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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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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 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 about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers, and consider adjuvant therapeutic options based on an evaluation of this information.
- 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 unresectable metastatic neuroendocrine tumors of the GI tract regarding novel treatment approaches and their associated risks and benefits.
- Evaluate therapeutic options — including surgery and the use of approved and novel kinase inhibitors — for patients with newly diagnosed gastrointestinal stromal tumors (GIST) and those with imatinib- and sunitinib-resistant GIST.
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular carcinoma.
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.

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INTERVIEW

Leonard B Saltz, MD

Dr Saltz is Attending Physician and Colorectal Disease Management Team Leader at Memorial Sloan-Kettering Cancer Center and Professor of Medicine at Weill Medical College of Cornell University in New York, New York.

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Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the recent clinical research developments in metastatic colorectal cancer (mCRC), specifically with regard to the CORRECT trial and regorafenib, given the agent's recent approval by the FDA in this setting?

DR SALTZ: Regorafenib is a molecule very similar to sorafenib. It's basically sorafenib with an additional fluorine atom. CORRECT was a large-scale, randomized Phase III trial in which patients were selected on the basis of having experienced disease progression on all standard therapy options — they had received oxaliplatin, irinotecan and a fluoropyrimidine, and those patients with K-ras wild-type disease had also exhausted anti-EGFR therapies. These are patients we see frequently in our practice who are still functioning at a high level and still have a reasonably good performance status with good end-organ function but unfortunately have run out of treatment options.

The median survival benefit was 1.4 months for the patient population receiving regorafenib as opposed to placebo (1.1). It's not a huge difference, but it was a statistically significant advantage and it invites discussion of what constitutes a clinically meaningful benefit. I would hope that using regorafenib in an earlier phase would be even more beneficial, but this is an agent with activity so it's exciting because that's new for us — we've been in the "doldrums" in colorectal cancer for approximately a decade.

1.1

CORRECT: A Phase III Trial of the Oral Multikinase Inhibitor 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[1]	6.4 mo	5.0 mo	0.79	0.0038
Median progression-free survival[2]	1.9 mo	1.7 mo	0.49	<0.000001
Disease control rate[2]	41.0%	14.9%	—	<0.000001

	Regorafenib + BSC (n = 500)		Placebo + BSC (n = 253)	
Select adverse events (AEs)[2]	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Hand-foot skin reaction	46.6%	16.6%	7.5%	0.4%
Fatigue	47.4%	9.6%	28.1%	5.1%
Hypertension	27.8%	7.2%	5.9%	0.8%
Diarrhea	33.8%	7.2%	8.3%	0.8%
Rash/desquamation	26.0%	5.8%	4.0%	0%
Mucositis, oral	27.2%	3.0%	3.6%	0%
AEs leading to permanent treatment discontinuation[3]	8.2%		1.2%	

* Standard therapies were required to include 5-FU, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if K-ras wild type).

[1] Van Cutsem E et al. *Proc ESMO* 2012;**Abstract LBA18**; [2] Van Cutsem E et al. *Proc ASCO* 2012;**Abstract 3502**; [3] Grothey A et al. Gastrointestinal Cancers Symposium 2012;**Abstract LBA385**.

Tracks 5-7

DR LOVE: What are your thoughts on the recent data from the TML study evaluating the continuation of bevacizumab beyond disease progression along with chemotherapy in mCRC?

DR SALTZ: In the TML trial, depending on which chemotherapy patients received in the first-line setting with bevacizumab, they were randomly assigned to an appropriate second-line regimen in combination with either bevacizumab or placebo. So if they had received an oxaliplatin-based regimen, they later received an irinotecan-based regimen and vice versa. The TML study also reported a 1.4-month survival benefit with continuation bevacizumab (Arnold 2012; [1.2]).

It's important to emphasize that this is not a validation of the BRiTE registry that reported on the use of bevacizumab beyond progression in clinical practice (Grothey 2008). In fact, I would interpret it as a refutation of the BRiTE registry results, which reported a 1-year median survival benefit. In TML the median survival benefit is

1.2

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 (Grade 3-5)	CT + bev (n = 401)	CT (n = 409)
Hypertension	2%	1%
Proteinuria	<1%	—
GI perforation	2%	<1%
Venous thromboembolism	5%	3%
Arterial thromboembolism	<1%	<1%
Wound-healing complications	<1%	<1%

Arnold D et al. *Proc ASCO* 2012;**Abstract CRA3503**.

approximately 6 weeks, so it's quite a different finding. I do believe that the data justify continued application of bevacizumab through multiple lines of therapy. The extrapolation is reasonable that continuation of anti-VEGF therapy provides a modest but statistically significant benefit. The data are reassuring that the downside to continuation bevacizumab appears to be modest.

This trial has changed my view of continuation bevacizumab because previously we didn't have data to support it. Now we have an appropriately powered, well-conducted randomized study that provides insight into the upsides and downsides.

DR LOVE: The other piece of the puzzle is the VELOUR study, which reported on the use in second-line treatment of FOLFIRI with the VEGF trap aflibercept and reported a survival advantage. How do you reconcile those data with the results of the TML trial?

DR SALTZ: It's an interesting parallel study and is a challenge to interpret. Aflibercept is difficult to differentiate from bevacizumab, and it's not a good idea to make cross-study comparisons. In this case it would raise concern with regard to increased toxicity with aflibercept compared to bevacizumab. We don't know whether that is real, but it's a cautionary flag to consider.

The VELOUR study is remarkably similar in outcome to the TML study. A weakness in the design of the VELOUR study is the variability as to whether the patients received front-line bevacizumab (Van Cutsem 2011; [1.3]). The focus of the recent ASCO presentation on VELOUR was to try to inform us on the issue of whether aflibercept has activity after disease progression on a bevacizumab-containing regimen (Allegra 2012; [1.4]).

The statistical analysis failed to show interaction that would definitively say it doesn't work, but it was also pointed out that the data don't directly say that it does work. From the interpretation of the data the possibility is reasonable, and if the TML bevacizumab study had not been presented we'd all be saying, "Okay, let's use bevacizumab and then the next chemotherapy with aflibercept." However, now we

have a problem. We have nothing to suggest that aflibercept by itself, any more than bevacizumab, has single-agent activity. In addition, we have nothing to suggest that either bevacizumab or aflibercept provides activity with inactive chemotherapy.

I don't know if aflibercept is a new therapeutic option, but it's creating a choice: If you administer first-line treatment with bevacizumab, do you want your second-line treatment with continuation bevacizumab or do you want second-line aflibercept? You have the benefit from the TML bevacizumab study and you have the benefit from the aflibercept study, but I'm not sure these trials are additive — I believe that a patient can receive treatment with one or the other, but I don't see a way to receive a benefit from both.

1.3

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

Survival	FOLFIRI + aflibercept (n = 614)	FOLFIRI + placebo (n = 612)	Hazard ratio	*p*-value
Median progression-free survival	6.9 mo	4.7 mo	0.76	0.00007
Median overall survival	13.5 mo	12.1 mo	0.82	0.0032

Van Cutsem E et al. World Congress on Gastrointestinal Cancer 2011;**Abstract O-0024**.

1.4

Effects of Prior Bevacizumab on Outcomes in the VELOUR Study

	Prior bevacizumab		No prior bevacizumab	
	Aflibercept + FOLFIRI	Placebo + FOLFIRI	Aflibercept + FOLFIRI	Placebo + FOLFIRI
Response rates	11.7%	8.4%	23.3%	12.4%
Overall survival	12.5 mo	11.7 mo	13.9 mo	12.4 mo
Progression-free survival	6.7 mo	3.9 mo	6.9 mo	5.4 mo
	Prior bevacizumab		**No prior bevacizumab**	
Select adverse events (Grade 3-4)	Aflibercept + FOLFIRI	Placebo + FOLFIRI	Aflibercept + FOLFIRI	Placebo + FOLFIRI
Proteinuria	9.4%	0.6%	7.3%	1.4%
Hypertension	16.4%	0.6%	20.5%	1.8%
Hemorrhage	3.5%	1.2%	2.7%	1.8%
Venous thromboembolic event Pulmonary embolism	7.0% 2.3%	5.8% 2.9%	8.2% 5.5%	6.5% 3.7%
Arterial thromboembolic event	1.8%	0.6%	1.8%	0.5%
GI perforation	0%	0%	0.7%	0.5%

Allegra C et al. *Proc ASCO* 2012;**Abstract 3505**.

Track 10

DR LOVE: What data came out of ASCO in terms of tissue testing for colon cancer in the adjuvant setting, and how is the clinical use of the Onco*type* DX Colon Cancer assay evolving?

DR SALTZ: I was encouraged to see a presentation in the poster session indicating that the NSABP is starting to evaluate Onco*type*'s potential to answer the question of who does not benefit from oxaliplatin-based therapy among patients with Stage II and Stage III disease (O'Connell 2012; [1.5]).

Considerable long-term neurotoxicity is associated with oxaliplatin. We don't want to miss an opportunity to help someone, but we also don't want to put someone in harm's way. It's clear that we're administering oxaliplatin to many patients who are experiencing long-term toxicities and might have been equally as well off without the exposure.

If we could be smart enough to use molecular signatures to identify a population for whom oxaliplatin doesn't provide benefit and offer those patients adjuvant therapy with only a fluoropyrimidine, which is less likely to cause serious and/or long-term toxicity, that would be a huge step forward. I hope we see positive results soon. ■

1.5

Validation of the Onco*type* DX Colon Cancer Recurrence Score (RS) in NSABP-C-07 as a Predictor of Recurrence in Patients with Stage II and Stage III Colon Cancer Treated with 5-FU/LV and 5-FU/LV with 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%

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

SELECT PUBLICATIONS

Allegra CJ et al. **Effects of prior bevacizumab (B) use on outcomes from the VELOUR study: A phase III study of aflibercept (Afl) and FOLFIRI in patients (pts) with metastatic colorectal cancer (mCRC) after failure of an oxaliplatin regimen.** *Proc ASCO* 2012;**Abstract 3505**.

Arnold D et al. **Bevacizumab (BEV) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with BEV plus CT: Results of a randomized phase III intergroup study (TML study).** *Proc ASCO* 2012;**Abstract CRA3503**.

Grothey A et al. **Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies.** Gastrointestinal Cancers Symposium 2012;**Abstract LBA385**.

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.

O'Connell M et al. **Validation of the 12-gene colon cancer recurrence score (RS) in NSABP C07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5FU/LV (FU) and 5FU/LV + oxaliplatin (FU + Ox).** *Proc ASCO* 2012;**Abstract 3512**.

Van Cutsem E et al. **Phase III CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC).** *Proc ASCO* 2012;**Abstract 3502**.

INTERVIEW

Suzanne George, MD

Dr George is Clinical Director at the Center for Sarcoma and Bone Oncology at Dana-Farber Cancer Institute and Assistant Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-16

Select Excerpts from the Interview

Tracks 6-7

DR LOVE: Would you summarize recent clinical trial results reported with regorafenib for patients with advanced gastrointestinal stromal tumors (GIST)?

DR GEORGE: Thirty-three patients received treatment on our Phase II trial evaluating regorafenib for patients with metastatic and/or unresectable GIST after disease progression on imatinib and sunitinib. The median progression-free survival (PFS) was 10 months (George 2012), which was a good hypothesis-generating PFS. The clinical benefit rate was 79%. Clinical benefit from regorafenib was noted in patients with

KIT wild-type GIST and those with mutations in exon 9 and 11 of KIT. The PFS for patients with exon 9 mutations was less than that for exon 11 mutations. With only 3 patients in the exon 9 group, it's difficult to draw any conclusions. Although dose modifications were required in approximately 80% of the patients, we did not observe any significant need to discontinue regorafenib as a result of toxicity.

Based on the data from the Phase II trial, the Phase III GRID trial evaluating regorafenib for patients with metastatic and/or unresectable GIST progressing despite prior treatment with at least imatinib and sunitinib was initiated. It was designed as a 2-to-1 randomization to regorafenib or placebo, respectively (Demetri 2012; [2.1]).

A significant improvement was reported in PFS with regorafenib, with a median PFS of approximately 5 months for regorafenib versus 0.9 months for placebo. Patients receiving the placebo were allowed to cross over to regorafenib at the time of disease progression. The PFS curves postcrossover indicated that disease control was equally as good as if the patient had initially received regorafenib. The overall survival data showed no difference between regorafenib and placebo, which was expected because of the crossover design.

We're hopeful that regorafenib will become available in this setting, and I believe its role will be in the third-line setting because that's where the current data were collected. A question that arises is whether we'll have an opportunity to test it earlier in the treatment algorithm. Some of the challenges with regorafenib, as with sunitinib,

2.1

GRID: Results from a Phase III Trial of Regorafenib for Metastatic and/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
Median overall survival*	Not reached	Not reached	0.77	0.199
Disease control rate	52.6%	9.1%	—	—

	Regorafenib (n = 132)		Placebo (n = 66)	
Select adverse events (AEs)	Any grade	Grade ≥3	Any grade	Grade ≥3
Hand-foot skin reaction	56.1%	19.7%	15.2%	1.5%
Hypertension	48.5%	23.5%	16.7%	3.0%
Diarrhea	40.9%	5.3%	7.6%	0%
Fatigue	38.6%	2.3%	27.3%	3%
Oral mucositis	37.9%	1.5%	9.1%	1.5%
Alopecia	23.5%	1.5%	3.0%	0%
Hoarseness	22.0%	0%	4.5%	0%
Treatment-emergent AE leading to permanent treatment discontinuation	6.1%		7.6%	

* Lack of statistical significance between regorafenib and placebo was expected due to the crossover design.

Demetri GD et al. *Proc ASCO* 2012;**Abstract LBA10008**.

are toxicity, dose-modification management and ensuring that the disease is well controlled and that patients are able to stay on treatment that is well tolerated for extended periods.

Tracks 11-13, 16

DR LOVE: Would you comment on the use of adjuvant imatinib therapy for patients with GIST?

DR GEORGE: Two large Phase III trials have investigated adjuvant imatinib therapy in GIST. The ACOSOG-Z9001 trial reported a recurrence-free survival benefit with 1 year of adjuvant imatinib versus placebo (Dematteo 2009). This study enrolled patients with tumors larger than 3 centimeters. No difference in overall survival was observed, but the follow-up period was short. In a subset analysis of data from the Z9001 study, patients with tumors larger than 10 centimeters experienced the greatest recurrence-free survival benefit, whereas those with smaller tumors had a much smaller differential in the curves.

The Scandinavian SSGXVIII/AIO study randomly assigned patients to either 1 or 3 years of adjuvant imatinib (Joensuu 2012; [2.2]). The trial included patients stratified as having high-risk disease using the modified NIH criteria. Patients who received treatment for 3 years experienced an overall survival benefit. In fact, this was the first study to report an overall survival benefit with adjuvant therapy for GIST. I believe it's important that we understand that patients with resected GIST may fall into the category considered to be at high risk, and these patients would potentially benefit from adjuvant therapy.

DR LOVE: What about patients at lower risk of recurrence?

2.2

SSGXVIII/AIO: A Randomized Phase III Clinical Trial of 12 versus 36 Months of Adjuvant Imatinib Therapy for Patients with High-Risk Gastrointestinal Stromal Tumors

Outcome	One-year arm (n = 198)	Three-year arm (n = 199)	Hazard ratio	*p*-value
Five-year RFS	47.9%	65.6%	0.46	<0.001
Five-year OS	81.7%	92.0%	0.45	0.02
	One-year arm (n = 194)		Three-year arm (n = 198)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Periorbital edema	59.3%	0.5%	74.2%	1.0%
Nausea	44.8%	1.5%	51.0%	0.5%
Diarrhea	43.8%	0.5%	54.0%	2.0%
Muscle cramps	30.9%	0.5%	49.0%	1.0%
Discontinued imatinib for reason other than GIST recurrence	12.6%		25.8%	

RFS = recurrence-free survival; OS = overall survival

Joensuu H et al. *JAMA* 2012;307(12):1265-72.

DR GEORGE: In the SSGXVIII study, approximately 25% of patients randomly assigned to the 3-year arm stopped treatment, not because of tumor recurrence but for some other reason, raising the issue of tolerance. Although imatinib is well tolerated, the discontinuation rate was nontrivial in that study. Toxicities such as fatigue, diarrhea and muscle cramping can be an issue. In general, it's difficult to justify extended therapy for patients at a low risk of recurrence.

The consensus from the United States and European groups is that consideration of adjuvant imatinib should be for patients with intermediate- and high-risk tumors. Although the FDA label is broad, patients with low-risk tumors should not receive adjuvant imatinib.

DR LOVE: Should patients at high risk have adjuvant imatinib therapy discontinued at 3 years?

DR GEORGE: These 2 trials consistently showed that patients fare well on adjuvant imatinib. When therapy is discontinued, patients continue to fare well for about 1 to 2 years before recurrence. The risk of recurrence tends to re-emerge the longer the patient is not receiving adjuvant therapy. Because we haven't seen a "plateau of curves" after adjuvant therapy is discontinued, the question of how long to continue therapy remains an issue.

DR LOVE: Have you administered adjuvant imatinib therapy for more than 3 years?

DR GEORGE: In my practice I have seen a couple of patients who underwent marginal resections of high-risk tumors at the outset, and I administered adjuvant imatinib for more than 3 years. In those cases I believed that the risk was not only a result of the characteristics of the tumor but also may have been further compounded by the way in which the surgery was performed due to the anatomy.

When initiating adjuvant therapy now, I usually aim for a 3-year duration because that's what the data show is most effective. Three years from now I will reassess the situation and consider what data are available.

A single-arm Phase II study of 5 years of imatinib for patients at high risk of recurrence recently completed accrual (NCT00867113). It will be interesting to see the outcome of this study. ■

SELECT PUBLICATIONS

Blay JY. **Management of imatinib-associated skin rash in a patient with metastatic gastrointestinal stromal tumor: A case report.** *Clin Sarcoma Res* 2012;2(1):23.

Dematteo RP et al. **Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: A randomised, double-blind, placebo-controlled trial.** *Lancet* 2009;373(9669):1097-104.

Demetri GD et al. **Randomized Phase III trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU): GRID trial.** *Proc ASCO* 2012;**Abstract LBA10008**.

Demetri GD. **Differential properties of current tyrosine kinase inhibitors in gastrointestinal stromal tumors.** *Semin Oncol* 2011;38(Suppl 1):10-9.

George S et al. **Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: A multicenter Phase II trial.** *J Clin Oncol* 2012;30(19):2401-7.

Joensuu H et al. **One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: A randomized trial.** *JAMA* 2012;307(12):1265-72.

INTERVIEW

Andrew X Zhu, MD, PhD

Dr Zhu is Director of Liver Cancer Research at Massachusetts General Hospital Cancer Center and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-7

Track 1 Critical assessment of local treatment modalities in hepatocellular carcinoma (HCC): Resection, transplantation or radiofrequency ablation

Track 2 Therapeutic interventional strategies based on differential blood flow of HCC versus normal liver

Track 3 TACE with or without sorafenib for patients with HCC and extrahepatic metastases

Track 4 Identification of patients with advanced Child-Pugh B HCC who may benefit from sorafenib

Track 5 Evaluation of performance status, hepatic function and age when considering initial and subsequent dosing of sorafenib for patients with advanced HCC

Track 6 Management of sorafenib-associated hand-foot syndrome

Track 7 Heterogeneity of biliary tract cancers and opportunities for development of novel treatments

Select Excerpts from the Interview

Track 1

DR LOVE: What curative treatment modalities should a physician consider when evaluating a patient with newly diagnosed hepatocellular carcinoma (HCC)?

DR ZHU: The key options that a medical oncologist should carefully assess when first evaluating a patient with HCC are surgical resection, liver transplant or local ablative therapy, particularly radiofrequency ablation, which can be curative in this setting.

If you diagnose HCC at an early stage, outcomes are overwhelmingly good, within the neighborhood of 70% to 80% survival at 5 years. This is in contrast to some of the aggressive tumors that we as GI medical oncologists deal with, for example, pancreatic cancer. Therefore, I always make a strong point to evaluate patients with HCC for definitive treatment.

Tracks 4-6

DR LOVE: Would you discuss the role of systemic therapies like sorafenib for patients with HCC who have Child-Pugh B and Child-Pugh C disease?

DR ZHU: A large number of patients with HCC present with underlying Child-Pugh B or C cirrhosis. Patients with Child-Pugh C disease should not receive systemic

therapies such as sorafenib. The best option for these patients with severe underlying cirrhosis is careful follow-up with a hepatologist. Cirrhosis-related complications need to be appropriately managed to ensure the control of ascites and to prevent encephalopathy and severe upper GI bleeding.

It's important to consider that not all Child-Pugh B disease is the same. The Child-Pugh classification is a rough estimate of the underlying hepatic function. But we know from extensive clinical experience that sorafenib can be safely administered to patients with Child-Pugh B disease, particularly if they have a B7 Barcelona Clinic Liver Cancer staging score. When sorafenib is administered to this population, duration of treatment and time to tumor progression are shorter compared to the benefits exhibited in patients with Child-Pugh A disease. Although patients with Child-Pugh B disease derive some benefit with sorafenib, the duration of benefit tends to be shorter.

DR LOVE: What dosing regimen of sorafenib do you follow for patients with HCC?

DR ZHU: The dose of sorafenib in patients with HCC remains controversial. Two pivotal Phase III studies, the SHARP trial and another study conducted in the Asian-Pacific region, evaluated the 400-mg dose twice daily and demonstrated that sorafenib improved overall survival compared to placebo (Llovet 2008; Cheng 2009).

Many community oncologists administer half that dose, either 200 mg twice daily or 400 mg daily (Venook 2011). If patients tolerate the drug at a reduced dose, then it can be gradually escalated to the full dose. I only use that strategy for patients with borderline performance status or those with Child-Pugh B disease. This avoids some of the toxicities associated with sorafenib that could potentially lead to its discontinuation. If the patient is young, has a good performance status and has compensated hepatic function, the standard 400-mg, twice-daily dose can be administered.

Currently we have no data to determine which dosing regimen is better tolerated and would lead to a longer time on treatment or time-to-tumor progression. I suggest that community oncologists assess the patient's performance status and the underlying hepatic function to determine the dosing regimen for sorafenib.

DR LOVE: Would you recommend the full dose of sorafenib for an elderly patient who has a robust performance status and good liver function?

DR ZHU: I would not discriminate based on the patient's age alone. I would use my earlier criteria and would consider the full dose if the patient's performance status was robust.

DR LOVE: What are your thoughts on the recent ASCO presentation (Ren 2012; [3.1]) on the use of a urea-based cream to treat the hand-foot skin reaction associated with sorafenib in patients with advanced HCC?

DR ZHU: Many strategies have been employed to manage sorafenib-associated skin toxicity. We have used the urea-containing cream in our practice. This study definitely has its merits, but I don't believe that the open-label study design was the best approach to determine whether a urea-based cream could decrease the skin toxicity associated with sorafenib. We need additional studies to definitively address this issue.

DR LOVE: Do you use any strategies preemptively to prevent hand-foot skin reaction?

DR ZHU: I always encourage patients to moisturize their skin carefully. Particular attention should be given to the palms of the hands and soles of the feet because the hand-

foot skin reaction tends to occur early and with more severity in those areas. Beyond that I do not currently use pharmacological intervention as a preventive strategy for the hand-foot syndrome associated with sorafenib. ■

3.1

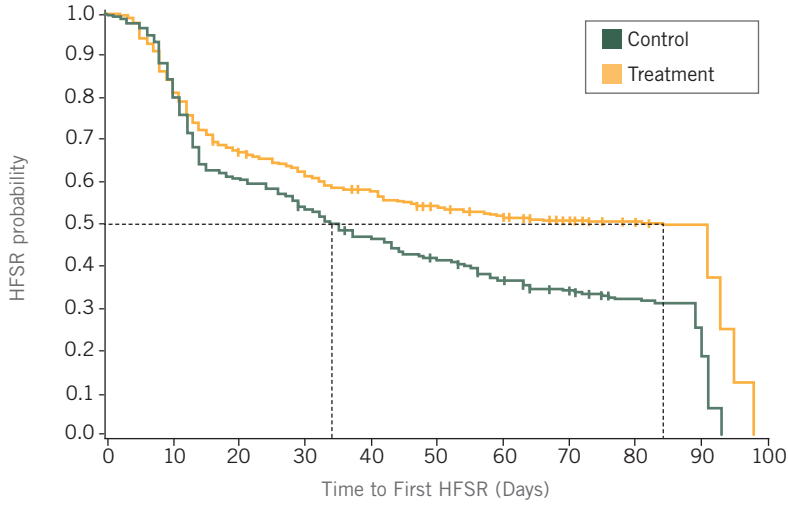
Randomized Phase II Study of the Prophylactic Effect of Urea-Based Cream on the Hand-Foot Skin Reaction (HFSR) Associated with Sorafenib in Advanced Hepatocellular Carcinoma

Primary endpoint: Incidence of all-grade HFSR

Grade of HFSR	Urea cream + BSC (n = 439)	BSC (n = 432)	*p*-value
All grades	56.0%	73.6%	<0.0001
Grade 2 or 3	20.7%	29.2%	0.004

Secondary endpoints include time to first HFSR event

The median time to first HFSR event was 2.5 times as long in the urea cream + BSC arm (n = 354) as in the BSC arm (n = 345) (84 days versus 34 days; $p < 0.0001$).



BSC = best supportive care

With permission from Ren Z et al. *Proc ASCO* 2012;**Abstract 4008**.

SELECT PUBLICATIONS

Cheng A et al. **Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial.** *Lancet Oncol* 2009;10(1):25-34.

Llovet JM et al. **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med* 2008;359(4):378-90.

Ren Z et al. **A randomized controlled phase II study of the prophylactic effect of urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced hepatocellular carcinoma.** *Proc ASCO* 2012;**Abstract 4008**.

Venook A et al. **First interim results of the global investigation of therapeutic decisions in hepatocellular carcinoma (HCC) and of its treatment with sorafenib (GIDEON) study: Use of sorafenib (Sor) by oncologists and nononcologists in the management of HCC.** Gastrointestinal Cancers Symposium 2011;**Abstract 157**.

INTERVIEW

Richard M Goldberg, MD

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

Tracks 1-12

Select Excerpts from the Interview

Track 1

DR LOVE: Would you provide your perspective on the role, if any, of the Onco*type* DX Colon Cancer assay in the management of Stage II disease?

DR GOLDBERG: We are observing better outcomes for patients with Stage II colon cancer based on improved surgical techniques and earlier screening. So now, even for untreated patients, we're seeing a 5-year survival rate of approximately 90%.

I believe that the Onco*type* DX assay and similar tests such as ColoPrint® and others have contributed somewhat to this. The Onco*type* DX Colon Cancer assay provides a Recurrence Score based on 7 cancer-related genes that can complement tumor stage and mismatch repair status in the assessment of a patient's risk. Unlike the Onco*type* DX assay for patients with breast cancer, which is both prognostic and predictive, the colon cancer assay is only prognostic.

I occasionally order the assay in my practice. My reflex for patients with Stage II disease is to tell them that I don't believe they need chemotherapy, but I do advise them of the QUASAR data, which reported a 3.6% improvement in 5-year survival for patients with Stage II colon cancer treated with chemotherapy versus surgery alone (QUASAR Collaborative Group 2007).

If patients strongly desire chemotherapy, I ask them, "If your Recurrence Score predicts that you have a 9% recurrence risk versus a 25% recurrence risk, will that make a difference to you in whether you take treatment or not?" If they reply yes, then I order the test (Gray 2011; [4.1]).

4.1

QUASAR/Oncotype DX Results: Assessment of Recurrence Risk for Patients with Stage II Colon Cancer

Recurrence risk group	Range of Recurrence Score	Surgery alone (proportion of patients)	Kaplan-Meier estimate of of recurrence risk at 3 years with surgery alone
Low (n = 311)	<30	43.7%	12%
Intermediate (n = 218)	30-40	30.7%	18%
High (n = 182)	≥41	25.6%	22%

Methods: Study analyzed relationship between the Recurrence Score (RS) and risk of recurrence in patients treated with surgery alone and between Treatment Score (TS) and benefits of adjuvant fluoropyrimidine chemotherapy.

Conclusions: The continuous 12-gene RS has been validated in a prospective study for assessment of recurrence risk in patients with Stage II colon cancer after surgery and provides prognostic value that complements T stage and MMR. The TS was not predictive of chemotherapy benefit.

Gray RG et al. *J Clin Oncol* 2011;29(35):4611-9.

Track 5

DR LOVE: What are your thoughts on the use of FOLFIRINOX in the systemic management of pancreatic cancer?

DR GOLDBERG: A study that was published last year investigating the use of FOLFIRINOX versus gemcitabine in pancreatic cancer demonstrated a median overall survival of approximately 1 year with FOLFIRINOX (Conroy 2011; [4.2]). The FOLFIRINOX regimen is intensive, and not every patient can tolerate it. The dose has to be adjusted for certain patients, but at least it is a step forward. Those of us who have experience with this regimen have been pleased with the tolerance and the response rate.

I administer FOLFIRINOX in practice, although the patients I see are often older, with comorbidities and a performance score of 2, so I'm not so enthusiastic. I give younger patients with metastatic disease and a performance score of 0 the option of receiving the more aggressive FOLFIRINOX regimen. I also tell patients that they could receive gemcitabine, which is easier to tolerate and has less toxicity but a modest response rate. I let the patient participate in the decision-making regarding which chemotherapy to use. ■

4.2

Efficacy of FOLFIRINOX versus Gemcitabine in a Phase II/III Study of Initial Therapy for Metastatic Pancreatic Cancer

	Gemcitabine (n = 171)	FOLFIRINOX (n = 171)	Hazard ratio	*p*-value
ORR	9.4%	31.6%	Not reported	<0.001
PFS	3.3 mo	6.4 mo	0.47	<0.001
OS	6.8 mo	11.1 mo	0.57	<0.001

Select Grade ≥3 adverse events occurring in >5% of patients

Adverse events	Gemcitabine (n = 171)	FOLFIRINOX (n = 171)	*p*-value
Neutropenia	21.0%	45.7%	<0.001
Febrile neutropenia	1.2%	5.4%	0.03
Thrombocytopenia	3.6%	9.1%	0.04
Diarrhea	1.8%	12.7%	<0.001
Sensory neuropathy	0%	9.0%	<0.001

Conclusions:

- FOLFIRINOX was associated with a survival advantage and had more toxicity compared to gemcitabine.
- FOLFIRINOX is an option for patients with metastatic pancreatic cancer and good performance status.

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

Conroy T et al. *N Engl J Med* 2011;364(19):1817-25.

SELECT PUBLICATIONS

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

Gray RG et al. **Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer.** *J Clin Oncol* 2011;29(35):4611-9.

Innocenti F et al. **A genome-wide association study of overall survival in pancreatic cancer patients treated with gemcitabine in CALGB 80303.** *Clin Cancer Res* 2012;18(2):577-84.

Lorgis V et al. **Influence of localization of primary tumor on effectiveness of 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) in patients with metastatic pancreatic adenocarcinoma: A retrospective study.** *Anticancer Res* 2012;32(9):4125-30.

Mahaseth H et al. **Safety and efficacy of modified FOLFIRINOX in pancreatic cancer: A retrospective experience.** *Proc ASCO* 2012;**Abstract e14614**.

Marshall JL. **Risk assessment in Stage II colorectal cancer.** *Oncology (Williston Park)* 2010;24 (1 Suppl 1):9-13.

O'Connell M et al. **Validation of the 12-gene colon cancer recurrence score (RS) in NSABP C07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5FU/LV (FU) and 5FU/LV + oxaliplatin (FU + Ox).** *Proc ASCO* 2012;**Abstract 3512**.

O'Connell MJ et al. **Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin.** *J Clin Oncol* 2010;28(25):3937-44.

QUASAR Collaborative Group. **Adjuvant chemotherapy versus observation in patients with colorectal cancer: A randomized study.** *Lancet* 2007;370(9604):2020-29.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III CORRECT trial of regorafenib in combination with best supportive care versus placebo for patients with mCRC who experience disease progression on standard therapy reported statistically significant improvements in _____ for patients who received regorafenib.**
   a. Median PFS
   b. Median overall survival
   c. Disease control rate
   d. All of the above

2. **The Phase III TML trial evaluating the addition of _____ to crossover fluoropyrimidine chemotherapy for patients with mCRC whose disease progressed while receiving first-line chemotherapy/bevacizumab indicated a 1.4-month improvement in median overall survival for patients who received treatment with bevacizumab beyond disease progression.**
   a. Aflibercept
   b. Bevacizumab
   c. Cetuximab

3. **Results from the Phase III VELOUR trial indicate that the addition of aflibercept to FOLFIRI chemotherapy is associated with increased PFS and overall survival compared to treatment with FOLFIRI alone as second-line therapy for patients with mCRC.**
   a. True
   b. False

4. **Data presented at the 2012 American Society of Clinical Oncology meeting evaluating patients who received 5-FU/LV versus 5-FU/LV and oxaliplatin on the NSABP-C-07 trial suggest that the Onco*type* DX Colon Cancer Recurrence Score was validated as a predictor of recurrence risk for patients with Stage II and Stage III colon cancer.**
   a. True
   b. False

5. **A Phase II trial of regorafenib for patients with metastatic and/or unresectable GIST after failure of imatinib and sunitinib demonstrated significant clinical benefit from regorafenib.**
   a. True
   b. False

6. **The Phase III SSGXVIII/AIO trial of 12 months versus 36 months of adjuvant imatinib therapy for patients with high-risk GIST reported a statistically significant improvement in 5-year overall survival with 36 months of imatinib therapy.**
   a. True
   b. False

7. **The randomized Phase III GRID trial of regorafenib for patients with metastatic and/or unresectable GIST progressing despite prior treatment with imatinib and sunitinib demonstrated statistically significant improvement in _____ for patients who received regorafenib.**
   a. Median PFS
   b. Median overall survival
   c. Both a and b

8. **An ongoing single-arm Phase II trial for patients at significant risk for tumor recurrence after complete resection of primary GIST is evaluating adjuvant imatinib therapy for _____.**
   a. One year
   b. Three years
   c. Five years
   d. Eight years

9. **A randomized Phase II study on the prophylactic effect of a urea-based cream on the hand-foot skin reaction associated with sorafenib demonstrated that the cream significantly reduced the incidence of all-grade hand-foot skin reaction versus placebo for patients with advanced HCC.**
   a. True
   b. False

10. **A Phase II/III study for patients with metastatic pancreatic cancer demonstrated that FOLFIRINOX was associated with a significant survival advantage but had more toxicity compared to gemcitabine.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 2, 2012

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
TML study of bevacizumab beyond first progression and VELOUR study of FOLFIRI/aflibercept in mCRC	4 3 2 1	4 3 2 1
Results of Phase III studies of regorafenib for patients with mCRC whose disease has progressed after standard therapies (CORRECT trial) or those with metastatic and/or unresectable GIST progressing despite prior treatment with at least imatinib and sunitinib (GRID trial)	4 3 2 1	4 3 2 1
Data supporting the utility of molecular markers (Onco*type* DX, ColoPrint) in guiding treatment planning for patients with Stage II colon cancer	4 3 2 1	4 3 2 1
Relative toxicity and side effects of FOLFIRINOX versus gemcitabine in the treatment of advanced pancreatic cancer	4 3 2 1	4 3 2 1
Management of sorafenib-related hand-foot skin reaction in advanced HCC	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:

- Counsel patients with Stage II colon cancer about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers, and consider adjuvant therapeutic options based on an evaluation of this information..... 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 unresectable metastatic neuroendocrine tumors of the GI tract regarding novel treatment approaches and their associated risks and benefits..... 4 3 2 1 N/M N/A
- Evaluate therapeutic options — including surgery and the use of approved and novel kinase inhibitors — for patients with newly diagnosed gastrointestinal stromal tumors (GIST) and those with imatinib- and sunitinib-resistant GIST..... 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
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials..... 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

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
Leonard B Saltz, MD	4 3 2 1	4 3 2 1
Suzanne George, MD	4 3 2 1	4 3 2 1
Andrew X Zhu, MD, PhD	4 3 2 1	4 3 2 1
Richard M Goldberg, 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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