: oxaliplatin (Oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Updated efficacy and quality of life (QOL) data from an intergroup study. Abstract 1009. Presented at: 39th annual meeting of the American Society of Clinical Oncology; May 31-June 1, 2003; Chicago, IL.

Greene FL, Stewart AK, Norton J. A new TNM staging strategy for node-positive (stage III) colon cancer. An analysis of 50,042 patients. *Ann Surg*. 2002;236:416-421.

Grothey A, Sugurue E, Hedrick E, et al. Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): results from a large observational study (BRiTE). Abstract: 4036. Presented at: 43rd annual meeting of the American Society of Clinical Oncology; June 1-5, 2007; Chicago, IL.

Hecht JR, Mitchell E, Chidiac T, 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). Abstract 273. Presented at: 2008 Gastrointestinal Cancers Symposium; January 25-27, 2008. Orlando, FL.

Hecht JR, Mitchell E, Chidiac T, et al. Interim results from PACCE: irinotecan (Iri)/bevacizumab (bev) ± panitumumab (pmab) as first-line treatment (tx) for metastatic colorectal cancer (mCRC). Abstract 279. Presented at: 2008 Gastrointestinal Cancers Symposium; January 25-27, 2008; Orlando, FL.

Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350:2335-2342.

Kalofonos HP, Aravantinos G, Kosmidis P, et al. Irinotecan or oxaliplatin combined with leucovorin and 5-fluorouracil as first-line treatment in advanced colorectal cancer: a multicenter, randomized, phase II study. *Ann Oncol*. 2005;16:869-877.

Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol*. 2007;25:3230-3237.

Kopetz J, Dang J, Overman M, et al. Bevacizumab toxicity and efficacy are unaffected by regimen or resection status: a single institution retrospective study. Abstract 243. Presented at: 2006 Gastrointestinal Cancers Symposium; January 26-28, 2006; San Francisco, CA.

Lievre A, Bachet J-B, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol*. 2008;26:374-379.

Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol*. 2006;24:3535-3541.

Meyerhardt JA, Niedzwiecki D, Hollis D, et al.et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. *JAMA*. 2007;298:754-764.

Saltz L, Clarke S, Diaz-Rubio E, et al. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: updated efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer. Abstract 4028. Presented at: 43rd annual meeting of the American Society of Clinical Oncology; June 1-5, 2007; Chicago, IL.

Saltz LB, Lenz H-J, Kindler HL, 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;25:4557-4561.

Skillings J, Johnson DH, Miller K, et al. Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy. Abstract 3019. Presented at: 41st annual meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL.

Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22:229-237.

Van Cutsem E, Nowacki M, Lang S, et al. Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): the CRYSTAL Trial. Abstract 4000. Presented at: 43rd annual meeting of the American Society of Clinical Oncology; June 1-5, 2007; Chicago, IL.

Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol*. 2007;25:1658-1664.

Venook A, Niedzwiecki D, Hollis D, et al. Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results. Abstract 3509. Presented at: 42nd annual meeting of the American Society of Clinical Oncology; June 2-6, 2006; Atlanta, GA.