INTERVIEW

David J Kerr, CBE, MA, MD, DSc

Dr Kerr is Professor of Cancer Medicine at the University of Oxford in Oxford, United Kingdom.

Tracks 1-13

Select Excerpts from the Interview

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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 KERR: We work closely with Norman Wolmark, and we codeveloped and validated the Onco*type* DX test with the NSABP. It does appear that when we evaluate patients with Stage III colon cancer, the Onco*type* DX assay provides useful discriminatory information (Yothers 2013; [1.1]).

It's not classically predictive, so it doesn't allow us to identify those patients who will be more or less responsive to a fluoropyrimidine. However, the huge advantage Onco*type* DX holds is that it can be delivered from paraffin-embedded tissue rather than from fresh or frozen tissue. I believe the Onco*type* DX assay is a beautiful piece of translational science.

1.1 **Validation of the Onco*type* DX 12-Gene Colon Cancer Recurrence Score (RS) in the Phase III NSABP-C-07 Study as a Predictor of Recurrence in Patients with Stage II and III Colon Cancer Treated with 5-FU/Leucovorin with or without Oxaliplatin**

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

Conclusions: "The 12-gene Recurrence Score predicts recurrence risk in stage II and stage III colon cancer and provides additional information beyond conventional clinical and pathologic factors. Incorporating Recurrence Score into the clinical context may better inform adjuvant therapy decisions in stage III as well as stage II colon cancer."

Yothers G et al. *J Clin Oncol* 2013;[Epub ahead of print].

This group of investigators are utterly committed to validating their gene signatures to the highest level. And the more we understand about the biology of cancer, the better the care we can provide for our patients.

DR LOVE: What are your thoughts on the recently published report of a subanalysis of elderly patients and patients with Stage II colon cancer treated on the adjuvant MOSAIC trial of 5-FU in combination with leucovorin with or without oxaliplatin (Tournigand 2012)?

DR KERR: When they updated these results, no benefits were reported in high-risk Stage II colon cancer. So I agree with Robert Mayer that we cannot recommend the use of oxaliplatin in Stage II disease (Mayer 2012; Midgley 2013). We have no discriminates now that would allow us to define a group of patients who would experience any benefits whatsoever.

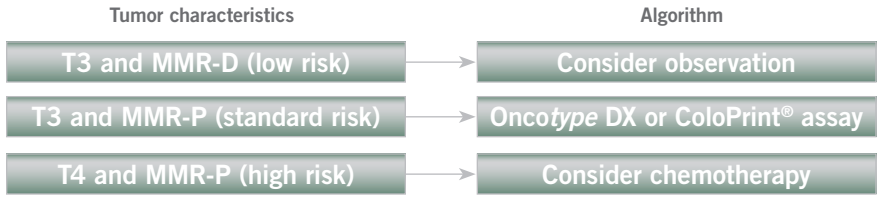
DR LOVE: Would you discuss the treatment algorithm you outlined in a recent publication (Kerr 2013; [1.2]) in terms of individualizing adjuvant therapy for patients with Stage II colon cancer?

DR KERR: We believe that with the degree of evidentiary support for the Onco*type* DX assay, a role exists for it in modern molecular pathology. When we performed a careful pathological review of all the specimens we'd collected from the QUASAR trial and conducted tight multivariate modeling with the Onco*type* DX assay against all these old pathologic variables — degree of differentiation, T3 versus T4 tumor staging, vascular and lymphatic invasion, et cetera — they all fell out at the bottom of the model. The factors that remained were Onco*type* DX Recurrence Score, T4 and MSI status. So for us in our new model, those were the 3 variables we believe we must take account of.

So with regard to the treatment of Stage II disease, in a patient with T4 status we'd be more inclined to offer chemotherapy. For patients whose tumors were MMR deficient,

1.2

Dr Kerr's Molecular Prognostic and Pathologic Algorithm for the Treatment of Resected Stage II Colon Cancer



T = tumor; MMR-D = mismatch repair deficient; MMR-P = mismatch repair proficient

Personal communication with David J Kerr, CBE, MA, MD, DSc August 2013; Kerr DJ, Shi Y. *Nat Rev Clin Oncol* 2013;10(8):429-30.

we'd be inclined to not offer chemotherapy because their 5-year survival rate will be around 90%. I don't believe we can do much better than that with chemotherapy.

In the middle, for the approximately 75% of patients who have T3 tumors that are MMR proficient, rather than deficient, then I believe something like Onco*type* DX, possibly an assay like ColoPrint, would offer useful additional information that would allow the treating physician and the patient to move toward saying, "I'm going to stick with surgery alone" or "I'm going to place my bets on more chemotherapy." It's a simple algorithm, but it's one that we're using in our hospital.

Track 5

DR LOVE: The 5-year follow-up data from the NSABP-C-08 trial were recently published and confirmed the initial findings that, even though there was a transient effect on disease-free survival, bevacizumab for 1 year with modified FOLFOX6 did not significantly prolong disease-free or overall survival in Stage II/III colon cancer (Allegra 2013). What are your thoughts on the role now of bevacizumab, if any, in this setting?

DR KERR: The adjuvant bevacizumab story in colon cancer appeared to be over after these results were originally presented. However, the trial did produce the observation that bevacizumab could be delivered safely in this setting (Allegra 2013; [1.3]), and we have now completed a large Phase III adjuvant trial called QUASAR 2 that is evaluating capecitabine alone versus capecitabine in combination with bevacizumab in Stage II and Stage III colon cancer.

This trial is a genome-wide association study, and we have identified a number of germline markers of toxicity for capecitabine. So I believe we have a relatively simple genetic test that will allow us to identify a priori those patients most at risk for Grade III and Grade IV toxicity.

We expect to have these data ready for next year's ASCO or ESMO meeting, so we'll see what the data show. I know that Norman Wolmark was keen to evaluate administering bevacizumab for a couple of years rather than for 1 year, and I believe some of these ideas are interesting — whether we end up pursuing those further with bevacizumab or with aflibercept.

1.3

Bevacizumab (Bev) in Stage II and III Colon Cancer: 5-Year Update of the Phase III NSABP-C-08 Trial Results

Efficacy	mFOLFOX6	mFOLFOX6 + bev	Hazard ratio	*p*-value
3-y DFS*	75.1%	77.9%	0.93	0.35
5-y overall survival	80.7%	82.5%	0.95	0.56
Select adverse events†	**mFOLFOX6**		**mFOLFOX6 + bev**	
Hypertension	0.6%		0.7%	
Pain	1.1%		1.1%	
Proteinuria	0.1%		0%	
ATE	0.1%		0.5%	
VTE	0.4%		0.2%	
Hemorrhage	0.3%		0.3%	

Conclusion: Bevacizumab for 1 year with modified FOLFOX6 does not significantly prolong DFS or OS in Stage II-III colon cancer. We observed no evidence of a detrimental effect of exposure to bevacizumab. A transient effect on disease-free survival was observed during bevacizumab exposure in the study's experimental arm.

* Exploratory analyses found that the effect of bevacizumab on DFS was different before and after a 1.25-year landmark (time-by-treatment interaction $p = 0.0001$). HR before the 15-month landmark strongly favored bevacizumab (HR, 0.61; $p = 0.0001$), whereas this benefit was entirely lost subsequently (HR, 1.19; $p = 0.059$).

† Grade ≥3 toxicities generally associated with bevacizumab during the 9-month period beginning 3 months after completion of all therapy

mFOLFOX6 = modified FOLFOX6; DFS = disease-free survival; ATE = arterial thrombotic event; VTE = venous thrombotic event

Allegra CJ et al. *J Clin Oncol* 2013;31(3):359-64.

We know that 80% of recurrences of colorectal cancer occur within the first 3 years after surgery. If we could lay down some "anti-angiogenic cover" during those 3 years, perhaps we'd be talking a different ballgame then. ■

SELECT PUBLICATIONS

Allegra CJ et al. **Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial.** *J Clin Oncol* 2013;31(3):359-64.

Kerr DJ, Shi Y. **Biological markers: Tailoring treatment and trials to prognosis.** *Nat Rev Clin Oncol* 2013;10(8):429-30.

Mayer RJ. **Oxaliplatin as part of adjuvant therapy for colon cancer: More complicated than once thought.** *J Clin Oncol* 2012;30(27):3325-7.

Midgley RS, Kerr DJ. **Adjuvant chemotherapy for stage II colon cancer: Less complicated than we thought.** *J Clin Oncol* 2013;31(12):1611.

O'Connell MJ et al. **Validation of the 12-gene colon cancer Recurrence Score result in NSABP C-07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5FU/LV (5FU) and 5FU/LV + oxaliplatin (5FU+Ox).** *Proc ASCO* 2012;**Abstract 3512**.

Tournigand C et al. **Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: Subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial.** *J Clin Oncol* 2012;30(27):3353-60.

Yothers G et al. **Validation of the 12-gene colon cancer Recurrence Score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin.** *J Clin Oncol* 2013;[Epub ahead of print].