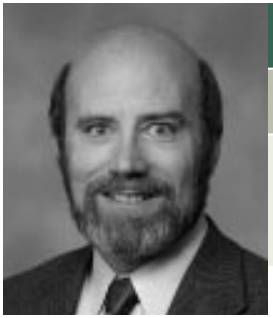


INTERVIEW

Steven R Alberts, MD

Dr Alberts is Professor of Oncology at the Mayo Clinic College of Medicine in Rochester, Minnesota.

Tracks 1-13

Track 1 Association of K-ras G13D mutation with outcome in patients with mCRC treated with cetuximab

Track 2 Prognostic web-based models for Stage II and III colon cancer: A population- and clinical trials-based validation of Numeracy and Adjuvant! Online

Track 3 Utility of the Onco*type* DX colon cancer assay

Track 4 **Case 8 discussion:** A 58-year-old man with resected Stage III colon cancer had several postoperative surgical complications precluding adjuvant chemotherapy and developed small, resectable hepatic metastases 18 months later

Track 5 Determining resectability of liver-limited mCRC

Track 6 Conversion therapy in potentially resectable colorectal hepatic metastases

Track 7 Perioperative FOLFOX/bevacizumab for patients with potentially resectable CRC hepatic metastases

Track 8 Perioperative chemotherapy versus surgery alone for patients with resectable mCRC

Track 9 **Case 9 discussion:** A 56-year-old woman with T3N0M0 colon cancer with a focal area of lymphovascular invasion, 0 of 47 positive lymph nodes and no MMR deficiencies has an Onco*type* DX Recurrence Score® of 20

Track 10 Perspective on the utility of Onco*type* DX for patients with Stage II colon cancer

Track 11 BRAF V600E mutation as a potential therapeutic target in CRC

Track 12 **Case 10 discussion:** A 63-year-old man with a T3 rectal tumor and nodal involvement receives neoadjuvant capecitabine and radiation therapy followed by adjuvant FOLFOX

Track 13 Use of radiation therapy in upper rectal cancer

Select Excerpts from the Interview

Track 1

DR LOVE: What are your thoughts about recent data suggesting a possible benefit from anti-EGFR antibodies in patients with a G13D K-ras mutation?

DR ALBERTS: A recent article in *JAMA* reported on this specific K-ras mutation. Patients with metastatic colorectal cancer and G13D still seem to

respond to EGFR inhibitors (de Roock 2010; [3.1]), and it was also reported in a presentation at ASCO 2011 that this subgroup benefits from cetuximab (Tejpar 2011). These data raise the point that when we're doing K-ras testing, we need to be aware of specific subgroups as to not exclude a patient population from potential therapeutic benefit. Although the proportion of patients with the K-ras mutation who have this G13D subtype is small — it represents roughly 20% of mutations — we certainly don't want to deprive them of the opportunity to receive an EGFR inhibitor.

Given these findings, we performed a retrospective analysis of patients who received cetuximab on our NCCTG-N0147 trial. Our results indicated no benefit in the adjuvant setting within the group of patients with the K-ras G13D mutation who received cetuximab (Alberts 2011).

3.1

Association of K-ras G13D Mutation with Outcome for Patients with Chemotherapy-Refractory Metastatic Colorectal Cancer Treated with Any Cetuximab-Based Therapy

	K-ras mutation		
	K-ras G13D mutation (n = 45)	**Other K-ras mutations** (n = 265)	**K-ras wild type** (n = 464)
Median overall survival	7.6 months Reference	5.7 months HR* = 0.50; $p = 0.005$	10.1 months HR* = 0.94; $p = 0.79$
Median progression-free survival	4.0 months Reference	1.9 months HR* = 0.51; $p = 0.004$	4.2 months HR* = 1.10; $p = 0.66$

* Hazard ratios are expressed for comparison of K-ras G13D mutation versus other status.

De Roock W et al. *JAMA* 2010;304(16):1812-20.

Tracks 3, 9-10

DR LOVE: What are your thoughts about the Onco*type* DX colon cancer assay?

DR ALBERTS: The Onco*type* DX assay for colon cancer was designed using a similar paradigm as for breast cancer. Retrospective analyses of large databases were performed to select genes that would provide a better understanding of which patients with Stage II colon cancer are more likely to experience relapse after surgery and who might benefit from adjuvant therapy if that risk of relapse is high enough.

The Onco*type* DX colon cancer assay focuses on patients at intermediate risk based on other clinical parameters. It is not meant for patients at high risk and also excludes patients with deficiency in mismatch repair who have a low risk of recurrence. So you're left with that group in between with an approximate 10% to 30% risk of recurrence. If we're going to administer chemotherapy,

we'd want to focus on that higher end of the spectrum. This assay is meant to help clarify where a patient fits along that spectrum.

Although the breast assay does provide some information about potential benefit with chemotherapy, the colon Onco*type* DX assay doesn't do so directly. We are unfortunately left with information derived from the NSABP-C-07 and MOSAIC trials to determine within that subgroup of patients who were enrolled with Stage II colon cancer how much benefit they gained from chemotherapy overall. We can then apply that to the risk of recurrence based on the Onco*type* DX colon assay and derive some potential benefit for a patient from those pieces of information.

The colon assay became available recently, and oncologists are still trying to understand how it fits into their daily practice and whether it changes their decision-making when they meet with a patient with Stage II colon cancer.

DR LOVE: Do you have any patients for whom you have used the Onco*type* DX colon assay?

DR ALBERTS: I used it for a young woman who had average-risk Stage II colon cancer. Due to her young age, the surgeon strongly recommended that she receive chemotherapy to ensure that the disease didn't recur, but other than focal lymphovascular invasion, no other risk factors suggested she would benefit from chemotherapy. We discussed the potential use of the Onco*type* DX assay. She agreed and the result came back as a Recurrence Score of 20, which translates to a risk of recurrence of about 13% (Kerr 2009; [3.2]).

She decided not to pursue chemotherapy unless the Recurrence Score came back indicating a high risk of recurrence. She is now being followed periodically for any evidence of recurrence.

3.2

QUASAR/Onco*type* DX Results: Recurrence Risk in Prespecified Recurrence Risk Groups (n = 711)

Recurrence risk group	Range of Recurrence Score	Proportion of patients	Kaplan-Meier estimate of recurrence risk at 3 years*
Low	<30	43.7%	12%
Intermediate	30-40	30.7%	18%
High	≥41	25.6%	22%

* With surgery alone

Kerr D et al. *Proc ASCO* 2009;**Abstract 4000**.

Track 8

DR LOVE: Would you comment on the important issue of preoperative systemic therapy for patients with colorectal cancer and resectable liver metastases?

DR ALBERTS: The question remains, does a benefit exist to perioperative versus postoperative chemotherapy in this setting? Part of the thought process has been that if we administer perioperative chemotherapy, then we're immediately gaining control of any metastatic disease either within or outside the liver and that ultimately should lead to better outcomes versus immediately taking patients to surgery and delaying the use of chemotherapy until they recover.

A European trial seemed to show a benefit to perioperative chemotherapy (Nordlinger 2008). An ongoing NSABP trial should help clarify this issue in a group of patients at somewhat higher risk (3.3).

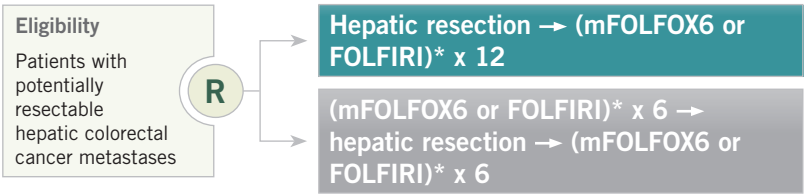
DR LOVE: What is your typical approach to a patient who presents with a single, easily resectable metastasis?

DR ALBERTS: For patients a year or more out from adjuvant therapy with a solitary metastasis, I tend to refer them directly to the surgeon and encourage proceeding to surgery. For a patient at higher risk with either multiple metastases, even if it's 3 or 4 metastases in 1 lobe or somebody who experiences relapse shortly after adjuvant therapy, I believe it's important to show that you can establish control of the disease prior to proceeding to surgery. ■

3.3

Phase III Study Evaluating the Role of Perioperative Chemotherapy for Patients with Potentially Resectable Hepatic Colorectal Cancer Metastases

Protocol ID: NSABP-C-11 **Accrual:** 670 (Open)



* Dependent upon prior exposure to oxaliplatin

NOTE: Protocol amended to no longer include bevacizumab in combination with chemotherapy

NSABP Protocol Summaries, March 2011.

SELECT PUBLICATIONS

Alberts SR et al. **Influence of KRAS and BRAF mutational status and rash on disease-free survival (DFS) in patients with resected stage III colon cancer receiving cetuximab (Cmab): Results from NCCTG N0147.** *Proc ASCO* 2011;**Abstract 3607**.

De Roock W et al. **Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab.** *JAMA* 2010;304(16):1812-20.

Nordlinger B et al. **Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial.** *Lancet* 2008;371(9617):1007-16.

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**.