REAL-LIFE DECISIONS

Clinical Investigators Provide Their Perspectives on Actual Patients with Metastatic Colorectal, Gastric and Pancreatic Cancer

CME Information

TARGET AUDIENCE

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

OVERVIEW OF ACTIVITY

Given the prevalent nature of the disease, extensive resources are allocated to colorectal cancer (CRC) research and education. Interestingly, however, although individually less frequently encountered, the collection of other "non-CRC" GI cancers account for more per annum cancer-related deaths than those attributed to tumors of the colon and rectum combined. Importantly, among this collection of distinct tumors, two areas in particular — gastric and pancreatic cancer — have witnessed several recent advances that have already drastically altered or have the potential to affect current treatment considerations and approaches.

These video highlights from a CME symposium held during the 2016 Gastrointestinal Cancers Symposium feature presentations given by leading investigators in the management of GI cancers. By providing information on important new developments, this activity will address the most pressing educational needs of practitioners involved in the multidisciplinary management of colorectal, gastric and pancreatic cancer.

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and changing practice standards in colorectal, gastric and pancreatic cancer, and integrate this information, as appropriate, into current clinical care.
- Develop a long-term care plan for individuals diagnosed with metastatic CRC, considering the patient's biomarker profile, exposure to prior systemic therapy, symptomatology, performance status and personal goals for treatment.
- Communicate with patients and their caregivers regarding the incidence and manifestation of side effects and toxicities associated with systemic agents and regimens commonly used in the management of advanced GI cancers.
- Individualize local and systemic treatment for patients with liver-only or liver-dominant metastatic CRC.
- Use HER2 status, clinical factors and patient perspectives to optimize the selection and sequence of systemic therapy for patients with locally advanced or metastatic gastric or gastroesophageal cancer.
- Consider age, performance status and other clinical and logistical factors in the selection of systemic therapy for patients with locally advanced or metastatic pancreatic cancer.
- Appraise the rationale for and clinical data with investigational anti-PD-1 and/or anti-PD-L1 antibodies in the treatment of GI cancers.
- Describe the proposed mechanisms of action of and recall new data with investigational agents demonstrating promising activity in colorectal, gastric and pancreatic cancer, and use this information to counsel appropriate patients regarding ongoing trials.

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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

Heinz-Josef Lenz, MD

Atreya CE et al. **Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with *BRAF* V600E mutated (BRAFm) metastatic colorectal cancer (mCRC).** *Proc ASCO* 2015;**Abstract 103**.

Bertotti A et al. **A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer.** *Cancer Discov* 2011;1(6):508-23.

Bollag G et al. **Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma.** *Nature* 2010;467(7315):596-9.

Corcoran RB et al. **Pharmacodynamic and efficacy analysis of the BRAF inhibitor dabrafenib (GSK436) in combination with the MEK inhibitor trametinib (GSK212) in patients with BRAFV600 mutant colorectal cancer (CRC).** *Proc ASCO* 2013;**Abstract 3507**.

Corcoran RB et al. **EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib.** *Cancer Discov* 2012;2(3):227-35.

Elez E et al. **Results of a phase 1b study of the selective BRAF V600 inhibitor encorafenib in combination with cetuximab alone or cetuximab + alpelisib for treatment of patients with advanced BRAF-mutant metastatic colorectal cancer.** *Proc ESMO* 2014;**Abstract LBA-08**.

Falchook GS et al. **Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: A phase 1 dose-escalation trial.** *Lancet* 2012;379(9829):1893-901.

Gomez-Roca CA et al. **Encorafenib (lGX818), an oral BRAF inhibitor, in patients (pts) with BRAF V600E metastatic colorectal cancer (mCRC): Results of dose expansion in an open-label, Phase 1 study.** *Proc ESMO* 2014;**Abstract 535P**.

Guinney J et al. **The consensus molecular subtypes of colorectal cancer.** *Nat Med* 2015;21(11):1350-6.

Hong DS et al. **Phase Ib study of vemurafenib in combination with irinotecan and cetuximab in patients with *BRAF*-mutated metastatic colorectal cancer and advanced cancers.** *Proc ASCO* 2015;**Abstract 3511**.

Kopetz S et al. **PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors.** *Proc ASCO* 2010;**Abstract 3534**.

Martin V et al. **HER2 gene copy number status may influence clinical efficacy to anti-EGFR monoclonal antibodies in metastatic colorectal cancer patients.** *Br J Cancer* 2013;108(3):668-75.

Missiaglia E et al. **Proximal and distal colon tumors as distinct biologic entities with different prognoses.** *Proc ASCO* 2013;**Abstract 3526**.

Prahallad A et al. **Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR.** *Nature* 2012;483(7387):100-3.

Ramanathan RK et al. **Low overexpression of HER-2/neu in advanced colorectal cancer limits the usefulness of trastuzumab (Herceptin) and irinotecan as therapy. A phase II trial.** *Cancer Invest* 2004;22(6):858-65.

Siena S et al. **Trastuzumab and lapatinib in HER2-amplified metastatic colorectal cancer patients (mCRC): The HERACLES trial.** *Proc ASCO* 2015;**Abstract 3508**.

Tabernero J et al. **VE-BASKET, a Simon 2-stage adaptive design, phase II, histology-independent study in nonmelanoma solid tumors harboring BRAF V600 mutations (V600m): Activity of vemurafenib (VEM) with or without cetuximab (CTX) in colorectal cancer (CRC).** *Proc ASCO* 2014;**Abstract 3518**.

Van Geel R et al. **Phase I study of the selective BRAF^{V600} inhibitor encorafenib (LGX818) combined with cetuximab and with or without the α-specific PI3K inhibitor BYL719 in patients with advanced *BRAF*-mutant colorectal cancer.** *Proc ASCO* 2014;**Abstract 3514**.

Yaeger R et al. **Pilot trial of combined BRAF and EGFR inhibition in BRAF-mutant metastatic colorectal cancer patients.** *Clin Cancer Res* 2015;21(6):1313-20.

Yang H et al. **Antitumor activity of BRAF inhibitor vemurafenib in preclinical models of BRAF-mutant colorectal cancer.** *Cancer Res* 2012;72(3):779-89.

Axel Grothey, MD

Burris HA 3rd et al. **Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial.** *J Clin Oncol* 1997;15(6):2403-13.

Select Publications

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

Hingorani SR et al. **High response rate and PFS with PEGPH20 added to *nab*-paclitaxel/gemcitabine in stage IV previously untreated pancreatic cancer patients with high-HA tumors: Interim results of a randomized phase II study.** *Proc ASCO* 2015;**Abstract 4006**.

Hurwitz HI et al. **Randomized, double-blind, phase II study of ruxolitinib or placebo in combination with capecitabine in patients with metastatic pancreatic cancer for whom therapy with gemcitabine has failed.** *J Clin Oncol* 2015;33(34):4039-47.

Hurwitz H et al. **A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC).** *Proc ASCO* 2014;**Abstract 4000**.

Ko AH et al. **A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer.** *Br J Cancer* 2013;109(4):920-5.

Ramanathan RK et al. **Pilot study in patients with advanced solid tumors to evaluate feasibility of ferumoxytol (FMX) as tumor imaging agent prior to MM-398, a nanoliposomal irinotecan (nal-IRI).** *Proc AACR* 2014;**Abstract CT224**.

Roy AC et al. **A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma.** *Ann Oncol* 2013;24(6):1567-73.

Von Hoff D et al. **NAPOLI-1: Randomized Phase 3 study of MM-398 (nal-IRI), with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer progressed on or following gemcitabine-based therapy.** ESMO World Congress on Gastrointestinal Cancer 2015;**Abstract O-0003**.

Von Hoff DD et al. **Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.** *N Engl J Med* 2013;369(18):1691-703.

Weinberg BA et al. **Current standards and novel treatment options for metastatic pancreatic adenocarcinoma.** *Oncology (Williston Park)* 2015;29(11):809-20, 886.

Tanios Bekaii-Saab, MD

Bekaii-Saab TS et al. **A phase Ib/II study of BBI608 combined with weekly paclitaxel in advanced pancreatic cancer.** Gastrointestinal Cancers Symposium 2016;**Abstract 196**.

Grothey A et al; CORRECT Study Group. **Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial.** *Lancet* 2013;381(9863):303-12.

Khoja L et al. **Evaluation of hypertension and proteinuria as markers of efficacy in antiangiogenic therapy for metastatic colorectal cancer.** *J Clin Gastroenterol* 2014;48(5):430-4.

Mayer RJ et al; RECOURSE Study Group. **Randomized trial of TAS-102 for refractory metastatic colorectal cancer.** *N Engl J Med* 2015;372(20):1909-19.

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.

Ricotta R et al. **Cavitation of lung metastases induced by regorafenib in patients with colorectal carcinoma: Data from the phase III CORRECT study.** *Proc ECCO* 2015;**Abstract 2015**.

Saavedra E et al. **Dysphonia induced by anti-angiogenic compounds.** *Invest New Drugs* 2014;32(4):774-82.

Strumberg D, Schultheis B. **Regorafenib for cancer.** *Expert Opin Investig Drugs* 2012;21(6):879-89.

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

Eunice L Kwak, MD, PhD

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

Barthélémy P et al. **Pertuzumab: Development beyond breast cancer.** *Anticancer Res* 2014;34(4):1483-91.

Cancer Genome Atlas Research Network. **Comprehensive molecular characterization of gastric adenocarcinoma.** *Nature* 2014;513(7517):202-9.

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Clarke JM, Hurwitz HI. **Understanding and targeting resistance to anti-angiogenic therapies.** *J Gastrointest Oncol* 2013;4(3):253-63.

Fuchs CS et al; REGARD Trial Investigators. **Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial.** *Lancet* 2014;383(9911):31-9.

Van Cutsem E et al. **HER2 screening data from ToGA: Targeting HER2 in gastric and gastroesophageal junction cancer.** *Gastric Cancer* 2015;18(3):476-84.

Wilke H et al; RAINBOW Study Group. **Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial.** *Lancet Oncol* 2014;15(11):1224-35.

Alberto F Sobrero, MD

Cunningham D et al. **Bevacizumab (bev) in combination with capecitabine (cape) for the first-line treatment of elderly patients with metastatic colorectal cancer (mCRC): Results of a randomized international phase III trial (AVEX).** Gastrointestinal Cancers Symposium 2013;**Abstract 337**.

Douillard J et al. **Final results from PRIME: Randomized phase III study of panitumumab (pmab) with FOLFOX4 for first-line metastatic colorectal cancer (mCRC).** *Proc ASCO* 2011;**Abstract 3510**.

Falcone A et al; Gruppo Oncologico Nord Ovest. **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.

Giantonio BJ et al; Eastern Cooperative Oncology Group Study E3200. **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.

Gibbs P et al. **SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC).** *Proc ASCO* 2015;**Abstract 3502**.

Gruenberger T et al. **Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: The OLIVIA multinational randomised phase II trial.** *Ann Oncol* 2015;26(4):702-8.

Heinemann V et al. **Cetuximab-based or bevacizumab-based first-line treatment in patients with *KRAS* p.G13D mutated metastatic colorectal cancer (mCRC) — A meta-analysis of 54 cases.** *Proc ASCO* 2012;**Abstract 511**.

Hochster HS et al. **Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): Final analysis of the TREE-Study.** *Proc ASCO* 2006;**Abstract 3510**.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42.

Kemeny NE et al. **Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma.** *J Clin Oncol* 2009;27(21):3465-71.

Loupakis F et al. **Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer.** *N Engl J Med* 2014;371(17):1609-18.

Maughan TS et al; MRC COIN Trial Investigators. **Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: Results of the randomised phase 3 MRC COIN trial.** *Lancet* 2011;377(9783):2103-14.

Ruers T et al. **Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC).** *Proc ASCO* 2015;**Abstract 3501**.

Sobrero AF et al. **EPIC: Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer.** *J Clin Oncol* 2008;26(14):2311-9.

Tebbutt NC et al. **International randomized phase III study of capecitabine (Cap), bevacizumab (Bev), and mitomycin C (MMC) in first-line metastatic colorectal cancer (mCRC): Final results of the AGITG MAX trial.** *Proc ASCO* 2009;**Abstract 4023**.

Select Publications

Tveit KM et al. **Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: The NORDIC-VII study.** *J Clin Oncol* 2012;30(15):1755-62.

Van Cutsem E 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.** *Proc ASCO* 2007;**Abstract 4000**.

Ye LC et al. **Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases.** *J Clin Oncol* 2013;31(16):1931-8.

Charles S Fuchs, MD, MPH

Cancer Genome Atlas Research Network. **Comprehensive molecular characterization of gastric adenocarcinoma.** *Nature* 2014;513(7517):202-9.

Muro K et al. **Relationship between PD-L1 expression and clinical outcomes in patients (Pts) with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (Pembro; MK-3475) in KEYNOTE-012.** Gastrointestinal Cancers Symposium 2015;**Abstract 03**.