Cetuximab with Chemotherapy as Treatment for Stage III Colon or Metastatic Colorectal Cancer

Cetuximab with Chemotherapy (CT) as First-Line Treatment for Metastatic Colorectal Cancer (mCRC): Analysis of the CRYSTAL and OPUS Studies According to KRAS and BRAF Mutation Status

Bokemeyer C et al.

Proc ASCO 2010;Abstract 3506.

Background

- Cetuximab (Cmab) added to chemotherapy (CT) as first-line treatment for patients with mCRC and KRAS wild-type (wt) tumors improved efficacy (CRYSTAL study, *NEJM* 2009;360:1408; OPUS study, *JCO* 2009;27:663).
- BRAF may be an additional biomarker for CRC:
  - BRAF gene mutations (mt) were detected in 8% of CRC tumors (*JCO* 2010;28:466).
  - BRAF mt are suggested to be predictive of Cmab efficacy in pre-treated patients with CRC (*JCO* 2008;26:5705).
- **Current study objective:**
  - To investigate the efficacy of Cmab in patients from CRYSTAL and OPUS trials according to KRAS and BRAF mutation status.

Bokemeyer C et al. *Proc ASCO* 2010;Abstract 3506.

Pooled Analyses: Overall Response Rate

Patient Group	ORR	*p*-value
KRAS wt CT (n = 447) Cmab + CT (n = 398)	 38.5% 57.3%	<0.0001
KRAS wt/BRAF wt CT (n = 381) Cmab + CT (n = 349)	 40.9% 60.7%	<0.0001
KRAS wt/BRAF mt CT (n = 38) Cmab + CT (n = 32)	 13.2% 21.9%	0.4606

ORR = overall response rate

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Pooled Analyses: Survival Data

Patient Group	Median OS	HR for OS (*p*-value)	Median PFS	HR for PFS (*p*-value)
KRAS wt				
CT (n = 447)	19.5 mos	0.81 (0.0062)	7.6 mos	0.66 (<0.0001)
CT + Cmab (n = 398)	23.5 mos		9.6 mos	
KRAS wt/BRAF wt				
CT (n = 381)	21.1 mos	0.84 (0.041)	7.7 mos	0.64 (<0.001)
CT + Cmab (n = 349)	24.8 mos		10.9 mos	
KRAS wt/BRAF mt				
CT (n = 38)	9.9 mos	0.63 (0.079)	3.7 mos	0.69 (0.267)
CT + Cmab (n = 32)	14.1 mos		7.1 mos	

OS = overall survival; PFS = progression-free survival

Bokemeyer C et al. *Proc ASCO* 2010;Abstract 3506.

Conclusions

- This pooled analysis confirms that the addition of Cmab to CT in first-line therapy for patients with mCRC and KRAS wt tumors achieves a statistically significant improvement in efficacy compared to CT alone.
- The best outcome was observed in patients with KRAS wt/BRAF wt tumors (90% of KRAS wt patients).
- Based on these results, BRAF mutation status does not appear to be a relevant predictive biomarker for use of Cmab in first-line therapy for mCRC.
  - BRAF mt appears to be an indicator of poor prognosis.
  - However, the sample size may be too small to be reliable.

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Investigator comment on the analysis of CRYSTAL and OPUS according to K-ras and B-raf mutation status

The CRYSTAL and the OPUS studies added cetuximab to either FOLFOX or FOLFIRI. OPUS study was a randomized Phase II study and CRYSTAL was a randomized Phase III study. The investigators pooled their data in order to tease out some issues that related to the mutation status of the tumors.

Interestingly, a number of people jumped on the notion that we ought to be performing B-raf testing routinely as we do K-ras testing. As it turns out, this analysis suggests that you can do that and learn about the prognostic features of having a B-raf mutation. Patients who have B-raf mutations in their tumors can still respond to cetuximab. So one shouldn't use B-raf mutation status as a “go/no-go” factor for whether or not to use cetuximab for these patients.

B-raf does carry an adverse prognosis, and response rates were about a third for patients with the B-raf mutation compared to those with B-raf wild-type tumors. So patients with B-raf mutations fare poorly, but they still fared better when cetuximab was added to chemotherapy than when chemotherapy was administered alone.

Interview with Richard M Goldberg, MD, June 23, 2010

Investigator comment on the analysis of CRYSTAL and OPUS according to K-ras and B-raf mutation status

Two interesting findings emerged from this analysis. First, B-raf is hugely prognostic. Patients with B-raf mutations live about a year less than patients without B-raf mutations, which I thought was shocking. We have always searched for a good prognostic marker in colon cancer, and now we have a marker, which identifies seven to eight percent of patients with a very poor prognosis. Personally, I test for B-raf mutations because this influences the way I approach a patient in terms of stop-and-go strategies. For patients with B-raf mutations, I have to be alert and cannot as easily consider stop-and-go and maintenance therapies.

Second, there was still a numerical benefit for the addition of cetuximab to chemotherapy in terms of response rate, progression-free survival and overall survival, which may refute the initial idea that a mutation in B-raf is a negative predictive marker like K-ras mutations. So my personal preference, if I have a patient with a B-raf mutation, is not to use cetuximab or panitumumab in an earlier-line setting. Would I use it in a last-line setting when the patient's back is against the wall? Based on these data, I might consider that.

Interview with Axel Grothey, MD, July 9, 2010

Adjuvant mFOLFOX6 with or without Cetuximab in Patients with KRAS Wild-Type or KRAS Mutant Resected Stage III Colon Cancer: Results from NCCTG Intergroup Phase III Trial N0147

Goldberg RM et al.
Proc ASCO 2010;Abstract 3508.

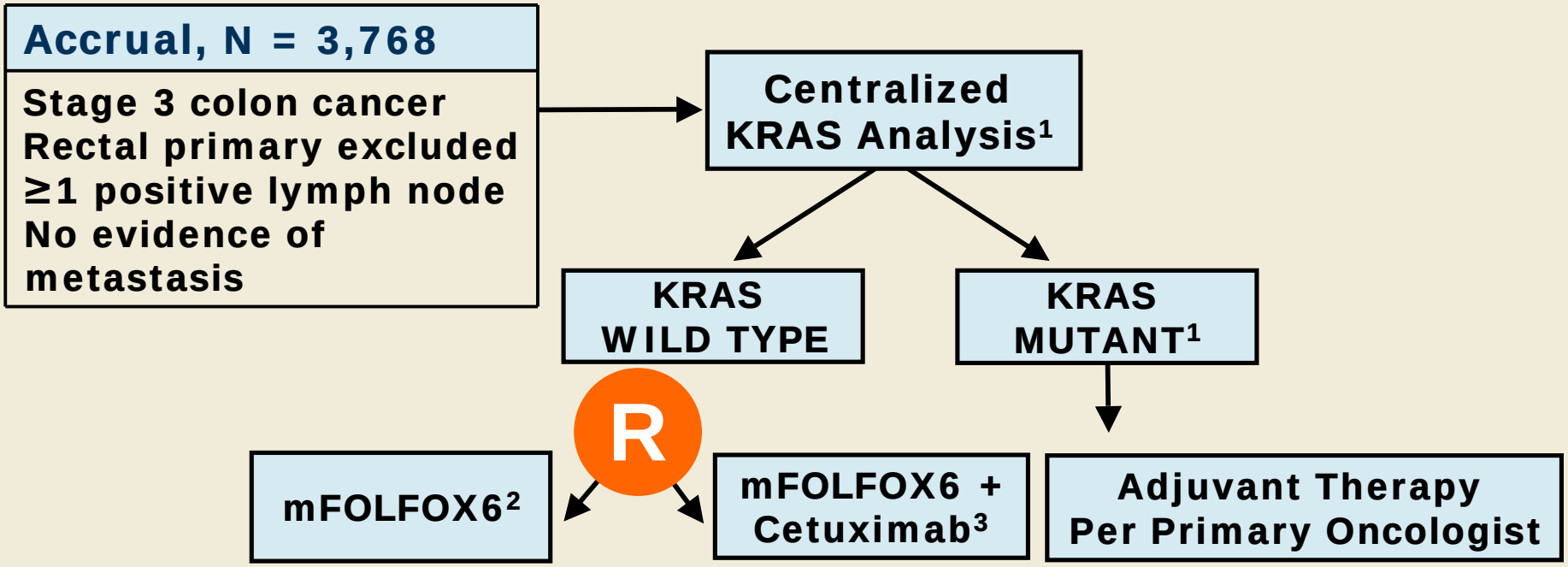
Alberts SR et al.
Proc ASCO 2010;Abstract CRA3507.

Background

- FOLFOX is standard adjuvant therapy and improves disease-free survival and OS in Stage III colon cancer (*JCO* 2009;27:3109).
- Combination of EGFR antibody and chemotherapy demonstrates improved outcome in metastatic colon cancer.
- KRAS wild type was established as a predictive marker for the addition of cetuximab to FOLFOX4 in Stage IV colon cancer (*JCO* 2009;27:663) leading to an N0147 amendment requiring prospective KRAS testing.
- **Current study objectives:**
  - Safety and efficacy of cetuximab added to mFOLFOX6 in patients with:
    - Colon cancer with KRAS wild type present
    - Colon cancer with KRAS mutation present

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508; Alberts SR et al. *Proc ASCO* 2010;Abstract CRA3507.

N0147 Final Design



[1] 717 patients with KRAS mutation were enrolled before an amendment requiring prospective KRAS testing. Patients who were enrolled pre-amendment had KRAS status analyzed retrospectively from paraffin-embedded blocks.

[2] mFOLFOX6 = Oxaliplatin 85 mg/m^2 d1, leucovorin 400 mg/m^2, 5-FU 400 mg/m^2 bolus IV d1, 5-FU 2,400 mg/m^2 d 1-2 (over 46 hours) every 2 wk

[3] Cetuximab 400 mg/m^2 loading dose, then 250 mg/m^2 qwk

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508; Alberts SR et al. *Proc ASCO* 2010;Abstract CRA3507.

Efficacy Endpoints

KRAS Wild Type (23-mo follow-up)	FOLFOX (n = 902)	FOLFOX + Cetuximab (n = 945)	Hazard Ratio	*p*-value
3-Year Disease-Free Survival	75.8%	72.3%	1.2	0.22
3-Year Overall Survival	87.8%	83.9%	1.3	0.13

KRAS Mutant (22.4-mo follow-up)	FOLFOX (n = 374)	FOLFOX + Cetuximab (n = 343)	Hazard Ratio	*p*-value
3-Year Disease-Free Survival	67.2%	64.2%	1.2	0.13
3-Year Overall Survival	88.0%	80.4%	1.5	0.12

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508; Alberts SR et al. *Proc ASCO* 2010;Abstract CRA3507.

Select Grade 3+ Adverse Events

Adverse Event	KRAS Wild Type		KRAS Mutants	
	FOLFOX (n = 883)	FOLFOX + Cetuximab (n = 919)	FOLFOX (n = 364)	FOLFOX + Cetuximab (n = 339)
Paresthesias	9%	7%	13%	9%
Neutropenia (Grade 4+)	10%	11%	12%	13%
Rash	0.1%	8%	0%	9%
Diarrhea	8%	15%	8%	15%
Nausea	3%	4%	2%	6%
Vomiting	3%	3%	3%	5%
Mucositis	2%	7%	3%	7%

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508.

Conclusions

- Cetuximab does not add benefit when added to adjuvant FOLFOX in patients with Stage III colon cancer and either KRAS wild type or KRAS mutation.
- Based on analysis of idealized patients (aged <70 years and with ≥80% dose intensity achieved), the failure of cetuximab added to FOLFOX is not primarily due to lower dose intensity of 5-FU and oxaliplatin when cetuximab was added (data not shown).
- Potential Explanations:
  - Related to tumor biology, cetuximab treatment of KRAS mutants may drive chemotherapy resistance
  - Overall decreased tolerance with addition of cetuximab
  - Lessened ability in older patients (≥70 years) to complete therapy with adjuvant FOLFOX when cetuximab was added (data not shown)

Goldberg RM et al. *Proc ASCO* 2010;Abstract 3508; Alberts SR et al. *Proc ASCO* 2010;Abstract CRA3507.

Investigator comment on the results of NCCTG-N0147: mFOLFOX6 with or without cetuximab for Stage III colon cancer

For NCCTG-N0147, we split the analysis, because we wanted to focus first on the entire group of patients and then on those patients with the K-ras mutations. Initially, the randomization was to FOLFOX with or without cetuximab for “all comers,” but once we became aware of the importance of K-ras status, we restricted enrollment to patients with K-ras wild-type tumors.

The bottom line is there was no overall value to the addition of cetuximab to chemotherapy in the entire population or in those patients with K-ras wild-type tumors. Unfortunately, there was a detriment when cetuximab was used in patients who were over 70 years old.

Perhaps more startling, for patients with K-ras mutations there was a statistically worse outcome among those who received cetuximab. We would not have predicted this outcome. In some manner that we do not understand, cetuximab interfered with the efficacy of chemotherapy. On the positive side, we did have tumor block requirements for enrollment, so hopefully we can unravel this unexpected finding.

Interview with Richard M Goldberg, MD, June 23, 2010

Investigator comment on the results of NCCTG-N0147: mFOLFOX6 with or without cetuximab for Stage III colon cancer

This study was started about seven years ago when nobody talked about K-ras status. In the end, the primary endpoint was adjusted to evaluate FOLFOX with or without cetuximab in patients with K-ras wild-type tumors. I was shocked when I saw the data because I believed we had our “HER2 in breast cancer.” We had our K-ras-enriched population and a drug like cetuximab, which had clear activity in colon cancer. We knew the population that should be treated with cetuximab and that this should work as adjuvant therapy. It failed miserably. We did not see benefit in patients with K-ras wild-type or mutant tumors. If anything, we observed a detrimental effect from cetuximab, which was pronounced in the elderly and those with K-ras mutations.

With the elderly, we probably compromised the dose of chemotherapy over time. In those with K-ras mutant tumors, we’ve seen more recent evidence in mCRC that the addition of cetuximab to an oxaliplatin-based regimen interferes with the activity of the underlying chemotherapy.

In the end, this was a disturbing and disappointing outcome. The question is, where do we go from here? I believe we are all pretty much at a loss right now.

Interview with Axel Grothey, MD, July 9, 2010