

# Beyond the Guidelines

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

### *Part II — Noncolorectal GI Cancers*

#### **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**

Given the prevalent nature of the disease, extensive resources are allocated to colorectal cancer (CRC) research and education. Of interest, however, although individually less frequently encountered, the collection of other “non-CRC” gastrointestinal (GI) cancers accounts for more per annum cancer-related deaths than those attributed to tumors of the colon and rectum combined. In addition to maintaining a sound understanding of the conventional but distinct treatment algorithms applicable to each subtype of non-CRC GI cancer, practicing oncologists must now rationally integrate targeted agents into their individualized therapeutic recommendations for the safe and effective clinical management of diseases they seldom encounter.

These proceedings from a CME symposium held during the 2013 Gastrointestinal Cancers Symposium use the perspectives of renowned GI cancers experts to explore the self-described practice patterns of 25 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 various non-CRC GI cancers.

#### **LEARNING OBJECTIVES**

- Effectively integrate the evidence-based use of chemotherapy into the individualized management of advanced pancreatic cancer.
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with locally advanced or metastatic hepatocellular cancer.

- Identify patients with GIST who are likely to benefit from adjuvant therapy, and determine treatment strategies for patients with imatinib-resistant disease.
- Educate patients with gastric cancer about novel treatment approaches in the locally advanced and metastatic disease settings.
- Identify the optimal sequencing of systemic therapies for patients with metastatic neuroendocrine tumors of the GI tract.
- Counsel patients with cancers of the GI tract about participation in ongoing clinical trials.

#### **ACCREDITATION STATEMENT**

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**FACULTY** — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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**Consulting Agreements:** Novartis Pharmaceuticals Corporation, Pfizer Inc.

**MODERATOR** — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

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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

### Charles S Fuchs, MD, MPH

Bang YJ et al. **A randomized, open-label, phase III study of lapatinib in combination with weekly paclitaxel versus weekly paclitaxel alone in the second-line treatment of HER2 amplified advanced gastric cancer (AGC) in Asian population: Tytan study.** *Gastrointestinal Cancers Symposium 2013;Abstract 11.*

Bang YJ et al. **Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or GE junction cancer (ToGA): A Phase 3, open-label, randomised controlled trial.** *Lancet* 2010;376(9742):687-97.

Fuchs CS et al. **REGARD: A Phase III, randomized, double-blinded trial of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum- and/or fluoropyrimidine-containing combination therapy.** *Gastrointestinal Cancers Symposium 2013;Abstract LBA5.*

Jung YD et al. **Effects of combination anti-vascular endothelial growth factor receptor and anti-epidermal growth factor receptor therapies on the growth of gastric cancer in a nude mouse model.** *Eur J Cancer* 2002;38(8):1133-40.

Ohtsu A et al. **Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A randomized, double-blind, placebo-controlled Phase III study.** *J Clin Oncol* 2011;29(30):3968-76.

### Philip A Philip, MD, PhD, FRCP

Conroy T et al. **FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.** *N Engl J Med* 2011;364(19):1817-25.

Von Hoff DD et al. **Randomized Phase III study of weekly nab-paclitaxel plus gemcitabine vs gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT).** *Gastrointestinal Cancers Symposium 2013;Abstract LBA148.*

### Alan P Venook, MD

Corless CL et al. **Molecular pathobiology of gastrointestinal stromal sarcomas.** *Annu Rev Pathol* 2008;3:557-86.

Debiec-Rychter M; EORTC Soft Tissue and Bone Sarcoma Group. **KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours.** *Eur J Cancer* 2006;42(8):1093-103.

Demetri GD et al. **Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID): An international, multicenter, randomised, placebo-controlled, phase 3 trial.** *Lancet* 2013;381(9863):295-302.

Demetri GD et al. **Randomized phase III trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU): GRID trial.** *Proc ASCO* 2012;Abstract LBA10008.

Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). **Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: A meta-analysis of 1,640 patients.** *J Clin Oncol* 2010;29(7):1247-53.

George S et al. **Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: A multicenter phase II trial.** *J Clin Oncol* 2012;30(19):2401-7.

Heinrich MC et al. **Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 study by Cancer and Leukemia Group B and Southwest Oncology Group.** *J Clin Oncol* 2008;26(33):5360-7.

Mross K et al. **A Phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors.** *Clin Cancer Res* 2012;18(9):2658-67.

**NCCN clinical practice guidelines in oncology: Gastrointestinal stromal tumors (GIST).** v.3.2012. Available at: [www.nccn.org](http://www.nccn.org).

Wilhelm SM et al. **Regorafenib (BAY 73-4506): A new multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity.** *Int J Cancer* 2011;129(1):245-55.

### Andrew X Zhu, MD, PhD

Cheng A et al. **Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial.** *Lancet Oncol* 2009;10(1):25-34.

Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. **A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma.** *N Engl J Med* 1995;332(19):1256-61.

Kudo M et al. **Phase III study of sorafenib after transarterial chemoembolization in Japanese and Korean patients with unresectable hepatocellular carcinoma.** *Eur J Cancer* 2011;47(14):2117-27.

Lencioni R et al. **Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial.** *Gastrointestinal Cancers Symposium 2012;Abstract LBA154.*

Llovet JM et al. **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med* 2008;359(4):378-90.

Llovet JM et al. **Updated treatment approach to hepatocellular carcinoma.** *J Gastroenterol* 2005;40(3):225-35.

Madden MV et al. **Randomised trial of targeted chemotherapy with lipiodol and 5-epidoxorubicin compared with symptomatic treatment for hepatoma.** *Gut* 1993;34(11):1598-600.

Marrero JA et al. **Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON) second interim analysis in more than 1,500 patients: Clinical findings in patients with liver dysfunction.** *Proc ASCO* 2011;Abstract 4001.

Pelletier G et al. **Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: A multicenter randomized trial.** *J Hepatol* 1998;29(1):129-34.

Pelletier G et al. **A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma.** *J Hepatol* 1990;11(2):181-4.

Rimassa L et al. **Tivantinib (ARQ 197) versus placebo in patients (Pts) with hepatocellular carcinoma (HCC) who failed one systemic therapy: Results of a randomized controlled phase II trial (RCT).** *Proc ASCO* 2012;Abstract 4006.

Zhu AX et al. **A Phase II study of ramucirumab as first-line monotherapy in patients (pts) with advanced hepatocellular carcinoma (HCC).** *Proc ASCO* 2010;Abstract 4083.

#### **Matthew Kulke, MD, MMSc**

Arnold R et al. **Placebo-controlled, double-blind, prospective, randomized study of the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID study group.** *Proc ASCO* 2009;Abstract 4508.

Ekeblad S et al. **Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors.** *Clin Cancer Res* 2007;13(10):2986-91.

Faiss S et al. **Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors — The International Lanreotide and Interferon Alfa Study Group.** *J Clin Oncol* 2003;21(14):2689-96.

Kouvaraki MA et al. **Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas.** *J Clin Oncol* 2004;22(23):4762-71.

Kulke MH et al. **O<sup>6</sup>-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors.** *Clin Cancer Res* 2009;15(1):338-45.

Kulke MH et al. **A phase II study of temozolomide and bevacizumab in patients with advanced neuroendocrine tumors.** *Proc ASCO* 2006;Abstract 4044.

Kulke MH et al. **Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors.** *J Clin Oncol* 2006;24(3):401-6.

Moertel CG et al. **Streptozocin-doxorubicin, streptozocin-fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma.** *N Engl J Med* 1992;326(8):519-23.

Niccoli P et al. **Updated safety and efficacy results of the phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of pancreatic neuroendocrine tumors (NET).** *Proc ASCO* 2010;Abstract 4000.

Pavel ME et al. **Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): A randomised, placebo-controlled, phase 3 study.** *Lancet* 2011;378(9808):2005-12.

Pavel M et al. **A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus + octreotide LAR vs placebo + octreotide LAR in patients with advanced neuroendocrine tumors (NET) (RADIANT-2).** *Proc ESMO* 2010;Abstract LBA8.

Strosberg JR et al. **First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas.** *Cancer* 2011;117(2):268-75.

Sun W et al. **Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group study E1281.** *J Clin Oncol* 2005;23(22):4898-904.

Yao JC et al. **Everolimus for advanced pancreatic neuroendocrine tumors.** *N Engl J Med* 2011;364(6):514-23.