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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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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

- Coordinate comprehensive biomarker analysis for patients diagnosed with advanced CRC, inclusive of broader RAS and RAF 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.
- Educate patients with metastatic gastric or pancreatic cancer regarding approved and novel treatment approaches and their associated risks and benefits.
- 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 systemic therapies for these patients.
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular carcinoma.

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INTERVIEW

Richard M Goldberg, MD

Dr Goldberg is Professor of Medicine and Physician-in-Chief at the OSUCCC – James Cancer Hospital and Richard J Solove Research Institute and Klotz Family Chair in Cancer Research at The Ohio State University in Columbus, Ohio.

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Select Excerpts from the Interview

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DR LOVE: What is your approach to treatment for a patient with metastatic colorectal cancer (mCRC) whose disease has progressed on first-line therapy?

DR GOLDBERG: You have to evaluate the data along with the patient and then make a decision because a single right or wrong approach does not exist. We've been successful in transforming metastatic colon cancer into more of a chronic disease than it was when you and I first started. And as a consequence, I want as many options as I can offer for my patients, and I want to use them in series.

I tend to administer first-line FOLFOX/bevacizumab and now tend to use FOLFIRI/bevacizumab in the second-line setting, even for patients with KRAS wild-type disease. Then I fall back to irinotecan with an EGFR inhibitor for third-line therapy. I believe that the mechanism of action of the EGFR inhibitors is so much different than that of the other agents we use earlier on that you often see satisfying and long responses.

The next question is, what about aflibercept? In my experience, the toxicity associated with this agent has been less than I expected based on the VELOUR trial results (Van Cutsem 2012). It seems to be as easy to administer as bevacizumab. I tend to consider aflibercept in the second-line setting for patients who "burn through" first-line therapy quickly and for whom I want to "reboot" and try a completely new regimen because I do believe that aflibercept is fundamentally different from bevacizumab.

Then, of course, we now have the option of regorafenib in the late-line setting. Regorafenib is a bit of a "dirty" kinase inhibitor and affects multiple important pathways in cancer cells. That may be an appealing approach in later-line therapy, with which you have a diversity of mutations that we've accentuated by putting pressure on the tumor with chemotherapy and targeted agents. My own experience with regorafenib in this setting is that it's been more difficult to administer than I thought it would be. I often have to reduce the dose, particularly for older patients.

Of interest, we are conducting a Phase II study of regorafenib in combination with FOLFIRI as second-line therapy for mCRC (NCT01298570), and I've found it much easier to administer in an earlier line of therapy. That may be in part because we are accruing patients who are both younger and healthier. Also, these patients are earlier on in their exposure to chemotherapy agents.

DR LOVE: Much debate is going on about what the starting dose of regorafenib should be. For practical purposes, what's the dosing range that you consider?

DR GOLDBERG: I don't start patients on 160 mg unless they are 40 or younger and fit. I generally start at 80 to 120 mg. For older patients or those with a number of comorbidities I will start at a half dose and escalate. For younger patients or older patients with a good performance status I'll start at 120 mg, although I find that I am almost never able to escalate in this group.

You need to monitor patients, especially early on. The nice aspect about oral agents is that you can intervene over the phone and say, "Take less tonight and from now on." So I believe it's a great idea to call patients receiving regorafenib a week after they start treatment to check in with them and see how they're faring.

DR LOVE: What points do you emphasize to patients beginning therapy on regorafenib, and do any preemptive approaches help prevent toxicity?

DR GOLDBERG: When I prescribe panitumumab and cetuximab to patients, I'm a big believer in using prophylactic measures to try to improve their rashes. But I haven't found a way to improve regorafenib-associated hand-foot syndrome other than to tell the patients to use moisturizing creams, which I'm not sure makes a big difference. The fatigue is not something you can manage. I don't think resting or not resting makes a difference. I don't want to start patients on other drugs for muscle aches unless they have them. So I haven't found an effective solution to preemptively ameliorate the toxicity as of yet.

Often these issues occur quickly. An analysis of data from the CORRECT study indicated that patients who were able to tough it out through the first cycle often fared better on later cycles (Grothey 2013b; [1.1]). Toxicity seems to present and peak early. In some ways this is akin to the skin toxicity observed with EGFR-targeted antibodies, with which the most vigorous skin reaction tends to be in the first month or so, and then it improves in many patients.

1.1

CORRECT Trial: Frequency of Treatment-Emergent Adverse Events Over Time in Patients with Metastatic Colorectal Cancer Treated with Regorafenib

	Cycle of therapy							
Adverse event	1 (n = 500)	2 (n = 417)	3 (n = 229)	4 (n = 193)	5 (n = 119)	6 (n = 91)	7 (n = 55)	8 (n = 43)
HFSR	32	26	24	24	26	25	15	5
Fatigue	45	23	16	24	17	22	11	9
Hypertension	21	11	3	4	4	2	0	5
Rash/ desquamation	24	7	3	4	5	1	0	0

HFSR = hand-foot skin reaction

Conclusion: In the CORRECT trial, the incidences of the most common adverse events in the regorafenib group peaked early during treatment and no evidence was apparent for cumulative toxicity with regorafenib.

Grothey A et al. Gastrointestinal Cancers Symposium 2013b;**Abstract 467**.

Track 11

DR LOVE: Would you comment on the role of the Onco*type* DX Colon Cancer assay in the management of Stage II and Stage III disease?

DR GOLDBERG: It is fairly well known that the difference between an Onco*type* high-risk Recurrence Score® (RS) and an Onco*type* low-risk RS is somewhere between 20% and 8%. So a patient at high risk would have a 1 in 5 chance of recurrence, and a patient with a low-risk RS would have a less than 1 in 10 chance of recurrence.

I usually discuss the modest benefit from 5-FU/leucovorin chemotherapy with my patients. I don't administer FOLFOX to patents with low-risk, Stage II disease. We perform microsatellite instability (MSI) testing on all of our patients. If their disease is MSI high, I talk them out of treatment if I can. I present the Onco*type* DX Colon Cancer assay data to patients with T2 and T3N0 disease and I say, "If a 20% risk of recurrence is going to lead you to take therapy and an 8% risk of recurrence is going to lead you to not take therapy, then it's worth ordering the test."

If you evaluate Stage III colon cancer as an example, the patients with the worst prognosis get the most benefit from adjuvant therapy. Patients with 15 positive nodes and a T3 tumor, or even a T4 tumor, have a terrible prognosis. However, you can modify their prognosis the most with adjuvant therapy in that setting. So the higher the risk, the higher the benefit. ■

SELECT PUBLICATIONS

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

Grothey A et al. **Time course of regorafenib-associated adverse events in the phase III CORRECT study.** Gastrointestinal Cancers Symposium 2013b;**Abstract 467**.

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

Philip A Philip, MD, PhD

Dr Philip is Professor of Oncology and Medicine, Director of GI and Neuroendocrine Tumors and Vice President of Medical Affairs at Wayne State University's Karmanos Cancer Institute in Detroit, Michigan.

Tracks 1-13

Select Excerpts from the Interview

Track 2

DR LOVE: What is your treatment approach for a patient with hepatocellular cancer (HCC) who is not a candidate for liver-directed therapy?

DR PHILIP: If a patient is deemed to be ineligible for liver-directed therapy, my next step is to administer sorafenib. The challenge here is that the patient who will not qualify for liver-directed therapy may also not have been represented on the SHARP trial (Abou-Alfa 2006), which included patients with Child-Pugh A disease and favorable performance statuses.

The question is, do you start these patients with a full or lower dose of sorafenib? This should be a personalized decision with each patient. I rarely administer sorafenib to patients with Child-Pugh C disease. For patients with Child-Pugh B disease, especially

the older patients, I tend to start with lower doses ranging from 200 to 600 mg. The key aspect here is to follow up frequently early on because I've seen patients in whom nontolerance can be discovered within a week or 2 of starting treatment.

Track 4

DR LOVE: What is your view on the use of therapies targeting the VEGF pathway in advanced HCC?

DR PHILIP: In HCC we believe that hypervascularity on a CAT or MRI scan translates into overactivation of the VEGF/VEGF receptor (VEGFR) pathway. We use liver-directed therapy because of the belief in the need to address the vascularity-related issues.

Ramucirumab is an interesting anti-VEGFR-2 monoclonal antibody. Before the ramucirumab era, bevacizumab initially showed benefit in a pilot study (Britten 2012), but in the randomized Phase II trials that followed, it failed to demonstrate much activity. Ramucirumab might prove to be a different and better agent because it targets the VEGF receptor rather than the growth factor itself and so has the potential to be effective.

The REACH trial of ramucirumab and best supportive care versus placebo/best supportive care as second-line therapy for patients with HCC after failure of first-line sorafenib is ongoing (2.1). Several agents, such as brivanib, have been tested after disease progression on sorafenib and have failed to be effective (Llovet 2013). Because sorafenib is a multikinase inhibitor that also targets VEGFR-2, it is unknown if its activity results from anti-angiogenesis. Although targeting the VEGF pathway is interesting, we do not know if ramucirumab after sorafenib failure will lead to major breakthroughs in the management of HCC.

Regorafenib is an oral small molecule anti-angiogenic agent being studied in the RESORCE trial in the second-line setting after sorafenib failure (2.1). Because both sorafenib and regorafenib inhibit VEGFR-2, among other targets, an important question to ask is whether they differ so much that regorafenib can elicit activity after sorafenib failure. At this time, we are in need of active agents targeting other biomarkers besides VEGF and VEGFRs.

2.1

Ongoing Trials of Anti-VEGF-Based Therapies for Patients with Advanced Hepatocellular Cancer

Trial ID	Phase	N	Setting	Treatment arms
NCT01140347 (REACH)	III	565	Second line (after sorafenib)	• Ramucirumab + BSC • Placebo + BSC
NCT01774344 (RESORCE)	III	530	Second line (after sorafenib)	• Regorafenib + BSC • Placebo + BSC
NCT02082210	I/II	55	Advanced	• Ramucirumab + LY2875358
NCT02069041	IB	9	Advanced	• Ramucirumab + FOLFOX4

BSC = best supportive care

www.clinicaltrials.gov. Accessed May 2014.

Tracks 7-8

DR LOVE: What factors do you consider when making a treatment decision for patients with metastatic pancreatic cancer (mPC) (Ghosn 2014; [2.2])?

DR PHILIP: The most important decision-making factor is the patient's performance status. I also consider age and liver function test results. I discuss the pros and cons of the treatment options with the patient, and their preference is important.

In my practice, about 10% to 15% of patients with unresectable or metastatic pancreatic cancer will receive gemcitabine alone, whereas 15% will receive FOLFIRINOX. Nowadays, the remaining 70% to 75% of patients will receive gemcitabine/*nab* paclitaxel.

I administer FOLFIRINOX to patients younger than age 75 with a performance status of 2 or lower and without major liver dysfunction. I don't believe any patients with mPC have a performance status of 0 because they all are symptomatic and have certain limitations. I do not administer FOLFIRINOX to any patient with elevations in bilirubin levels. I may consider administering FOLFIRINOX for patients with borderline enzyme elevations 2 or fewer times the upper limit of normal.

DR LOVE: In your experience, what are the side effects of gemcitabine/*nab* paclitaxel (Ghosn 2014; [2.2])?

DR PHILIP: Initially, patients may experience Grade II fatigue and myelosuppression. Continued treatment for longer periods is associated with increased fatigue and cumulative myelosuppression. In this situation, we may dose reduce by 20% while carefully monitoring symptoms as treatment is continued. If symptoms don't improve, I would administer therapy biweekly at the reduced dose.

2.2

Efficacy and Safety Results Across Trials of 3 FDA-Approved Regimens for Metastatic Pancreatic Cancer

Trial (authors)	Regimens evaluated	ORR	Median OS	Median PFS
ACCORD-11/0402 (Conroy et al)[1]	FOLFIRINOX	31.6%	11.1 mo	6.4 mo
	Gem	9.4%	6.8 mo	3.3 mo
MPACT (Von Hoff et al)[2]	Gem/*nab* pac	23%	8.5 mo	5.5 mo
	Gem	7%	6.7 mo	3.7 mo
Adverse events (≥Grade 3)[3]		**FOLFIRINOX**[1]	**Gem**[1]	**Gem/*nab* pac**[2]
Neutropenia		45.7%	21%	38%
Febrile neutropenia		5.4%	1.2%	3%
Thrombocytopenia		9.1%	3.6%	13%
Fatigue		23.6%	17.8%	17%
Diarrhea		12.7%	1.8%	6%
Peripheral neuropathy		9.0%	0%	17%

ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Gem = gemcitabine; *nab* pac = *nab* paclitaxel

[1] Conroy T et al. *N Engl J Med* 2011;364(19):1817-25; [2] Von Hoff DD et al. *Proc ASCO* 2013;**Abstract 4005**; [3] Ghosn M et al. *World J Gastroenterol* 2014;20(9):2352-7.

In my practice, neurotoxicity has not posed much of a problem with *nab* paclitaxel use during the first 6 months of therapy. This may be because we commonly dose reduce and are more proactive with managing the associated side effects. However, with extended treatment beyond this time, patients may experience some neurotoxic effects.

Track 9

DR LOVE: What is the status of the Phase II RECAP trial of capecitabine with or without ruxolitinib as second-line therapy for mPC?

DR PHILIP: Ruxolitinib targets the JAK-STAT pathway, which plays a key role in the signaling of many cytokines and growth factors. A recent press release reported that ruxolitinib was beneficial for a subset of patients on the RECAP trial (2.3). It is probable that those patients have disease that is characterized by a higher or constitutional activity of the circulating cytokines.

A biomarker that relates to cytokine release is serum C-reactive protein (CRP). I have been conducting tests to determine serum CRP levels in my patients for the past few weeks, and the results are interesting. The normal level is 9 ng/mL, but one of my patients expressed a level of 132 ng/mL and another had 10 ng/mL. It is reasonable to expect a spread in the CRP levels because some patients with pancreatic cancer have constitutional symptoms such as leukocytosis. Such patients possibly will benefit from ruxolitinib therapy. Hopefully, the results from the RECAP trial will be presented soon. (Editor's note: Subsequent to this interview results of the RECAP trial were presented [Hurwitz H et al. *Proc ASCO* 2014;**Abstract 4000**].) ■

2.3

Phase II RECAP Trial of Capecitabine with or without Ruxolitinib as Second-Line Therapy for Patients with Refractory Metastatic Pancreatic Cancer

Protocol ID: NCT01423604

Target accrual (n = 138)

- Metastatic pancreatic cancer (mPC)
- Karnofsky performance status ≥60
- Failure of first-line gemcitabine for mPC **or** other first-line chemotherapy for patients intolerant to or ineligible for gemcitabine

R

- Ruxolitinib + capecitabine
- Placebo + capecitabine

www.clinicaltrials.gov. Accessed May 2014.

Press release (8/21/13): "Results of the RECAP trial provide the first evidence that JAK inhibition is active in this disease and suggest a demonstrable survival benefit in a well-defined group of patients with refractory metastatic pancreatic cancer who can be identified without the development of a companion diagnostic test."

SELECT PUBLICATIONS

Abou-Alfa GK et al. **Phase II study of sorafenib in patients with advanced hepatocellular carcinoma.** *J Clin Oncol* 2006;24(26):4293-300.

Britten CD et al. **Transarterial chemoembolization plus or minus intravenous bevacizumab in the treatment of hepatocellular cancer: A pilot study.** *BMC Cancer* 2012;12:16.

Llovet JM et al. **Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: Results from the randomized phase III BRISK-PS study.** *J Clin Oncol* 2013;31(28):3509-16.

INTERVIEW

Pamela L Kunz, MD

Dr Kunz is Assistant Professor of Medicine in the Division of Oncology at Stanford University School of Medicine in Stanford, California.

Tracks 1-15

Select Excerpts from the Interview

Track 4

DR LOVE: Could you comment on some of the ongoing trials evaluating HER2-directed therapies for HER2-positive advanced gastric cancer (GC) or gastroesophageal junction (GEJ) cancer?

DR KUNZ: Different anti-HER2 agents are currently under investigation in advanced GC and GEJ cancer (3.1). Pertuzumab and trastuzumab emtansine (T-DM1) are being investigated in prospective clinical trials. An ongoing prospective study is evaluating triweekly T-DM1 versus weekly T-DM1 or a taxane. It is anticipated that the trial will

complete accrual in about 2 years, but results may not be available for a few more years. We're all excited about the study.

3.1 **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 (BO25114)	780	• Pertuzumab + TFP • Placebo + TFP
NCT00680901 (LOGiC)	545	• Lapatinib + CAPOX • Placebo + CAPOX
NCT01641939 (BO27952)	412	• Triweekly trastuzumab emtansine (3.6 mg/kg) • Weekly trastuzumab emtansine (2.4 mg/kg) • Taxane (paclitaxel or docetaxel)

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

www.clinicaltrials.gov. Accessed May 2014.

Tracks 7-8

DR LOVE: Would you discuss the results of the Phase III REGARD and RAINBOW trials of second-line ramucirumab in metastatic GC or GEJ cancer?

DR KUNZ: The REGARD trial of ramucirumab versus placebo demonstrated that accrual to a second-line trial in metastatic GC/GEJ cancer is possible (Fuchs 2014; [3.2]). We're seeing more patients who are eligible to receive second-line therapy. The RAINBOW study of second-line paclitaxel with or without ramucirumab demonstrated that combination therapy was more effective than paclitaxel alone (Wilke 2014; [3.2]). Based on the results of these trials, I believe ramucirumab will be approved (3.3).

3.2 **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		0.0169	
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	

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

[1] Fuchs CS et al. *Lancet* 2014;383(9911):31-9; [2] Wilke H et al. Gastrointestinal Cancers Symposium 2014;**Abstract LBA7**.

Most oncologists will combine ramucirumab with other cytotoxic backbones, even without available data. I'm excited about the potential for ramucirumab in combination with other agents.

3.3

Editor's Note: FDA Approves Ramucirumab for Metastatic Gastric or Gastroesophageal Junction (GEJ) Cancer

Subsequent to this interview, on April 21, 2014, the FDA approved ramucirumab for use as a single agent for the treatment of advanced or metastatic gastric or GEJ adenocarcinoma that progresses during or after treatment with fluoropyrimidine- or platinum-containing chemotherapy.

www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm394260.htm. Accessed May 27, 2014.

Tracks 9, 12-14

DR LOVE: Can you provide a global view of the key features in the management of neuroendocrine tumors (NETs)?

DR KUNZ: A key decision branch point is to determine if the disease is poorly or well differentiated. It also is important to know whether the disease grade is low, intermediate or high. The Ki-67 value, which is a proliferative index, and the mitotic index are also key features. One needs to ask for these details if they are not included in the pathologist's report because they are important features needed to prognosticate.

These features group patients in different treatment categories. For example, patients with well-differentiated NETs — which include both the low- and intermediate-grade tumors — receive different therapies than those with poorly differentiated NETs. Another major decision branch point is to determine if the tumor is of pancreatic or nonpancreatic origin.

DR LOVE: Does adjuvant therapy have a role in gastrointestinal NET?

DR KUNZ: Currently, even with lymph node-positive disease, adjuvant therapy has no known role. This partly depends on the disease pathology. For a patient with poorly differentiated NET at the time of resection, one would likely offer adjuvant therapy with platinum/etoposide. However, for those with well-differentiated tumors, even with node-positive disease, I would not offer adjuvant therapy.

The Phase II ECOG-E2212 trial will evaluate whether the addition of adjuvant everolimus to the R0 or R1 surgical resection of metastatic pancreatic NETs to the liver will yield improvements in disease-free survival (NCT02031536). Patients will be randomly assigned to receive everolimus or placebo for 1 year. This is exciting because it's the first time the adjuvant question will be asked. I hope that after the completion of that study, we will evaluate the role of adjuvant therapy in earlier settings.

DR LOVE: How do you select patients with NETs for treatment?

DR KUNZ: It is known that adjuvant octreotide controls symptoms of true carcinoid syndrome, like diarrhea and flushing. We also know that somatostatin analogs have an effect on controlling hormones in addition to having antiproliferative effects. The PROMID study of octreotide or placebo for patients with metastatic small-bowel NETs demonstrated a prolonged progression-free survival (PFS) with octreotide (Rinke 2009). So octreotide is my first-line choice for patients with slowly progressive disease.

Also, the Phase III CLARINET study, in patients with nonfunctioning enteropancreatic NETs, demonstrated prolonged PFS with the long-acting aqueous preparation of lanreotide, a slightly different somatostatin analog from octreotide (Caplin 2013). A key take-home message is that patients with progressive disease, hormone-related symptoms or tumor bulk-related symptomatic disease need to be appropriately selected for therapy. For a patient with newly diagnosed metastatic asymptomatic disease with no evidence of progression, I would offer no treatment.

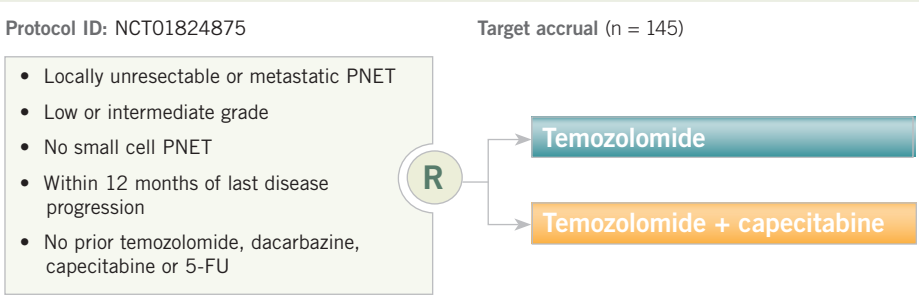
DR LOVE: What's your treatment algorithm for metastatic pancreatic NET?

DR KUNZ: For metastatic NETs of pancreatic origin, the FDA-approved agents are everolimus, an mTOR inhibitor, and sunitinib, a VEGF tyrosine kinase inhibitor. These agents are oral, taken daily and used separately. In comparison to placebo, both showed a 5- to 6-month PFS benefit. The choice of one versus the other sometimes depends on the patient's comorbidities. I will choose sunitinib for a patient with existing hypertension. Everolimus may cause lipid disorders such as hypertriglyceridemia. In a patient with pre-existing lung disorders, everolimus may cause pneumonitis. Streptozocin is the only FDA-approved cytotoxic chemotherapy. It's an alkylating agent thought to have considerable toxicity. Even now, it's not widely available.

We've been trying to look at newer, less toxic cytotoxic therapies. In the past few years, we've been interested in temozolomide, an oral alkylating agent approved for glioblastoma treatment. A retrospective review of the combination of temozolomide with oral capecitabine for 30 patients with metastatic pancreatic NET demonstrated a response rate of 70% (Strosberg 2011). This combination has not been well studied prospectively. A Phase II trial of temozolomide/capecitabine versus temozolomide alone in advanced pancreatic NET is ongoing (3.4). Some believe the combination may be synergistic. ■

3.4

Ongoing Phase II Trial of Temozolomide with or without Capecitabine for Patients with Advanced Pancreatic Neuroendocrine Tumors (PNET)



www.clinicaltrials.gov. Accessed May 2014.

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Caplin M et al. **A randomized double-blind placebo-controlled study of lanreotide antiproliferative response in patients with enteropancreatic neuro endocrine tumours (CLARINET).** *Proc ESMO* 2013;**Abstract E17-7103**.

Rinke A et al. **Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group.** *J Clin Oncol* 2009;27(28):4656-63.

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

INTERVIEW

J Randolph Hecht, MD

Dr Hecht is Professor of Clinical Medicine, Carol and Saul Rosenzweig Chair in Cancer Therapies Development and Director of the UCLA GI Oncology Program in Santa Monica, California.

Tracks 1-9

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the importance of RAS/BRAF mutations as predictive markers of resistance to anti-EGFR antibodies for patients with CRC?

DR HECHT: KRAS mutations are a validated genetic marker of resistance to anti-EGFR therapy in patients with CRC. Studies have demonstrated that in about 40% of patients with KRAS mutations in codons 12 and 13 of exon 2, anti-EGFR antibodies have no benefit (Amado 2008).

Expanded RAS analysis indicates that outside of exon 2, a small number of mutations can be found in various hot spots. Mutations in NRAS occur in less than 10% of CRC tumors. HRAS mutations are also rare. The incidence of BRAF mutations varies from about 10% to 15% in the early stage to 5% in the salvage setting, and they confer a poor prognosis in CRC. Initially it was thought that BRAF mutations were a predictive marker for response to anti-EGFR antibodies, but that has not borne out.

The PRIME study, which assessed the efficacy and safety of panitumumab in combination with FOLFOX4 versus FOLFOX4 alone as first-line therapy, demonstrated

that patients with the nonclassical RAS mutations experienced worse outcomes with the addition of panitumumab to chemotherapy for mCRC. This is consistent with the findings in patients with KRAS mutations in exon 2 (Douillard 2013).

The hazard ratios are more than 1 in studies when panitumumab or cetuximab is administered to patients who have RAS-mutant CRC, which is interesting from a biological standpoint. We may be tweaking the biology in a bad way by administering anti-EGFR therapy to these patients.

Tracks 2-5

DR LOVE: What do we know about the efficacy and side effects of bevacizumab versus anti-EGFR antibodies for patients with KRAS wild-type mCRC?

DR HECHT: Three trials have compared or are comparing chemotherapy with an anti-EGFR antibody to chemotherapy with bevacizumab head to head in patients with KRAS wild-type mCRC.

The PEAK trial was a randomized Phase II trial of panitumumab with modified fluorouracil/leucovorin/oxaliplatin (mFOLFOX6) versus bevacizumab with mFOLFOX6 for patients with untreated, unresectable, wild-type KRAS exon 2 mCRC. Improvement was observed in overall survival (OS) with panitumumab versus bevacizumab for patients with wild-type disease with respect to KRAS exon 2. A subgroup of patients with wild-type KRAS and NRAS exons 2, 3 and 4 seemed to experience more clinical benefit with panitumumab (Schwartzberg 2014; [4.1]).

A large trial presented last year was the FIRE-3 study, which evaluated chemotherapy in combination with either cetuximab or bevacizumab as first-line treatment for

4.1

PEAK: A Randomized, Multicenter Phase II Study of Panitumumab/mFOLFOX6 versus Bevacizumab/mFOLFOX6 for Untreated, Unresectable, Wild-Type (WT) KRAS Exon 2 Metastatic Colorectal Cancer

Efficacy	Panitumumab/ mFOLFOX6	Bevacizumab/ mFOLFOX6	HR	*p*-value
WT KRAS exon 2 (n = 142, 143)*				
Median progression-free survival	10.9 mo	10.1 mo	0.87	0.353
Median overall survival	34.2 mo	24.3 mo	0.62	0.009
WT KRAS and NRAS exons 2, 3, 4 (n = 88, 82)				
Median progression-free survival	13.0 mo	9.5 mo	0.65	0.029
Median overall survival	41.3 mo	28.9 mo	0.63	0.058

	Panitumumab/ mFOLFOX6 (n = 139)		**Bevacizumab/ mFOLFOX6** (n = 139)	
Select adverse events*	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin disorders	97%	32%	45%	1%
Thrombocytopenia	24%	1%	12%	0%
Hypertension	4%	0%	25%	7%

mFOLFOX6 = modified fluorouracil, leucovorin and oxaliplatin; HR = hazard ratio
* Intent to treat

Schwartzberg LS et al. *J Clin Oncol* 2014;[Epub ahead of print].

patients with KRAS wild-type mCRC. The primary endpoint was objective response rate, and it was similar in both arms. No difference was observed in PFS either, but OS was significantly improved in the cetuximab arm. The curves diverged after most of the patients would have been off the therapy, and this was unexpected (Heinemann 2013; [4.2]). Expanded RAS testing confirmed the previously reported results (Stintzing 2013).

It has been postulated that perhaps the biology of the tumor was altered differently with bevacizumab versus with cetuximab. The CALGB-C80405 trial is evaluating bevacizumab and/or cetuximab in combination with irinotecan or oxaliplatin and 5-FU/leucovorin as first-line therapy for KRAS wild-type locally advanced or metastatic CRC (4.3). OS is the primary endpoint, and the results, which will be presented at ASCO, may provide a more definitive answer. (Editor's note: Subsequent to this interview results of the CALGB-C80405 trial were presented [Venook AP et al. *Proc ASCO* 2014;**Abstract LBA3**].)

DR LOVE: What is your usual first-line therapy for patients with KRAS wild-type mCRC?

DR HECHT: I typically administer CAPOX in combination with bevacizumab. This is partly because the schedule of administration is convenient for patients who travel long distances. If we need to achieve resectability, we use 5-FU/irinotecan and oxaliplatin.

We use bevacizumab as the biologic agent for the majority of patients receiving front-line therapy because of the side effects associated with anti-EGFR antibodies. The side effects of bevacizumab, which include hypertension, arterial thromboembolic events and gastrointestinal perforation, are rare, but if they occur, they can be catastrophic. The results of the FIRE-3 study are interesting, but we haven't changed our practice because of those results.

Anti-EGFR therapy may increase the preoperative response rate and may facilitate resection for patients with marginally resectable disease. The new EPOC trial evaluated the benefit of cetuximab in addition to standard chemotherapy versus chemotherapy alone for patients with KRAS wild-type, operable liver metastasis from CRC. The addition of cetuximab to chemotherapy improved response rates but resulted in significantly worse PFS outcomes (Primrose 2013).

4.2

FIRE-3: A Phase III Study of FOLFIRI in Combination with Cetuximab versus FOLFIRI in Combination with Bevacizumab as First-Line Treatment for KRAS Wild-Type (WT) Metastatic Colorectal Cancer

Efficacy	Cetuximab/ FOLFIRI	Bevacizumab/ FOLFIRI	*p*-value
KRAS WT (n = 592)*			
Objective response rate	62%	58%	0.183
Median progression-free survival	10.0 mo	10.3 mo	0.547
Median overall survival	28.7 mo	25.0 mo	0.017
WT KRAS and NRAS exons 2, 3, 4 (n = 301)			
Objective response rate	76.0%	65.2%	0.026
Median progression-free survival	10.5 mo	10.4 mo	0.627
Median overall survival	33.1 mo	25.9 mo	0.010

* Intent to treat

Heinemann V et al. *Proc ASCO* 2013;**Abstract LBA3506**; Stintzing S et al. *Proc ECC* 2013;**Abstract E17-7073**.

DR LOVE: What is your approach to first-line therapy for mCRC when you need a response?

DR HECHT: The Phase III TRIBE trial, presented at ASCO 2013, compared FOLFOXIRI/bevacizumab to FOLFIRI/bevacizumab as first-line treatment in unresectable mCRC. The results demonstrated a significantly better response rate and PFS with FOLFOXIRI compared to FOLFIRI (Falcone 2013). So particularly in young, healthy patients who need downstaging prior to surgery, we use FOLFOXIRI.

Should patients receive chemotherapy before surgery, after surgery or both? We have no right answer. Patients with small tumors can go right to surgery followed by adjuvant therapy. We tend to administer chemotherapy before resection to patients with extrahepatic disease. For these patients, chemotherapy-associated steatohepatitis is a concern.

FOLFOXIRI can elicit high response rates in patients without extrahepatic disease who have tumors that are difficult to resect because they are large or are near a blood vessel. As far as the role of bevacizumab, it can be associated with complications like impaired wound healing when administered preoperatively. The current wisdom is to perform the surgery at least 6 to 8 weeks after bevacizumab administration. ■

4.3

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

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

Eligibility

- Locally advanced (unresectable) or metastatic colon or rectal cancer
- KRAS wild type
- No history of significant bleeding within the past 6 months unless the bleeding source has been resected
- No prior anti-VEGF or anti-EGFR therapy

R

- Oxaliplatin/5-FU/LV/bev or irinotecan/5-FU/bev
- Oxaliplatin/5-FU/LV/cet or irinotecan/5-FU/LV/cet
- Oxaliplatin/5-FU/LV/bev/cet or irinotecan/5-FU/LV/bev/cet

www.clinicaltrials.gov. Accessed May 2014.

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Douillard JY et al. **Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer.** *N Engl J Med* 2013;369(11):1023-34.

Falcone A et al. **FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group.** *Proc ASCO* 2013;**Abstract 3505**.

Primrose JN et al. **A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in KRAS wild-type patients with operable metastases from colorectal cancer: The new EPOC study.** *Proc ASCO* 2013;**Abstract 3504**.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **An ongoing Phase II study (NCT01298570) is evaluating regorafenib in combination with FOLFIRI as _____ for patients with mCRC.**
   a. First-line therapy
   b. Second-line therapy
   c. Late-line therapy

2. **The ongoing Phase II RECAP trial is evaluating treatment with capecitabine in combination with _____ or placebo for patients with recurrent or treatment-refractory mPC after failure of first-line gemcitabine for metastatic disease or an alternate first-line chemotherapy for those who are intolerant to or ineligible for gemcitabine as first-line therapy.**
   a. Ruxolitinib
   b. Brivanib
   c. *Nab* paclitaxel

3. **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 a statistically significant improvement in _____ with the addition of ramucirumab.**
   a. OS
   b. PFS
   c. Objective response rate
   d. All of the above

4. **An ongoing Phase II trial is evaluating temozolomide with or without _____ for patients with locally unresectable or metastatic low- or intermediate-grade pancreatic NET.**
   a. Capecitabine
   b. 5-fluorouracil
   c. Cisplatin

5. **The Phase II ECOG-E2212 trial will evaluate whether the addition of adjuvant _____ versus placebo to the R0 or R1 surgical resection of metastatic pancreatic NET to the liver will yield improvements in disease-free survival.**
   a. Ramucirumab
   b. Everolimus
   c. Etoposide
   d. Sunitinib

6. **_____ is an anti-angiogenic agent targeting VEGFR-2 and is currently undergoing investigation in combination with best supportive care in a Phase III trial comparing it to placebo/best supportive care as second-line therapy for patients with HCC after first-line therapy with sorafenib.**
   a. Ramucirumab
   b. Regorafenib
   c. Both a and b

7. **An analysis of patients with mCRC treated with regorafenib on the CORRECT trial demonstrated that the most common adverse events did not present until late in the course of therapy.**
   a. True
   b. False

8. **Adverse events associated with the long-term treatment of mPC with gemcitabine in combination with *nab* paclitaxel include_____.**
   a. Peripheral neuropathy
   b. Myelosuppression
   c. Fatigue
   d. All of the above

9. **The Phase III FIRE-3 study, which evaluated FOLFIRI in combination with either cetuximab or bevacizumab as first-line treatment for patients with KRAS wild-type mCRC, demonstrated a statistically significant difference in _____ in favor of the cetuximab arm in the intent-to-treat population.**
   a. Objective response rate
   b. PFS
   c. OS
   d. All of the above

10. **The randomized, Phase II PEAK study evaluating a modified regimen of FOLFOX6 in combination with panitumumab or bevacizumab demonstrated a statistically significant improvement in OS with panitumumab therapy for patients with previously untreated, unresectable mCRC harboring wild-type KRAS (exon 2).**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 1, 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 the REGARD trial of ramucirumab monotherapy and the RAINBOW trial of paclitaxel with or without ramucirumab for patients with metastatic gastric or GEJ cancer	4 3 2 1	4 3 2 1
RECAP: A Phase II trial of capecitabine with or without the selective oral JAK1 and JAK2 inhibitor ruxolitinib as second-line therapy for mPC	4 3 2 1	4 3 2 1
Efficacy of somatostatin analogs — octreotide and lanreotide — in NETs	4 3 2 1	4 3 2 1
Impact of performance status and age on the initial dosing of regorafenib for patients with mCRC	4 3 2 1	4 3 2 1
Efficacy and safety results across trials of 3 FDA-approved regimens for mPC: FOLFIRINOX versus gemcitabine versus gemcitabine/*nab* paclitaxel	4 3 2 1	4 3 2 1
Integration of expanded RAS analysis and implications for clinical decision-making for patients with mCRC	4 3 2 1	4 3 2 1

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 and RAF 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
- 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
- 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 systemic therapies for these patients. . . . . 4 3 2 1 N/M N/A
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular carcinoma. . . . . 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:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.

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

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
Richard M Goldberg, MD	4 3 2 1	4 3 2 1
Philip A Philip, MD, PhD	4 3 2 1	4 3 2 1
Pamela L Kunz, MD	4 3 2 1	4 3 2 1
J Randolph Hecht, 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:

.....

.....

.....

REQUEST FOR CREDIT — Please print clearly

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