GASTROINTESTINAL CANCER TUMOR PANEL

Clinical Investigators Provide Their Perspectives on Current Cases and Clinical Issues in the Management of Colorectal, Gastric and Pancreatic Cancer

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists, hematology-oncology fellows and other allied healthcare professionals involved in the treatment of colorectal, gastric and pancreatic cancer.

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 8% of all cancer deaths. Although individually less frequently encountered, the collection of noncolorectal gastrointestinal (GI) cancers account for more per annum cancer-related deaths than those attributed to tumors of the colon and rectum combined. Two noncolorectal GI tumors in particular — gastric and pancreatic cancer — have witnessed several recent advances that have drastically altered current treatment considerations and approaches. As such, educational opportunities relevant to the clinical management of colorectal, gastric and pancreatic cancers are essential for medical oncologists responsible for delivering comprehensive care.

These video proceedings from a CME symposium held during the 2015 ASCO Annual Meeting feature discussions with leading researchers with an expertise in colorectal, gastric and pancreatic cancer regarding actual patient cases and related clinical research findings. By providing information on the latest research developments and their potential application to routine practice, this activity is designed to not only improve clinicians' knowledge of recent data related to the rapidly evolving GI cancer treatment landscape but also to provide them with practical perspectives to help them become better and more effective caregivers.

LEARNING OBJECTIVES

- Coordinate comprehensive biomarker analysis for patients diagnosed with advanced colorectal cancer (CRC), and use this information to guide evidence-based care.
- Communicate the benefits and risks of approved anti-VEGF, anti-EGFR and other targeted biologic therapies to patients with metastatic CRC, and develop an evidence-based algorithm to sequence these available options based on disease- and patient-specific characteristics.
- Individualize local and systemic treatment for patients with metastatic CRC that is isolated to the liver.
- Implement a clinical plan for the management of advanced HER2-positive gastric cancer, incorporating existing and emerging targeted treatments.
- Appreciate available clinical research data documenting the efficacy of ramucirumab in advanced gastric or gastro-esophageal junction cancer, and discern how this agent can be optimally integrated into clinical practice for patients with HER2-negative and HER2-positive disease.
- Appraise the rationale for and clinical data with investigational anti-PD-1 and/or anti-PD-L1 antibodies in patients with gastric cancer.
- Consider age, performance status and other clinical factors in the selection of systemic therapy for patients with metastatic pancreatic adenocarcinoma (PAD).
- Appreciate available safety and efficacy data with nanoparticle albumin-bound (*nab*) paclitaxel in combination with gemcitabine, and develop effective strategies to appropriately integrate this regimen into the management of metastatic PAD.
- Describe the proposed mechanism of action and available research data with ruxolitinib in pancreatic cancer, and use this information to counsel appropriate patients regarding ongoing trials evaluating this novel approach.
- Recall new data with other investigational agents demonstrating promising activity in colorectal, gastric and pancreatic cancers.

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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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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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Expiration date: September 2016

Select Publications

Peter C Enzinger, MD

Folprecht G et al. **Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study).** *Ann Oncol* 2014;25(5):1018-25.

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.

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.

Petrelli F et al. **Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: A meta-analysis.** *Int J Colorectal Dis* 2012;27(8):997-1004.

Schwartzberg LS et al. **PEAK: A randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer.** *J Clin Oncol* 2014;32(21):2240-7.

Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases: CAIRO5 — A randomized phase 3 study of the Dutch Colorectal Cancer Group (DCCG). NCT02162563

Ychou M et al. **A randomized phase II trial of three intensified chemotherapy regimens in first-line treatment of colorectal cancer patients with initially unresectable or not optimally resectable liver metastases. The METHEP trial.** *Ann Surg Oncol* 2013;20(13):4289-97.

Axel Grothey, MD

A randomized, open-label phase III Intergroup study: Effect of adding bevacizumab to cross over fluoropyrimidine based chemotherapy (CTx) in patients with metastatic colorectal cancer and disease progression under first-line standard CTx/bevacizumab combination. NCT00700102

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.

Peeters M et al. **Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer.** *J Clin Oncol* 2010;28(31):4706-13.

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.

Tabernero J et al. **RAISE: A randomized, double-blind, multicenter phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab (RAM) or placebo (PBO) in patients (pts) with metastatic colorectal carcinoma (CRC) progressive during or following first-line combination therapy with bevacizumab (bev), oxaliplatin (ox), and a fluoropyrimidine (fp).** Gastrointestinal Cancers Symposium 2015;**Abstract 512.**

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.

J Randolph Hecht, MD

A phase 1b/2 study of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma. NCT02340975

A phase Ib clinical study of BBI608 in combination with standard chemotherapies in adult patients with advanced gastrointestinal cancer. NCT02024607

Garon EB et al. **Pembrolizumab for the treatment of non-small-cell lung cancer.** *N Engl J Med* 2015;372(21):2018-28.

KEYNOTE-059: A phase II clinical trial of pembrolizumab as monotherapy and in combination with cisplatin+5-fluorouracil in subjects with recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma. NCT02335411

KEYNOTE-061: A phase III, randomized, open-label clinical trial of pembrolizumab (MK-3475) versus paclitaxel in subjects with advanced gastric or gastroesophageal junction adenocarcinoma who progressed after first-line therapy with platinum and fluoropyrimidine. NCT02370498

Select Publications

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**.

Phase I study of soluble LAG-3 (IMP321) and gemcitabine in patients with advanced pancreas cancer. NCT00732082

Postow MA et al. **Immune checkpoint blockade in cancer therapy.** *J Clin Oncol* 2015;33(17):1974-82.

Todaro M et al. **Tumorigenic and metastatic activity of human thyroid cancer stem cells.** *Cancer Res* 2010;70(21):8874-85.

Topalian SL et al. **Cancer immunotherapy comes of age.** *J Clin Oncol* 2011;29(36):4828-36.

Tumeh PC et al. **PD-1 blockade induces responses by inhibiting adaptive immune resistance.** *Nature* 2014;515(7528):568-71.

Wagle N et al. **Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling.** *J Clin Oncol* 2011;29(22):3085-96.

Yates LR, Campbell PJ. **Evolution of the cancer genome.** *Nat Rev Genet* 2012;13(11):795-806.

Eileen M O'Reilly, MD

A phase 1b study of the safety and tolerability of ruxolitinib in combination with gemcitabine with or without *nab*-paclitaxel in subjects with advanced solid tumors. NCT01822756

A phase 2, randomized, double-blind study of gemcitabine and *nab*-paclitaxel combined with momelotinib in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma preceded by a dose-finding, lead-in phase. NCT02101021

A randomized multicenter phase Ib/II study to assess the safety and the immunological effect of chemoradiation therapy (CRT) in combination with pembrolizumab (MK-3475) compared to CRT alone in patients with resectable or borderline resectable pancreatic cancer. NCT02305186

A randomized pilot/pharmacodynamic/genomic study of neoadjuvant paricalcitol to target the microenvironment in resectable pancreatic cancer. NCT02030860

An exploratory phase 2 study of neoadjuvant chemotherapy followed by stereotactic body radiation therapy (SBRT) with algen-pantucel-L (HyperAcute®-pancreas) immunotherapy in subjects with borderline resectable pancreatic cancer. NCT02405585

Ancrile B et al. **Oncogenic RAS-induced secretion of IL6 is required for tumorigenesis.** *Genes Dev* 2007;21(14):1714-9.

Becker C et al. **TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling.** *Immunity* 2004;21(4):491-501.

Fearon KC et al. **Pancreatic cancer as a model: Inflammatory mediators, acute-phase response, and cancer cachexia.** *World J Surg* 1999;23(6):584-8.

Fukuda A et al. **STAT3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression.** *Cancer Cell* 2011;19(4):441-55.

Harrison DA. **The JAK/STAT pathway.** *Cold Spring Harb Perspect Biol* 2012;4(3).

Hidalgo M. **Pancreatic cancer.** *N Engl J Med* 2010;362(17):1605-17.

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**.

JANUS 1: Randomized, double-blind, phase 3 study of the Janus kinase (JAK) 1/2 inhibitor, ruxolitinib, or placebo in combination with capecitabine in subjects with advanced or metastatic adenocarcinoma of the pancreas who have failed or are intolerant to first-line chemotherapy. NCT02117479

JANUS 2: A randomized, double-blind, phase 3 study of the JAK 1/2 inhibitor, ruxolitinib or placebo in combination with capecitabine in subjects with advanced or metastatic adenocarcinoma of the pancreas who have failed or are intolerant to first-line chemotherapy. NCT02119663

Koskela HL et al. **Somatic STAT3 mutations in large granular lymphocytic leukemia.** *N Engl J Med* 2012;366(20):1905-13.

MacKenzie S et al. **A pilot phase II multicenter study of *nab*-paclitaxel (*nab*-P) and gemcitabine (G) as preoperative therapy for potentially resectable pancreatic cancer (PC).** *Proc ASCO* 2013;**Abstract 4038**.

Neoadjuvant FOLFIRINOX and chemoradiation followed by definitive surgery and postoperative gemcitabine for patients with borderline resectable pancreatic adenocarcinoma: An Intergroup single-arm pilot study. NCT01821612

Select Publications

NEOPAC: Adjuvant gemcitabine versus NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable PAncreatic Cancer: A randomized multicenter phase III study. NCT01521702

Phase 1/2 safety and feasibility of gemcitabine and *nab*-paclitaxel in combination with LDE-225 as neoadjuvant therapy in patients with borderline resectable pancreatic adenocarcinoma. NCT01431794

Phase II study of preoperative FOLFIRINOX versus gemcitabine/*nab*-paclitaxel in patients with resectable pancreatic cancer. NCT02243007

Steele CW et al. **Exploiting inflammation for therapeutic gain in pancreatic cancer.** *Br J Cancer* 2013;108(5):997-1003.

Philip A Philip, MD, PhD

Fuchs CS et al. **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.

GATSBY: A randomized, multicenter, adaptive phase II/III study to evaluate the efficacy and safety of trastuzumab emtansine (T-DM1) versus taxane (docetaxel or paclitaxel) in patients with previously treated locally advanced or metastatic HER2-positive gastric cancer, including adenocarcinoma of the gastroesophageal junction. NCT01641939

HELOISE study: A study of Herceptin (trastuzumab) in combination with cisplatin/capecitabine chemotherapy in patients with HER2-positive metastatic gastric or gastro-esophageal junction cancer. NCT01450696

JACOB: A double-blind, placebo-controlled, randomized, multicenter phase III study evaluating the efficacy and safety of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastroesophageal junction or gastric cancer. NCT01774786

Kang YK et al. **A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer.** *Br J Cancer* 2014;111(4):660-6.

RAINBOW: A randomized, multicenter, double-blind, placebo-controlled phase 3 study of weekly paclitaxel with or without ramucirumab (IMC-1121B) drug product in patients with metastatic gastric adenocarcinoma, refractory to or progressive after first-line therapy with platinum and fluoropyrimidine. NCT01170663

RAINFALL: A randomized, double-blind, placebo-controlled phase 3 study of capecitabine and cisplatin with or without ramucirumab as first-line therapy in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. NCT02314117

Eric Van Cutsem, MD, PhD

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

Li J et al. **Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet Oncol* 2015;16(6):619-29.

Mayer RJ et al. **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.

RECOURSE: A randomized, multicenter, adaptive phase II/III study to evaluate the efficacy and safety of trastuzumab emtansine (T-DM1) versus taxane (docetaxel or paclitaxel) in patients with previously treated locally advanced or metastatic HER2-positive gastric cancer, including adenocarcinoma of the gastroesophageal junction. NCT01607957

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.

Yoshino T et al. **TAS-102 monotherapy for pretreated metastatic colorectal cancer: A double-blind, randomised, placebo-controlled phase 2 trial.** *Lancet Oncol* 2012;13(10):993-1001.