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Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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EDITOR

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OVERVIEW OF ACTIVITY

Colorectal cancer (CRC) is a common and potentially lethal type of cancer, and its clinical management is continuously evolving. Although "non-CRC" gastrointestinal (GI) tumors are less frequently encountered individually, the cancer-related deaths in that subcategory surpass those attributed to CRC. Published results from ongoing trials continuously lead to the emergence of novel biomarkers and new therapeutic targets and regimens, thereby altering existing management algorithms. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, *Gastrointestinal Cancer Update* uses one-on-one discussion with leading GI oncology investigators. By providing access to the latest scientific developments and the perspectives of experts in the field, this CME activity assists medical oncologists with the formulation of up-to-date management strategies.

LEARNING OBJECTIVES

- Coordinate comprehensive biomarker analysis for patients diagnosed with advanced CRC, inclusive of broader RAS mutational assessments, and use this information to guide evidence-based care for these patients.
- Effectively apply the results of practice-changing clinical research to the selection and sequencing of chemobiologic regimens for patients with metastatic CRC.
- Consider clinical scenarios in which treatment rather than observation is warranted for patients with metastatic neuroendocrine tumors of the GI tract, and identify the optimal sequence of available systemic therapies for these patients.
- Understand the importance of expanded RAS testing in selection of treatment for patients with advanced CRC.
- Educate patients with metastatic gastroesophageal or pancreatic cancer regarding approved and novel treatment approaches and their associated risks and benefits.
- Appreciate the recent FDA-approved indications for ramucirumab alone or in combination with paclitaxel for advanced gastric or GEJ cancer, and discern how this agent can be optimally integrated into clinical practice.
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with biliary tract cancer.
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.

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INTERVIEW

David H Ilson, MD, PhD

Dr Ilson is Professor of Medicine at Weill Cornell Medical College and Attending Physician at Memorial Hospital and Memorial Sloan Kettering Cancer Center in New York, New York.

Tracks 1-11

Track 1	**Case discussion:** A 54-year-old non-smoker with a history of breast cancer presents with a squamous cell carcinoma of the esophagus
Track 2	Use of PET-CT to evaluate response to induction chemotherapy in esophageal cancer
Track 3	Addition of anti-EGFR antibodies to chemoradiation therapy and outcomes in esophageal cancer
Track 4	Investigation of immune checkpoint inhibitors in esophageal and gastric cancers
Track 5	**Case discussion:** A 50-year-old patient presents with weight loss, dysphagia and abdominal pain and is diagnosed with HER2-negative adenocarcinoma of the gastroesophageal junction (GEJ) with hepatic metastases
Track 6	Clinical experience with the recently FDA-approved agent ramucirumab as monotherapy or in combination with paclitaxel as second-line therapy for metastatic gastric or GEJ adenocarcinoma
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Track 8	Trials of T-DM1 and pertuzumab in HER2-positive metastatic gastric cancer
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Track 11	Clinical experience with alternative schedules and doses of regorafenib

Select Excerpts from the Interview

Track 4

DR LOVE: Would you comment on the research investigating immune checkpoint inhibitors for patients with gastric or esophageal cancers?

DR ILSON: Anti-PD-1 and anti-PD-L1 inhibitors are being studied in gastroesophageal adenocarcinoma. Squamous cell carcinomas are rare, and they haven't been specifically studied in this context. Anecdotal responses to anti-PD-1/anti-PD-L1 agents have been noted. A signal of activity is observed, though it is not as strong as that with other cancers, such as lung cancer (Muro 2014).

I believe further evaluation in Phase II studies is of interest. Ongoing studies are evaluating anti-PD-1 and anti-PD-L1 drugs alone or in combination with CTLA-4 inhibitors. This is not a home run yet, but some patients may benefit from this strategy.

An interesting area of study, based on the abscopal effect, is administration of therapy to prime the immune response followed by radiation therapy to release antigens and enhance the immune response. We've seen much interest in sequencing radiation therapy with immune checkpoint inhibitors to determine if we can induce responses by creating an antigen burst. This is an exciting area of future research.

Track 6

DR LOVE: Would you discuss the results of the Phase III REGARD and RAINBOW trials investigating ramucirumab as second-line therapy for metastatic gastric or gastroesophageal junction (GEJ) cancer?

DR ILSON: The REGARD trial demonstrated that treatment with single-agent ramucirumab resulted in improvement in progression-free and overall survival versus placebo in the second-line setting for patients whose disease had progressed on fluoropyrimidine/platinum-based chemotherapy (Fuchs 2014). Ramucirumab monotherapy was approved by the FDA as second-line therapy based on these data. It was fairly well tolerated, and the only Grade 3 toxicity that was noteworthy was an increase in hypertension. Epistaxis was reported, but bleeding and gastrointestinal perforation were not serious adverse events.

The RAINBOW trial showed even more compelling data with ramucirumab in combination with paclitaxel. A significant improvement was observed in progression-free and overall survival with the combination. An almost 2-fold increase in response rate with the combination versus paclitaxel alone was also noted (Wilke 2014; [1.1]).

A slight increase in neutropenia was observed with the combination. Ramucirumab may augment some of the toxicity of chemotherapy, but that does not translate into clinically significant neutropenic fever. I believe that most practitioners would use ramucirumab in combination with paclitaxel, unless the patient has a poor performance status and cannot tolerate chemotherapy. In my practice, I generally administer the combination because taxanes are now standard second-line chemotherapy.

1.1

Efficacy Results of the Phase III REGARD and RAINBOW Trials of Ramucirumab (Ram) in Metastatic Gastroesophageal Junction and Gastric Adenocarcinoma After Disease Progression on First-Line Platinum- and/or Fluoropyrimidine-Containing Combination Therapy

	REGARD trial[1]		RAINBOW trial[2]	
Clinical outcome	Ram (n = 238)	Placebo (n = 117)	Ram + pac (n = 330)	Pac (n = 335)
Median OS	5.2 mo	3.8 mo	9.6 mo	7.4 mo
p-value	0.047		0.017	
Median PFS	2.1 mo	1.3 mo	4.4 mo	2.9 mo
p-value	<0.0001		<0.0001	
ORR	3%	3%	28%	16%
p-value	0.76		0.0001	

Pac = paclitaxel; OS = overall survival; PFS = progression-free survival; ORR = objective response rate

[1] Fuchs CS et al. *Lancet* 2014;383(9911):31-9; [2] Wilke H et al. *Lancet Oncol* 2014;15(11):1224-35.

Editor's Note: FDA Expands Approval for Ramucirumab for Advanced GEJ Cancer

Subsequent to this interview, on November 5, 2014, the FDA approved ramucirumab for use in combination with paclitaxel for the treatment of advanced gastric or GEJ adenocarcinoma.

Tracks 8-9

DR LOVE: What are your thoughts on therapies targeting HER2 for HER2-positive gastric cancer or GEJ cancer?

DR ILSON: Trastuzumab is approved in combination with a fluoropyrimidine/cisplatin as first-line therapy for patients with HER2-positive metastatic gastric or GEJ cancer. I generally administer trastuzumab in combination with chemotherapy because we have no data to support its use as monotherapy.

For patients who experience disease progression, extrapolating from data in breast cancer, I continue trastuzumab as second-line therapy. If patients experience rapid disease progression while receiving second-line therapy, it's difficult to rationalize continuing trastuzumab in the third-line setting.

Pertuzumab has been validated in breast cancer and is now being investigated in gastric cancer. The JACOB trial is an ongoing Phase III trial of chemotherapy/trastuzumab with or without pertuzumab as first-line therapy for patients with HER2-positive metastatic gastric or GEJ cancer with an estimated enrollment of more than 700 patients. In the second-line setting, the GATSBY trial is studying T-DM1 versus a taxane for patients with HER2-positive locally advanced or metastatic gastric cancer who have experienced disease progression during or after first-line therapy and has a target accrual of more than 400 patients (1.2).

A recent trial suggested benefit from lapatinib in Asian patients in the second-line setting (Satoh 2014). However, in Western patients, lapatinib in combination with capecitabine and oxaliplatin did not improve survival in the first-line setting (Hecht 2013). I believe that lapatinib is not likely to move forward in the West.

1.2

Ongoing Phase III Trials of HER2-Directed Therapies in HER2-Positive Locally Advanced or Metastatic Gastroesophageal Junction Cancer or Gastric Adenocarcinoma

Trial ID	N	Treatment arms
NCT01774786 (JACOB)	780	• Pertuzumab + TFP • Placebo + TFP
NCT01641939 (GATSBY)	412	• Triweekly T-DM1 (3.6 mg/kg) • Weekly T-DM1 (2.4 mg/kg) • Taxane (paclitaxel or docetaxel)
NCT00680901 (LOGiC)	545	• Lapatinib + CAPOX • Placebo + CAPOX

TFP = trastuzumab, cisplatin and fluoropyrimidine (capecitabine or 5-fluorouracil);
CAPOX = capecitabine/oxaliplatin

www.clinicaltrials.gov. Accessed December 2014.

Tracks 10-11

DR LOVE: What is the rationale behind the Phase II study of adjuvant regorafenib versus placebo for patients with node-positive esophageal or GEJ cancer who completed preoperative therapy?

DR ILSON: The impetus for this study came from a Phase II study of single-agent sorafenib in patients with metastatic esophageal or GEJ cancer who had received 1 or 2 prior lines of therapy. The median progression-free survival was approximately 4 months, with 1 durable complete remission reported with sorafenib (Ku 2013). Patients were receiving the agent for approximately 4 months, and some patients were able to continue therapy for 1 to 2 years.

Based on that signal, we're going to investigate regorafenib, an analogous drug, for patients with high-risk disease in the adjuvant setting. This study is being conducted through the Alliance and compares adjuvant regorafenib to placebo for patients with node-positive esophageal or GEJ cancer who have completed preoperative therapy (NCT02234180). We will prospectively explore potential biomarkers like VEGF-A. Our objective is to determine if we can significantly increase disease-free survival with this adjuvant approach.

DR LOVE: Regorafenib was approved for colorectal cancer in a late-line setting, but there have been concerns about toxicity. How do you manage regorafenib dosing to prevent toxicity?

DR ILSON: The recommended dose of regorafenib is 160 mg a day, 3 weeks on, 1 week off. Administering drugs that cause cutaneous toxicity 2 or 3 weeks in a row is often problematic. We are conducting a Phase II trial of regorafenib combined with FOLFOX as first-line therapy for unresectable or metastatic esophageal and gastric cancer (NCT01913639), and regorafenib will be administered for 1 week on, 1 week off. With this schedule, you achieve approximately 75% of the 160-mg daily dose, and we have observed virtually no toxicity.

My message to practitioners is to think about alternative doses and schedules. If patients start treatment on the full dose, they should be monitored every week for the first couple of months and dose reductions should be made promptly so that patients don't run into problems. ■

SELECT PUBLICATIONS

Hecht JR et al. **Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC trial.** *Proc ASCO* 2013;**Abstract LBA4001**.

Ku GY et al. **Phase II trial of sorafenib in esophageal (E) and gastroesophageal junction (GEJ) cancer: Response and prolonged stable disease observed in adenocarcinoma.** Gastrointestinal Cancers Symposium 2013;**Abstract 91**.

Muro K et al. **A phase 1b study of pembrolizumab (pembro; MK-3475) in patients (pts) with advanced gastric cancer.** *Proc ESMO* 2014;**Abstract LBA15**.

Satoh T et al. **Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN — A randomized, phase III study.** *J Clin Oncol* 2014;32(19):2039-49.

Yoon H et al. **Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial.** *Proc ASCO* 2014;**Abstract 4004**.

INTERVIEW

Eric Van Cutsem, MD, PhD

Prof Van Cutsem is Professor of Medicine and Digestive Oncology at University Hospital Gasthuisberg/Leuven in Leuven, Belgium.

Tracks 1-8

Track 1 Approach to counseling patients with Stage II colon cancer about adjuvant therapeutic options and risk of recurrence

Track 2 Treatment for elderly patients with Stage III colon cancer

Track 3 Use of the Onco*type* DX® Colon Cancer assay in the United States versus Europe

Track 4 Expanded RAS testing in metastatic colorectal cancer (mCRC)

Track 5 CALGB/SWOG-80405: Results of a Phase III trial of FOLFOX or FOLFIRI with bevacizumab or cetuximab for patients with KRAS wild-type, untreated metastatic adenocarcinoma of the colon or rectum

Track 6 Continuation of anti-angiogenic treatment after disease progression on first-line therapy for mCRC

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Track 8 Tolerability of regorafenib in patients with mCRC versus those with advanced gastrointestinal stromal tumors

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: What is your approach to making adjuvant treatment decisions for patients with Stage II colon cancer?

PROF VAN CUTSEM: The outcome for patients with Stage II colon cancer is already quite good and is improving. We still use the concept of high-risk versus low-risk Stage II disease and take different factors into account. If fewer than 12 lymph nodes are removed and examined by the pathologist, the patient is classified as having high-risk disease. We also consider differentiation grades. Patients with poorly differentiated tumors fare worse.

Other factors taken into account include bowel obstruction at initial presentation, T4 tumors, tumors with lymphatic vessel, perineural or vascular invasion, young patients and patients with elevated CA19.9 levels. These criteria are used to categorize patients as having high-risk Stage II disease.

In addition to these features, we now have microsatellite instability (MSI) testing. Patients with MSI unstable (MSI-H) status have a good prognosis, and those with microsatellite stable (MSS) status have an unfavorable prognosis. If a patient has Stage II colon cancer without the poor characteristics previously mentioned and an MSI-H

status, we do not treat. We discuss the treatment options with patients and inform them that the benefit of adjuvant chemotherapy is limited.

For a patient with an MSS tumor with one or more of the poor characteristics, we discuss adjuvant chemotherapy with 5-FU or capecitabine. In exceptional cases, such as a young patient with several poor prognostic characteristics and MSS status, we consider 5-FU/oxaliplatin.

DR LOVE: How do you care for elderly patients and those with Stage III colon cancer?

PROF VAN CUTSEM: For Stage III disease, treatment decisions are easier to make. Most of these patients are offered adjuvant 5-FU/oxaliplatin for 6 months without biologics. That's the standard treatment in this situation. An important discussion is whether to offer that to all patients with Stage III colon cancer.

For elderly patients, 3 factors come into play: the biology of the disease, other comorbidities and physiological age. Age by itself is not a crucial decision factor. One must also consider the concomitant pathology and diseases that the patient has. I would offer a 75-year-old fit patient with clear Stage III colon cancer without any concomitant adverse pathology 5-FU/oxaliplatin. For a 70-year-old patient who has a physiological age above 70 with T2N1 disease, poor kidney function and myocardial infarction, I may offer only 5-FU.

DR LOVE: What do you envision as the current and/or future role of multigene assays such as the Onco*type* DX assay in this decision-making paradigm?

PROF VAN CUTSEM: Increasing evidence suggests that they may play a role in the treatment algorithm for patients with Stage II disease in addition to consideration of the different factors I have mentioned.

Although these different clinical factors are more prognostic and they are not proven to be predictive, we still use them in making our clinical decisions to predict benefit of a treatment. The same holds true with these gene signatures — they have a prognostic role, but they are not predictive of benefit from 5-FU or 5-FU/oxaliplatin. These assays are currently used more in the United States than elsewhere. At the moment we don't use gene signatures as much in Europe, but I believe they have some utility. I believe that in 5 to 10 years we will integrate them much more. Some work is being done in this regard to try to prove predictive value, but we do not yet have the data.

DR LOVE: In your practice, do you perform routine RAS tests for patients with metastatic colorectal cancer (mCRC)? What is the clinical effect of knowing the RAS status of the disease in making treatment decisions for patients with mCRC?

PROF VAN CUTSEM: I believe that expanded RAS testing is mandatory for patients with mCRC. The biology of the disease and evidence from preclinical and retrospective studies are all going in the same direction. Even though we must be cautious with data from retrospective studies, if all the evidence is consistent with the biology and pointing in the same direction, it should be believed.

RAS testing is important for a number of different reasons. First, we can increase the likelihood of benefit from an anti-EGFR antibody. This is true for both cetuximab and panitumumab. Second, if a patient with a rare RAS mutation receives treatment, especially with an oxaliplatin-based regimen, it may be harmful. Data on the combination of oxaliplatin with panitumumab or cetuximab for patients with rare RAS mutations show a deleterious or harmful effect (Douillard 2013). Third, it is economically advanta-

geous to not administer treatment to patients who will not benefit from therapy. Fourth, it prevents unnecessary exposure to the toxic side effects of the drug or drugs.

Track 5

DR LOVE: Would you discuss the results of the Phase III CALGB/SWOG-80405 trial for patients with untreated metastatic adenocarcinoma of the colon and rectum (2.1)?

PROF VAN CUTSEM: Several important lessons and messages came out of this study. First, it showed that the overall survival for patients with mCRC has become longer, at about 30 months. If you go back to the 5-FU era 15 years ago, the median survival was 10 to 11 months. With incremental steps, the survival is improving. I believe that this is mainly because of strategic thinking and treatment with different agents. Also, the multidisciplinary approach to therapy contributes to the improved survival observed. Every time a new agent is integrated into therapy, we see an incremental benefit.

Second, the CALGB/SWOG-80405 study did not confirm the results of the FIRE-3 trial, which reported that survival for patients who received chemotherapy/cetuximab was longer than that with chemotherapy/bevacizumab (Heinemann 2014). Instead, it tells us that we have equivalent options, including oxaliplatin-based and irinotecan-based chemotherapy. In theory, we can combine oxaliplatin or irinotecan with bevacizumab or an anti-EGFR antibody. Third, the data pertain to patients with wild-type KRAS exon 2 colon cancer. The results did not change my standard practice because I administer

2.1

CALGB/SWOG-80405: Results of a Phase III Trial of FOLFIRI or mFOLFOX6 with Bevacizumab (Bev) or Cetuximab (Cet) for Patients with KRAS Wild-Type Untreated Metastatic Adenocarcinoma of the Colon or Rectum

	Chemo + bev (n = 559)	Chemo + cet (n = 578)	HR	*p*-value
Median OS	29.0 mo	29.9 mo	0.92	0.34
Median PFS	10.8 mo	10.4 mo	1.04	0.55
ORR	57.2%	65.6%	NR	0.02
KRAS wt exon 2/all RAS mt*	n = 42	n = 53	HR	*p*-value
Median OS	22.3 mo	28.7 mo	0.74	0.21
FOLFOX-based chemo (all RAS wt)	**FOLFOX + bev** (n = 192)	**FOLFOX + cet** (n = 198)	HR	*p*-value
Median OS	29.0 mo	32.5 mo	0.86	0.2
Median PFS	11.0 mo	11.3 mo	1.1	0.3
FOLFIRI-based chemo (all RAS wt)	**FOLFIRI + bev** (n = 64)	**FOLFIRI + cet** (n = 72)	HR	*p*-value
Median OS	35.2 mo	32.0 mo	1.1	0.7
Median PFS	11.9 mo	12.7 mo	1.1	0.7

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; NR = not reported; mt = mutation; wt = wild type

* Findings may not apply to KRAS mutations in codons 12 and 13.

Venook A et al. *Proc ASCO* 2014;**Abstract LBA3**; Lenz H et al. *Proc ESMO* 2014;**Abstract 501O**.

first-line oxaliplatin and bevacizumab to most of my patients, regardless of RAS status. The anti-EGFR antibody is administered in the second or third line.

Track 7

DR LOVE: You were involved in the Phase III RECOURSE trial of the novel fluoropyrimidine TAS-102 for patients with refractory mCRC. Would you discuss the results of the study (Yoshino 2014; [2.2])?

PROF VAN CUTSEM: TAS-102 is a new fluoropyrimidine with a different mechanism of action from classic 5-FU. It combines cytotoxic pyrimidine analog trifluridine and a thymidine phosphorylase inhibitor. A placebo-controlled Phase II trial for patients with pretreated mCRC reported an overall survival benefit and limited toxicity (Yoshino 2012).

The Phase III RECOURSE trial randomly assigned 800 patients who had received at least 2 prior lines of standard therapy including fluoropyrimidines, irinotecan and oxaliplatin. Most of the patients' disease was refractory to fluoropyrimidines. Surprisingly, we found a statistically and clinically significant benefit in overall survival. Progression-free survival was improved, but no improvement in response rate was recorded. Of interest, toxicity associated with TAS-102 was limited. The most frequent toxicity was neutropenia, but only about 4% of patients experienced febrile neutropenia. ■

2.2

RECOURSE: Efficacy and Safety Results of a Phase III Trial of TAS-102 or Placebo and Best Supportive Care (BSC) for Patients with Metastatic Colorectal Cancer Refractory to Standard Therapies

Outcome	TAS-102/BSC (n = 534)	Placebo/BSC (n = 266)	HR	*p*-value
Median OS	7.1 mo	5.3 mo	0.68	<0.0001
Median PFS	2.0 mo	1.7 mo	0.48	<0.0001
ORR	1.6%	0.4%	NR	NS
DCR	44.0%	16.3%	NR	<0.0001
Grade ≥3 AEs	**TAS-102/BSC**		**Placebo/BSC**	
Neutropenia	37.9%		0%	
Anemia	18.2%		3.0%	
Febrile neutropenia	3.8%		0%	

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; NR = not reported; NS = not significant; DCR = disease control rate; AEs = adverse events

Yoshino T et al. *Proc ESMO WCGC* 2014;**Abstract O-0022**.

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Heinemann V et al. **FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial.** *Lancet Oncol* 2014;15(10):1065-75.

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.

INTERVIEW

Eileen M O'Reilly, MD

Dr O'Reilly is Associate Director of the Rubenstein Center for Pancreatic Cancer Research at Memorial Sloan Kettering Cancer Center and Associate Professor of Medicine at Weill Medical College of Cornell University in New York, New York.

Tracks 1-15

Select Excerpts from the Interview

Track 2

DR LOVE: To date, we only have indirect comparisons of the efficacy of FOLFIRINOX and gemcitabine/*nab* paclitaxel in advanced pancreatic cancer. What is your perspective on these regimens?

DR O'REILLY: Compared to single-agent gemcitabine, both regimens have shown improved tumor response, disease control and overall survival. The numerical outcomes

in terms of median survivals favor FOLFIRINOX, but one has to consider that these studies were conducted in somewhat different patient populations.

FOLFIRINOX was studied in patients with an ECOG performance status of 0 to 1 and an upper age limit of 75. Gemcitabine/paclitaxel was studied in a broader community-/academic-based setting, including patients with a lower performance status and without an upper age limit.

The US Oncology Network reported some interesting data from a retrospective analysis of patients in their database suggesting that in equivalent populations, FOLFIRINOX fared favorably compared to gemcitabine and *nab* paclitaxel, but this is not a direct head-to-head comparison in a randomized study (Cartwright 2014). I believe the choice of chemotherapy largely depends on what toxicities are acceptable to patients.

Track 4

DR LOVE: Would you discuss the results of the Phase III NAPOLI-1 trial evaluating nanoliposomal irinotecan, or MM-398, for patients with metastatic pancreatic cancer (Von Hoff 2014; [3.1, 3.2])?

DR O'REILLY: The NAPOLI-1 trial evaluated nanoliposomal irinotecan with or without infusional 5-FU and leucovorin (5-FU/LV) versus 5-FU/LV. This was a pragmatic study in terms of its design. The eligibility criteria were interesting. Patients had to have received at least one prior gemcitabine-based regimen, and that could have been first-line treatment for metastatic disease, a neoadjuvant regimen or a front-line treatment in the locally advanced disease setting.

The bottom line was that a survival benefit was seen with the addition of MM-398 to 5-FU/LV compared to the control arm of 5-FU/LV. We're still awaiting the detailed breakdown of those who benefited to see if any subgroups of patients within the broad inclusion criteria benefited more than others. The toxicity profile appeared fairly similar to what one might see with irinotecan in its parent form. We're hopeful that this may offer an additional option in the previously treated disease setting. However, it is unlikely to replace currently available therapies.

3.1

NAPOLI-1: Efficacy Results of a Phase III Trial of MM-398, with or without 5-Fluorouracil (5-FU) and Racemic Leucovorin (LV) versus 5-FU/LV in Metastatic Pancreatic Cancer After Gemcitabine-Based Therapy

Outcome	MM-398 + 5-FU/LV (n = 1,117)	5-FU/LV (n = 149)	MM-398 (n = 151)
Median overall survival	6.1 mo	4.2 mo	4.9 mo
Hazard ratio (*p*-value) vs 5-FU/LV	0.67 (0.012)	Reference	0.99 (0.9416)
Median progression-free survival	3.1 mo	1.5 mo	2.7 mo
Hazard ratio (*p*-value) vs 5-FU/LV	0.56 (0.0001)	Reference	0.81 (0.1001)
Objective response rate (*p*-value) vs 5-FU/LV	16% (<0.001)	1% Reference	6% (0.019)

Von Hoff D et al. *Proc ESMO WCGC* 2014;**Abstract O-0003**.

3.2

NAPOLI-1 Trial: Select Adverse Events of Grade 3 or Higher

Grade ≥3 adverse events	MM-398 + 5-FU/LV (n = 117)	5-FU/LV (n = 134)	MM-398 (n = 147)
Decreased neutrophil count	20%	2%	16%
Fatigue	14%	4%	6%
Diarrhea	13%	5%	21%
Vomiting	11%	3%	14%
Nausea	8%	3%	5%

Von Hoff D et al. *Proc ESMO WCGC* 2014;**Abstract O-0003**.

Tracks 6-7

DR LOVE: What are your thoughts on the results of the Phase II SWOG-S0809 trial of adjuvant capecitabine/gemcitabine followed by concurrent capecitabine and radiation therapy for extrahepatic cholangiocarcinoma and gallbladder carcinoma?

DR O'REILLY: This nonrandomized adjuvant trial that was presented at ASCO 2014 was for patients with either a margin-positive or a node-positive extrahepatic cholangiocarcinoma or gallbladder carcinoma (Ben-Josef 2014; [3.3]). The median overall survival was 34 months. This is a study that will likely provide the reference arm for a future randomized Phase III trial in North America, but we need prospective data to better guide treatment decision-making in these scenarios.

DR LOVE: In what situations outside of a trial setting will you use adjuvant systemic therapy and/or radiation therapy?

DR O'REILLY: It depends on whether the patient has intrahepatic or extrahepatic biliary cancer. The intrahepatic biliary cancers are different. In general, factors such as node-positive or margin-positive disease, many satellite tumors or significant vascular and/

3.3

SWOG-S0809: Efficacy and Safety Results from the Phase II Trial of Adjuvant Capecitabine and Gemcitabine Followed by Concurrent Capecitabine and Radiation Therapy in Extrahepatic Cholangiocarcinoma (EHCC) and Gallbladder Carcinoma (GBCA)

Outcome	All patients (n = 79)	R0 cohort (n = 54)	R1 cohort (n = 25)	EHCC (n = 49)	GBCA (n = 30)
Median OS	34 months	33 months	36 months	NR	NR
Two-year OS	64%	67%	57%	68%	57%
Two-year DFS	51%	54%	45%	54%	47%
Two-year LR	12%	9%	16%	11%	13%

R0 and R1 = margin of resection; OS = overall survival; NR = not reported; DFS = disease-free survival; LR = local relapse

In 79 evaluable patients (54 R0, 25 R1), Grade 3/4 adverse events (AEs) were observed in 52% and 11% of patients. The most common Grade 3/4 AEs included neutropenia (44%), hand-foot syndrome (13%), diarrhea (8%), lymphopenia (8%) and leukopenia (6%).

Ben-Josef E et al. *Proc ASCO* 2014;**Abstract 4030**.

or perineural invasion sway me in favor of considering adjuvant treatment, the mainstay being systemic therapy.

A big question is whether to include radiation therapy. For intrahepatic cholangiocarcinoma, margins are usually not the issue, and I am less convinced that radiation therapy has a role. For extrahepatic cholangiocarcinoma, however, margins are usually challenging and often may be technically negative, close and/or positive, and I believe a role exists for adjuvant radiation therapy in that setting.

For gallbladder cancer, I keep an open mind. The patterns of failure are different and are typically more metastatic and more peritoneal for gallbladder cancer. And in the absence of positive margins, it has been our practice not to routinely consider the inclusion of radiation therapy for those patients outside of a study setting.

We have adopted the SWOG-S0809 regimen of 4 cycles of gemcitabine administered on day 1 and day 8 and capecitabine on days 1 through 14 every 3 weeks followed by capecitabine-based radiation therapy. We more selectively incorporate, outside of a trial setting, the use of 5-FU-based chemoradiation therapy, depending on whether it's gallbladder versus extrahepatic or intrahepatic cholangiocarcinoma.

Tracks 12-14

DR LOVE: Let's talk about pancreatic neuroendocrine tumors (NET). How do you sequence everolimus and sunitinib for advanced disease and what are the side effects?

DR O'REILLY: Sequencing of these agents depends on physician and patient biases and preferences. Everolimus has an established oncologic value in terms of disease stabilization. Even though the overall response rate to everolimus is low, it is my preferred choice compared to sunitinib. I believe that the toxicity profile is better, but I know one can't say that from the Phase III data. It's generally well tolerated but is associated with hyperglycemia. The more problematic toxicities are mucositis, fatigue and pneumonitis (Yao 2011).

I believe that fatigue is worse with sunitinib, and this may be my subjective opinion, but mucositis and myelosuppression are more complicated. That's not based on hard data. Both everolimus and sunitinib are acceptable choices for treating pancreatic NET. It is unclear if an optimal sequence exists and whether the sequence matters.

DR LOVE: What's your clinical experience with temozolomide and capecitabine?

DR O'REILLY: It is an active, generally well-tolerated regimen. We currently have data from a single-institution, multicenter Phase II study (Fine 2014) but no prospective randomized Phase III study data. Our approach is to administer capecitabine for 14 days and temozolomide with prophylactic antiemetics on days 10 through 14. For some patients receiving this regimen, fatigue, myelosuppression and hand-foot symptoms are problematic. ■

SELECT PUBLICATIONS

Cartwright TH et al. **Use of first-line chemotherapy for advanced pancreatic cancer: FOLFIRINOX versus gemcitabine-based therapy.** *Proc ASCO* 2014;**Abstract 4132**.

Fine RL et al. **Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors.** Gastrointestinal Cancers Symposium 2014;**Abstract 179**.

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

INTERVIEW

Herbert I Hurwitz, MD

Dr Hurwitz is Professor of Medicine in the Division of Medical Oncology, Clinical Director of the Phase I Program and Co-Leader of the GI Oncology Program at Duke University Medical Center in Durham, North Carolina.

Tracks 1-8

Track 1 Efficacy, tolerability and sequencing of FOLFIRINOX and *nab* paclitaxel/gemcitabine in metastatic pancreatic cancer (mPC)

Track 2 Results of the Phase II RECAP trial of capecitabine with or without the selective oral JAK1 and JAK2 inhibitor ruxolitinib as second-line therapy for mPC

Track 3 Ongoing Phase III trials — JANUS 1 and 2 — evaluating capecitabine and ruxolitinib for patients with metastatic adenocarcinoma of the pancreas with disease progression or intolerance to first-line chemotherapy

Track 4 Discussing risk stratification and treatment options for patients with Stage II colon cancer

Track 5 Investigating potential predictors of benefit for bevacizumab in mCRC and other solid tumors

Track 6 STEAM: An ongoing Phase II trial of sequential and concurrent FOLFOXIRI/bevacizumab versus FOLFOX/bevacizumab as first-line therapy for mCRC

Track 7 Understanding and targeting resistance to anti-angiogenic therapies

Track 8 Novel approach to the management of regorafenib-associated hand-foot syndrome

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss the data set you presented at the ASCO 2014 meeting evaluating capecitabine and the oral JAK1/JAK2 inhibitor ruxolitinib in metastatic pancreatic cancer?

DR HURWITZ: This study was a randomization of 127 patients to capecitabine/placebo versus capecitabine/ruxolitinib. The main endpoint was overall survival, and in the unselected population a modest improvement in overall survival was observed. The hazard ratio was 0.79, but the key message was found in the preplanned subgroup analysis of patients with a C-reactive protein (CRP) above the median, which was 13 mg/L.

In this subgroup the hazard ratio was 0.47, and the *p*-value was highly significant at 0.01 (Hurwitz 2014; [4.1]). A similar trend was also observed in the unselected and high CRP groups related to progression-free survival.

The study also evaluated inflammation, via the so-called Modified Glasgow Prognostic Score, which is essentially 2 components: CRP, cut off at 10 mg/L rather than 13 mg/L,

4.1 **RECAP: A Phase II Study of Ruxolitinib (Rux) or Placebo (Pbo) with Capecitabine (Cape) as Second-Line Therapy for Patients with Metastatic Pancreatic Cancer**

Efficacy	Rux/cape (n = 64)	Pbo/cape (n = 63)
Overall survival (intent-to-treat population)		
Median overall survival*	136.5 days	129.5 days
3-month survival rate	64%	58%
6-month survival rate	42%	35%
12-month survival rate	22%	11%
Efficacy	**Rux/cape (n = 31)**	**Pbo/cape (n = 29)**
Overall survival (patients with CRP >13 mg/L)		
Median overall survival†	83.0 days	55.0 days
3-month survival rate	48%	29%
6-month survival rate	42%	11%
12-month survival rate	11%	0%
Select Grade 3/4 adverse events	**Rux/cape (n = 59)**	**Pbo/cape (n = 60)**
Anemia	15.3%	1.7%
Thrombocytopenia	1.7%	3.3%
Neutropenia	0%	1.7%

* Hazard ratio = 0.79; 2-sided *p*-value = 0.25
† Hazard ratio = 0.47; 2-sided *p*-value = 0.01

Hurwitz H et al. *Proc ASCO* 2014;**Abstract 4000**.

and serum albumin, classified as low or normal. The patients with high CRP and low albumin benefited from ruxolitinib most.

Interestingly, patients gained weight on the ruxolitinib arm more than patients on the placebo arm, and the weight gain had to be qualified as both sustained and not associated with fluid retention. In the intent-to-treat, high CRP and low CRP groups, the amount of weight gain was greater with ruxolitinib — the percent of patients with some degree of weight gain varied between 20% and 40% on the ruxolitinib arm across those different subgroups, compared to between 5% and approximately 10% on the capecitabine/placebo arm.

The positive results from this trial led to 2 Phase III studies, JANUS 1 and JANUS 2 (NCT02117479; NCT02119663). I suspect, considering the amount of attention now placed on immunity and inflammation being linked to biology, that we will see many other strategies to try to target this axis beyond ruxolitinib.

Track 6

DR LOVE: Would you discuss the randomized Phase II STEAM trial comparing sequential and concurrent FOLFOXIRI/bevacizumab regimens to FOLFOX/bevacizumab as first-line therapy for patients with mCRC (NCT01765582)?

DR HURWITZ: This study is the US follow-up to the European Phase III TRIBE trial, which evaluated FOLFIRI/bevacizumab versus FOLFOXIRI/bevacizumab. The data looked good, with a higher response rate and better progression-free and overall survival by front-loading the more intense chemotherapy for a limited induction period, followed by maintenance (Loupakis 2014).

The American version, the STEAM trial, uses FOLFOX/bevacizumab as the control group and FOLFOXIRI/bevacizumab, as used in TRIBE, as the experimental arm. The second experimental group, so-called modified FOLFOXIRI in combination with bevacizumab, is essentially sequential FOLFOX followed by FOLFIRI (Bendell 2014). This may be a way of mitigating some of the significant myelosuppression that's sometimes observed and the side effects that come with the whole package. The study is ongoing, and it's accruing well with no unexpected side effects, at least initially, from the dose and schedule here in the US population.

Considering the activity in the TRIBE trial and the frequent use of the cousin regimen of FOLFIRINOX in pancreatic cancer, I believe that having good data on whether the triplet is better in patients with colorectal cancer would be useful, particularly for those patients who may have so-called borderline resectable disease, in which case a little extra response may be especially useful.

Track 8

DR LOVE: What's your experience with regorafenib, and how does it figure into your practice in the management of mCRC?

DR HURWITZ: The main issue with regorafenib, at least as it appears in patients in the United States, is tolerability. The 160-mg/day dose that was used in the CORRECT study, which is also in the package insert, is challenging to tolerate for many patients. A number of strategies are being evaluated to try to avoid the toxicity problems, including starting at a lower dose such as 80 mg or 120 mg instead.

The side effects tend to include fatigue, liver function changes and hand-foot syndrome, and they can be mitigated with dose adjustments. Our group is interested in a potential treatment for the associated hand-foot syndrome. We believe that it may be related to a conserved biology of the vasculature in the palms and soles and that some of it may be mediated by nitric oxide.

Agents that could be applied topically that would modulate nitric oxide might be useful, and one of them, ironically, would be a phosphodiesterase-5 inhibitor such as sildenafil. We only have anecdotal data, but you can apply it topically. You would have to obtain either the active pharmaceutical ingredient with a compounding pharmacy or grind it up — I would discourage oral administration. The dose intensity you'd be likely to observe on the skin would probably not be adequate. I am hopeful that we can garner support for a proper randomized study to ascertain whether the anecdotes can be confirmed. ■

SELECT PUBLICATIONS

Bendell JC et al. **STEAM: A randomized, open-label, phase 2 trial of sequential and concurrent FOLFOXIRI-bevacizumab (BEV) versus FOLFOX-BEV for the first-line (1L) treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC).** *Proc ASCO* 2014;**Abstract TPS3652**.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The ongoing Phase III JACOB trial is evaluating chemotherapy/trastuzumab with or without _____ as first-line therapy for patients with HER2-positive metastatic gastric or GEJ cancer.**
   a. Lapatinib
   b. Afatinib
   c. Pertuzumab

2. **The Phase III RAINBOW trial of paclitaxel with or without ramucirumab for patients with metastatic gastric or GEJ adenocarcinoma after disease progression on first-line platinum- and fluoropyrimidine-based combination therapy demonstrated statistically significant improvement(s) in _____ with the addition of ramucirumab.**
   a. Overall survival
   b. Progression-free survival
   c. Objective response rate
   d. All of the above

3. **Which of the following is true about the results from the Phase III CALGB/SWOG-80405 trial for patients with untreated metastatic adenocarcinoma of the colon and rectum?**
   a. The median overall survival was significantly improved for patients on the chemotherapy/cetuximab arm compared to the chemotherapy/bevacizumab arm
   b. Treatment with either chemotherapy/bevacizumab or chemotherapy/cetuximab resulted in a median overall survival of approximately 30 months
   c. Patients with RAS wild-type disease benefited more from FOLFIRI/cetuximab as compared to FOLFIRI/bevacizumab
   d. All of the above

4. **The results from the Phase III RECOURSE trial of TAS-102 for patients with mCRC that is refractory to standard therapies demonstrated statistically significant improvement(s) in _____with TAS-102 and best supportive care (BSC) compared to placebo/BSC.**
   a. Median overall survival
   b. Median progression-free survival
   c. Overall response rate
   d. Disease control rate
   e. All except c
   f. None of the above

5. **The ongoing Phase III GATSBY trial is evaluating _____ versus a taxane for patients with HER2-positive locally advanced or metastatic gastric cancer who have experienced disease progression during or after first-line therapy.**
   a. Lapatinib
   b. Pertuzumab
   c. T-DM1

6. **The Phase III NAPOLI-1 trial of MM-398 with or without 5-FU/LV for patients with metastatic pancreatic cancer after gemcitabine-based therapy demonstrated statistically significant improvement(s) in _____ with the combination of MM-398 and 5-FU/LV versus 5-FU/LV only.**
   a. Median overall survival
   b. Median progression-free survival
   c. Objective response rate
   d. All of the above

7. **Side effects associated with MM-398, a nanoliposomal irinotecan, in the treatment of metastatic pancreatic cancer may include _____.**
   a. Neutropenia
   b. Fatigue
   c. Diarrhea
   d. All of the above

8. **The Phase II SWOG-S0809 trial of adjuvant capecitabine and _____ followed by concurrent capecitabine and radiation therapy for patients with extrahepatic cholangiocarcinoma or gallbladder carcinoma demonstrated a median overall survival of 34 months.**
   a. 5-FU
   b. Gemcitabine
   c. Both a and b

9. **Results from the Phase II RECAP trial of capecitabine in combination with _____ or placebo as second-line therapy for patients with metastatic pancreatic cancer indicated improved overall survival in both the intent-to-treat population and a subgroup of patients with high CRP levels.**
   a. Ruxolitinib
   b. Brivanib
   c. *Nab* paclitaxel

10. **STEAM is an ongoing Phase II trial of sequential and concurrent _____ versus FOLFOX/bevacizumab as first-line therapy for mCRC.**
    a. FOLFIRI/bevacizumab
    b. FOLFOXIRI/bevacizumab
    c. Neither a nor b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 2, 2014

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Results of RECOURSE: A Phase III trial of the novel fluoropyrimidine TAS-102 with BSC for patients with mCRC refractory to standard therapies	4 3 2 1	4 3 2 1
Implications of the CALGB/SWOG-80405 trial results (FOLFOX or FOLFIRI with bevacizumab or cetuximab) on the selection of first-line chemobiologic therapy for patients with KRAS wild-type metastatic adenocarcinoma of the colon or rectum	4 3 2 1	4 3 2 1
RECAP: Results of a Phase II trial of capecitabine with or without the selective oral JAK1 and JAK2 inhibitor ruxolitinib as second-line therapy for metastatic pancreatic cancer	4 3 2 1	4 3 2 1
Alternative schedules and doses of regorafenib and a novel approach to the management of treatment-associated hand-foot syndrome	4 3 2 1	4 3 2 1
SWOG-S0809: Results of a Phase II trial of adjuvant capecitabine/gemcitabine → concurrent capecitabine and radiation therapy for extrahepatic cholangiocarcinoma and gallbladder carcinoma	4 3 2 1	4 3 2 1

Practice Setting:

☐ Academic center/medical school ☐ Community cancer center/hospital ☐ Group practice

☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify).....

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No If no, please explain:.....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain):.....

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Coordinate comprehensive biomarker analysis for patients diagnosed with advanced CRC, inclusive of broader RAS mutational assessments, and use this information to guide evidence-based care for these patients..... 4 3 2 1 N/M N/A
- Effectively apply the results of practice-changing clinical research to the selection and sequencing of chemobiologic regimens for patients with metastatic CRC..... 4 3 2 1 N/M N/A
- Consider clinical scenarios in which treatment rather than observation is warranted for patients with metastatic neuroendocrine tumors of the GI tract, and identify the optimal sequence of available systemic therapies for these patients..... 4 3 2 1 N/M N/A
- Understand the importance of expanded RAS testing in selection of treatment for patients with advanced CRC..... 4 3 2 1 N/M N/A
- Educate patients with metastatic gastroesophageal or pancreatic cancer regarding approved and novel treatment approaches and their associated risks and benefits..... 4 3 2 1 N/M N/A
- Appreciate the recent FDA-approved indications for ramucirumab alone or in combination with paclitaxel for advanced gastric or GEJ cancer, and discern how this agent can be optimally integrated into clinical practice..... 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

As a result of this activity, I will be able to:

- Communicate the benefits and risks of existing and emerging systemic interventions to patients with biliary tract cancer. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials. . . . . 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

. . . . . .

Would you recommend this activity to a colleague?

☐ Yes ☐ No If no, please explain: . . . . . .

Additional comments about this activity:

. . . . . .

. . . . . .

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☐ Yes, I am willing to participate in a follow-up survey.
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PART 2 — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
David H Ilson, MD, PhD	4 3 2 1	4 3 2 1
Eric Van Cutsem, MD, PhD	4 3 2 1	4 3 2 1
Eileen M O'Reilly, MD	4 3 2 1	4 3 2 1
Herbert I Hurwitz, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Other comments about the faculty and editor for this activity:

. . . . . .

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