INTERVIEW

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Tracks 1-9

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the importance of RAS/BRAF mutations as predictive markers of resistance to anti-EGFR antibodies for patients with CRC?

DR HECHT: KRAS mutations are a validated genetic marker of resistance to anti-EGFR therapy in patients with CRC. Studies have demonstrated that in about 40% of patients with KRAS mutations in codons 12 and 13 of exon 2, anti-EGFR antibodies have no benefit (Amado 2008).

Expanded RAS analysis indicates that outside of exon 2, a small number of mutations can be found in various hot spots. Mutations in NRAS occur in less than 10% of CRC tumors. HRAS mutations are also rare. The incidence of BRAF mutations varies from about 10% to 15% in the early stage to 5% in the salvage setting, and they confer a poor prognosis in CRC. Initially it was thought that BRAF mutations were a predictive marker for response to anti-EGFR antibodies, but that has not borne out.

The PRIME study, which assessed the efficacy and safety of panitumumab in combination with FOLFOX4 versus FOLFOX4 alone as first-line therapy, demonstrated

that patients with the nonclassical RAS mutations experienced worse outcomes with the addition of panitumumab to chemotherapy for mCRC. This is consistent with the findings in patients with KRAS mutations in exon 2 (Douillard 2013).

The hazard ratios are more than 1 in studies when panitumumab or cetuximab is administered to patients who have RAS-mutant CRC, which is interesting from a biological standpoint. We may be tweaking the biology in a bad way by administering anti-EGFR therapy to these patients.

Tracks 2-5

DR LOVE: What do we know about the efficacy and side effects of bevacizumab versus anti-EGFR antibodies for patients with KRAS wild-type mCRC?

DR HECHT: Three trials have compared or are comparing chemotherapy with an anti-EGFR antibody to chemotherapy with bevacizumab head to head in patients with KRAS wild-type mCRC.

The PEAK trial was a randomized Phase II trial of panitumumab with modified fluorouracil/leucovorin/oxaliplatin (mFOLFOX6) versus bevacizumab with mFOLFOX6 for patients with untreated, unresectable, wild-type KRAS exon 2 mCRC. Improvement was observed in overall survival (OS) with panitumumab versus bevacizumab for patients with wild-type disease with respect to KRAS exon 2. A subgroup of patients with wild-type KRAS and NRAS exons 2, 3 and 4 seemed to experience more clinical benefit with panitumumab (Schwartzberg 2014; [4.1]).

A large trial presented last year was the FIRE-3 study, which evaluated chemotherapy in combination with either cetuximab or bevacizumab as first-line treatment for

4.1

PEAK: A Randomized, Multicenter Phase II Study of Panitumumab/mFOLFOX6 versus Bevacizumab/mFOLFOX6 for Untreated, Unresectable, Wild-Type (WT) KRAS Exon 2 Metastatic Colorectal Cancer

Efficacy	Panitumumab/ mFOLFOX6	Bevacizumab/ mFOLFOX6	HR	*p*-value
WT KRAS exon 2 (n = 142, 143)*				
Median progression-free survival	10.9 mo	10.1 mo	0.87	0.353
Median overall survival	34.2 mo	24.3 mo	0.62	0.009
WT KRAS and NRAS exons 2, 3, 4 (n = 88, 82)				
Median progression-free survival	13.0 mo	9.5 mo	0.65	0.029
Median overall survival	41.3 mo	28.9 mo	0.63	0.058

	Panitumumab/ mFOLFOX6 (n = 139)		**Bevacizumab/ mFOLFOX6** (n = 139)	
Select adverse events*	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin disorders	97%	32%	45%	1%
Thrombocytopenia	24%	1%	12%	0%
Hypertension	4%	0%	25%	7%

mFOLFOX6 = modified fluorouracil, leucovorin and oxaliplatin; HR = hazard ratio
* Intent to treat

Schwartzberg LS et al. *J Clin Oncol* 2014;[Epub ahead of print].

patients with KRAS wild-type mCRC. The primary endpoint was objective response rate, and it was similar in both arms. No difference was observed in PFS either, but OS was significantly improved in the cetuximab arm. The curves diverged after most of the patients would have been off the therapy, and this was unexpected (Heinemann 2013; [4.2]). Expanded RAS testing confirmed the previously reported results (Stintzing 2013).

It has been postulated that perhaps the biology of the tumor was altered differently with bevacizumab versus with cetuximab. The CALGB-C80405 trial is evaluating bevacizumab and/or cetuximab in combination with irinotecan or oxaliplatin and 5-FU/leucovorin as first-line therapy for KRAS wild-type locally advanced or metastatic CRC (4.3). OS is the primary endpoint, and the results, which will be presented at ASCO, may provide a more definitive answer. (Editor's note: Subsequent to this interview results of the CALGB-C80405 trial were presented [Venook AP et al. *Proc ASCO* 2014;**Abstract LBA3**].)

DR LOVE: What is your usual first-line therapy for patients with KRAS wild-type mCRC?

DR HECHT: I typically administer CAPOX in combination with bevacizumab. This is partly because the schedule of administration is convenient for patients who travel long distances. If we need to achieve resectability, we use 5-FU/irinotecan and oxaliplatin.

We use bevacizumab as the biologic agent for the majority of patients receiving front-line therapy because of the side effects associated with anti-EGFR antibodies. The side effects of bevacizumab, which include hypertension, arterial thromboembolic events and gastrointestinal perforation, are rare, but if they occur, they can be catastrophic. The results of the FIRE-3 study are interesting, but we haven't changed our practice because of those results.

Anti-EGFR therapy may increase the preoperative response rate and may facilitate resection for patients with marginally resectable disease. The new EPOC trial evaluated the benefit of cetuximab in addition to standard chemotherapy versus chemotherapy alone for patients with KRAS wild-type, operable liver metastasis from CRC. The addition of cetuximab to chemotherapy improved response rates but resulted in significantly worse PFS outcomes (Primrose 2013).

4.2

FIRE-3: A Phase III Study of FOLFIRI in Combination with Cetuximab versus FOLFIRI in Combination with Bevacizumab as First-Line Treatment for KRAS Wild-Type (WT) Metastatic Colorectal Cancer

Efficacy	Cetuximab/ FOLFIRI	Bevacizumab/ FOLFIRI	*p*-value
KRAS WT (n = 592)*			
Objective response rate	62%	58%	0.183
Median progression-free survival	10.0 mo	10.3 mo	0.547
Median overall survival	28.7 mo	25.0 mo	0.017
WT KRAS and NRAS exons 2, 3, 4 (n = 301)			
Objective response rate	76.0%	65.2%	0.026
Median progression-free survival	10.5 mo	10.4 mo	0.627
Median overall survival	33.1 mo	25.9 mo	0.010

* Intent to treat

Heinemann V et al. *Proc ASCO* 2013;**Abstract LBA3506**; Stintzing S et al. *Proc ECC* 2013;**Abstract E17-7073**.

DR LOVE: What is your approach to first-line therapy for mCRC when you need a response?

DR HECHT: The Phase III TRIBE trial, presented at ASCO 2013, compared FOLFOXIRI/bevacizumab to FOLFIRI/bevacizumab as first-line treatment in unresectable mCRC. The results demonstrated a significantly better response rate and PFS with FOLFOXIRI compared to FOLFIRI (Falcone 2013). So particularly in young, healthy patients who need downstaging prior to surgery, we use FOLFOXIRI.

Should patients receive chemotherapy before surgery, after surgery or both? We have no right answer. Patients with small tumors can go right to surgery followed by adjuvant therapy. We tend to administer chemotherapy before resection to patients with extrahepatic disease. For these patients, chemotherapy-associated steatohepatitis is a concern.

FOLFOXIRI can elicit high response rates in patients without extrahepatic disease who have tumors that are difficult to resect because they are large or are near a blood vessel. As far as the role of bevacizumab, it can be associated with complications like impaired wound healing when administered preoperatively. The current wisdom is to perform the surgery at least 6 to 8 weeks after bevacizumab administration. ■

4.3

CALGB-C80405: A Phase III Trial of Irinotecan/5-FU/Leucovorin (LV) or Oxaliplatin/5-FU/LV with Bevacizumab (Bev) or Cetuximab (Cet) or Bev/Cet for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum

Other Protocol IDs: SWOG-C80405; NCT00265850 **Target Accrual:** 2,900

Eligibility

- Locally advanced (unresectable) or metastatic colon or rectal cancer
- KRAS wild type
- No history of significant bleeding within the past 6 months unless the bleeding source has been resected
- No prior anti-VEGF or anti-EGFR therapy

R

- Oxaliplatin/5-FU/LV/bev or irinotecan/5-FU/bev
- Oxaliplatin/5-FU/LV/cet or irinotecan/5-FU/LV/cet
- Oxaliplatin/5-FU/LV/bev/cet or irinotecan/5-FU/LV/bev/cet

www.clinicaltrials.gov. Accessed May 2014.

SELECT PUBLICATIONS

Amado RG et al. **Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer.** *J Clin Oncol* 2008;26(10):1626-34.

Douillard JY et al. **Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer.** *N Engl J Med* 2013;369(11):1023-34.

Falcone A et al. **FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group.** *Proc ASCO* 2013;**Abstract 3505**.

Primrose JN et al. **A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in KRAS wild-type patients with operable metastases from colorectal cancer: The new EPOC study.** *Proc ASCO* 2013;**Abstract 3504**.

Schwartzberg LS et al. **PEAK: A randomized, multicenter Phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer.** *J Clin Oncol* 2014;[Epub ahead of print].