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Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Charles S Fuchs, MD, MPH
Tanios Bekaii-Saab, MD
Emily K Bergsland, MD
Josep Tabernero, MD

EDITOR

Neil Love, MD

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2 Audio CDs
Monograph

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Gastrointestinal Cancer Update

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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

- Counsel patients with Stage II colon cancer on appropriate adjuvant therapeutic options based on an evaluation of their individual risk of recurrence estimated from clinical, pathologic and genomic biomarkers.
- Effectively apply the results of practice-changing clinical research to the selection and sequencing of chemobiologic regimens for patients with metastatic CRC.
- Evaluate clinical scenarios in which treatment rather than observation is warranted for patients with metastatic neuroendocrine tumors of the GI tract, and identify the optimal sequencing of systemic therapies for these patients.
- Educate patients with metastatic gastric or pancreatic cancer regarding approved and novel treatment approaches and their associated risks and benefits.
- Evaluate therapeutic options for patients with imatinib- and sunitinib-resistant GI stromal tumors.
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.

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EDITOR

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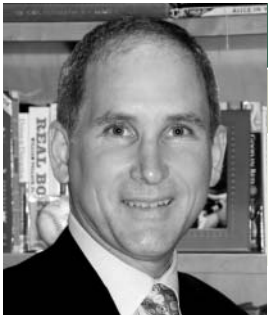

INTERVIEW

Charles S Fuchs, MD, MPH

Dr Fuchs is Director of the Center for Gastrointestinal Cancer at Dana-Farber/Harvard Cancer Center and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-15

Track 1 New options for continued anti-angiogenic treatment after disease progression on first-line therapy for metastatic colorectal cancer (mCRC)

Track 2 Mechanism of action, side effects and future directions for aflibercept in mCRC

Track 3 Rationale for a proposed trial evaluating irinotecan, cetuximab or panitumumab with or without bevacizumab as third-line therapy for mCRC

Track 4 Role for indefinite anti-angiogenic therapy in mCRC

Track 5 Underuse of EGFR monoclonal antibodies in mCRC

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Select Excerpts from the Interview

Track 1

DR LOVE: How have the recent data on new options for continued anti-angiogenic treatment after disease progression on first-line therapy and on the use of the tyrosine kinase inhibitor regorafenib influenced your approach to the treatment of metastatic colorectal cancer?

DR FUCHS: The data from the TML study are convincing. Whereas we were potentially administering second-line or continuation bevacizumab based on observational data (Grothey 2008), we now have sound Phase III data that I have integrated into my practice (Bennouna 2013; [4.1, page 15]). Many of my patients start with FOLFOX/bevacizumab and then move on to FOLFIRI/bevacizumab in the second line, and the TML data support that.

Also, I use regorafenib. The CORRECT study reported a benefit that is modest but undeniably robust statistically (Grothey 2013; [4.3, page 16]), so for patients who have experienced disease progression on all approved standard therapies and aren't eligible for a clinical trial I routinely administer regorafenib.

As for aflibercept, the data appeared convincing (Van Cutsem 2012; [4.2, page 15]), and bevacizumab and aflibercept are both effective options in terms of second-line therapy. I haven't had the chance to use aflibercept yet, but I am looking forward to doing so.

DR LOVE: How do you choose between aflibercept and bevacizumab in the second-line setting, particularly for patients with EGFR-mutant disease who received FOLFOX/bevacizumab as first-line therapy?

DR FUCHS: At the moment I am administering more bevacizumab because it has been our practice — we have a chemotherapy order entry template that includes it. However, I believe that we will see more aflibercept use in the future. We are studying it in other settings and in clinical trials — namely in neuroendocrine tumors (NET) and gastric cancer (GC). We are interested in aflibercept, and I anticipate that we will use it more routinely. Bevacizumab and aflibercept are equivalent options in the second line, and I would be comfortable using either.

Track 8

DR LOVE: Our group recently conducted a survey of 102 US-based oncologists, and we presented a poster at the 2013 Gastrointestinal Cancers Symposium on the treatment data with oxaliplatin in both Stage II and Stage III colon cancer (Love 2013; [1.1]). What is your approach to the use of adjuvant oxaliplatin?

DR FUCHS: I have curtailed my use of oxaliplatin in Stage II disease, and I applaud your efforts because we need to understand this more clearly. Patients who receive adjuvant oxaliplatin experience neuropathy for the rest of their lives, a lesson learned since the original publication of the MOSAIC trial data (André 2004). We must be mindful of who we expose to this agent. The current Intergroup study of 3 months versus 6 months of FOLFOX will also be important. We shouldn't deviate from the 6-month schedule

1.1

Is Adjuvant Oxaliplatin Overused in Colon Cancer?
408 Cases from the Practices of 102 Oncologists

	Stage II N = 306					Stage III N = 102	
Adjuvant treatment	T2 N = 16	T3 N = 229	T4 N = 61	Age <70 N = 200	Age ≥70 N = 106	Age <70 N = 84	Age ≥70 N = 18
None	12 **75%**	142 **62%**	5 **8%**	78 **39%**	81 **76%**	1 **1%**	1 **6%**
5-FU	1 **6%**	11 **5%**	3 **5%**	11 **5%**	4 **4%**	0 **0%**	0 **0%**
Capecitabine	2 **13%**	32 **14%**	13 **21%**	31 **16%**	16 **15%**	4 **5%**	1 **6%**
Oxaliplatin/ fluoropyrimidine	1 **6%**	44 **19%**	40 **66%**	80 **40%**	5 **5%**	79 **94%**	16 **88%**

Love N et al. Gastrointestinal Cancers Symposium 2013;**Abstract 479**.

yet, but I hope that 3 months is as good as 6. You won't completely eliminate the neuropathy by limiting oxaliplatin to 6 cycles, but I believe it will make a difference.

DR LOVE: One of the questions we asked the oncologists taking the survey was how much absolute benefit is needed to justify the addition of oxaliplatin. The answer was about 5%, but if you review the cases and add the numbers, it was actually less than 5%. Why do you think that is?

DR FUCHS: As gastrointestinal oncologists, I believe that we design studies for bigger differences, but we still act on the smaller ones. In fact, to ASCO's credit, their current statement is to tell patients that, on average, adjuvant chemotherapy for Stage II disease provides approximately a 2% benefit. That's what they think we should be telling patients, and it's a small difference to act on.

Tracks 9-11

DR LOVE: What are your thoughts on the use of ramucirumab monotherapy in GC, and would you discuss the results of the Phase III REGARD trial that you presented at the 2013 Gastrointestinal Cancers Symposium?

DR FUCHS: Ramucirumab is an antibody against the VEGF receptor 2, and it's well tolerated. We were particularly interested in studying it in GC as second-line therapy. In the Phase I setting, some patients with GC seemed to benefit with the single agent (Spratlin 2010), and we thought that as proof of principle it was valuable to know how the antibody acts on its own in GC because we now have ample evidence that the VEGF pathway is important in stomach cancer. That said, the RAINBOW study is evaluating paclitaxel with or without ramucirumab in patients with metastatic GC who have experienced disease progression on first-line therapy (NCT01170663). That trial is now complete, and we should have the data later this year.

On the REGARD trial patients had experienced disease progression on front-line therapy that contained either a fluoropyrimidine or a platinum agent, and at disease progression they were randomly assigned to single-agent ramucirumab or best supportive care. It was a 2-to-1 randomization, so one third of the 355 patients received best supportive care. Patients who received ramucirumab experienced a statistically significant improvement in overall survival (OS), which was the primary endpoint, and a significant improvement in progression-free survival (PFS) (Fuchs 2013; [1.2]). Compared to placebo, the only notable difference in terms of toxicity with ramucirumab was hypertension. For the most part, more higher-grade adverse events were recorded on the placebo arm than on the ramucirumab arm.

Median survival with ramucirumab was 5.3 months versus 3.8 months with placebo. That seems modest, but in the studies of docetaxel or irinotecan versus best supportive care — one example of such a study was recently published in the *Journal of Clinical Oncology* (Kang 2012) — they found the same outcome, 5.3 months with docetaxel or irinotecan and 3.8 months with placebo. Similarly, the results of the British COUGAR-02 trial evaluating docetaxel versus best supportive care were reported at the 2013 Gastrointestinal Cancers Symposium with nearly the same median survivals (Ford 2013). So the OS benefit with ramucirumab is almost identical to that of chemotherapy.

We also observed a 52% improvement in PFS. The response rate was about 3.5%. Now, you might say, "That's less than we see with docetaxel." But the response to docetaxel on the COUGAR-02 study was 7%, so is 3.5% all that different from 7%? My conclusion

1.2

REGARD: A Phase III, Randomized, Double-Blind Trial of Ramucirumab and Best Supportive Care (BSC) versus Placebo and BSC as Second-Line Therapy for Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Efficacy	Ramucirumab (n = 238)	Placebo (n = 117)	Hazard ratio	Log-rank *p*-value
Median overall survival	5.2 mo	3.8 mo	0.776	0.0473
Median progression-free survival	2.1 mo	1.3 mo	0.483	<0.0001
Response rate (CR + PR)	3.4%	2.6%	—	0.756
Select adverse events	Ramucirumab (n = 236)		Placebo (n = 115)	
Fatigue	6.4%		9.6%	
Hypertension	7.6%		2.6%	
Anemia	6.4%		7.8%	

CR = complete response; PR = partial response

Fuchs S et al. Gastrointestinal Cancers Symposium 2013;**Abstract LBA5**.

is that ramucirumab is an agent with activity in the second-line setting. The benefit is comparable to that observed with docetaxel or irinotecan in second-line therapy, and the toxicity profile is probably superior to chemotherapy. ■

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Ford H et al. **Cougar-02: A randomized phase III study of docetaxel versus active symptom control in advanced esophagogastric adenocarcinoma.** Gastrointestinal Cancers Symposium 2013;**Abstract LBA4**.

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

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.

Grothey A et al. **Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: Results from a large observational cohort study (BRiTE).** *J Clin Oncol* 2008;26(33):5326-34.

Kang JH et al. **Salvage chemotherapy for pretreated gastric cancer: A randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone.** *J Clin Oncol* 2012;30(13):1513-8.

Love N et al. **Is adjuvant oxaliplatin (Ox) overutilized in colon cancer (CC)? 408 cases from the practices of 102 oncologists.** Gastrointestinal Cancers Symposium 2013;**Abstract 479**.

Spratlin JL et al. **Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2.** *J Clin Oncol* 2010;28(5):780-7.

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.

INTERVIEW

Tanios Bekaii-Saab, MD

Dr Bekaii-Saab is Gastrointestinal Oncology Section Chief, Chair of the CCC Gastrointestinal Disease Research Group and Associate Professor of Medicine and Pharmacology at The Ohio State University – James Cancer Hospital in Columbus, Ohio.

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Track 1 MPACT: Results from a Phase III study of weekly nanoparticle albumin-bound (*nab*) paclitaxel with gemcitabine versus gemcitabine alone for metastatic adenocarcinoma of the pancreas

Track 2 Results from a Phase II study of bevacizumab/gemcitabine/5-FU in advanced pancreatic cancer (PC)

Track 3 Phase III trial results with bevacizumab/gemcitabine with or without erlotinib for metastatic PC

Track 4 Validation of the Onco*type* DX® Colon Cancer assay Recurrence Score® as a predictor of recurrence in patients with Stage II and III colon cancer treated with 5-FU/leucovorin with or without oxaliplatin on the NSABP-C-07 trial

Track 5 Utility of the Onco*type* DX and ColoPrint® assays in colon cancer

Track 6 PEAK: Results from a Phase II study of FOLFOX with panitumumab or bevacizumab as first-line therapy for unresectable K-ras wild-type mCRC

Track 7 Therapeutic approach for patients with CRC and hepatic-only metastasis

Track 8 **Case discussion:** A 48-year-old woman with poorly differentiated adenocarcinoma of the pylorus and 7 of 13 positive nodes

Track 9 Addition of trastuzumab to neoadjuvant therapy for HER2-positive GC

Track 10 Ongoing clinical trials in HER2-positive esophageal cancer

Track 11 Adjuvant therapy options and rates of local recurrence for patients with GC and R1 resection

Select Excerpts from the Interview

Track 1

DR LOVE: Can you comment on the MPACT trial that was recently presented evaluating *nab* paclitaxel with gemcitabine in advanced pancreatic cancer (PC)?

DR BEKAII-SAAB: The MPACT trial provided the first proof of principle that the activity of gemcitabine can be improved — in this case with the addition of *nab* paclitaxel (Von Hoff 2013; [2.1]). We know that the combination of a taxane with gemcitabine or 5-FU demonstrated activity in PC in Phase II studies. However, these combinations were never tested in the Phase III setting. Taxanes are active in PC, and the MPACT study confirmed this by demonstrating a survival advantage with the addition of *nab* paclitaxel to gemcitabine versus gemcitabine alone. It is intriguing that the response rate was at least 3-fold more with *nab* paclitaxel. Although *nab* paclitaxel may induce neurotoxicity, this regimen is manageable.

As you know, a year and a half ago we saw much excitement surrounding FOLFIRINOX because it induced responses and improved survival versus gemcitabine as first-line therapy

2.1

MPACT: A Phase III Trial of Weekly *Nab* Paclitaxel (*nab*-P)/Gemcitabine (Gem) versus Gem Alone for Patients with Metastatic Pancreatic Cancer

Efficacy outcome	*nab*-P/Gem (n = 431)	Gem (n = 430)	Hazard ratio	*p*-value
Median OS	8.5 months	6.7 months	0.72	0.000015
Six-month OS	67%	55%	—	0.00074
Median PFS	5.5 months	3.7 months	0.69	0.000024
ORR (independent review)	23%	7%	—	1.1×10^{-10}
ORR (investigator review)	29%	8%	—	3.3×10^{-16}

Grade ≥3 adverse events	*nab*-P/Gem (n = 421)	Gem (n = 402)
Neutropenia	38%	27%
Leukopenia	31%	16%
Fatigue	17%	7%
Peripheral neuropathy	17%	<1%

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

Von Hoff DD et al. Gastrointestinal Cancers Symposium 2013;**Abstract LBA148**.

for patients with metastatic PC (Conroy 2011). However, it is highly toxic and can't be used easily in a community setting. I have not adopted FOLFIRINOX except in cases in which it can be used for a limited time for patients with resectable or locally advanced PC when a response is needed within 3 to 4 months. Thus, the results from the MPACT trial will change my approach to first-line therapy.

DR LOVE: What interesting questions might come out of this report, with an obvious one being, would you consider this regimen in the adjuvant setting?

DR BEKAII-SAAB: FOLFIRINOX is already being evaluated in the adjuvant setting, but I would anticipate it to be an incredibly difficult regimen to administer as adjuvant treatment. This is where gemcitabine/*nab* paclitaxel will likely get the upper hand because it's relatively tolerable compared to the triplet regimen and it's also a feasible regimen for most patients. Older patients are generally excluded from receiving more aggressive regimens such as FOLFIRINOX.

I envision a broader applicability for gemcitabine/*nab* paclitaxel in the adjuvant setting for both younger and older patients. Evaluating this regimen in the adjuvant setting will be our next step, and I will wait for those data before using such an approach.

Track 2

DR LOVE: Would you discuss your Phase II study of bevacizumab/gemcitabine/5-FU in advanced PC and the role of anti-angiogenic agents in this disease?

DR BEKAII-SAAB: Our study and others have suggested that gemcitabine is the wrong backbone for anti-VEGF therapy and that a 5-FU backbone would be more likely to induce response. Our study met its primary endpoint with a 6-month PFS of 49% and a response rate higher than 25% (Martin 2012). We also reported that VEGF-A

levels and normal or above-normal baseline albumin levels might predict response to bevacizumab. The assumption is that low albumin levels are associated with a faster clearance of bevacizumab than normal or high albumin levels.

We may be able to dose modify or exclude patients with low albumin from receiving bevacizumab and focus on those with normal and high albumin levels as a way to select patients more likely to respond to VEGF inhibitors.

Track 4

DR LOVE: What are your thoughts on the report from the NSABP-C-07 trial for patients with Stage II and III colon cancer who received 5-FU/leucovorin with or without oxaliplatin? It seemed as though the Onco*type* DX Colon Cancer assay could identify patients who would or would not benefit from oxaliplatin (O'Connell 2012; [2.2]).

DR BEKAII-SAAB: Those data were interesting, particularly in regard to patients with Stage III disease. These findings have 2 aspects. One, you identify the patients who will truly benefit from adjuvant oxaliplatin, or to say that another way, you can identify those patients who will not benefit. Two, neurotoxicity remains one of the biggest limiting factors with oxaliplatin. It's clear that we're administering oxaliplatin to many patients who will have to cope with significant neurotoxicity when in fact they may have fared equally as well without the oxaliplatin.

The Onco*type* DX Colon Cancer assay must be further validated because it could serve a great purpose in the adjuvant setting. This test is currently a prognostic tool in colon cancer, unlike in breast cancer, for which it's also predictive.

2.2 **Validation of the Onco*type* DX Colon Cancer Recurrence Score (RS) in the Phase III NSABP-C-07 Study as a Predictor of Recurrence in Patients with Stage II and Stage III Colon Cancer Treated with 5-FU/Leucovorin with or without Oxaliplatin**

		Five-year recurrence risk by RS	
		5-FU	5-FU + oxaliplatin
Stage II	Low RS	7%	12%
	Intermediate RS	8%	10%
	High RS	23%	9%
Stage IIIA/B	Low RS	19%	17%
	Intermediate RS	30%	19%
	High RS	43%	31%
Stage IIIC	Low RS	41%	38%
	Intermediate RS	48%	40%
	High RS	67%	59%

Conclusions: "RS predicts recurrence risk in Stage II and III colon cancer, capturing underlying biology and providing risk information beyond conventional factors. RS is not predictive of relative benefit of oxaliplatin added to adjuvant 5-FU but enables better discrimination of absolute oxaliplatin benefit as a function of risk. For certain patients with Stage IIIA/B disease, the finding of low RS (<30), and thus low recurrence risk and low absolute oxaliplatin benefit, may not justify the risk of potential toxicity from adding oxaliplatin."

O'Connell M et al. *Proc ASCO* 2012;**Abstract 3512**.

Tracks 6-7

DR LOVE: Would you discuss the PEAK trial results presented at the 2013 Gastrointestinal Cancers Symposium, and what other interesting studies of antibody therapy are ongoing in advanced colorectal cancer?

DR BEKAII-SAAB: Being a Phase II trial, the PEAK study of first-line FOLFOX/panitumumab versus FOLFOX/bevacizumab for metastatic colorectal cancer has limitations (Schwartzberg 2013). The study reported no difference in PFS between the 2 arms. The addition of FOLFOX to an EGFR inhibitor versus bevacizumab yielded similar response rates despite the hypothesis that FOLFOX/panitumumab would produce better response rates than FOLFOX/bevacizumab.

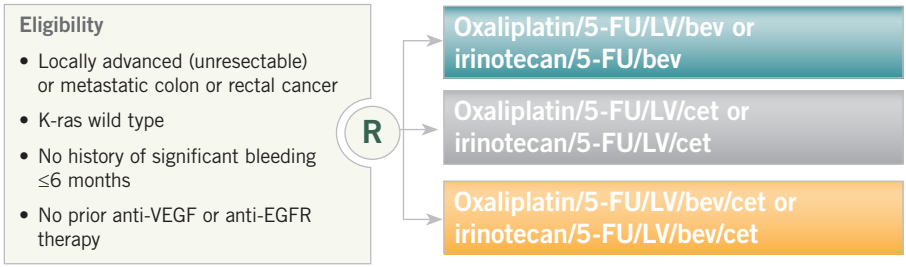
We're also awaiting the results of the CALGB-C80405 trial, which is evaluating chemotherapy/cetuximab versus chemotherapy/bevacizumab for patients with liver-only metastases (2.3). At present, the treatment strategy for these patients should be similar to that used overall for metastatic colorectal cancer.

I treat up front with bevacizumab/chemotherapy, and I would apply my standard choice of therapy across the board. I am unaware of results from a randomized study comparing VEGF inhibitors to EGFR inhibitors. The treatment of this population is a contentious issue, and it is hoped that CALGB-C80405 will shed more light on this. ■

2.3

CALGB-C80405: A Phase III Trial of Irinotecan/5-FU/Leucovorin (LV) or Oxaliplatin/5-FU/LV with Bevacizumab (Bev) or Cetuximab (Cet) or the Combination for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum

Other Protocol IDs: SWOG-C80405; NCT00265850 **Target Accrual:** 2,900



www.clinicaltrials.gov, May 2013.

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Schwartzberg LS et al. **PEAK (study 20070509): A randomized phase II study of mFOLFOX6 with either panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) in patients (pts) with unresectable wild-type (WT) KRAS metastatic colorectal cancer (mCRC).** Gastrointestinal Cancers Symposium 2013;**Abstract 446**.

INTERVIEW

Emily K Bergsland, MD

Dr Bergsland is Professor of Clinical Medicine at the University of California, San Francisco in San Francisco, California.

Tracks 1-12

Select Excerpts from the Interview

Tracks 1, 6

DR LOVE: Would you discuss the management of carcinoid and pancreatic NET?

DR BERGSLAND: Over the past 5 years there has been a greater appreciation for the differences between pancreatic and carcinoid NET. In general, pancreatic NET is more responsive to therapy. Two biologic agents are now FDA approved for advanced pancreatic NET — sunitinib and everolimus (3.1, 3.2). Neither of them have proven efficacy in carcinoid tumors.

Ongoing studies are evaluating mTOR and VEGF inhibitors in carcinoid NET. SWOG-S0518 is a Phase III study investigating bevacizumab versus interferon in combination with octreotide for patients with high-risk nonpancreatic NET (NCT00569127). The RADIANT-4 trial is investigating everolimus in advanced, carcinoid NET (NCT01524783).

DR LOVE: What is your algorithm for optimally sequencing systemic agents for patients with NET?

DR BERGSLAND: For pancreatic NET, the treatment algorithm is individualized depending on the extent and location of disease and whether the tumor is functional and/or symptomatic. First-line treatment might consist of observation in an asymptomatic patient or proceeding with resection if the patient had limited disease. For a patient with metastatic disease, I observe for a couple of months to get a sense of the pace of the disease before recommending surgery. In patients with bulky, symptomatic disease I recommend chemotherapy with capecitabine and temozolomide up front.

Everolimus and sunitinib are also reasonable considerations for a patient with progressive pancreatic NET (3.1, 3.2). I make a decision between the 2 based on the patient's comorbidities and preferences. The side-effect profiles are a little different. With everolimus you can experience a worsening of hyperglycemia, whereas with sunitinib the risk of hypertension is higher. Liver-directed therapy is an option for both pancreatic and carcinoid NET.

3.1

Results from a Phase III Trial of Sunitinib Malate for Patients with Advanced or Metastatic, Well-Differentiated Pancreatic Neuroendocrine Tumors

Efficacy	**Sunitinib** (n = 86)	**Placebo** (n = 85)	Hazard ratio	*p*-value
Median progression-free survival	11.4 mo	5.5 mo	0.42	<0.001
Median overall survival	Not reached	Not reached	0.41	0.02
	Sunitinib (n = 83)		**Placebo** (n = 82)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	59%	5%	39%	2%
Nausea	45%	1%	29%	1%
Neutropenia	29%	12%	4%	0%
Hypertension	26%	10%	5%	1%

Raymond E et al. *N Engl J Med* 2011;364(6):501-13.

3.2

RADIANT-3: Results from the Phase III Study of Everolimus for Advanced Pancreatic Neuroendocrine Tumors

Efficacy	**Everolimus** (n = 207)	**Placebo** (n = 203)	Hazard ratio	*p*-value
Median progression-free survival	11.0 mo	4.6 mo	0.35	<0.001
Median overall survival	Not reached	Not reached	1.05	0.59
	Everolimus (n = 204)		**Placebo** (n = 203)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Stomatitis	64%	7%	17%	0%
Anemia	17%	6%	3%	0%
Pneumonitis	17%	2%	0%	0%
Hyperglycemia	13%	5%	4%	2%
Thrombocytopenia	13%	4%	<1%	0%

Yao JC et al. *N Engl J Med* 2011;364(6):514-23.

For carcinoid tumors, treatment options are limited because the only approved agent is octreotide and this disease is not particularly chemotherapy sensitive. I watch patients up front if they're asymptomatic. I start octreotide in patients with functional tumors. If a patient is experiencing disease progression and not yet receiving octreotide, it is typically my first-line therapy. If the disease progresses on octreotide, I would consider regional therapy such as embolization. If the disease progressed on octreotide and the patient had extrahepatic disease or wasn't a candidate for regional therapy, I would consider enrollment on a clinical trial. RADIANT-2, a Phase III trial, evaluated everolimus with octreotide for patients with advanced NET associated with carcinoid syndrome and reported an improvement in PFS with the combination (Yao 2012). Everolimus is not approved for carcinoid tumors, however. It has a Category 3 recommendation level in the NCCN guidelines, so it may be considered for patients for whom we need additional options.

Track 12

DR LOVE: Would you comment on the Phase III GRID trial investigating the multikinase inhibitor regorafenib in patients with metastatic GIST progressing despite prior imatinib and sunitinib (Demetri 2013; [3.3])?

DR BERGSLAND: Regorafenib was effective for patients in this setting and is now approved for this indication. However, we do not yet have data to determine if it should replace sunitinib in the second-line setting. My practice would be to consider sunitinib after failure of imatinib. Regorafenib should also be considered in this setting. ■

3.3

GRID: Results from a Phase III Trial of Regorafenib for Metastatic or Unresectable GIST Progressing Despite Prior Treatment with at Least Imatinib and Sunitinib

Efficacy	Regorafenib (n = 133)	Placebo (n = 66)	Hazard ratio	*p*-value
Median progression-free survival	4.8 mo	0.9 mo	0.27	<0.0001
Overall survival events	22%	26%	0.77	0.199
Disease control rate	52.6%	9.1%	—	<0.0001
	Regorafenib (n = 132)		**Placebo** (n = 66)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hand-foot skin reaction	56%	20%	14%	0%
Hypertension	49%	24%	17%	3%
Diarrhea	40%	5%	5%	0%
Oral mucositis	38%	2%	8%	2%

Conclusion: "The results of this study show that oral regorafenib can provide a significant improvement in progression-free survival compared with placebo in patients with metastatic GIST after progression on standard treatments… This is the first clinical trial to show benefit from a kinase inhibitor in this highly refractory population of patients."

Demetri GD et al. *Lancet* 2013;381(9863):295-302.

SELECT PUBLICATION

Yao JC et al. **Multivariate analysis including biomarkers in the phase III RADIANT-2 study of octreotide LAR plus everolimus or placebo among patients with advanced neuroendocrine tumors.** Gastrointestinal Cancers Symposium 2012;**Abstract 157**.

INTERVIEW

Josep Tabernero, MD

Dr Tabernero is Head of the Medical Oncology Department at Vall d'Hebron University in Barcelona, Spain.

Tracks 1-13

Track 1 Current therapeutic options and promising investigational regimens for advanced PC

Track 2 REGARD: Ramucirumab as second-line therapy for metastatic gastric or GEJ cancer

Track 3 Ongoing Phase III trial of FOLFIRI with or without ramucirumab in mCRC

Track 4 Reconciling the TML — bevacizumab beyond progression — and VELOUR — aflibercept/FOLFIRI — trial results in mCRC

Track 5 Tumor responses to aflibercept/FOLFIRI in mCRC

Track 6 CORRECT: Results from a Phase III trial of regorafenib with best supportive care (BSC) versus BSC for refractory mCRC

Track 7 CORRECT study analysis correlating mutation status with clinical response to regorafenib

Track 8 Similarities among toxicity profiles of regorafenib, sorafenib and sunitinib

Track 9 Potential use of regorafenib prior to an EGFR inhibitor or as maintenance therapy for mCRC

Track 10 Clinical and technical validation of the ColoPrint assay for predicting outcome of patients with Stage II colon cancer

Track 11 Duration of adjuvant oxaliplatin-based chemotherapy in colon cancer

Track 12 Adjuvant therapy with 5-FU and oxaliplatin in Stage II colon cancer and elderly patients: Subgroup analyses of the MOSAIC trial

Track 13 Therapeutic algorithms for oxaliplatin use in Stage II and Stage III colon cancer

Select Excerpts from the Interview

Track 4

DR LOVE: What are your thoughts about data from the TML study of bevacizumab beyond progression and the VELOUR study investigating the VEGF Trap aflibercept for patients with metastatic colorectal cancer?

DR TABERNERO: Studies evaluating different anti-angiogenic treatment options report that maintenance of angiogenesis inhibition in the second-line setting results in a benefit in patient survival (Bennouna 2013; [4.1]; Van Cutsem 2012; [4.2]).

The TML study included patients whose disease had progressed in the first-line setting on bevacizumab and chemotherapy. Patients receiving all chemotherapy regimens were eligible to participate in the trial, and this could have diluted the effect of bevacizumab in combination with a specific chemotherapy regimen. I believe it is important to have large numbers of patients and clear data with a specific chemotherapy. Otherwise, the real magnitude of the effect of a particular chemotherapy may be unclear.

4.1

ML18147 (TML): Results from a Phase III Trial Evaluating the Addition of Bevacizumab (Bev) to Crossover Fluoropyrimidine-Based Chemotherapy (CT) for Patients with Metastatic Colorectal Cancer Experiencing Disease Progression on First-Line CT/Bev

Efficacy	**CT + bev** (n = 409)	**CT** (n = 410)	Hazard ratio	*p*-value
Median overall survival	11.2 mo	9.8 mo	0.81	0.0062
Median progression-free survival	5.7 mo	4.1 mo	0.68	<0.0001

Select adverse events (Grades 3-5)	**CT + bev** (n = 401)	**CT** (n = 409)
Neutropenia	16%	13%
Leukopenia	4%	3%
Hypertension	2%	1%
GI perforation	2%	<1%
Venous thromboembolic events	5%	3%
Bleeding or hemorrhage	2%	<1%

Bennouna J et al. *Lancet Oncol* 2013;14(1):29-37.

4.2

VELOUR: A Phase III Trial of Aflibercept versus Placebo in Combination with FOLFIRI as Second-Line Therapy for Metastatic Colorectal Cancer

Survival	**FOLFIRI + aflibercept** (n = 612)	**FOLFIRI + placebo** (n = 614)	Hazard ratio	*p*-value
Median progression-free survival	6.9 mo	4.7 mo	0.758	<0.0001
Median overall survival	13.5 mo	12.1 mo	0.817	0.0032

Select adverse events (Grades 3-4)	**FOLFIRI + aflibercept** (n = 611)	**FOLFIRI + placebo** (n = 605)
Neutropenia	36.7%	29.5%
Anemia	3.8%	4.3%
Thrombocytopenia	3.4%	1.6%
Hypertension	19.3%	1.5%
Hemorrhage	3.0%	1.7%

Van Cutsem E et al. *J Clin Oncol* 2012;30(28):3499-506.

The VELOUR study is a cleaner study in that all patients received FOLFIRI in the second-line setting. Approximately one third of the population had received bevacizumab in the first-line setting. The magnitude of the benefit with aflibercept may be similar to that with bevacizumab. However, I believe that due to the design of the VELOUR study the results may be more consistent.

DR LOVE: The FDA recently approved bevacizumab in combination with chemotherapy for patients with metastatic colorectal cancer who experienced disease progression on bevacizumab in the first-line setting. How do you decide between continuing bevacizumab versus administering aflibercept for patients in the second-line setting?

DR TABERNERO: This is a challenging decision because both options are feasible. The decision has to be based on the available data for each particular chemotherapy regimen of choice and dependent on individual clinical scenarios.

The side effects of bevacizumab in the TML study were manageable. With aflibercept, we're still trying to determine how to manage the side effects. Aflibercept targets several ligands, including VEGF-A, VEGF-B and placental growth factor (PlGF) and is associated with more side effects than bevacizumab in the second-line setting. In studies in which aflibercept was added to conventional chemotherapy, the rate of neutropenia increased. Its effects on PlGF may explain why it causes more neutropenia and other hematologic side effects (4.1, 4.2).

Tracks 6-7

DR LOVE: Would you discuss the mechanism of action of regorafenib and the results of the CORRECT trial of this agent versus placebo in combination with best supportive care for patients with metastatic colorectal cancer?

DR TABERNERO: Regorafenib inhibits several kinase receptors, including VEGFR-1, 2 and 3, Kit, PDGFR, RET and FGFR. All of these proteins play an important role in colorectal cancer, especially in the late stage of the disease when tumors have become resistant. Patients were enrolled on the CORRECT trial if their disease had progressed on all standard therapies. The study demonstrated that regorafenib treatment resulted in a survival benefit and a significant increase in the disease control rate versus placebo (Grothey 2013; [4.3]). Patients with late-stage colon cancer are usually quite sick, and an oral therapy such as regorafenib can be advantageous. Promiscuous inhibitors like regorafenib have toxic effects, and one of the future challenges will be to determine how to manage the side effects in this patient population.

4.3

CORRECT: A Phase III Trial of Regorafenib with Best Supportive Care (BSC) versus Placebo with BSC for Patients with Metastatic Colorectal Cancer Who Experience Disease Progression After Standard Therapies

Efficacy	Regorafenib + BSC (n = 505)	Placebo + BSC (n = 255)	Hazard ratio	*p*-value
Median overall survival	6.4 mo	5.0 mo	0.77	0.0052
Median progression-free survival	1.9 mo	1.7 mo	0.49	<0.0001
Disease control rate	41.0%	15%	—	<0.0001
	Regorafenib + BSC (n = 500)		**Placebo + BSC (n = 253)**	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Hand-foot skin reaction	47%	16.6%	8%	0.4%
Fatigue	47%	9.6%	28%	5.1%
Hypertension	28%	7.2%	6%	0.8%
Diarrhea	34%	7.2%	8%	0.8%
Rash/desquamation	26%	5.8%	4%	0%
Mucositis, oral	27%	3.0%	4%	0%

Grothey A et al. *Lancet* 2013;381(9863):303-12.

DR LOVE: Recently, a retrospective biomarker analysis of samples from patients on the CORRECT trial was performed to determine if mutational status correlated with clinical response to regorafenib (Jeffers 2013). Would you comment on the results?

DR TABERNERO: The results of that study reported that the clinical benefit of regorafenib did not correlate with mutations in conventional biomarkers like K-ras. This is reasonable because these biomarkers are involved in signaling pathways in malignant cells, whereas regorafenib mainly inhibits the receptor kinases in the stroma.

Tracks 12-13

DR LOVE: Would you discuss the recent results from follow-up of the MOSAIC trial investigating adjuvant therapy with oxaliplatin, fluorouracil and leucovorin in elderly patients with Stage II colon cancer?

DR TABERNERO: Patients older than age 70 derived little or no benefit from the addition of oxaliplatin to fluorouracil/leucovorin as adjuvant therapy (Tournigand 2012; [4.4]). This is in contrast to other data with the combination of oxaliplatin/capecitabine, which was beneficial in patients who were older than age 70. Colorectal cancer is a disease of the elderly population, so it is important to investigate the use and effects of oxaliplatin in elderly patients.

DR LOVE: In what situations do you recommend oxaliplatin in colon cancer?

DR TABERNERO: I administer oxaliplatin-based chemotherapy for Stage II and Stage III disease after discussion with the patient. For patients with poor-risk tumors, even with Stage II disease, I tend to use more oxaliplatin-based chemotherapy because the disease-free survival rate is rather low. ■

4.4

Subgroup Analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil and Leucovorin in the Adjuvant Treatment of Colon Cancer: Cox Analysis for Disease-Free Survival (DFS) and Overall Survival (OS) with Fluorouracil/Leucovorin (FL) with or without Oxaliplatin (FOLFOX4) by Stage and Age

FOLFOX4 versus FL	Five-year DFS HR, *p*-value	Six-year OS HR, *p*-value
Stage III (n = 1,347)	0.78, 0.005	0.8, 0.023
Stage II (n = 899)	0.84, 0.258	1.00, 0.986
Age <70 y, all stages (n = 1,931)	0.78, 0.003	0.8, 0.02
Age >70 y, all stages (n = 315)	0.93, 0.71	1.1, 0.661

Tournigand C et al. *J Clin Oncol* 2012;30(27):3353-60.

SELECT PUBLICATIONS

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.

Jeffers M et al. **Mutational analysis of biomarker samples from the CORRECT study: Correlating mutation status with clinical response to regorafenib.** Gastrointestinal Cancers Symposium 2013;**Abstract 381**.

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.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III REGARD trial comparing ramucirumab/best supportive care (BSC) to placebo/BSC demonstrated a significant improvement in _____ with ramucirumab for patients with metastatic gastric or gastroesophageal junction adenocarcinoma after disease progression on first-line platinum- and/or fluoropyrimidine-based regimens.**
   a. PFS
   b. OS
   c. Both a and b

2. **The results of the Phase III MPACT trial of weekly *nab* paclitaxel in combination with gemcitabine versus gemcitabine alone demonstrated a statistically significant improvement in _____ with the addition of *nab* paclitaxel for patients with metastatic pancreatic cancer.**
   a. OS
   b. PFS
   c. Overall response rate
   d. All of the above

3. **The RAINBOW study is evaluating paclitaxel versus paclitaxel and _____ as second-line therapy for patients who have experienced disease progression on first-line therapy.**
   a. Regorafenib
   b. Ramucirumab
   c. Neither a nor b

4. **The Phase III CALGB-C80405 trial is evaluating irinotecan or oxaliplatin in combination with leucovorin and 5-FU/leucovorin with bevacizumab and/or cetuximab for patients with untreated metastatic colorectal cancer harboring the _____ gene.**
   a. K-ras-mutant
   b. K-ras wild-type
   c. Both a and b

5. **Data evaluating patients enrolled in the Phase III NSABP-C-07 trial suggest that the Onco*type* DX Colon Cancer Recurrence Score predicts recurrence risk for patients with Stage II and Stage III colon cancer.**
   a. True
   b. False

6. **A Phase III trial of sunitinib malate versus placebo for patients with advanced or metastatic well-differentiated pancreatic NET demonstrated a statistically significant increase in PFS with sunitinib.**
   a. True
   b. False

7. **The Phase III GRID trial of regorafenib for metastatic or unresectable GIST reported that the side effects associated with regorafenib treatment included _____.**
   a. Hypertension
   b. Diarrhea
   c. Hand-foot skin reaction
   d. All of the above

8. **The Phase III CORRECT trial of regorafenib in combination with BSC versus placebo with BSC for patients with metastatic colorectal cancer who experience disease progression on standard therapy reported statistically significant improvements in _____ for patients who received regorafenib.**
   a. Median PFS
   b. Median OS
   c. Disease control rate
   d. All of the above

9. **The Phase III TML trial evaluating the addition of _____ to crossover fluoropyrimidine-based chemotherapy versus chemotherapy alone for patients with metastatic colorectal cancer who experienced disease progression while receiving first-line chemotherapy/bevacizumab demonstrated a statistically significant improvement in median OS.**
   a. Aflibercept
   b. Bevacizumab
   c. Cetuximab
   d. Regorafenib

10. **Results from the Phase III VELOUR trial indicated that the addition of aflibercept to FOLFIRI was associated with statistically significant improvements in PFS and OS compared to FOLFIRI alone as second-line therapy for patients with metastatic colorectal cancer.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 1, 2013

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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
MPACT: Results from a Phase III study of weekly *nab* paclitaxel in combination with gemcitabine versus gemcitabine alone for metastatic adenocarcinoma of the pancreas	4 3 2 1	4 3 2 1
Validation of the Onco*type* DX Colon Cancer assay RS as a predictor of recurrence for patients with Stage II and III colon cancer treated with 5-FU/leucovorin with or without oxaliplatin on the NSABP-C-07 trial	4 3 2 1	4 3 2 1
Mechanism of action, efficacy and tolerability of ramucirumab for metastatic gastric or gastroesophageal junction cancer (REGARD trial)	4 3 2 1	4 3 2 1
TML study of bevacizumab beyond first progression and VELOUR study of FOLFIRI/aflibercept in metastatic colorectal cancer	4 3 2 1	4 3 2 1
CORRECT study analysis correlating mutation status with clinical response to regorafenib	4 3 2 1	4 3 2 1
Differential management of carcinoid and pancreatic NET	4 3 2 1	4 3 2 1

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

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

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☐ 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: .....

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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:

- Counsel patients with Stage II colon cancer on appropriate adjuvant therapeutic options based on an evaluation of their individual risk of recurrence estimated from clinical, pathologic and genomic biomarkers. . . . . 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
- Evaluate clinical scenarios in which treatment rather than observation is warranted for patients with metastatic neuroendocrine tumors of the GI tract, and identify the optimal sequencing of systemic therapies for these patients. . . . . 4 3 2 1 N/M N/A
- Educate patients with metastatic gastric or pancreatic cancer regarding approved and novel treatment approaches and their associated risks and benefits. . . . . 4 3 2 1 N/M N/A
- Evaluate therapeutic options for patients with imatinib- and sunitinib-resistant GI stromal tumors. . . . . 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?

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.....

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☐ No, I am not willing to participate in a follow-up survey.

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Charles S Fuchs, MD, MPH	4	3	2	1	4	3	2	1
Tanios Bekaii-Saab, MD	4	3	2	1	4	3	2	1
Emily K Bergsland, MD	4	3	2	1	4	3	2	1
Josep Tabernero, 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

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

.....

.....

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