

Beyond the Guidelines

Clinical Investigators Provide Their Perspectives on Current Strategies and Ongoing Research in the Management of Gastrointestinal Cancers

Part I — Cancers of the Colon and Rectum

TARGET AUDIENCE

This activity is intended for medical oncologists, hematology-oncology fellows, surgeons and other healthcare providers involved in the treatment of gastrointestinal cancers.

OVERVIEW OF ACTIVITY

Cancer of the colon and rectum is the fourth most frequently diagnosed cancer and the second most common cause of death among all neoplasms in the United States, accounting for approximately 9% of all cancer deaths. In the year 2012 it was estimated that 103,170 new cases of colon cancer and 40,290 new cases of rectal cancer were documented in the United States. Current therapeutic management of colorectal cancer (CRC) is dependent on tumor stage at the time of initial diagnosis, status of surgical margins, patient performance status, age, prior treatment exposure and sites of metastasis for those with disease recurrence or de novo advanced cancer. Although these variables are helpful in guiding selection of treatment, the introduction of novel biomarkers, multigene signatures and molecular-targeted systemic agents has significantly refined the clinical algorithm such that individualized therapeutic approaches have become the standard. This rapid paradigm shift presents a challenge to practicing oncologists who must grapple with the presentation of ambiguous data sets and their immediate impact on treatment decisions.

These proceedings from a CME symposium held during the 2013 Gastrointestinal Cancers Symposium use the perspectives of renowned experts in the field of CRC to explore the self-described practice patterns of 25 gastrointestinal cancer clinical investigators and the supporting research database in a number of commonly encountered clinical situations. By providing information on the latest research developments and their potential application to routine practice, this activity is designed to assist medical oncologists, hematology-oncology fellows, surgeons and other healthcare providers with the formulation of up-to-date clinical management strategies for CRC.

LEARNING OBJECTIVES

- Apply the results of emerging clinical research to the best-practice management of cancers originating within the colon and rectum.
- Counsel patients with Stage II colon cancer about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers, and consider adjuvant therapeutic options based on this information.
- Effectively apply the results of practice-changing clinical research in the selection and sequencing of biologic agents alone or in combination with chemotherapy for patients with metastatic CRC (mCRC).
- Develop an evidence-based algorithm for the prevention and amelioration of side effects associated with chemotherapeutic and biologic agents used in the management of mCRC.
- Individualize local and systemic treatment for patients with mCRC that is isolated to the liver.
- Identify ongoing clinical trials evaluating innovative investigational approaches for CRC, and obtain consent from appropriate patients for study participation.

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RESEARCH TO PRACTICE STAFF AND EXTERNAL

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Hardware/Software Requirements:

A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

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Select Publications

Howard S Hochster, MD

- André T et al. **Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial.** *J Clin Oncol* 2009;27(19):3109-16.
- De Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of 6 years.** *Proc ASCO* 2007b;Abstract 4007.
- Kuebler JP et al. **Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07.** *J Clin Oncol* 2007;25(16):2198-204.
- O'Connell JB et al. **Colon cancer survival rates with the new American Joint Committee on Cancer Sixth Edition Staging.** *JNCI* 2004;96(19):1420-5.
- O'Connell M et al. **Validation of the 12-gene colon cancer recurrence score (RS) in NSABP C07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5FU/LV (FU) and 5FU/LV+oxaliplatin (FU+Ox).** *Proc ASCO* 2012;Abstract 3512.
- Tournigand C et al. **Adjuvant therapy with fluorouracil and oxaliplatin in Stage II and elderly patients (between ages 70 and 75 years) with colon cancer: Subgroup analyses of the multicenter international study of oxaliplatin, fluorouracil, and leucovorin in the adjuvant treatment of colon cancer.** *J Clin Oncol* 2012;30(27):3353-60.

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- Arnold D et al. **Bevacizumab (BEV) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with BEV plus CT: Results of a randomized phase III intergroup study (TML study).** *Proc ASCO* 2012;Abstract CRA3503.
- Bennouna J et al. **Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): A randomised phase 3 trial.** *Lancet Oncol* 2013;14(1):29-37.
- Cohn AL et al. **Clinical outcomes in bevacizumab (BV)-treated patients (pts) with metastatic colorectal cancer (mCRC): Results from ARIES observational cohort study (OCS) and confirmation of BRiTE data on BV beyond progression (BBP).** *Proc ASCO* 2010;Abstract 3596.
- De Roock W et al. **Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab.** *JAMA* 2010;304(16):1812-20.
- 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.

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- Amado RG et al. **Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer.** *J Clin Oncol* 2008;26(10):1626-34.
- Arnold D et al. **Bevacizumab (BEV) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with BEV plus CT: Results of a randomized phase III intergroup study (TML study).** *Proc ASCO* 2012;Abstract CRA3503.
- Douillard J et al. **Final results from PRIME — A Phase III study of panitumumab with FOLFOX4 for first-line mCRC.** *Proc ASCO* 2011;Abstract 3510.
- Ellis LM et al. **VEGF-targeted therapy: Mechanisms of anti-tumor activity.** *Nat Rev Cancer* 2008;8:579-91.
- Giantonio BJ 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;25(12):1539-44.
- Goldberg RM et al. **The continuum of care: A paradigm for the management of metastatic colorectal cancer.** *Oncologist* 2007;12(1):38-50.
- Grothey A, Sargent D. **Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line.** *J Clin Oncol* 2005;23(36):9441-2.
- Holash J et al. **VEGF-Trap: A VEGF blocker with potent antitumor effects.** *PNAS* 2002;99:11393-8.
- Karapetis CS et al. **K-ras mutations and benefit from cetuximab in advanced colorectal cancer.** *N Engl J Med* 2008;359(17):1757-65.
- Khayat D et al. **Intravenous aflibercept administered in combination with irinotecan, 5-fluorouracil and leucovorin in patients with advanced solid tumors: Results from the expansion cohort of a phase I study.** *Eur J Cancer* 2013;49(4):790-7.

Pericay C et al. **Phase 2 randomized, noncomparative, open-label, study of aflibercept and modified FOLFOX6 in the first-line treatment of metastatic colorectal cancer (AFFIRM).** ESMO 14th World Congress on Gastrointestinal Cancer 2012;Abstract O-0024.

Tew WP et al. **Phase 1 study of aflibercept administered subcutaneously to patients with advanced solid tumors.** *Clin Cancer Res* 2010;16(1):358-66.

Van Cutsem E et al. **Phase I dose-escalation study of intravenous aflibercept administered in combination with irinotecan, 5-fluorouracil and leucovorin in patients with advanced solid tumors.** *Eur J Cancer* 2013;49:17-24.

Van Cutsem E et al. **Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a Phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen.** *J Clin Oncol* 2012;30(28):3499-506.

Van Cutsem E et al. **Lessons from the adjuvant bevacizumab trial on colon cancer: What next?** *J Clin Oncol* 2011;29(1):1-4.

Van Cutsem E et al. **Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment.** *Ann Oncol* 2010;21(Suppl 5):v93-7.

Richard M Goldberg, MD

Grothey A. **S-1 in colorectal cancer: A new standard of care?** *Lancet Oncol* 2012;13(11):1068-70.

Siena S et al. **Biomarkers predicting clinical outcome of epidermal growth factor receptor-targeted therapy in metastatic colorectal cancer.** *JNCI* 2009;101(19):1308-24.

Josep Taberner, MD

Abad A et al. **Colorectal cancer metastasis resectability after treatment with the combination of oxaliplatin, irinotecan and 5-fluorouracil. Final results of a phase II study.** *Acta Oncol* 2008;47(2):286-92.

Alberts SR et al. **Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: A North Central Cancer Treatment Group Phase II study.** *J Clin Oncol* 2005;23(36):9243-9.

Barone C et al. **Final analysis of colorectal cancer patients treated with irinotecan and 5-fluorouracil plus folinic acid neoadjuvant chemotherapy for unresectable liver metastases.** *Br J Cancer* 2007;97(8):1035-9.

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.

Falcone A et al. **Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest.** *J Clin Oncol* 2007;25(13):1670-6.

Folprecht G et al. **Randomized multicenter study of cetuximab plus FOLFOX or cetuximab plus FOLFIRI in neoadjuvant treatment of non-resectable colorectal cancer liver metastases (CELIM-study).** *Proc ESMO* 2011. No abstract available

Folprecht G et al. **Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: The CELIM randomised phase 2 trial.** *Lancet Oncol* 2010;11(1):38-47.

Masi G et al. **Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer.** *Ann Surg Oncol* 2006;13(1):58-65.

Okines A et al. **Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer — First BEAT and the randomized phase-III NO16966 trial.** *Br J Cancer* 2009;101(7):1033-8.

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.

Seium Y et al. **Oxaliplatin combined with irinotecan and 5-fluorouracil/leucovorin (OCFL) in metastatic colorectal cancer: A Phase I-II study.** *Ann Oncol* 2005;16(5):762-6.

Tournigand C et al. **FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study.** *J Clin Oncol* 2004;22(2):229-37.

Van Cutsem E et al. **Outcome according to metastatic site in patients with KRAS wild-type tumors: Analysis from the CRYSTAL and OPUS studies.** *Gastrointestinal Cancers Symposium 2011;Abstract 472.*

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

Ychou M et al. **Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): A phase II study in colorectal cancer patients with non-resectable liver metastases.** *Cancer Chemother Pharmacol* 2008;62(2):195-201.