INTERVIEW

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Track 1

DR LOVE: Would you discuss your treatment decision-making process when considering adjuvant therapy for a patient with Stage II colon cancer?

DR ARNOLD: Without chemotherapy, a subset of patients with Stage II disease have a worse prognosis than those with Stage III disease, whereas another group of patients with Stage II disease have a high likelihood of being cured.

The tools we currently have to help identify these patient groups are clinical risk factors and molecular information from single markers and complex gene arrays. The problem is that the information we obtain from clinical and molecular markers is only prognostic. We need predictive markers to inform us about which patients might benefit from a distinct treatment.

The Onco*type* DX assay provides additional information in terms of predicting the patient's prognosis with surgery alone. However, it tells us nothing about the relative benefit of 5-FU treatment (Gray 2011; [4.1]).

DR LOVE: I understand that no genomic assay is currently available in the colon cancer setting that can identify a group of patients with greater or lesser relative risk reduction as the Onco*type* DX assay does in patients with ER-positive, HER2-negative breast cancer. But if you evaluate the results of the article recently published in the *Journal of Clinical Oncology* analyzing the QUASAR trial of single-agent 5-FU versus surgery alone, it appears that the relative risk reduction with chemotherapy in the various risk categories is about the same. Thus you can attain a quantitative projected absolute benefit, although it's a fairly narrow range (Gray 2011).

DR ARNOLD: It is, and I believe this holds true. The relative risk reduction allows you to calculate an absolute risk reduction. I agree with the accompanying editorial in which Dr Al Benson recommends using the Onco*type* DX assay in patients who have adverse clinical pathologic factors (Benson 2011).

DR LOVE: Outside a research setting, how do you treat Stage II disease?

DR ARNOLD: My decision is based on clinical information. Only a small percentage of patients who are at a high clinical risk of recurrence should receive an oxaliplatin-based combination because of the lack of benefit and adverse effects of oxaliplatin. 5-FU as a single agent or capecitabine should be considered for other patients.

Once the patient is at a certain intermediate risk — when the tumor is well differentiated — we consider treating with 5-FU. The patients are informed that the absolute benefit of a 5-FU-based treatment will be between 3% and 7%.

If all the patient wants to know is if his or her risk level is at 3% or at 7%, I would consider ordering a genomic assay. This area is becoming more complicated, however. We primarily order the Onco*type* DX assay, but there is also ColoPrint and another test called Predictor-C, which was reported at ASCO last year (Adams 2011; Tan 2011).

4.1

QUASAR/Onco*type* 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.

DR LOVE: If you opt to administer a fluoropyrimidine, how do you decide between 5-FU and capecitabine?

DR ARNOLD: In patients who have no contraindications we administer capecitabine. In younger patients we do everything to achieve a cure and the acceptance of 5-FU-based treatment is higher. Oxaliplatin may also be an option for younger patients, but its long-term toxicity must be considered.

Track 4

DR LOVE: What is currently known about K-ras testing, and which patients might benefit from an EGFR antibody?

DR ARNOLD: K-ras testing is standard for decision-making regarding first-line treatment. K-ras mutation is a predictive marker for not using an EGFR antibody. Initial decision-making should be based on the clinical situation and depends on the intensity of treatment needed. FOLFIRI/cetuximab has a higher intensity and higher response rate and is the standard approach for patients in need of a high response rate. For the majority of asymptomatic patients FOLFOX and bevacizumab are alternatives. The aim is to prolong progression-free survival and to prevent unnecessary toxicity.

Analyses of data from the CRYSTAL and the OPUS trials report that patients with the K-ras G13D mutation might benefit from treatment with an EGFR antibody (Tejpar 2011; [4.2]). Because these are retrospective studies, one should be cautious. The only situation in which I would consider an EGFR antibody is for patients with the K-ras G13D mutation whose disease is progressing after treatment with FOLFIRI.

4.2 **Influence of K-ras G13D Mutations on Outcomes in Patients with Metastatic Colorectal Cancer Treated with First-Line Chemotherapy (CT) with and without Cetuximab (Cet)**

	N	Response (%)		PFS (mo)		OS (mo)	
		CT	CT + Cet	CT	CT + Cet	CT	CT + Cet
K-ras wild type	845	38.5	57.3	7.6	9.6	19.5	23.5
Odds ratio/HR *p*-value		2.17 <0.0001		0.66 <0.0001		0.81 0.0063	
K-ras G13D	83	22.0	40.5	6.0	7.4	14.7	15.4
Odds ratio/HR *p*-value		2.41 0.0748		0.60 0.1037		0.80 0.37	
K-ras other mutations	450	43.8	30.5	8.5	6.4	17.7	15.5
Odds ratio/HR *p*-value		0.56 0.0037		1.42 0.0069		1.14 0.1964	

PFS = progression-free survival; OS = overall survival; HR = hazard ratio

Tejpar S et al. *Proc ASCO* 2011;**Abstract 3511**.

Track 6

DR LOVE: Do you ever use biologic agents along with chemotherapy in the neoadjuvant setting for patients with potentially resectable liver-only metastases?

DR ARNOLD: Patients with clearly resectable liver metastases have the best prognosis, with a 5-year survival rate of 25% to 37% (Adson 1984; Fong 1999). Targeted agents or combination chemotherapy could be a consideration, especially in the preoperative setting.

However, most patients with resectable metastases are not receiving treatment preoperatively but in the adjuvant setting, and we do not know if these agents provide benefit in that setting. Disappointing results from Stage III trials leave me skeptical about bevacizumab and cetuximab.

DR LOVE: Outside a research setting, do you treat resectable liver metastases preoperatively?

DR ARNOLD: I treat most of these cases preoperatively. The exceptions are patients with 1 or 2 small liver metastases. If you can get good access with surgery, I would proceed with surgery first. In patients with 2 or more metastases or with large metastases that might make surgery difficult, I would consider preoperative treatment.

I offer most patients FOLFOX with or without bevacizumab, depending on the size of the tumor. If the tumor is clearly resectable, we limit treatment to chemotherapy to avoid unnecessary toxicity.

DR LOVE: What is your treatment approach when a patient's disease is borderline resectable and your goal is to "convert" the patient to being eligible for resection?

DR ARNOLD: Patients in this setting with K-ras wild-type disease are ideal candidates for EGFR-based treatment with either FOLFOX/panitumumab or FOLFIRI/cetuximab.

DR LOVE: How would you compare chemotherapy with bevacizumab to chemotherapy with panitumumab in patients with K-ras wild-type tumors?

DR ARNOLD: Response rates and tumor shrinkage are greater with the panitumumab regimen. An interesting trial from the EORTC will evaluate the efficacy of FOLFOX alone, FOLFOX in combination with bevacizumab and FOLFOX in combination with panitumumab as perioperative treatment for patients with resectable liver metastases from K-ras wild-type CRC (NCT01508000). This trial will shed light on the biologic activity of these agents in patients with metastases to the liver. ■

SELECT PUBLICATIONS

Adams H et al. **Independent validation of a prognostic classifier (Predictor-C) in a set of 292 patients with colorectal cancer of UICC stage II.** *Proc ASCO* 2011;**Abstract 3558**.

Adson MA et al. **Resection of hepatic metastases from colorectal cancer.** *Arch Surg* 1984;119(6):647-51.

Benson AB et al. **Path toward prognostication and prediction: An evolving matrix.** *J Clin Oncol* 2011;29(35):4599-601.

Fong Y et al. **Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases.** *Ann Surg* 1999;230(3):309-18.

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.

Tan IB et al. **Genetics: An 18-gene signature (ColoPrint®) for colon cancer prognosis.** *Nat Rev Clin Oncol* 2011;8(3):131-3.

Tejpar S et al. **Influence of KRAS G13D mutations on outcome in patients with metastatic colorectal cancer (mCRC) treated with first-line chemotherapy with or without cetuximab.** *Proc ASCO* 2011;**Abstract 3511**.