ImClone Systems Incorporated

33 ImClone Drive
Branchburg, NJ 08876
Tel: (908) 218-9588
Fax: (908) 704-8325
www.imclone.com

Targeted Oncology®

Re: Briefing Document for December 16, 2008
ODAC Advisory Committee Meeting

December 2, 2008

Nicole Vesely, Pharm.D.
Advisors and Consultants Staff
FDA, CDER, OEP
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20857-1734

Dear Ms. Vesely:

Reference is made to the upcoming December 16, 2008 Oncologic Drugs Advisory Committee meeting and to your December 2, 2008 email to Ms. Cheryl Anderson.

Enclosed are seven electronic copies (CD-Roms) and five paper copies of the briefing document, entitled: "Background Document: K-*ras* Oncology Drugs, Advisory Committee (ODAC)". As requested, each CD and each page of the briefing document have been clearly marked: "AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION."

If you have any questions, please contact me by telephone at (908) 541-8060 or by facsimile at (908) 218-0555.

Sincerely,

Heather Lynne Manna
Associate Director, Regulatory Operations
Phone: (908) 541-2336
Email: heather.manna@imclone.com

BRISTOL-MYERS SQUIBB
RESEARCH AND DEVELOPMENT

BMS-564717
(ERBITUX®; cetuximab)

Background Document: *K-ras* Oncology Drugs Advisory Committee (ODAC)

Report Date: 07-November-2008

Bristol-Myers Squibb Research and Development
P.O. Box 4000
Princeton, NJ 08543-4000

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1 EXECUTIVE SUMMARY

Summarized in this document are the results of a retrospective analysis of efficacy based upon *K-ras* status from four randomized studies conducted by the sponsor (NCIC CO.17 /BMS-025, CRYSTAL, EPIC, OPUS) in subjects with metastatic colorectal cancer (mCRC). The data make a compelling argument that patients with *K-ras* wild-type (WT) tumors derive enhanced benefit from the addition of cetuximab to their therapeutic regimen compared to the overall study population unselected for K-*ras* mutational status, but patients with tumors harboring *K-ras* mutations will probably not benefit from anti-EGFR antibodies. There may be limitations of such retrospective analyses in terms of (i) the studies not having been originally designed to test this hypothesis, (ii) analyses were conducted on a subset of the study population, and (iii) though performed in a blinded manner, the data were analyzed subsequent to the analysis of efficacy results. Nevertheless, the consistency of results across studies strongly suggests that *K-ras* status is a predictive biomarker for cetuximab activity in mCRC. The implications of these findings in terms of their impact (ie, modification of study design and endpoints to primarily focus on benefit in K-*ras* WT patients only) on two Phase 3 studies in mCRC currently ongoing in North America (CALBG 80405 and NCCTG 147), the rationale for testing *K-ras* status in making treatment decisions in patients with mCRC in any future trials with anti-EGFR antibodies, and the possibility of using the *K-ras* data from these studies to support revised labeling for ERBITUX™ (cetuximab) in the US are presented in this document.

2 INTRODUCTION AND RATIONALE FOR *K-RAS* TESTING

Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR), improves overall and progression-free survival (OS and PFS) in patients with mCRC that has not responded to chemotherapy. ERBITUX™ (cetuximab) was initially approved by the FDA (Feb-2004) for use in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal cancer in patients who are refractory to irinotecan-based chemotherapy and as a single agent in patients who are intolerant to irinotecan-based chemotherapy. Subsequently, in a randomized Phase 3 trial (NCIC CO.17/BMS-025), cetuximab as a single-agent demonstrated significantly improved overall survival versus best supportive care (BSC), and confirmed the positive effects on PFS and response rate (RR). Median overall survival (OS) in cetuximab + BSC arm was

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6.1 months versus 4.6months with BSC alone (hazard ratio = 0.77, log-rank p = 0.0046). Based upon these data, the use of cetuximab was expanded in the US (Oct-2007) as a single-agent in patients who had failed all available chemotherapeutic agents, including an irinotecan-containing regimen and an oxaliplatin-containing regimen, and for whom no standard anti-cancer therapy was available.

The effectiveness of cetuximab for the first-line treatment of patients with EGFR-expressing mCRC was also investigated in a randomized Phase 3 study of 5-FU, irinotecan and leucovorin (FOLFIRI) with or without cetuximab (CRYSTAL). This study met its primary endpoint of PFS, and demonstrated a significant improvement of PFS when cetuximab was added to FOLFIRI in the overall population (N=599 in each arm). Median PFS in cetuximab + FOLFIRI arm was 8.9 months versus 8.0 months with FOLFIRI alone (hazard ratio = 0.851, log-rank p = 0.0479).

Like other therapies that target the EGFR, the working hypothesis at the beginning of the pre-clinical and clinical development of cetuximab was that only EGFR-expressing tumors would be responsive to treatment. However, an increasing body of evidence now indicates that immunohistochemical detection of the EGFR on tumor cells of patients with CRC is a poor marker for predicting the efficacy of cetuximab.[1] Thus, further research in this area has focused on detecting more reliable predictive markers for EGFR-targeted therapies. *K-ras* mutation status has emerged as a predictive marker for EGFR-targeted monoclonal antibody therapies.

The analysis of efficacy based upon *K-ras* status from NCIC CO.17/BMS-025 (cetuximab monotherapy) and 3 other randomized studies conducted by the sponsor, CRYSTAL, EPIC, OPUS (cetuximab in combination with chemotherapy), suggest that patients with K-*ras* WT tumors in advanced CRC benefit from the addition of cetuximab to other therapy, whereas patients with tumors harboring *K-ras* mutations will not benefit from anti-EGFR antibodies.

In 2004, FDA had identified pharmacogenomics as a key opportunity in its Critical Path Initiative. Since then a number of Agency guidance documents have been issued to encourage and assist sponsors in evaluating pharmacogenomic data. One key component of those guidelines is the encouragement to make Voluntary Genomics Data Submissions (VGCS) when provision of such data would not otherwise be required by the regulations. The sponsor had made a Voluntary Genomics Data Submission (VGDS) for cetuximab to

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the FDA in April 2008. Included in the VGDS were (i) results of retrospective pharmacogenomic data analysis from five trials conducted in mCRC patients, and (ii) an overview of the assay methods used for biomarker analyses, including available cross-validation work.

On 06-June-2008, NIH/NCI issued an action letter asking the investigators to suspend accrual for all CTEP-sponsored and Cooperative Group trials that contained cetuximab in the protocol regimen for patients with CRC until appropriate modifications to the protocol and informed consent were made, new information concerning *K-ras* was added, and patients with mutated *K-ras* (MT) in tumors were excluded. This action letter was issued after the results of *K-ras* analysis from the CRYSTAL trial were presented at the ASCO Annual Meeting (01-Jun-2008). This study had met its primary endpoint (PFS assessed in blinded manner by an IRC), and demonstrated a significant improvement of PFS when cetuximab was added to FOLFIRI in the intent-to-treat (ITT) population (median PFS in cetuximab + FOLFIRI arm was 8.9 months versus 8.0 months with FOLFIRI alone; hazard ratio = 0.851, log-rank p = 0.0479). The results presented at ASCO were based on a retrospective analysis of *K-ras* status in subjects with tumor tissues evaluable for analysis of *K-ras* mutation (N=540), and showed that the benefit of adding cetuximab to FOLFIRI was only demonstrated in subjects with *K-ras* WT in their tumors (hazard ratio = 0.68, p = 0.017). Subjects with *K-ras* mutations in their tumors derived no benefit from the addition of cetuximab over and above chemotherapy alone (hazard ratio = 1.07, p = 0.75).

The effectiveness of cetuximab for the first line treatment of patients with EGFR-expressing mCRC was also observed in a randomized Phase 2 study of 5-FU/FA plus oxaliplatin (FOLFOX-4) with or without cetuximab (OPUS). This study demonstrated an improvement in RR by independent review (primary endpoint of the study) in the intent-to-treat (ITT) population when cetuximab was added to FOLFOX-4 (ORR in cetuximab + FOLFOX-4 arm was 46% versus 36% with FOLFOX-4 alone; p = 0.064). Median PFS was 7.2 months in both treatment arms (hazard ratio = 0.931, p = 0.62). The results based on a retrospective analysis of *K-ras* status in subjects with tumor tissues available for analysis of *K-ras* mutation (N=233) showed that subjects with K-ras WT in their tumors receiving cetuximab and FOLFOX-4 had a greater RR than subjects receiving FOLFOX-4 alone (p = 0.011). Subjects with *K-ras* mutations in their tumors derived no benefit in terms of RR from the addition of cetuximab to chemotherapy alone (p = 0.108).

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Similarly, for PFS, the benefit of adding cetuximab to FOLFOX-4 was only demonstrated in subjects with *K-ras* WT in their tumors (hazard ratio = 0.57, p = 0.016). Subjects with *K-ras* mutations in their tumors derived no benefit in PFS from the addition of cetuximab to chemotherapy alone (hazard ratio = 1.83, p = 0.019).

Although this was a retrospective subgroup analysis, it represented one of the largest data sets for the association of *K-ras* mutation and the role of cetuximab in combination with chemotherapy. Accordingly, subsequent to the action letter issued by NIH/NCI, the sponsor also endorsed similar action and wrote to all investigators participating in sponsor-conducted and/or investigator-sponsored trials (ISTs) in CRC asking them to limit further accrual to patients with *K-ras* WT tumors. Similarly, enrollment was temporarily suspended for the two large cooperative Phase 3 studies in CRC currently ongoing in North America (CALBG 80405 and NCCTG 147) until, in collaboration with the FDA, the study design had been amended to allow only patients with *K-ras* WT tumors to be enrolled in these studies. The K-*ras* mutational status in tumors is based on an assay that is validated with the recommendations of FDA. This has been achieved and accrual in both studies was resumed (August 2008 for NCCTG and September 2008 for CALBG study; see Section 4). The sponsor considers testing for *K-ras* mutation status as medically important information necessary for making treatment decision in patients with mCRC. The NCCN has recently updated treatment guidelines for CRC with a key recommendation that the EGFR inhibitors (cetuximab and panitumumab), either as single agents or in combination with other agents, are now recommended only for patients with tumors characterized by the wild-type *K-ras* gene.[2]

2.1 Biology of *K-ras*

The *K-ras* (Kirsten rat sarcoma 2 viral oncogene homolog) gene encodes an important signaling protein that is present in both normal and malignant cells. The KRAS protein relays a variety of signals from cell surface receptors, such as the EGFR, to the nucleus that result in survival, angiogenesis, proliferation, and metastasis. In tumors with *K-ras* WT, the protein is only temporarily activated in response to certain stimuli such as EGFR signaling. In tumors with *K-ras* MT, the KRAS protein is constitutively activated independent of EGFR-mediated signaling (Figure 1), resulting in unregulated downstream signaling that lead to tumor growth. Consequently, inhibition of growth-factor receptor signaling by anti-EGFR antibodies such as cetuximab and panitumumab

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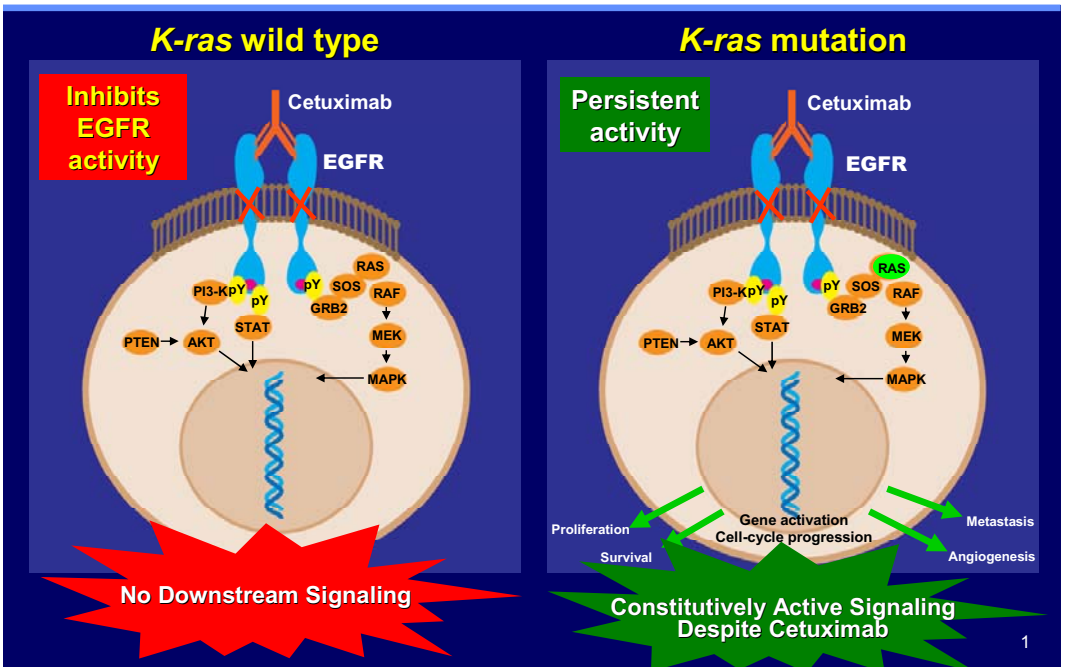
does not have an inhibitory effect on signaling events that are down-stream of oncogenic *K-ras*, and thus, are generally associated with a poor prognosis for treatment with anti-EGFR therapies. In colorectal cancer, up to 65% of the patients have *K-ras* WT and the incidence of *K-ras* mutations is in the range of 30-50%.[3, 4, 5, 6, 7, 8, 9, 10, 11]

Figure 1: EGFR Signaling Cascade and *K-ras*



K-ras mutations can be detected in either formalin fixed paraffin-embedded tumors or fresh tumor biopsies by a quantitative polymerase chain reaction (PCR)–based assay or a DNA sequencing method:

1) Quantitative PCR: The locked nucleic acid (LNA)–mediated qPCR-based assay is a unique qPCR technique using fluorescent hybridization probes and a wild-type DNA competing LNA oligomer.[12] By adding the LNA oligomer to the qPCR reaction, amplification of WT *K-ras* is suppressed (used for CRYSTAL and OPUS).
2) DNA sequencing: This assay involves PCR amplification of genomic DNA isolated from formalin fixed paraffin embedded tissues. The PCR products are subjected to bidirectional sequencing of exon 2. The sequencing traces are analyzed using Mutation Surveyor software and visual inspection. (Used for NCIC CO.17/BMS-025, EPIC and BMS-045).

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The two assays described above were not validated against each other in a single study. However, each of these assays was compared with results obtained on a small subset of samples using a commercial qPCR based assay (TheraScreen™ *K-ras* Mutation Test Kit from DxS Genotyping). The results of such comparison showed a satisfactory correlation: (i) 97% concordance between the LNA-mediated qPCR clamping assay and DxS assay, and (ii) 86% concordance between the bidirectional sequencing assay and the DxS assay.

3 ANALYSIS OF *K-RAS* DATA FROM NCIC CO.17/ BMS-025

NCIC CO.17/BMS-025 was a randomized Phase 3 study of cetuximab and best supportive care (BSC) versus BSC in subjects with pretreated EGFR-positive mCRC. Addition of cetuximab prolonged survival in the overall study population; the median survival was 6.1 months in cetuximab plus BSC arm versus 4.6 months in BSC alone arm. The hazard ratio (HR) for cetuximab plus BSC over BSC alone was 0.77 (p = 0.0046).[13] A prospectively planned retrospective analysis of efficacy data based upon *K-ras* status was conducted for this study.[14] Of the overall study population (N = 572), tumor samples evaluable for *K-ras* analyses were available from 68.9% (394/572; Table 4.1) of subjects. Mutational analysis of *K-ras* was performed by robust analytic methods (i.e. bidirectional sequencing of K-Ras exon 2) and without knowledge of clinical outcome, including tumor response.

The demographics and other baseline characteristics of the subset of subjects evaluable for *K-ras* analyses were representative of the overall population. Within this subset of 394 subjects, the demographic and baseline characteristics of subjects with WT *K-ras* (N = 230) and MT *K-ras* (N = 164) were similar except for ECOG PS 2, which was lower in the cetuximab + BSC arm compared with the BSC arm (13.0% versus 26.3%) among subjects with the WT *K-ras*.

Cetuximab had demonstrated a survival benefit over BSC when given as a monotherapy to subjects with metastatic CRC in the overall study population (Table 4.2). Identifying patients with CRC who optimally benefit from cetuximab treatment would further enhance the clinical utility of this therapy. A retrospective analysis of efficacy data based upon *K-ras* status (Table 4.3) showed that:

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- Cetuximab provided significant improvement in OS in subjects with *K-ras* WT tumors (median OS 9.5 months versus 4.8 months in BSC alone). The HR for cetuximab plus BSC over BSC alone was 0.55.
- Cetuximab provided significant improvement in PFS in subjects with *K-ras* WT tumors (median PFS 3.8 months versus 1.9 months in BSC alone). The HR for cetuximab plus BSC over BSC alone was 0.40.
- Subjects with *K-ras* mutations in their tumors did not derive benefit from the addition of cetuximab to BSC (median OS 4.5 months versus 4.6 months in BSC alone; median PFS 1.8 months versus 1.8 months in BSC alone). The HR for cetuximab plus BSC over BSC alone was 0.98 for OS and 0.99 for PFS.
- Moreover, the results showed that *K-ras* is not a predictor of efficacy with BSC but is a strong predictor for cetuximab activity.

The safety profile of cetuximab + BSC in the subset evaluated for *K-ras* status was consistent with that in the overall study population. The overall safety profile was similar in subset of subjects with WT *K-ras* and those with MT *K-ras*. Whereas higher incidences of skin toxicities, dyspnea and neuropathy were observed in the subset of subjects with WT *K-ras*, this difference may be due to a longer duration of treatment in this subset than those in the *K-ras* MT subset.

These findings support the use of *K-ras* status as a strong predictive marker for EGFR-targeted monoclonal antibody therapies in patients with advanced CRC, and provide a strong foundation for considering testing for *K-ras* status prior to making treatment decision in patients with mCRC.

4 SUPPORTING DATA FROM OTHER CLINICAL STUDIES FOR KRAS AS A PREDICTIVE BIOMARKER

The findings in NCIC CO.17/BMS-025 support the use of *K-ras* status as a strong predictive marker for EGFR-targeted monoclonal antibody therapy in subjects with advanced CRC. The compelling data on the predictive nature of *K-ras* status in NCIC CO.17/BMS-025 were also supported by 4 other studies (CRYSTAL and OPUS in 1st line CRC, EPIC in 2nd line CRC, and an exploratory study BMS-045 in refractory CRC; Table 4.1). Review of the aggregate data across these clinical studies demonstrates consistency of results suggesting patients with *K-ras* MT tumors derive little or no

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benefit from adding cetuximab regardless of whether it was administered as monotherapy or in combination with other chemotherapy.

BMS-045, an exploratory single-arm, single-agent, Phase 2 study, was designed to systematically identify biomarkers associated with disease control to cetuximab monotherapy. This was the largest prospective cohort treated with an anti-EGFR antibody with the goal of identifying candidate predictive markers that were correlated with clinical activity. One of the key findings of this exploratory study was that subjects with tumors without *K-ras* mutations had a significantly higher disease control rate than subjects with MT *K-ras*.[15]

The results from BMS-045 provided a rationale for further testing of *K-ras* status in tumor specimens obtained from subjects enrolled in 4 other randomized clinical trials in mCRC, and to determine if *K-ras* was a predictive biomarker for cetuximab activity. Summarized in this section are results on PFS, overall survival (OS) and response rate in relation to *K-ras* status from CRYSTAL[16] and OPUS[17] (both in 1st line CRC), EPIC[18] (2nd line CRC), and NCIC CO.17/BMS-025 (refractory CRC).

Tumor samples evaluable for *K-ras* analyses were available from 44.0% (1547/3515) of subjects in these five studies. Within the *K-ras* evaluable population, 61.7% (954/1547) of subjects had tumors with *K-ras* WT genes (Table 4.1). The data summarized in Table 4.3 show that:

- Across all studies, subjects with *K-ras* WT tumors derived a benefit from the addition of cetuximab to their therapy regimen; there was an improvement in PFS with cetuximab in subjects with *K-ras* WT tumors. In three of the four studies, a statistically significant difference in PFS between the treatment groups was established at the 5% significance level although the power was limited due to the reduced sample size.
- Subjects with *K-ras* mutations in their tumors did not derive any benefit from the addition of cetuximab to either BSC or chemotherapy alone.

Overall, the results on overall response rate (ORR) showed the same trend as was shown for PFS. A relevant treatment effect in terms of enhanced response rate to cetuximab was apparent in subjects with WT *K-ras* in their tumors in three out of four studies (CRYSTAL, OPUS and NCIC CO.17/BMS-025; Table 4.4).

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Table 4.1: An overview of clinical studies included in *K-ras* analysis

Study Name	Study Number	Stage	Regimen	Number / Proportion of *K-ras* Evaluable Subjects	*K-ras* Population	Number (%) of Subjects in Population		
						Cetuximab ± Control	Control	Total
NCIC CO.17	BMS-025	CRC Refractory	Randomized Phase 3	394*/ 572 (68.9%)	Wild type	117	113	230 (58.0%)
			BSC ± Cetuximab		Mutant	81	83	164 (42.0%)
CRYSTAL	EMR-013	CRC 1st line	Randomized Phase 3	540 / 1198 (45.1%)	Wild type	172	176	348 (64.4%)
			FOLFIRI ± Cetuximab		Mutant	105	87	192 (35.6%)
OPUS	EMR-047	CRC 1st line	Randomized Phase 2	233 / 337 (69.1%)	Wild type	61	73	134 (57.5%)
			FOLFOX-4 ± Cetuximab		Mutant	52	47	99 (42.5%)
EPIC	BMS-006	CRC 2nd line	Randomized Phase 3	300** / 1298 (23.1%)	Wild type	97	95	192 (64.0%)
			Irinotecan ± Cetuximab		Mutant	49	59	108 (36.0%)
--	BMS-045	CRC Refractory	Exploratory Single arm	80 / 110 (72.7%)	Wild type	50	NA	50 (62.5%)
			Phase 2 PGx		Mutant	30	NA	30 (37.5%)
			Cetuximab monotherapy					
TOTAL				**1547 / 3515 (44.0%)**	**Wild type**	**497**	**457**	**954 (61.7%)**
					Mutant	**317**	**276**	**593 (38.3%)**

NA = not applicable since it was a cetuximab monotherapy

*Reflects an interim analysis and availability of additional tumor samples will ultimately increase this database to approximately 75% of the overall study populations

** Tumor samples from US subjects only

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Table 4.2: Overall Survival, Progression Free Survival and Response Rate in Intent-to-Treat (ITT) Population

		PROGRESSION FREE SURVIVAL		OVERALL SURVIVAL		RESPONSE RATE	
Study Name/ Number	**Parameter**	**Cetuximab + Control**	**Control**	**Cetuximab + Control**	**Control**	**Cetuximab + Control**	**Control**
NCIC CO.17/ BMS-025[13]	Median (mo) / Rate (%)	1.9	1.8	6.1	4.6	6.62%	0%
	Hazard Ratio*	**0.676**		**0.77**		**--**	
	95% CI	0.568, 0.804		0.64, 0.92		--	
	Log rank p-value	<0.0001		0.0046		<0.0001	
CRYSTAL/ EMR-013[19]	Median (mo) / Rate (%)	8.9	8.0	19.9	18.6	47%	39%
	Hazard Ratio*	**0.85**		**0.93**		---	
	95% CI	0.726, 0.998		0.81, 1.07		---	
	Log rank p-value	0.048		0.30		0.0038	
OPUS/ EMR-047[20]	Median (mo) / Rate (%)	7.2	7.2			46%	36%
	Hazard Ratio*	0.931				---	
	95% CI	0.705, 1.23				---	
	Log rank p-value	0.62				0.064	
EPIC / BMS-006[21]	Median (mo) / Rate (%)	3.98	2.56	10.71**	9.99	16.36%	4.15%
	Hazard Ratio*	**0.692**		**0.975**		---	
	95% CI	0.617, 0.776		0.854, 1.114		---	
	p-value***	<0.0001		0.7115		0. <0.0001	

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NA = not applicable since it was a cetuximab monotherapy

* Hazard ratio for cetuximab + control over control

** Proportion of subjects receiving EGFR inhibitors in the post-treatment phase of the study was 15.8% (23/146 subjects) in cetuximab plus irinotecan arm and 59.1% (91/154 subjects) in irinotecan alone arm.

*** Fisher's Exact Test p-value for difference in response.

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Table 4.3: Overall and Progression Free Survival in *K-ras* Subpopulations

		PROGRESSION FREE SURVIVAL				OVERALL SURVIVAL			
		***K-ras* Wild Type**		***K-ras* Mutant**		***K-ras* Wild Type**		***K-ras* Mutant**	
Study Name/ Number	**Parameter**	**Cetuximab + Control**	**Control**	**Cetuximab + Control**	**Control**	**Cetuximab + Control**	**Control**	**Cetuximab + Control**	**Control**
NCIC CO.17/ BMS-025	Median (mo)	3.8	1.9	1.8	1.8	9.5	4.8	4.5	4.6
	95% CI	3.1, 5.1	1.8, 2.0	1.7, 1.8	1.7, 1.8	7.7, 10.3	4.2, 5.5	3.8, 5.6	3.6, 5.5
	Hazard Ratio*	**0.40**		**0.99**		**0.55**		**0.98**	
	95% CI	0.30, 0.54		0.73, 1.35		0.41, 0.74		0.70, 1.37	
	Log rank p-value	<0.0001		0.96		<0.0001		0.89	
Interaction p-value† (predictive effect)		**0.0001**				**0.011**			
CRYSTAL/ EMR-013	Median (mo)	9.9	8.7	7.6	8.1	24.9	21.0	17.5	17.7
	95% CI	8.7, 14.6	7.4, 9.9	6.7, 9.4	7.5, 9.4	22.2, 27.8	19.2, 25.7	15.6, 20.2	14.4, 20.6
	Hazard Ratio*	**0.684**		**1.069**		0.844		1.031	
	95% CI	0.501, 0.934		0.710, 1.610		0.644, 1.105		0.741, 1.436	
	Log rank p-value	0.0167		0.7496		0.2166		0.8540	
Interaction p-value† (predictive effect)		**0.0721**				**0.27**			
OPUS/ EMR-047	Median (mo)	7.7	7.2	5.5	8.6	NA			
	95% CI	7.1, 12.0	5.6, 7.4	4.0, 7.4	6.5, 9.5				
	Hazard Ratio*	**0.570**		**1.830**					
	95% CI	0.358, 0.907		1.095, 3.056					
	Log rank p-value	0.0163		0.0192					
Interaction p-value† (predictive effect)		**0.0007**							

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Table 4.3: Overall and Progression Free Survival in *K-ras* Subpopulations

		PROGRESSION FREE SURVIVAL				OVERALL SURVIVAL			
		***K-ras* Wild Type**		***K-ras* Mutant**		***K-ras* Wild Type**		***K-ras* Mutant**	
Study Name/ Number	**Parameter**	**Cetuximab + Control**	**Control**	**Cetuximab + Control**	**Control**	**Cetuximab + Control**	**Control**	**Cetuximab + Control**	**Control**
EPIC / BMS-006	Median (mo)	3.98	2.79	2.60	2.69	10.94***	11.56	8.41	10.68
	95% CI	2.79, 5.36	2.37, 3.25	1.54, 3.58	1.51, 2.79	7.79, 13.24	9.46, 18.63	6.14, 11.01	8.41,13.96
	Hazard Ratio*	**0.77**		**1.00**		1.29		1.28	
	95% CI	0.57, 1.04		0.67, 1.49		0.89, 1.85		0.81, 2.01	
	Log rank p-value	0.0954		0.9853		0.1755		0.2874	
Interaction p-value† (predictive effect)		**0.4010**				**0.9889**			

NA = not applicable since it was a cetuximab monotherapy

* Hazard ratio for cetuximab + control over control

** Hazard ratio for WT over MT *K-ras*

*** Proportion of subjects receiving EGFR inhibitors in the post-treatment phase of the study was 15.8% (23/146 subjects) in cetuximab plus irinotecan arm and 59.1% (91/154 subjects) in irinotecan alone arm.

†Significance of *K-ras*/treatment interaction term in Cox model with *K-ras* status, treatment, and interaction. The p-value is statistical evidence of heterogeneity in the relative treatment effect across WT and MT subgroups.

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Table 4.4: Overall Response Rate and *K-ras* Subpopulations

Study Name / Number	Parameter	*K-ras* Wild Type		*K-ras* Mutant	
		Cetuximab + Control	Control	Cetuximab + Control	Control
NCIC CO.17/ BMS-025	ORR, n (%)	13 (12.8)	0 (0)	1 (1.2)	0 (0)
	95% CI	6.8, 18.9	0	--	0
	p-value*	**<0.0001**		**0.494**	
CRYSTAL/ EMR-013	ORR, n (%)	102 (59.3)	76 (43.2)	38 (36.2)	35 (40.2)
	95% CI	51.6, 66.7	35.8, 50.9	27.0, 46.2	29.9, 51.3
	p-value*	**0.0025**		**0.46**	
Interaction p-value† (predictive effect)		**0.026**			
OPUS/ EMR-047	ORR, n (%)	37 (60.7)	27 (37.0)	17 (32.7)	23 (48.9)
	95% CI	47.3, 72.9	26.0, 49.1	20.3, 47.1	34.1, 63.9
	p-value*	**0.011**		**0.106**	
Interaction p-value† (predictive effect)		**0.003**			
EPIC/ BMS-006	ORR, n (%)	10 (10.31)	7 (7.37)	6 (12.24)	3 (5.08)
	95% CI	5.05, 18.14	3.01, 14.59	4.63, 24.77	1.06, 14.15
	p-value*	**0.6130**		**0.2947**	

* Fisher's Exact Test for treatment difference within *K-ras* subpopulation

†Significance of *K-ras*/treatment interaction term in Cox model with *K-ras* status, treatment, and interaction

5 OVERVIEW OF ONGOING CLINICAL STUDIES

On 06-June-2008, NIH/NCI issued an action letter asking the investigators to suspend accrual for all CTEP-sponsored and Cooperative Group trials that contained cetuximab in the protocol regimen for patients with CRC until appropriate modifications to the protocol and informed consent were made, new information concerning *K-ras* was added, and patients with mutated *K-ras* (MT) in tumors were excluded.

Subsequent to this action letter, the sponsor also endorsed similar action and temporarily suspended enrollment for the two NCI-sponsored Phase 3 studies in mCRC currently ongoing in North America (CALBG 80405 and NCCTG 147) in which chemotherapy is administered with or without cetuximab (Table 5.1). In collaboration with the FDA, the

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study design for both studies was amended to limit accrual only to subjects with *K-ras* WT tumors. The K-*ras* mutational status in tumors is based on an assay that is validated with the recommendations of FDA. In addition, the sample size was expanded in both clinical studies and accrual has resumed (August 2008 for NCCTG and September 2008 for CALBG study). It is no longer feasible to conduct clinical trials in patients with MT *K-ras* in their tumors, and these two Phase 3 studies will provide an opportunity to prospectively assess cetuximab activity in patients with WT *K-ras* tumors.

Accrual in another ongoing study (S0600) was put on hold until the protocol was similarly amendment. As of Sept 2008, enrollment in this study had not resumed. A similar action has been taken on the part of the European cooperative group with the PETACC-8 adjuvant study.

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Table 5.1: An overview of ongoing clinical studies with prospectively planned *K-ras* analysis

Study Name/Number	Stage	Regimen	Primary End Point	No. of Subjects Enrolled		
				As of April-08	As of Sept-08*	*K-ras* WT
STUDIES IN NORTH AMERICA						
CALGB 80405/ BMS-245	CRC 1st line	Phase 3 FOLFOX or FORFIRI + Cetuximab, Avastin or Cetuximab / Avastin	OS	1326 / 2300	1421 / 3610*	2850
NCCTG 147/ BMS-074	CRC adjuvant	FOLFOX +/- Cetuximab	DFS	2344 / 2300	2506 / 3768*	2070
S0600	CRC 2nd line	FOLFIRI + Cetuximab ± Bev	OS	44 / 1260	Accrual on hold	TBD
STUDIES IN REST OF THE WORLD (RoW)						
COIN	CRC 1st line	Continuous FOLFOX or XELXOX ± Cetuximab or Intermittent FOLFOX or XELXOX	OS	2400 / 2421	Accrual on hold	TBD
PETACC-8	CRC adjuvant	FOLFOX-4 ± Cetuximab	DFS	1830 / 2000	1946 / 2549	1875

* After protocol amendment and increase in sample size

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6 OVERALL CONCLUSIONS AND NEXT STEPS

The impact of *K-ras* mutation on the efficacy of EGFR antibodies is based on a strong biologic rationale. Results of retrospective analysis show a clear benefit of adding cetuximab in patients with *K-Ras* WT in their tumors and suggest no such benefit in patients with tumors harboring K-ras mutations. Whereas *K-ras* is not a prognostic factor, it is a strong predictor of efficacy for cetuximab activity in mCRC. In spite of the limitations of retrospective analyses presented in Section 3 and 4 above, the consistency of results across multiple studies strongly supports *K-ras* a predictive biomarker for cetuximab activity.

Prospective clinical evaluation of *K-ras* subgroups (WT versus MT) is no longer feasible. In addition, the limited prospective data that will be available from ongoing studies are unlikely to substantially supplement the large and internally consistent body of evidence from retrospective analyses across multiple studies. Therefore, there is a need to clearly communicate these important findings on the predictive nature of *K-ras* to medical practitioners as they provide a unique opportunity to optimize patient care.

Although the medical and scientific community have already implemented *K-ras* testing in response to these data, constraints imposed by the current product label on sponsors to communicate *K-ras* data for risk-benefit assessment need to be addressed. A precedence has been set for regulatory approval / label change based on retrospective biomarker data for: (i) ERBITUX™ (cetuximab) and Vectibix (panitumumab) for *K-ras* in CRC (Europe), and (ii) Alimta (pemetrexed) for non-squamous histology in non-small cell lung cancer (NSCLC) in US and Europe. Keeping the significance of the relationship between efficacy and *K-ras* mutation status in view, it can be argued that patients with mCRC that have MT *K-ras* in their tumors do not derive benefit from administration of any EGFR-targeted therapies. Accordingly, the sponsor has initiated a dialogue and requested a meeting with the FDA in order to discuss the possibility of including *K-ras* data in the ERBITUX™ (cetuximab) label. This would allow for the appropriate communication of these important findings to oncologists on the best treatment options for their patients.

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