1) Regarding Cetuximab-induced skin reactions

As described in the table above (Common Adverse Events), cetuximab-induced skin reactions were among the most common adverse events observed during the clinical development of the product.

In addition to standard analyses of skin toxicity, the applicant performed further analyses to summarize duration and time to first occurrence of these AEs. The applicant-derived case definition for "acne-like rash", which consisted of a concatenation of the COSTART terms acne, rash, maculopapular rash or pustular rash, was used for analyses. When multiple events in the category overlapped in time, the last resolution date and the earliest onset date were used (i.e., the overall duration).

As mentioned in section V.C.2.b, FDA changed used an alternate case definition for "acne-like rash" since the applicant's definition slightly under-reported relevant reactions for purposes of providing optimal labeling incidence information. The FDA's alternate case definition was not used to generate time-to-event analyses, since the conclusions reached (perspectives on time to event, time to resolution, etc.) could be generalized from the analyses conducted using the applicant's case definition due to the large overlap between the populations identified by the applicant's and FDA's case definitions.

Table 42: Time to Event, Time to Recovery from Cetuximab-Induced Skin Toxicity

	Colorectal carcinoma	
	Cetux + Irino (N=354)	Monotherapy (N=279)
Patients (%) with Acne-like rash	285 (80.5)	232 (83.2)
Time of First occurrence		
Week 1	74 (26.0)	75 (32.3)
Week 2-3	164 (57.5)	134 (57.8)
Week 4-5	27 (9.5)	15 (6.5)
Week 6-10	13 (4.6)	8 (3.4)
> Week 10	7 (2.5)	0
Duration		
1-7 days	3 (1.1)	0
8-21 days	21 (7.4)	6 (2.6)
22-60 days	54 (18.9)	45 (19.4)
61-90 days	21 (7.4)	25 (10.8)
>90 days	83 (29.1)	61 (26.3)

At least one episode ongoing	78 (27.4)	84 (36.2)
Unknown	25 (8.8)	11 (4.7)
Patients (%) with Acne-like rash ongoing at Cetuximab discont'n	214 (60.5)	210 (75.3)
Time until resolution		
1-7 days	7 (3.3)	9 (4.3)
8-28 days	47 (22.0)	42 (20.0)
> 28 days	64 (29.9)	72 (34.3)
Unresolved	96 (44.9)	87 (41.4)

The skin toxicity due to cetuximab begins within the first three weeks of treatment, and does not appear to be influenced by the concomitant administration of irinotecan. After discontinuation of therapy, only about 25% of patients have resolved form the toxicity after 28 days. The reasons for the lengthy and incomplete reversibility of these adverse events are uncertain.

a) Significant adverse events with cetuximab combined with XRT

The most notable effect observed in patients receiving both cetuximab and radiation therapy (Trial IMCL-CP02-9813; EGFr-positive Stage III/IV or recurrent SCCHN) was increased skin reactions at the port area of treatment relative to those observed during either normal XRT or observed in other patients receiving cetuximab. Formal analyses were not performed, due to the small number of patients in the study (n=21), but the toxicity interaction effect appeared to be additive.

b) Other Skin Toxicity Analyses

During the latter stages of the review period, the applicant submitted small datasets and analyses to support comments in the proposed labeling regarding dose modification relative to development of Grade 3 skin toxicity

Language in the proposed labeling for cetuximab included recommendations that, if a patient were to develop a Grade 3 skin toxicity, that the subsequent dose of the product should be delayed, and subsequently decreased incrementally (200, then 150 mg/m^2) if the event did not improve. However, the applicant did not provide analyses from the clinical trial data set to substantiate these dosing recommendations.

Subsequent to conversation between FDA and the applicant, the applicant provided data and analyses that, although limited in quantity, indicated that delay of dose did indeed improve Grade 3 toxicity, and that dose reductions as recommended, in the circumstance of continued toxicity, did indeed lead to improvement in skin condition.

2) Subgroup analyses of common adverse events

Age, race and gender did not appear to affect the safety profile of cetuximab (see section IX. A. and B.).

3) Common Grade 3 / 4 Adverse Events (occurred in >5% of Phase 2 Patient Groups)

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Table 43: Grade 3 / 4 Adverse Events Occurring in >5% of Patients

Patients (%) with Grade 3 or 4 AE: (1)	Colorectal carcinoma		Other Indications	
	Cetux + Irino (N=354)	Monotherapy (N=279)	Cetux + Chemo (N=224)	Monotherapy (N=54)
Body as a Whole (2)				
Asthenia	53 (15.0)	28 (10.0)	38 (17.0)	4 (7.4)
Abdominal pain	27 (7.6)	19 (6.8)	14 (6.3)	1 (1.9)
Carcinoma	23 (6.5)	5 (1.8)	24 (10.7)	0
Pain	20 (5.6)	14 (5.0)	22 (9.8)	1 (1.9)
Cardiovascular System (3)				
Digestive System (4)				
Diarrhea	79 (22.3)	5 (1.8)	18 (8.0)	0
Vomiting	24 (6.8)	8 (2.9)	16 (7.1)	0
Nausea	21 (5.9)	5 (1.8)	14 (6.3)	0
Intestinal obstruction	12 (3.4)	17 (6.1)	7 (3.1)	0
Hemic / Lymphatic System				
Leukopenia	59 (16.7)	0	421 (18.8)	0
Anemia	16 (4.5)	11 (3.9)	23 (10.3)	3 (5.6)
Thrombocytopenia	4 (1.1)	1 (0.4)	12 (5.4)	0
Metab. / Nutritional D/o (5)				
Dehydration	23 (6.5)	6 (2.2)	26 (11.6)	1 (1.9)
Hypokalemia	15 (4.2)	5 (1.8)	13 (5.8)	0
Hyponatremia	5 (1.4)	1 (0.4)	20 (8.9)	0
Respiratory System				
Dyspnea	8 (2.3)	20 (7.2)	5 (2.2)	2 (3.7)
Skin and Appendages				
Rash	24 (6.8)	4 (1.4)	6 (2.7)	2 (3.7)
Acne	21 (5.9)	20 (7.2)	15 (6.7)	9 (16.7)

Source: Table 3.3A; Amended ISS pages 58-59

(1) Patients may have had more than one event within a body system

(2) Grade 3/4 Cellulites, Mucous membrane disorder and Bacterial infection was observed in 19%, 9.5% and 9.5%, respectively, of Cetuximab + XRT patients, but <5% in other groups

(3) Grade 3/4 Syncope was observed in 9.5% of Cetuximab + XRT patients, but <5% in other groups

(4) Grade 3/4 Anorexia, Constipation and Stomatitis was observed in 9.5%, 14.3% and 19.0%, respectively, of Cetuximab + XRT patients, but <5% in other groups

(5) Grade 3/4 Hyperglycemia was observed in 14.3% of Cetuximab + XRT patients, but <5% in other groups

Reviewer Comment: the pattern of severe adverse events due to cetuximab + irinotecan and cetuximab monotherapy were also reflected in the pattern observed with serious adverse events.

f. Less Common Adverse Events

Table 44: Grade 3 / 4 Events in <5 but > 1% of Patients

	Colorectal carcinoma		Other Indications	
	Cetux + Irino (N=354)	Monotherapy (N=279)	Cetux + Chemo (N=224)	Monotherapy (N=54)
Body as a Whole				
Infection	4 (1.1)	2 (0.7)	8 (3.6)	0
Fever	13 (3.7)	0	3 (1.3)	0.0
Headache	6 (1.7)	8 (2.9)	3 (1.3)	0.0
Back pain	10 (2.8)	8 (2.9)	8 (3.6)	2 (3.7)
Ascites	8 (2.3)	7 (2.5)	4 (1.8)	0
Sepsis	15 (4.2)	7 (2.5)	8 (3.6)	0
Allergic reaction	3 (0.8)	4 (1.4)	5 (2.2)	0
Cardiovascular System				
Hypotension	7 (2.0)	3 (1.1)	9 (4.0)	0
Hemorrhage	0	0	7 (3.1)	0
Thrombosis	7 (2.0)	2 (0.7)	1 (0.4)	0
Digestive System				
Anorexia	14 (4.0)	8 (2.9)	9 (4.0)	1 (1.9)
Diarrhea	79 (22.3)	5 (1.8)	18 (8.0)	0
Constipation	6 (1.7)	3 (1.1)	8 (3.6)	1 (1.9)
Jaundice	10 (2.8)	4 (1.4)	4 (1.8)	0
GI hemorrhage	2 (0.6)	1 (0.4)	5 (2.2)	0

Metab / Nutritional d/o				
Hypomagnesemia	2 (0.6)	0	9 (4.0)	0
Weight loss	0	4 (1.4)	7 (3.1)	0
Hyperglycemia	10 (2.8)	1 (0.4)	8 (3.6)	2 (3.7)
Bilirubinemia	14 (4.0)	3 (1.1)	0	0
Hypocalcemia	5 (1.4)	1 (0.4)	5 (2.2)	0
Respiratory System				
Pleural effusion	2 (0.6)	8 (2.9)	0	0
Pneumonia	7 (2.0)	5 (1.8)	10 (4.5)	1 (1.9)
Lung disorder	1 (0.3)	1 (0.4)	5 (2.2)	0
Apnea	0	3 (1.1)	7 (3.1)	0

Source: Amended ISS, Table S.3.2A, pages 85-140

g. Laboratory Findings

Amended ISS Tables S.3.10.1 (hematology, pages 213-214) and S.3.10.2 (serum chemistries. Pages 215-222) were reviewed. The number and percentage developing Grade 3 / 4 laboratory values are presented. Severity was assessed according to the toxicity criteria defined in the NCI Common Toxicity Criteria version 2.0.

Table 45. Incidence of Grade 3/4 Laboratory Changes

	Colorectal cancer # (%) of patients with development of Grade 3/4	
	Cetuximab + Irinotecan (n=354)	Cetuximab monotherapy (n=279)
Hematology		
Hemoglobin, low	14 (4.0)	7 (2.6)
WBC, low	33 (9.3)	1 (0.4)
Platelet, low	1 (0.3)	1 (0.4)
Chemistries		
Albumin, low	6 (1.7)	3 (1.3)
Alk Phos, high	30 (9.5)	34 (12.2)
AST, high	5 (1.6)	12 (4.9)
Total bilirubin, high	11 (3.4)	15 (5.4)
Potassium, high	1 (0.3)	2 (0.7)
Potassium, low	12 (3.4)	5 (2.0)
Sodium, low	10 (3.1)	14 (5.0)
Calcium, low	7 (2.0)	6 (2.2)
Glucose, high	11 (3.4)	6 (2.2)
Glucose, low	0	1 (0.4)
Creatinine, high	3 (0.8)	1 (0.4)

Source: Amended ISS Table S.3.10, pages 79-80

Reviewer Comment: Although most lab abnormalities were consistent with known toxicities of irinotecan, cetuximab monotherapy was associated with occasional bilirubinemia and hyponatremia possibly above the background incidence expected with advanced colorectal carcinoma.

h. Withdrawal Phenomenon / Abuse Potential

There is no evidence of abuse potential by cetuximab.

i. Human Reproduction and Pregnancy Data

No studies have been conducted to assess the human reproduction toxicity potential of Cetuximab. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the

developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore cetuximab has the potential to be transmitted from the mother to the developing fetus. As part of phase IV commitment, the applicant will conduct nonclinical reproductive toxicology studies (ies) of cetuximab in a suitable animal species.

j. Overdose Experience

In the Serious Adverse Event database, there was one reported case of overdose of cetuximab (Patient EMR62202-007-302-1). Upon review of the case report form and the narrative of the case, the patient received the appropriate dose, however, it was administered intravenously over a 30 minutes period instead of the prescribed 39.5 minute period. Thus the investigator noted the event to be an overdose. There were no clinical sequelae of this event.

k. Post-Marketing Experience in U.S. and Foreign Markets

At the time of the filing of the BLA, the product had not been approved in U.S. or foreign markets.

D. Adequacy of Safety Testing

The safety population represents a population of advanced stage, previously heavily treated patients with colorectal carcinoma and other solid tumors. The population is likely to represent the usual patient with co-morbid illnesses and previous therapy. Adverse events related to ERBITUX were commonly observed, suggesting that near maximal dosing was achieved. As such, for the specific labeled indication, the safety testing is adequate and credible.

E. Summary of Critical Safety Findings and Limitations of Data

1. Summary of Critical Safety Findings

More than 1123 cancer patients were treated with cetuximab during its clinical development program. Clinical information from 911 patients enrolled in Phase 2 studies was used to assess the overall toxicity profile of cetuximab; this was supplemented by data from Phase 1 studies, studies conducted outside of the IND (in Europe), and studies conducted with product from an alternate manufacturing site in order to characterize unusual and serious adverse events. In the Phase 2 studies, treatment with cetuximab was either as a single agent, or in combination with chemotherapy or radiation therapy. The majority of patients in the Phase 2 safety database had colorectal cancer. The chemotherapeutic agent most commonly used in combination with cetuximab was irinotecan.

Acneform-rash skin toxicity was the most common adverse event associated with cetuximab. The reaction was described by a variety of terms (acne, rash, pustular rash, dry skin, exfoliative dermatitis, etc.), usually occurred within the first three weeks of therapy, and was often severe. Associated incidences of blephitis, cheilitis, skin ulcerations and boils were observed, and an unusual adverse event, paronychial inflammation/infection, was observed in a significant percentage (13%) of the patients who received cetuximab. In most patients there was improvement in severe skin reactions with dose reduction or cessation of cetuximab, however even in those patients with improvement, complete resolution of toxicity did not occur prior to death or discontinuation from study. In a small number of cases, patients with severe (Grade 3) skin toxicity developed concomitant *Staph aureus* septicemia and sepsis.

Infusion reactions occurred in 19% of patients who received ERBITUX plus irinotecan and 25% of the patients who received ERBITUX monotherapy, even in the presence of antihistamine prophylaxis. Occasionally infusion reactions were severe, including a report of a patient death in an ongoing study not associated with the BLA ISS population. Severe infusion reactions usually occurred at the time of first infusion of cetuximab, even while being premedicated with antihistamines. Treatment of patients with a test dose of cetuximab was found to not be predictive of occurrence of severe infusion reaction.

Pulmonary toxicity in the form of interstitial lung disease was a rare but significant toxicity associated with cetuximab. Two patients developed interstitial pneumonitis following administration of cetuximab, and one of the patients died as a result of their ILD. Two patients with pre-existing pulmonary fibrosis experienced a worsening of their disease while receiving cetuximab in a manner similar to that observed in another EGF receptor / pathway based therapy.

Diarrhea and neutropenia in the clinical studies were most often due to concomitant chemotherapy. Addition of cetuximab did not appear to worsen adverse events associated with chemotherapy, and concomitant chemotherapy treatment did not appear to impact cetuximab-associated adverse events.

There did not appear to be differences according to gender or age on the relative incidence or severity of cetuximab-induced adverse events.

2. Limitations of Data

During the BLA review period, various questions emerged that could not be resolved due to limitations in the data provided. Other search strategies were necessary to apply to the clinical safety database to resolve these issues.

a. Comparison of irinotecan toxicities alone versus in combination with cetuximab

Reviewer's Comments: In response to FDA request, the applicant addressed the issue of whether cetuximab was increasing or potentiating any of the adverse events associated with irinotecan. Table 46 compares information about relevant adverse events associated with irinotecan. The information was copied from the irinotecan product label and incidence rates were presented and compared to incidence data from the cetuximab + irinotecan combination group with colorectal cancer in the current BLA submission for cetuximab.

Table 46: Between-trial Comparison of Adverse Events Related to Irinotecan versus Cetuximab + Irinotecan

	AE Data from Current Irinotecan Label		AE Data from Cetuximab + Irinotecan Groups	
Body System / Event	% subjects reporting (N=304) NCI Grades 1-4	NCI Grades 3-4	% subjects reporting (N=354) NCI Grades 1-4	NCI Grades 3-4
Body as a Whole				
Asthenia	76	12	71	15
Chills	14	0	11	1
Gastrointestinal				
Diarrhea (late)	88	31	72	22
Nausea	86	17	55	6
Vomiting	67	12	41	7
Anorexia	55	6	36	4
Stomatitis	12	1	26	2
Hematologic				
Leukopenia	63	28	25	17
Anemia	60	7	16	5

Reviewer's Comments:
Although the clinical trials were performed at different times and under different conditions, this comparison represents a reasonable attempt to discern potential toxic interactions between the two components. It does not appear that cetuximab or irinotecan worsen the toxicities associated with the other component of the combination.

b. Discontinuation of the initial practice of a cetuximab test dose
Refer to section VII.C.2.c (1), Serious Adverse Events / Infusion Reaction Analyses

c. Infusion rate change for Grade 1 / 2 Infusion Reaction
Refer to section VII.C.2.c (1), Serious Adverse Events / Infusion Reaction Analyses.

d. Skin Toxicity Analyses
Refer to section VII.C.2.e (1) (b), Common Adverse Events / Other Skin Toxicity Analyses

VIII. Dosing, Regimen, and Administration Issues

The recommended dose of ERBITUX in combination with irinotecan is an initial dose of 400mg/m^2 intravenously a 120-minutes infusion with subsequent weekly doses of 250mg/m^2 infused over 60 minutes. Premedicaiton with an H1 antagonist (e.g. 50 mg of (diphenhydramine) should be used. Patients should be observed for at least 1 hour following infusion of ERBITUX. Appropriate medical resources for the treatment of severe infusion reactions should be available during ERBITUX infusions.

In the colorectal studies submitted in this application, a 20 mg test dose was administered prior to the loading dose to all patients on day 1. Analysis of subsequent clinical data submitted to the application indicated that the test dose did not reliably identify patients at risk for severe allergic reactions. Therefore, the test dose is no longer required.

In the event of infusion reactions, the following dose modification parameters should be applied: For grade 1 or 2 infusion reactions, the infusion rate should be permanently reduced by 50%. In the event severe (grade 3 or 4) infusion reactions, ERBITUX should be immediately and permanently discontinued.

The following guidelines for dose adjustments in the event of severe acneform rash (grade 3 or 4) are recommended:

Table 47 ERBITUX Dose Modification Guidelines

Severe Acneform Rash	ERBITUX	Outcome	ERBITUX Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No Improvement	Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No Improvement	Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

The following irinotecan schedules can be used in combination with ERBITUX: 350mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks or 125 mg/m^2 weekly times 4 doses with 2 weeks rest. In the event

the patient receives irinotecan on the same day, irinotecan should be administered after the 1-hour observation period following the ERBITUX infusion.

IX. Special Issues Related to Biological Products:

A. Integrated Summary of EGFr Expression:

Patients enrolled in the all three colorectal studies were required to have immunohistochemical evidence of positive EGFr expression. Primary tumor or tumor from metastatic site (paraffin embedded tissue blocks or slides) were sent to a central laboratory for testing. The detection of EGFr was performed by immunohistochemical staining using a Dako Cytomation EGFr pharmDx™ kit.

For the EMR62 202-007 study, specimens were scored based on the percentage of cells expressing EGFr and intensity (faintly/barely, weak to moderate or strong).
For IMCL-CP02-9923 and IMCL-CP02-0141, specimens were scored as 1+, 2+, or 3+.

Of a total of 1118 colorectal cancer tumor samples tested for EGFr expression, 77.7% (869) had EGFr expression scored as 1+ or greater. The results of EGFr screening from the three colorectal trials as summarized in Table 48.

Table 48. EGFr Expression in Colorectal Cancer

Colorectal Study	Screened	EGFr 1+ or greater (%)	Enrolled
EMR 662-02- 007	577	472 (82.1%)	329
IMCL-CP02-9923	401	292 (73%)	139
IMCL-CP-02-0141	140	105 (75%)	61
Total	1118	869 (77.7%)	529

The relationship between level of EGFr expression and tumor response was analyzed and are shown in Table 49 and 50.

Table 49. EGFr Expression in the ITT Population and all Responders (EMR662-02-007 Study)

EGFr expression	ITT population N=329 (%)	All responders N= 62 (%)
% Of positive cells		
0	2 (0.6)	-
0 - < 10%	163 (49.5)	29 (46.7)
10 - < 20%	36 (10.9)	9 (14.5)
20 - ≤35%	34 (10.3)	6 (9.6)
≥35%	94 (28.5)	18 (29.0)
Staining intensity		
Faint/barely	74 (22.7)	12 (19.0)
Weak or moderate	144 (43)	29 (46.7)
Strong	109 (33)	21 (33.8)
Missing	2 (0.6)	-

Table 50. EGFr Expression in all Enrolled Patients and all Responders (IMCL-CP02-9923 and 0141 studies)

	All treated patients	All responders
IMCL-CP-02-9923	N=138 (%)	N= 21 (%)
EGFr status		
1+	66 (47.8)	11 (16.7)
2+	48 (34.8)	7.48 (14.6)
3+	24 (17.4)	3/24 (12.5)
IMCL-CP-02-0141	N = 57 (%)	N = 5 (%)
EGFr status		
1+	17 (29.8)	1 (5.9)
2+	30 (52.6)	4 (13.3)
3+	10 (17.5)	0 (0.0)

Reviewer's comment: based on the available data, 77.7 % of the colorectal tumor samples tested positive for EGFr staining using the Dako Cytomation EGFr pharmDx™ kit. There are no clear correlation between tumor response and EGFr expression. No efficacy data are available on patients whose tumor are negative by EGFr staining.

B. Human Anti-Cetuximab Antibody (HACA)

As with all therapeutic proteins, ERBITUX has the potential for immunogenicity.

Antibody responses to ERBITUX were assessed using either a double antigen radiometric assay or an enzyme linked immunosorbant assay. These assays have not yet been validated, therefore the

incidence of antibody development in patients receiving ERBITUX presented here has to be interpreted with caution.

Patient population: 17 clinical studies contributed to the anti-cetuximab antibody database. The incidence of anti-cetuximab antibody response was examined in 614 patients treated with cetuximab from studies in which multiple doses of cetuximab were administered. Of these, 534 patients were considered evaluable for anti-cetuximab antibody responses, i.e., patients had a pre- and post-baseline sample available for analysis. In the EMR 62 202-007 study, the protocol was amended to collect blood samples at 6 weeks after the last dose of cetuximab when studies indicated that presence of cetuximab interfere with ELISA assay to measure HACA.

Anti-Cetuximab Assays: In the EMR 62 202-007 and all other studies conducted by Merck K.G, (EMR protocols), a sandwich ELISA was used to determine the anti-cetuximab responses. In the IMCL-CP02-9923 and 014 studies and all studies conducted by ImClone (IMCL protocols), double-antigen, radiometric assay specific for cetuximab was used. (For additional information regarding assay procedures, assay sensitivity, assay positivity criteria, refer to CMC review by Dr. Chana Fuchs)

The incidence of HACA in the clinical trials, as per applicant are summarized in Table 51.

Table 51. Anti-Cetuximab Incidence by Study

	NUMBER OF PATIENTS				
Study Number[1]	Treated	Tested	Evaluable	Positive Response[2]	Incidence (% patients)
IMCL CP02-9401	13	-	-	0	-
IMCL CP02-9502	17	16	13	3	23.1
IMCL CP02-9503	22	19	13	3	23.1
IMCL CP02-0504	36	35	31	1	3.2
IMCL CP02-9605	12	10	8	0	0.0
IMCL CP02-9607	16	14	11	0	0.0
IMCL CP02-9608	12	11	9	1	11.1
IMCL CP02-9709	5	2	2	0	0.0
IMCL CP02-9710	54	52	49	0	0.0
IMCL CP02-9813	21	21	18	5	22.2
IMCL CP02-9814	41	40	35	0	0.0
IMCL CP02-9816	130	98	83	1	1.2
IMCL CP02-9923	**138**	**136**	**110**	**2**	**1.8**
IMCL CP02-0038	30	30	29	0	0.0
IMCL CP02-0141	**57**	**56**	**50**	**0**	**0.0**
EMR 62-202-007	**327**	**60**	**59**	**5**	**8.5**
EMR 62-202-012	14	14	14	0	0.0
Overall	945	614	534	20	3.7

1. For additional information regarding each study, please refer to Tables 3-6
2. cut point = upper 95%CI of mean or 7 ng/mL cut point

The overall incidence of HACA was 5.3% (28 of 534) of evaluable patients. In patients positive for anti-cetuximab antibody, the median time to onset was 44 days (range 8-281 days). The incidence of HACA in the colorectal studies are highlighted in the table X. Five out of 59 evaluable patients developed HACA (8.5%) in the EMR 62-202-007 study. In the IMCL CP02-0023 study, the incidence of HACA was 1.8 % (2/110) and no patients had detectable HACA in the IMCL CP02-0141 study (0/50)

The time to onset did not appear to correlate with maximum level of response. The mean and median duration of observed anti-cetuximab responses was 40 and 28 days, respectively (range 6 to 99 days). Duration could not be calculated in a large number of patients since the final sample was positive.

HACA and safety concerns:

Review of the clinical data from the 28 patients with positive HACA was conducted with close attention to possible signs and symptoms of allergic or anaphylactic reactions.

Six out of 28 patients had signs or symptoms of infusion/allergic reactions, however on closer reviewer, none of them appear to be related to the presence of HACA.

- Patient 9813-061319 was noted to have an unspecified "allergic reaction" to oxycodone as per investigator on week 5 of ERBITUX treatment/ Reaction was solved and the patient received additional doses of ERBITUX with out incidences. Positive HACA was detected 12 weeks after the last infusion of ERBITUX.

- Patient 9608-001303 had fever and chills associated with ERBITUX infusion. This patient had a baseline anti-cetuximab level ≥10ng/ml, however subsequent blood samples did not show HACA positivity. Patient received additional doses of ERBITUX with no infusion or allergic reactions.

- Patient 9816-040-593 had a grade 1 chills and hypotension after ERBITUX infusion on day one. Positive HACA was detected on day 43 of treatment.

- Patient CP02-9503-003-603 was noted to have facial swelling, recorded after the 4th dose, but else where in the CRF, it was mentioned as pre-existing prior to study.

- Patient CP02-9813-061-308 was found to have wheezing on physical exam prior to the second infusion (along with findings of diaphoresis, tachycardia, unsteady gait). The dose that week was withheld, but the patient went on to receive additional doses of ERBITUX with no allergic reactions.

- In the EMR-6202-007, 14 patients had blood samples collected 6 weeks after the last dose of ERBITUX as per protocol amendment 3 (Refer to Section X) . HACA was detected in one patient (ID 502-02). An additional 47 patients were selected for determination of HACA based on AEs associated with inflammatory or hypersensitivity reactions (e.g. chills, fever). Of these, 4/47 patients had positive HACA (402-2, 405-16, 801-6, 906-7). Patient ID 502-02 had no reactions. Patients ID 402-2, 405-16, 801-6, 906-7 had grade 1 fever and chills related to ERBITUX infusion (day1) or other intercurrent illnesses.

Reviewer's conclusion: based on the available data, development of anti-cetuximab antibody does not appear to be associated with allergic or anaphylactic reactions. The reviewers note that the assays used in these trials have not yet been validated, therefore the results must be taken with caution.

X. Use in Special Populations

A. Evaluation of Applicant's Gender Effects Analyses and Adequacy of Investigation

In the pivotal trial, 206 (62.6%) patients were male and 123 (37.4 %) female. Of the 50 responders in the combination arm, 36 were male and 14 female yielding response rates of 25.2% [36/143] and 18.7% [14/75], respectively. Of the 12 responders in the monotherapy arm, 10 were male and 2 were female. In the supporting trial CP02-9923, there were 21/138 responders, 14 were male and 7 were female (18.4 [14/76] and 11.2% [7/62], respectively. Definitive conclusions regarding the comparability of efficacy cannot be made due to the small number of patients. On population pharmacokinetic analysis based on data from approximately 900 patients, female patients had a 25% lower intrinsic ERBITUX clearance than male patients. Regarding gender effects on safety outcomes, although adverse event incidences differed between gender groups, there was no consistent pattern or category of events suggesting differences in the adverse event profile by gender.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Age

The median age of patients on the EMR 62 202-007 study was 59 years (range 39-80). Eighty-nine patients (27%) were 65 years old or older. Responses were observed in patients 65 years and older, however due to the small number of patients studied, definitive conclusions regarding comparable efficacy cannot be made. Regarding age effect on safety outcomes, although adverse event incidences differed between the age groups, there was no consistent pattern or category of events suggesting differences in the adverse event profile in elderly as compared to younger patients.

2. Race

Since blacks, Asians, Hispanics, and other racial groups each constituted 5% or fewer of the patients who received cetuximab, there are insufficient numbers of patients to permit valid comparisons of relative efficacy and relative

incidence/severity of adverse events in these ethnic groups as compared to Caucasians. There was no evidence of differences in pharmacokinetic profile by race, although the numbers of patients studied in each group are small.

C. Evaluation of Pediatric Program

The product has not been evaluated in pediatric patients. As part of the phase IV commitment, the applicant will conduct phase I and II studies in children and adolescents who have EGFr expressing, pediatric solid tumors.

D. Comments on Data Available or Needed in Other Populations

No clinical data available on EGFr-negative patients. As part of phase IV commitment, the Applicant will conduct and submit the results of a Phase 2 study with ERBITUX monotherapy, to enroll patients with refractory, EGFr-negative, metastatic colorectal cancer to estimate the response rate and duration of response.

XI. Conclusions and Recommendations

A. Conclusions Regarding Safety and Efficacy

EMR-62 202-007 is a well-conducted, randomized phase 2 trial in a refractory, metastatic colorectal patient population who had failed a prior irinotecan-containing regimen. Stringent criteria were applied to confirm irinotecan refractoriness of the efficacy population. In addition, to having failed irinotecan and 5-fluorouracil, 38% of the patients (124/329) had also failed prior therapy with oxaliplatin. There has been no effective therapy found for this patient population.

In the ERBITUX plus irinotecan arm, the objective tumor response rate was 22.9% in the ITT population . A similar response rate was confirmed in the IRC-PD (25.8%) and IRC-PD oxaliplatin refractory population (23.8%). A clinically meaningful objective tumor response rate was also confirmed for ERBITUX monotherapy ITT population (12.1%) and secondary populations, IRC-PD (11.3%) and IRC-PD oxaliplatin failure (12.4%). A statistically significant improvement of tumor response rate was observed in the ERBITUX and irinotecan arm in the ITT population (p-value 0.0074), however the study was not powered to detect statistical significance for the secondary populations. The median time to progression for the ERBITUX plus irinotecan was 4.1 months compared to 1.5 month for ERBITUX monotherapy (p value < 0.0001).

Both supporting trials IMCL-CP-02-9923 and 0141 confirm that ERBITUX in combination with irinotecan or as monotherapy can induce objective tumor responses in this refractory colorectal cancer population.

The most serious adverse reactions associated with cetuximab were infusion reactions, dermatologic toxicity, interstitial lung disease, fever, sepsis, kidney failure and pulmonary embolus. In general, however, patients tolerated the adverse events caused by cetuximab. In the indicated population (patients with metastatic colorectal cancer), there appeared to be a higher likelihood of adverse events in patients that received cetuximab + irinotecan relative to cetuximab monotherapy. However, since there also appears to be improved efficacy in the combination therapy, the benefits of the combination therapy would seem to outweigh the risks.

Acneform-rash skin toxicity was the most common adverse event associated with cetuximab. The reaction was described by a variety of terms (acne, rash, pustular rash, dry skin, exfoliative dermatitis, etc.), usually occurred within the first three weeks of therapy, and was often severe. Associated incidences of blephitis, cheilitis, skin ulcerations and boils were observed, and an unusual adverse event, paronychial inflammation/infection, was observed in 13% of the patients who received cetuximab. In most patients there was improvement in severe skin reactions with dose reduction or cessation of cetuximab, however even in those patients with improvement, complete resolution of toxicity did not occur prior to death or discontinuation from study. In a small number of cases, patients with severe (Grade 3) skin toxicity developed concomitant *Staph aureus* septicemia and sepsis.

Infusion reactions occurred in 19% of the patients who received ERBITUX plus irinotecan and 25% of the patients who received ERBITUX monotherapy, even in the presence of antihistamine prophylaxis. Occasionally infusion reactions were severe, and death has been reported. Severe infusion reactions usually occurred at the time of first infusion of cetuximab, even while being premedicated with antihistamines.

Pulmonary toxicity in the form of interstitial lung disease was a rare but significant toxicity associated with cetuximab. Death was reported in one as a result of their ILD.

Diarrhea and neutropenia in the clinical studies were most often due to concomitant chemotherapy. Addition of cetuximab did not appear to worsen adverse events associated with chemotherapy, and concomitant chemotherapy treatment did not appear to impact cetuximab-associated adverse events.

B. Recommendations

We recommend accelerated approval of ERBITUX for the following indications

- ERBITUX in combination with irinotecan, is indicated for the treatment of patients with EGFr-expressing metastatic colorectal cancer, which has progressed or recurred after an irinotecan-containing chemotherapy regimen.

- ERBITUX monotherapy is indicated for the treatment of patients with EGFr-expressing metastatic colorectal cancer, which has progressed or recurred after an irinotecan-containing chemotherapy regimen, and who are intolerant to irinotecan.

XII. Appendix

A. Imaging Efficacy Review

Diagnostic Imaging Review: Independent Review Committee Charter

BLA 128778
Sponsor ImClone Systems Inc.
Product Cetuximab

Contract Research Organization

[redacted]

Reviewer Mary Andrich, MD

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Executive Summary

1.0 Recommendations

1.1 Recommendation on Approvability

Reviewer Comment:

The FDA verified that the Independent Review Committee (IRC) Charter, providing the procedure for an independent evaluation of the radiographic response to therapy, was followed. For selected subjects listed below, the IRC evaluation of imaging studies was reviewed. Comparisons were made between the IRC analysis of imaging studies, response data in the BLA line listings, and imaging data in the BLA Case Report Forms (CRFs). The IRC database is reliable with regard to confirmation of tumor response to therapy, and supports the approval of cetuximab for the proposed indication—use in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy.

2.0 Summary of Diagnostic Imaging Review

2.1 Submission of Imaging Data

The sponsor submitted patient imaging data for the following three studies. (Archival Copy dated 14 August 2003, including DVD 1, 1a, 2-49; BLA 125084/0/000)

- EMR 62 202-007: BOND – Bowel Oncology with Cetuximab Antibody: Open, Randomized, Multicenter, Phase 2 Study of Cetuximab Alone or in Combination with Irinotecan in Patients with Metastatic Colorectal Adenocarcinoma Expressing the Epidermal Growth Factor Receptor (EGFR) and Progressing on a Defined Irinotecan-Based Regimen.

- IMCL CP02-9923: Phase II Study of Anti-Epidermal Growth Factor Receptor (EGFR) Antibody Cetuximab in Combination with Chemotherapy in Patients with Advanced Colorectal Carcinoma

- IMCL CP02-0141: Phase II Study of an Anti-Epidermal Growth Factor Receptor (EGFR) Antibody, Cetuximab, in Patients with Irinotecan-Refractory, Stage IV Colorectal Carcinoma

Reviewer Comment:

For 97 subjects in EMR 62 202-007, 8 in IMCL CP02-0141, and 28 in IMCL CP02-9923, the FDA verified that images submitted by the sponsor were adequate for review, and

that the IRC charter was followed. Subjects were chosen using the criteria listed below in Section 2.2. The FDA did not readjudicate the image interpretations of the IRC radiologists.

2.2 Review of Imaging Data

Reviewer Comment:

For all of the subjects listed below, the FDA reviewed the [redacted] IRC data and compared it to the CRF imaging data submitted to the BLA. Other than minor differences in dates, no significant discrepancies were noted.

2.2.1 Subjects Responding to Therapy—Pre-Study Scans

This group included subjects who demonstrated an On-Study response to therapy. Pre-Study scan data were reviewed to confirm PD or OT.

Study	Subjects
EMR 62 202-007	104-004, 200-002, 201-005, 202-001, 204-001, 204-002, 208-001, 208-003, 300-007, 300-011, 301-006, 301-010, 301-020, 305-001, 306-014, 401-002, 402-003, 403-001, 404-002, 405-003, 405-015, 500-010, 502-002, 503-001, 600-010, 600-011, 600-012, 600-013, 600-021, 600-039, 600-040, 600-046, 600-064, 601-007, 601-010, 602-003, 602-007, 603-001, 603-003, 603-006, 603-014, 603-015, 603-026, 603-035, 800-004, 800-005, 802-006, 802-009, 804-003, 804-007, 901-004, 903-005, 904-004, 904-043, 905-004, 906-009, 1001-003, 1002-002, 1002-008, 1100-001, 1100-002, 1100-010
IMCL CP02-0141	001-1135, 002-1150, 002-1151, 003-1154, 061-1108
IMCL CP02-9923	020-624, 020-627, 020-635, 020-649, 028-661, 029-704, 035-685, 035-728, 036-678, 043-643, 060-621, 060-660, 060-667, 060-738, 061-615, 061-683, 061-718, 066-632, 068-724, 502-699, 502-715

Study	Number of Subjects	Pre-Study PD	Pre-Study OT	No Pre-Study Images*
EMR 62 202-007	62	50	9	3
IMCL CP02-0141	5	4	1	0
IMCL CP02-9923	21	11	10	0

2.2.2 Subjects Responding to Therapy—On-Study Scans

After subjects were confirmed to have PD on the Pre-Study Scans, the On-Study scans were reviewed to verify response.

Study	Subjects	Number of Subjects with PD Pre-Study / Number of Subjects with Response On-Study
EMR 62 202-007	104-004, 200-002, 201-005, 202-001, 204-001, 204-002, 208-001, 208-003, 300-007, 301-006, 301-010, 301-020, 305-001, 306-014, 401-002, 403-001, 404-002, 405-015, 502-002, 503-001, 600-010, 600-012, 600-013, 600-040, 600-046, 600-064, 601-007, 602-003, 603-001, 603-003, 603-006, 603-014, 603-015, 603-026, 603-035, 800-004, 800-005, 802-006, 802-009, 804-003, 804-007, 901-004, 904-004, 904-043, 905-004, 906-009, 1001-003, 1002-002, 1002-008, 1100-002	50/62
IMCL CP02-0141	001-1135, 002-1150, 003-1154, 061-1108	4/5
IMCL CP02-9923	020-649, 028-661, 043-643, 060-667, 060-738, 061-615, 061-683, 061-718, 066-632, 502-699, 502-715	11/21

Study	Number of Subjects with Confirmed PR On-Study / Number with PD Pre-Study and Response On-Study
EMR 62 202-007	50/50
IMCL CP02-0141	4/4
IMCL CP02-9923	11/11

2.2.3 Subset of Subjects Not Responding to Therapy—Pre-Study and On-Study Scans

From the patients who did not respond to therapy, Pre-Study and On-Study imaging data were reviewed for approximately 10% who were randomly selected.

Study	Subjects	Number of Subjects	No Images
EMR 62 202-007	103-002, 104-002, 304-001, 306-010, 400-004, 401-004, 405-017, 502-004, 502-007, 503-002, 505-006, 600-032, 600-036, 602-006, 602-009, 603-008, 603-027, 702-002, 801-006, 804-011, 904-007, 904-016, 904-034, 907-004, 1002-001, 1100-005, 1100-006	27	4*
IMCL CP02-0141	001-1132, 001-1153, 002-1152	3	0
IMCL CP02-9923	001-611, 023-630, 060-604, 060-653, 061-631, 063-716, 065-684	7	1**

* No Pre-Study scans for 502-007. No On-Study scans for 304-001, 306-010, 502-007.

** No On-Study scans for 002-1152.

3.0 IRC Charter

Reviewer Comment:

The FDA reviewed and approved the IRC Charter prospectively prior to the performance of the Independent Review by —. The IRC Charter submitted to the BLA is consistent with the prospectively approved Charter. The provisions of the IRC Charter are acceptable, and consistent with its implementation.

3.1 IRC Objective

The objective of the IRC was to provide an unbiased, independent review of subject data based on the following:

- Refractoriness to prior irinotecan therapy.
- Response to either Cetuximab alone versus Cetuximab plus irinotecan.

3.2 Provisions of the IRC Charter

For study EMR 62 202-007, the independent review process is described in the IRC charter, dated 15 August 2002, and modified on 28 October 2002, prior to the start of the review. A similar charter was used for the other two protocols, IMCL CP02-9923 and IMCL CP02-0141.

The IRC was composed of three board-certified radiologists (or national equivalent), and an oncologist.

Pre-study scans and limited clinical data (details of prior irinotecan therapy) were used to establish whether the patient had a pre-study status of Progressive Disease (PD) or a pre-study status of non-PD.

The radiologists assessed on-study scans and clinical data (patient listings of adverse events, physical examination, concomitant medications and laboratory safety variables) to determine the primary efficacy endpoint of best overall response, date of first response, date of response confirmation, date of progression, and date of last tumor assessment (provided by —).

The clinical data presented during independent review did not include lesion measurements or response assessments as reported by the clinical investigators. The IRC members were blinded with regard to institution, patient, and treatment group.

In the original protocol, the IRC was to assess tumor responses according to the RECIST criteria. This was changed to modified WHO criteria in Amendment 2 in order to ensure that the results were consistent with those of other studies being conducted with Cetuximab in the United States.

The Contract Research Organization, [redacted] conducted the independent review process. Subject imaging data, on optical or magnetic media and films, were sent to [redacted] from the study sites. The imaging data were transferred to a computer system and converted into a digitized format.

Review of the pre-study scans and the on-study scans was conducted separately. The database was locked after each time point of the blinded reading to ensure that the next time point of the evaluation would not influence the previous part.

Images from each subject were evaluated independently by two radiologists (Readers 1 and 2). Adjudication was performed by a third radiologist (Reader 3). Finally, Reader 3 and the oncologist re-assessed the subject response based on both images and clinical data.

Scans were evaluated in six separate reading sessions.

- Session I
  - Confirmation and measurement of index lesions at baseline.
  - Display of baseline images.
  - Reader 1 and Reader 2 could confirm or change the selection of lesions and measurements made by [redacted] in their preliminary measurement.

- Session II
  - Measurement and follow-up of index lesions.
  - Display of follow-up (post-baseline) images, with the baseline images available as reference.
  - Reader 1 and Reader 2 measured index lesions selected in Session I.

- Session III
  - Assessment of objective radiological responses with incremental sequential display of CT images.
  - Display of scans and diameter measurements for baseline and subsequent follow-up time points in a sequential manner, with responses assessed incrementally for each time point.

- Session IV
  - Assessment of overall radiological response.
  - Review all time points and assignment of a best overall response by Reader 1 and by Reader 2.
  - Readers 1 and 2 reported the dates of first response, response confirmation, and progression.

- Session V
  - Radiological agreement.
  - If Reader 1 and Reader 2 disagreed on any of the endpoints determined in Session IV, Reader 3 had to adjudicate the differences.

- Session VI
  - Combined assessment of response by radiologist and oncologist.
  - Reader 3 and the Oncologist re-assessed the patient response based on integration of the clinical data with the existing radiological findings.

The primary imaging data evaluated by the IRC were computerized tomography (CT) scans. Magnetic resonance imaging (MRI) scans were performed in some instances, e.g., allergy to CT contrast media.

For the pre-study phase, scans were collected for the most recent irinotecan therapy.

On-study scans were collected as follows:

- EMR 62 202-007
  - CT scans of the chest, abdomen, and pelvis for all time points

- IMCL CP02-0141 and IMCL CP02-9923
  - Scans selected based on sites of disease.

For all three protocols, pre-study data were collected for dates of prior irinotecan therapy. In addition, for protocol EMR 62 202-007, on-study data (physical examination findings, adverse events, concomitant medications, laboratory results) were provided.

At the baseline time point, all measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, were identified as index lesions. Selection of lesions was based on: size, suitability for repeated measurements on scans, and ability to represent the subject's tumor burden.

Index lesions were measured in two dimensions, with the size estimated by the following equation:

Cross Product = Longest Diameter x Greatest Perpendicular Diameter.

The sum of the cross products (SOP) was reported for the different time points. For lesions with tumor dimensions less than 1.0 cm, a default value of 1.0 cm was assigned.

After selection of the index lesions, all other lesions were identified as non-index lesions. Measurable non-index lesions were not included in the calculation of the SOP.

The reviews of pre-study scans and on-study scans were conducted separately for each study.

Study Period	**Objective**	**Response Data**
Pre-Study	To confirm eligibility	Progressive Disease (PD) versus Other (OT = not PD) Date of Progression
On-Study	To assess efficacy	Complete Response (CR), Partial Response (PR), Stable Disease (SD), or PD; Best Overall Response Date of Response (first observation) Date of Response Confirmation Date of Progression Date of Last Tumor Assessment

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A table describing the reading sessions is given below:

Reading Session	Data	Reader(s)	Objective
Session I	Baseline scan	Reader 1* Reader 2*	Identify and measure index lesions
Session II	Follow-up scans paired with baseline scan	Reader 1* Reader 2*	Identify and measure index lesions
Session III	All scans	Reader 1* Reader 2*	Incremental display of time points for response
Session IV	All scans	Reader 1* Reader 2*	Simultaneous display of time points for response
Session V	All scans	Reader 3	Adjudication of discrepant results
Session VI	Scans and clinical data	Reader 3 and Oncologist	Joint review of images along with clinical data for response

* Reader 1 and Reader 2 conducted Sessions I through IV independently.

Readers 1 and 2 identified index and non-index lesions, and followed them through the subsequent time points. Adjudication was performed by Radiologist 3 for discrepancies between the following:

- Date of First Response
- Date of Response Confirmation
- Date of Progression
- Date of Last Scan
- Best Overall Response.

In Session VI, Radiologist 3 and the Oncologist reassessed the subject imaging response data with clinical information available. The database was locked after each reading to prevent future results from affecting previous time points.

During Session III, the overall response at a time point was considered to be the response from the index lesions and non-index lesions, with or without the appearance of new lesions. The radiologic response criteria per time point for index lesions is given below:

Response Determination for Index Lesions	Definition
CR = Complete Response	Disappearance of all index lesions
PR = Partial Response	≥ 50% decrease in Sum of Products (SOP) of index lesions compared to baseline SOP and no evidence of PD
PD = Progressive Disease	≥ 25% increase in SOP of index lesions compared to nadir SOP
SD = Stable Disease	Neither PR nor PD

The radiologic response criteria per time point for non-index lesions is given below:

Response Determination for Non-Index Lesions	Definition
CR = Complete Response	Disappearance of all non-index lesions and no new lesions
PD = Progressive Disease	Progression of non-index lesions and/or one or more new non-index lesions
NC = No Change	Neither CR nor PD

The overall response per time point assessment was determined in the following manner:

Index Lesions	Non-Index Lesions	New Lesions	Overall Response Per Time Point
CR	CR	No	CR
CR	NC	No	PR
PR	CR or NC	No	PR
SD	CR or NC	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

In Session VI, after an overall response was assigned to each follow-up time point. The radiologists determined the best overall response across all time points, applying the confirmation criteria:

- CR must be confirmed by a repeat, consecutive scan no less than 4 weeks after the criteria for CR are first met.
- PR must be confirmed to show a $\geq$ 50% decrease in SOP compared to baseline by a repeat assessment (not necessarily consecutive) no less than 4 weeks after the first PR.
- SD must be at least once no less than 5 weeks after the first dose of therapy.
- If a temporary overall response of PD was assigned to a time point due to missing scan data, and that time point was followed by another time point with no evidence of progression, then the previous time point was to be "overruled" in the determination of best overall response.
- The objective response was considered to have stayed the same, or improved over time, until progression was observed.

- Once a CR was observed, any reappearance of disease was considered progression. (Neither a PR nor an SD followed a CR.)

- After confirmation of a PR, the status was maintained as PR until CR or PD criteria were met. In other words, an SD could not follow a confirmed PR.

- For subjects with confirmed CR or PR, the date of response was the date when the CR or PR criteria were first met.

The confirmation process and the best overall response are summarized below, where the best 2 time points are considered.

Earlier Best (Unconfirmed) Response	**Later Best Response**	**Best Overall Response**
CR	CR	CR
CR	No CR or missing	SD
PR	CR or PR	PR
PR	SD or PD or missing	SD
SD	N/A	SD
PD	N/A	PD

Except for CR, the two time points did not have to be consecutive. The second column applied only when the best response at the earlier time point was either CR or PR.

The best overall response was Not Evaluable (NE) when:

- No baseline scans and/or no follow-up scans were available.
- No index lesion was present at baseline, a protocol deviation, and there was no evidence of PD.

4.0 Reviewer's Aid Disk

On 4 September 2003, the sponsor submitted the Reviewer's Aid Disk containing information requested by the FDA.

Reviewer Comment:

The FDA reviewed the information on the Reviewer's Aid Disk, including the following:

- — slide presentations from the installation of the Medical Imaging Review System on 14 August 2003 entitled ImClone ———— Oncology Reading Protocols (BLA 125084/0/003\other\Request #1 [PreStudy PD_OnStudy Baseline Scan].pdf) and Lesion Calcification (BLA 125084/0/003\other\Request #2 [Calcified Tumors].pdf)

- Independent Review Committee (IRC) charter deviations affecting overall response for Study EMR 202 62-007 (BLA 125084/0/003\statistical\Request #3 Define [IRCDev].pdf)

- — User's Manual (BLA 125084/0/003\other\Request #4a — Users Manual.doc)

- Summary of Clinical Efficacy (BLA 125084/0/003\other\Request #5a Clinical Efficacy Summary.doc)

- IRC-PD Responders Subject Narratives (BLA 125084/0/003\other\Request #6 Narratives Clinical Efficacy Summary-App03.doc)

- Medical Imaging Submission tracking documents for IMCL CP02-0141 (BLA 125084/0/003\other\Request #7 [007].pdf), IMCL CP02-9923 (BLA 125084/0/003\other\Request #7 [9923].pdf), and EMR 62 202-007 (BLA 125084/0/003\other\Request #7 [007].pdf)

- List of archive DVDs of the Medical Imaging Review Submission (BLA 125084/0/003\other\Request #8 [49 Archive DVD listing].pdf)

4.1 — slide presentations

Reviewer Comment:

The FDA reviewed the —— slide presentations. The information was acceptable and consistent with the conduct of the independent review.

A summary of the slides is given below.

Reading Sessions

- Pre-study reads to confirm eligibility
- On-study reads to assess efficacy
- Total number of subjects = 329 + 195

Outline of Reading Sessions

- Session I: Baseline study--select, characterize, and measure index lesions
- Session II: Follow-up scans--characterize and measure index lesions
- Session III: Response assessment with incremental display of images.
- Session IV: Response assessment review with all images displayed.
- Session V: Adjudication for subjects with discrepant results.
- Session VI: Joint review of images/clinical data by Radiologist/Oncologist

Adjudication Criteria

- Pre-study: Disagreement of Progressive Disease (PD) vs. non-PD assessment.
- On-study: Disagreement of any of the following endpoints—Date of first response, Date of response confirmation, Date of progression, Date of last scan, Best overall response.

Number of Response Assessments

- For each subject, studies could be assessed up to a total of four times in Sessions III, IV, V, and VI.
- If complete agreement of Session IV endpoints between Radiologists is achieved, then Reader 1 assessments will be the final Radiology results.
- Response assessment changes in Session VI can only be the result of input from the clinical information.

Measurement Issues

- Protocol EMR 202 62-007 used RECIST unidimensional criteria.
- The FDA requested that all Cetuximab protocols use the same (World Health Organization) response criteria.
- Unidimensional lesions were transformed into bidimensional lesions by the following formula:
  Unidimensional Measurement x 1 cm =
  Lesion Measurement in cm^2
- All lesions less than 1 cm x 1 cm at follow-up time points, but clearly visible were assigned a cross product value of 1 cm^2.

Response Rules and Confirmation

- Confirmation time points for Partial Response (PR) or Complete Response (CR) do not need to be consecutive.
- A 50% tumor size reduction must be maintained.
- Stable Disease (SD) can be assigned following an unconfirmed PR.

Subjective Response Assessments

- Subjects with < 50% reduction in the sum of the products (SOPs), but deemed to have PR.

Shared Scans: Pre-Study and On-Study

- PD scan for pre-study was often used for on-study baseline.
- For the review, Pre-Study and On-Study scans were treated as belonging to separate subjects.
- Two sets of ROIs (Pre-Study and On-Study).
  - Pre-Study (PS): Time points given numeric values.
  - On-Study (OS): Time points designated by letters.

No Shared Scans

- Pre-Study
  - PS Time point 1 = Early Baseline
  - PS Time point 2 = Interim
  - PS Time point 3 = PD Confirmation
- On-Study
  - OS Time point A = Baseline
  - OS Time point B = 1st Follow-up
  - OS Time point C = 2nd Follow-up

Shared Scans

- Pre-Study
  - PS Time point 1 = Early Baseline
  - PS Time point 2 = Interim
  - PS Time point A = PD Confirmation
- On-Study
  - OS Time point A = Baseline
  - OS Time point B = 1st Follow-up
  - OS Time point C = 2nd Follow-up

4.2 SAS transport file of IRC charter deviations affecting overall response for Study EMR 202 62-007

Reviewer Comment:

The FDA reviewed the SAS transport file of charter deviations and verified that they were consistent with the data submitted to the BLA.

For study EMR 202 62-007, there were 11 subjects with charter deviations that affected the overall response: 404-12, 500-10, 502-2, 600-8, 600-36, 600-45, 600-59, 601-5, 602-10, 903-14, and 904-9.

All eleven subjects were included in the IRC-PD population (subset of intent-to-treat population determined to have pre-study PD by IRC, and who met all of the additional criteria for irinotecan refractoriness as defined in the statistical analysis plan).

Two of eleven, 500-10 and 502-2, were responders.

- Subject 500-10 was excluded from the final group of responders because the pre-study scans did not show progressive disease.
- For subject 502-2, reader 3 determined that the best overall response was PR during Session VI.

Reviewer Comment:

The FDA reviewed the following information, and verified that it was comparable to the data submitted to the BLA.

Subject	IRC Charter Deviation	Details
404-12	On-study Downgrade of overall response from SD by both Readers 1 and 2 in session IV to PD in session VI without comment.	On-study, at time-point B, both Readers 1 and 2 observed a +13.9% increase in SOP and determined SD for that time-point, as well as best overall response. In Session VI, Reader 3 and the oncologist downgraded the best overall response to PD without any comments.
500-10	Pre-study Change in overall radiologic response from PD by both Readers 1 and 2 in Session IV to OT in Session VI	Pre-study, both Readers 1 and 2 determined PD at time-point 3 in Session IV. In Session VI, Reader 3 and the oncologist determined OT at time-point 3 with a comment: "Review of images made the reader unable to validate a PD and clinical additional information was requested on Session VI. On Session VI, the oncologist did not see any signs for progression. It was decided that we could not validate the PD. Patient rated OT."

Subject	IRC Charter Deviation	Details
502-2	On-study Upgrade of overall radiologic response from SD by both Radiologic Readers 1 and 2 in session IV to PR in session VI.	At time-points B & C, on-study, both Readers 1 and 2 determined SD with SOP changes of -38.2% and -39.4%, respectively. At time-point D, both Readers determined a SOP change of +34.5% from nadir, but Reader 1 determined a SD and Reader 2 determined a PD. Both Readers determined SD as the best overall response. Because of the disagreement in PD date, this case was adjudicated in Session V, where Reader 1's opinion was selected, with best overall response of SD. At Session VI, Reader 3 and the oncologist upgraded the Session V determination of SD to PR, with a comment: "Reader 3 found lesions shrinking at time-points B & C. Confirmed by measurements. Clinical info unremarkable patient declared PR at Time-points B & C and PD at Time-point D as felt more representative of patient's history."
600-8	On-study Downgrade of overall response from SD by both Radiologic Readers 1 and 2 in session IV to PD in session VI without comment.	On-study, both Readers 1 and 2 made determination of SD as the best overall response, but disagreed on the date of subsequent progression. In Session V, Reader 2's date of progression was selected with the best overall response remaining unchanged (SD). However, in Session VI, the Reader 3 and the oncologist changed the best overall response to PD without any comments.

Subject	IRC Charter Deviation	Details
600-36	On-study Ugrade of overall radiologic response from PD by both Radiologic Readers 1 and 2 in session IV to SD in session VI.	On-study, both Readers 1 and 2 determined PD at time-point B for a +37.8% increase of SOP from baseline. In addition, Reader 1 observed appearance of a new lesion/site at time-point B. The best overall response was PD by both Readers. In Session VI, the best overall response was upgraded to SD, with a comment: "2 Lesions - right adrenal lesion small, unchanged, hypodense c/w benign disease. Pelvic lymph node small & difficult to measure. Reader 3 felt it unusual for PD for little change over 30 weeks. No clinical PD was declared, SD more representative of patient history."
600-45	On-study Downgrade of overall response from SD in session V to PD in session VI without comment.	On-study, Reader 1 determined SD and Reader 2 determined PD as the best overall response. In Session V, Reader 3 selected Reader 1's determination of SD with a comment: "Large peritoneal mass is seen. Measurements are difficult to assess but the tumor is growing slowly but continuously without any stabilization. Measurements of Reader A are valid, tumor does not exceed the rules for PD until time-point D. Reader A's opinion". However, in Session VI, Reader 3 and the oncologist changed the best overall response to PD without any comments.

Subject	IRC Charter Deviation	Details
600-59	Pre-study Change in overall radiologic response from PD by both Radiologic Readers 1 and 2 in Session IV to OT in Session VI.	Pre-study, both Readers 1 and 2 determined PD at time-point 2 in Session IV. In Session VI, Reader 3 and the oncologist determined OT at time-point 2 with a comment: "OT is chosen because cannot compare baseline X-ray to follow-up CT."
601-5	On-study Downgrade of overall response from SD by both Radiologic Readers 1 and 2 in session IV to PD in session VI without comment.	On-study, both Readers 1 and 2 made determination of SD but disagreed on the date of progression. In Session V, the Reader 2's date of progression was selected by Reader 3 with a comment: "This patient has a huge mesenteric mass, clearly progressing early. Reader B's is closer to the observed progression and his opinion is validated although it is clear that no stabilization has been observed in this patient." The best overall response remained unchanged (SD) in Session V. However, in Session VI, Reader 3 and the oncologist changed the best overall response to PD without any comment.

Subject	IRC Charter Deviation	Details
602-10	On-study Downgrade of overall response from SD by both Radiologic Readers 1 and 2 in session IV to PD in session VI without comment.	On-study, both Readers 1 and 2 made determination of SD but disagreed on the date of progression. In Session V, the Reader 2's date of progression was selected by Reader 3 with a comment: "Major increase in segment IV liver lesion indicates PD at time-point D. Radiologic Reader A's opinion validated." The best overall response remained unchanged (SD) at Session V. However, in Session VI, Reader 3 and the oncologist changed the best overall response to PD without any comment.
903-14	On-study Best overall response of SD from session IV changed to NE at session VI without comments	On-study, in Session IV, the best overall response was SD by both Readers 1 and 2. In Session VI, Reader 3 changed the best overall response to "NE" without any comments. (However, in pre-study Session VI, Reader 3 and the oncologist made a comment: "Biopsy of liver lesion was negative for malignancy.")
904-9	Pre-study Downgrade of overall radiologic response from PD by both Radiologic Readers 1 and 2 in Session IV to OT in Session VI	Pre-study, both Readers 1 and 2 determined PD at time-point "A" in Session IV. In Session VI, Reader 3 and the oncologist determined OT at the time-point with a comment: "Review of images made the reader unable to validate a PD and clinical additional information was requested on Session VI. In Session VI, Reader 3 did not see any signs for PD. Patient OT.

4.3 — User's Manual

Reviewer Comment:

Both the User's Manual and the filters provided by the sponsor were reviewed and found acceptable.

The ImClone ——— /Base application is a Microsoft Windows based program, with an associated database to review electronic images. The application allows the user to navigate through a database listing of study subjects and their associated images.

The application communicates with the local display systems to tell what images to display. To assist in the review, filters were generated from the database fields of the BLA. The purpose of the filters is to allow the selection, or deselection, of subjects based on criteria defined in the filtering process.

Filter Number and Description	Comments
1. Treatment Group (EMR 202 62-007 only)	EMR 202 62-007 only For selecting population receiving either combination therapy or monotherapy
2. IRC-PD-2-Cycles Population (EMR 202 62-007 only)	EMR 202 62-007 only Subset of IRC-PD population who also received at least 2 cycles of prestudy irinotecan.
3. IRC-PD Oxaliplatin-Failure Population (EMR 202 62-007 only)	EMR 202 62-007 only Subset of IRC-PD oxaliplatin population for whom the reason for oxaliplatin failure is known
4. IRC-PD Oxaliplatin Population (EMR 202 62-007 only)	EMR 202 62-007 only Subset of IRC-PD population who received pre-study oxaliplatin
5. IRC-PD Population (EMR 202 62-007 only)	EMR 202 62-007 only Subset of ITT population determined to have pre-study PD by IRC and who met all of the additional criteria for irinotecan refractoriness as defined in the statistical analysis plan (SAP) Criteria for refractoriness (IRC-PD) in the SAP more stringent than those in the clinical protocol, explaining the number of patients excluded from IRC-PD population
6. ITT-Oxaliplatin Population (EMR 202 62-007 only)	EMR 202 62-007 only Subset of ITT population who received both pre-study irinotecan and pre-study oxaliplatin
7. Final Best Overall Response (Session VI, Reader 3 + Oncologist)	Final best overall response determination by Reader 3 and the oncologist in Session VI
8. Best Overall Radiologic Response (Session IV, Reader 1)	Reader 1 only. For the on-study "NE/UK" selection, this filter does not pick up the on-study cases that were not evaluated by IRC. For the pre-study "OT" selection, this filter does not pick up the cases with no available pre-study scans.

Filter Number and Description	Comments
9. Best Overall Radiologic Response (Session IV, Reader 2)	Reader 2 only. For the on-study "NE/UK" selection, this filter does not pick up the on-study cases that were not evaluated by IRC. For the pre-study "OT" selection, this filter does not pick up the cases with no available pre-study scans.
10. Adjudicated Cases (Session V, Reader 3)	Cases that were adjudicated by Reader 3 in Session V.
11. Measurement Alone Not Basis for Individual Timepoint Response Determintation (Session III, Reader 1 or 2) – PR while SOP decreased < 50% – PD while SOP increased < 25% – No PD while SOP increased ≥ 25% – Not Applicable	In Session III, Readers 1 and 2 independently performed individual timepoint response assessments with incremental display of images. If any of one or more of the timepoint response assessment for either Reader 1 or 2 satisfies the condition, the case is selected by the filter. PD determination, while SOP is increased by < 25%, commonly occurs due to appearance of a new lesion, which is a part of PD definition.
12. Changed Individual Timepoint Response (Session IV, Reader 1 or 2)	This is a comparison between individual timepoints.
13. Changed Individual Timepoint Response (Session VI, Reader 3 + Oncologist)	This is a comparison between individual timepoints
14. Changed Endpoints (Best Overall Response, Response Date, Confirmation Date, or Progression Date), (Session VI, Reader 3 + Oncologist)	This filter picks up any change in any one of the four end points during Session VI.
15. Unidimensional Disease at Baseline (One Diameter < 1 cm)	This filter picks up patients with any baseline index lesion with either dimension < 1 cm.
16. Default Value of 1 cm Used for a Diameter Less than 1 cm	Applies to any time point, any index lesion.
17. Unreadable or Missing F/U Images of Lesion Present at Baseline	Applies to Readers 1 and 2

Filter Number and Description	Comments
18. At Least One Baseline Lesion with Longest Diameter Greater than (Enter Below Right)	A search will be performed on the entered value through all baseline lesions.
19. Largest Baseline Lesion with Longest Diameter Less than (Enter Below Right)	A search will be performed on the entered value through all baseline timepoints.
20. Unreadable Baseline Images (or CXR only), OR Unreadable or Missing Baseline Images with Lesion(s) Present in F/U Images	This filter does not pick up the cases where pre-study scans were not available nor the cases where on-study scans were not read by the IRC.
21. Charter Deviations Affecting Overall Response (Session VI, Reader 3 + Oncologist)	EMR 202 62-007 only. The IRC charter deviations are independent of, and distinct from, the EMR-007 clinical protocol deviations. This filter selects cases that were either up-graded or down-graded overall best response by Reader 3 and the oncologist during Session VI. Detailed written rationale for such up-grades or down-grades of overall best response were usually documented by Reader 3 in Computer Assisted Masked Reading Database Changes/ Edits forms found in the "screen shots" section of —

4.4 IRC-PD Responders Subject Narratives (Attachment 3)

Reviewer Comment:

The FDA reviewed the subject narrative summaries, and compared the imaging data in the summaries with the — database and the CRF imaging data.

The first date of PR, as determined by the independent review, was compared with the date of first PR determined by the clinical investigators. While the following differences were noted, the review did not reveal any significant trends.

Study	Subject	IRC PR Date	Clinical Site Investigator PR Date
EMR 62 202-007	202-1	4/19/02	3/11/02
EMR 62 202-007	208-3	5/31/02	(SD 5/31/02)
EMR 62 202-007	305-1	6/24/02	(SD 6/24/02)
EMR 62 202-007	401-2	6/4/02	4/16/02
EMR 62 202-007	404-2	3/6/02	(SD 3/6/02)
EMR 62 202-007	502-2	5/29/02	(SD 5/29/02)
EMR 62 202-007	600-46	2/13/02	2/19/02
EMR 62 202-007	601-7	3/21/02	(SD 3/21/02)
IMCL CP02-0141	1-1135	8/2/01	9/13/01
IMCL CP02-9923	20-649	8/25/00	5/31/00
IMCL CP02-9923	60-667	6/29/00	5/18/00
IMCL CP02-9923	60-738	8/31/00	10/10/00
IMCL CP02-9923	61-615	3/29/00	2/14/00

Of the subjects included in the narratives; 10 were initially randomized to receive Cetuximab monotherapy:

- 201-5
- 208-1
- 301-6
- 301-20
- 503-1
- 600-12
- 600-40
- 603-3
- 904-4
- 1001-3

Reviewer Comment:

The FDA verified that the — database has scans for all 10 subjects for Part 1 of the study, where they received Cetuximab monotherapy.

Of the 10 subjects listed above, 7 went on to receive Cetuximab + Irinotecan during Part 2 of the study:

- 201-5
- 301-6
- 503-1
- 600-12
- 603-3
- 904-4
- 1001-3

The subject narratives describe the responses based on imaging studies that were determined by the clinical investigators. However, the — database does not contain the scans for Part 2 of the study except for the Part 2 baseline scan (the same scan used to determine PD in Part 1).

Reviewer Comment:

For the seven subjects listed above who went on to receive Cetuximab + Irinotecan during Part 2 of the study, the FDA could not confirm the responses because the imaging data were not submitted to the BLA..

In addition, narratives for the five subjects were not included in the submission. The subjects are listed below.

- 204-2
- 600-10
- 600-13
- 804-3
- 904-43

Reviewer Comment: Because the narratives for the five subjects listed above were not submitted, the FDA was unable to review them.

4.5 Summary listing of the archive DVDs of the Medical Imaging Review System, consisting of 49 Archive DVDs (50 disks because two disks were labeled 1—#1 and #1a)

DVD Number	Content
1, 1a, and 2 through 9	Pre- and On-study Images for IMCL CP02-9923
10 through 13	Pre- and On-study Images for IMCL CP02-0141
14 through 45	Pre- and On-study Images for EMR 62 202-007
46 and 47	CAMR Edit Forms for IMCL CP02-9923 and IMCL CP02-0141
48 and 49	CAMR Edit Forms for EMR 62 202-007

4.6 Project Tracking

[redacted] submitted project tracking documents as PDF files for all three clinical studies: EMR 62 202-007, IMCL CP02-9923, and IMCL CP02-0141.

- The following information was provided:
- Clinical site number
- Patient number
- Logged time point, e.g., Baseline, 6 weeks, etc.
- Scan date
- Date films received
- Date digital data received
- Date of initial quality control
- Anatomic site imaged
- Date films returned to site
- [redacted] queries and clinical site responses to queries

Reviewer Comment:

Review of the project tracking documents showed that there was adequate documentation for all three trials.

5.0 Conclusions

Reviewer Comment:

For studies, EMR 62 202-007, IMCL CP02-9923, and IMCL CP02-0141, the FDA reviewed the IRC evaluation of Pre-Study and On-Study imaging studies.
The FDA review verified the following:

Study	Number of Subjects with PD Pre-Study / Number Responding to Therapy On-Study	Number of Subjects with Confirmed PR On-Study / Number of Subjects with PD Pre-Study
EMR 62 202-007	50/62	50/50
IMCL CP02-0141	4/5	4/4
IMCL CP02-9923	11/21	11/11

The IRC followed the charter, and the data are reliable for determination of response to therapy.

Appendix B

Reference

1. Cancer Statistics, 2004. CA Cancer J Clin 2004, 54:8-29
2. American Joint Committee on Cancer, Manual for Staging of Cancer, 6th ed, Springer, 2003
3. US FDA. Center for Drug Evaluation and Research. Listing of Approved Oncology Drugs with Approved Indications: http://www.fda.gov/cder/cancer/druglistframe.htm
4. McIntyre BS, Birkenfeld HP, Sylvester PW. Relationship between epidermal growth factor receptor levels, autophosphorylation and mitogenic-responsiveness in normal mouse mammary epithelial cells in vitro. Cell Prolif. 1995 Jan; 28(1): 45-56.
5. Serum-free growth of normal and tumor mouse mammary epithelial cells in primary culture. Imagawa W, Tomooka Y, Nandi S. Proc Natl Acad Sci U S A. 1982 Jul; 79(13): 4074-7.
6. Carpenter G. Employment of the epidermal growth factor receptor in growth factor-independent signaling pathways. K Cell Biol 1999: 146(4): 697-702
7. Moniola AO, Neve RM, Lane HA, et al: that erbB-signaling network. Receptor heterodimerization in development and cancer. EMBO J. 19:3[59-3] 67, 2000
8. Yarde Y, Sliwkowski MX: Untangling the erbB-signaling network. Nature Rev Mol Cell Biol 2:127-137, 20
9. Dassonville O, Formento JL, Francoual M, Ramaioli A., Santini J, Schneider M, et al. Expression of epidermal growth factor receptor and survival in upper aero digestive tract cancer. J Clin Oncol 1993; 11 (1): 1873-8
10. Etienne MC, Pivot, X, Formento JL, Bensadoun RJ, Formento P, Dassonville O, et al. A multifactorial approach including tumoral epidermal growth factor receptor, p53, thymidylate synthase and dihydropyrimidine dehydrogenase to predict treatment outcome in head and neck cancer patients receiving 5-flourouracil. Br J Cancer 1999; 79: 1864-9
11. Nicholson RI, Gee JMW, Harper ME. EGFr and cancer prognosis. Eur J Cancer 2001; 37: S9-S15
12. Sibilia, M, Wagner EF. Strain-dependent epithelial defects in mice lacking the EGF receptor, Science 1995, 269, 234-238
13. Miettinen PK, Berger JE, Meneses J, et al. Epithelial immaturity and multiorgan failure in mice lacking epidermal growth factor receptor. Nature 1995, 376, 3337-341