INTERVIEW

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Select Excerpts from the Interview

CD 1, 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**.

CD 1, 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

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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**.

CD 1, 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**.