

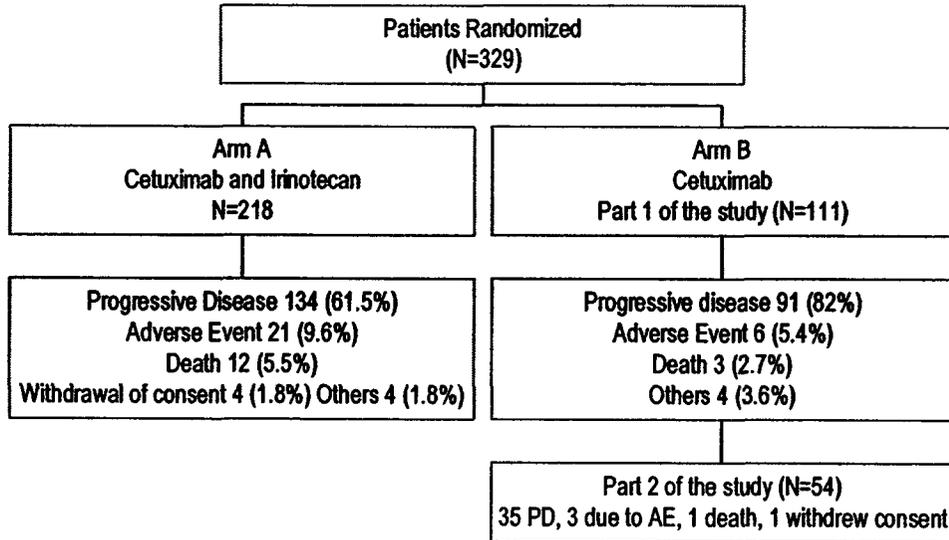
EGFr staining of the tumor biopsies is shown in Table14:

Table 14. EGFr Staining of the Tumor Biopsies

EGFr expression	ERBITUX plus irinotecan N=218 (%)	ERBITUX monotherapy N=111 (%)	All randomized patients N=329 (%)
% Of positive cells			
0	1 (0.4)	1 (0.9)	2 (0.6)
0 - < 10%	108 (49.5)	55 (49.5)	163 (49.5)
10 - < 20%	20 (9.1)	16 (14.4)	36 (10.9)
20 - ≤35%	27 (12.3)	7 (6.3)	34 (10.3)
≥35%	62 (28.4)	32 (28.8)	94 (28.5)
Staining intensity			
Faint/barely	53 (24.3)	21 (18.9)	74 (22.7)
Weak or moderate	89 (40.8)	55 (49.5)	144 (43)
Strong	75 (34.4)	34 (30.6)	109 (33)
Missing	1 (0.5)	1 (0.9)	2 (0.6)

Approximately 50% of the patients had tumors with less than 10% EGFr positive cells. The majority of the patients had tumors with weak or moderate staining to EGFr.

The disposition of all randomized patients are shown in Figure 1:



Protocol deviations

Major protocol violations were pre –specified in the protocol and are defined as:

- No evidence of metastatic colorectal cancer at baseline
- Lack of the least one uni-dimensionally measurable index lesion
- First on-study irinotecan dose exceeded the most recent pre-study irinotecan dose
- No evidence of positive EGFr expression
- Additional non-permitted chemotherapy under treatment
- Randomization failure (i.e. incorrect treatment group allocation)

There were 3 major violations identified in the EMR 62 202-007 study. One patient in each treatment group had no evidence of positive EGFr expression (patient 904-1 and 200-6) and one patient in the monotherapy had no evidence of metastatic colorectal cancer at baseline (patient 903-14).

Reviewer's Comment: The number of patients with major violations was small and did not impact the efficacy or safety analysis.

Minor protocol deviations as per applicant (5.3.5.1.1) are as follow:

1. Inclusion/exclusion violations
 - Patient did not provide 2 signed consents: 1(0.3%)
 - None of the defined irinotecan treatment at most recent chemotherapy: 10 (3.0%)
 - No documented progression on the defined irinotecan therapies: 4 (1.2%)
 - Neutrophils not $\geq 1.5 \times 10^9/L$ or platelets not $\geq 100 \times 10^9$ or Hb not $\geq 9g/dL$: 5 (1.5%)
 - Bilirubin either not normal and not $< 1.5 \times uln$: 3 (0.9%)
 - ALAT or ASAT not $\leq 1.5 \times uln$: 1 (0.3%)
 - Serum creatinine not $< 1.5 \times uln$: 2 (0.6%)
 - Surgery or radiation within 4 weeks prior to study entry: 1(0.3%)
2. Post randomization violation
 - Strata as randomized discordant to strata as reported in CRF: 16 (4.9%)
 - > 7 days between randomization and start of treatment: 14 (4.3%)

Reviewer's Comment: These minor violations did not impact on efficacy or safety analysis and were similar in both arms.

Study Population:

The number of patients in each of the populations of interest is shown in Table 15. Randomization stratification, baseline characteristics were well balanced in between arms, as observed in the ITT population.

Table 15 – Number of patients in each Study Population

Population	Cetuximab plus irinotecan (%)	Cetuximab monotherapy (%)	Total (%)
ITT	218 (100%)	111 (100%)	329 (100%)
Safety	212 (97.2%)	115 (103.6%)	327 (100%)
Per protocol	122 (56.0%)	66 (59.5%)	188 (57.1%)
IRC-PD	135 (61.9%)	71 (61.9%)	206 (62.6%)
IRC-PD oxaliplatin failure	80 (36.6%)	44 (39.6%)	124 (37.6%)
IRC-PD 2 cycles	132 (60.5%)	69 (62.1%)	201 (60.1%)

Of the 329 patients randomized 61.9% (206) of the patients fulfilled the pre-specified IRC-PD criteria. The remaining 123 (37.3%) patients were excluded from the IRC PD population. The reasons for exclusion from the IRC-PD population are shown in Table 16.

Table 16: Reasons for exclusion from IRC-PD population

Reason for Exclusion from IRC-PD	ERBITUX plus irinotecan N=83 (%)	ERBITUX monotherapy N = 40 (%)
No progression on prior irinotecan determined by IRC	26 (31)	13 (32)
No progression within 30 days after the last treatment course	56 (67)	24 (60)
Pre-study comparison scan is not in defined interval to 1 st dose of irinotecan	23 (28)	17 (42)
Pre-study comparison scan and pre-study scan documenting PD not in defined interval	33 (40)	27 (67)

The IRC-PD oxaliplatin failure population represents a group of special interest to the FDA, given that oxaliplatin was approved for second line use in the USA on August 2002, after acceptance of this trial to support accelerated approval for ERBITUX. Eighty and 44 patients were included in the combination and monotherapy arms, respectively.

Reviewer's comment: the pre-specified criteria of inclusion to the IRC-PD population and other secondary populations were followed by the IRC and were confirmed by the clinical reviewer.

Analysis of tumor response:

For additional details of statistical analysis, please refer to review by Clare Gnecco, Ph.D., statistical reviewer

The primary analysis of efficacy was based on analysis of the best overall response in the ITT population as assessed by the IRC. The primary target variable is the confirmed objective response rate. A summary of the overall response rate submitted by the applicant is shown in Table 17.

Table 17: Best Overall Response in ITT population (IRC assessment)

BEST RESPONSE	CETUXIMAB PLUS IRINOTECAN (N=218)		CETUXIMAB MONOTHERAPY (N=111)		DIFFERENCE IN PROPORTIONS	
	N	%	N	%	%	P-value*
Best Response						
CR	0	0	0	0		
PR	50	22.9	12	10.8		
SD	71	32.6	24	21.6		
PD	68	31.2	59	53.2		
Not evaluable	29	13.3	16	14.4		
Objective Response (CR + PR)	50	22.9	12	10.8	12.1	0.0074
95% CI		17.5, 29.1		5.7, 18.1	4.1, 20.2	
Disease Control	121	55.5	36	32.4	23.1	0.0001
95% CI		48.6, 62.2		23.9, 42.0	12.1, 34.0	

* P-value for difference between treatment groups was obtained from Fisher's exact test (2-tailed)

The objective response rate in the cetuximab plus irinotecan group was 22.9% (95% CI: 17.5%, 29.1%) compared to 10.8% (95% CI: 5.7%, 18.1%) in the monotherapy group. The difference in response proportions between the two treatment groups was 12.1% (95% CI: 4.1%, 20.2%) and statistically significant (p=0.0074, Fisher's exact test). When adjusted for randomization strata (KPS and prior treatment), results were confirmed; Cochran Mantel-Haenszel test (CMH) p=0.0069. The lower limit of the 95% CI for the combination therapy group was 17.5% and thus far above the 12% regarded as clinically relevant in the study.

The clinical and imaging reviewers confirmed the objective response rate submitted by the applicant. Results of the review of all clinical documentation and CT scans were in 100% accord with the IRC's assessment (see Appendix X, Imaging Review). The FDA statistical reviewer confirmed all statistical analyses summarized in the above table as well as the CMH stratified analysis.

Objective Response Rates in Sub-populations of interest

Table 18 summarized the objective response rates in subpopulations of interest based on the IRC assessments of tumor response and confirmation by the FDA reviewers.

Table 18. Objective Response Rates in Secondary Populations

Population	ERBITUX plus irinotecan		ERBITUX monotherapy		Δ In proportions	
	n/N	%	n/N	%	% 95% CI	P-value*
ITT oxaliplatin	30/135	22.2	6/71	8.5	13.8 (4.2, 23.3)	0.0127
Per protocol	34/122	27.0	10/66	15.2	12.7 (1.0, 24.5)	0.0702
IRC-PD	34/135	25.2	10/71	14.1	11.1 (0.2, 22.0)	0.0747
IRC-PD oxaliplatin	21/84	25.0	5/46	10.9	14.1 1.2, 27.0	0.0673
IRC-PD oxaliplatin failure	19/80	23.8	5/44	11.4	12.4 (-0.8, 25.6)	0.104
IRC-PD 2 cycles	34/132	25.8	10/69	14.5	11.3 (0.1, 22.4)	0.074

* Value for difference in proportions between groups obtained by Fisher's exact test (2-tailed)

In the secondary population analysis, objective response rates were consistent, ranging between 22.2-27.0% in combination arm and varied between 8.5-15.2% in the monotherapy arm.

In the IRC-PD oxaliplatin-failure subset, objective tumor response was consistent with the results observed in the ITT population. The response rate was 23.8% (95% CI: 14.9, 34.6) for the combination arm and 11.4% (95% CI: 3.8, 24.6) for the monotherapy arm. The difference between the observed response rates in the two treatment arms was 12.4% and the 95% CI around this observed were -0.8 and 25.6. The Fisher's exact test for assessing whether this difference was significantly different from zero was p=0.104 and the p-value for the stratified Cochran Mantel-Haenszel test (stratifying on randomization balancing factors) was p=0.089.

In the IRC-PD 2 cycle subset, objective tumor was consistent with the results observed in the ITT population. The objective response rate was 25.8% (95% CI: 18.5, 34.1) for the combination arm and 14.5% with a 95% CI of (7.2, 25.0) in the monotherapy arm. The difference in response rates in favor of combination therapy was 11% (95% CI: 0.1, 22.4). The Fisher's exact test p-value for testing if this difference is significantly different from zero was p=0.074, and the p-value for the stratified Cochran Mantel-Haenszel test was p=0.068.

Reviewer's comment: statistical significance using exact Fisher tests was reached for ITT and ITT oxaliplatin population, but not for the IRC-PD populations. However, the study was not powered to

Clinical Review Section

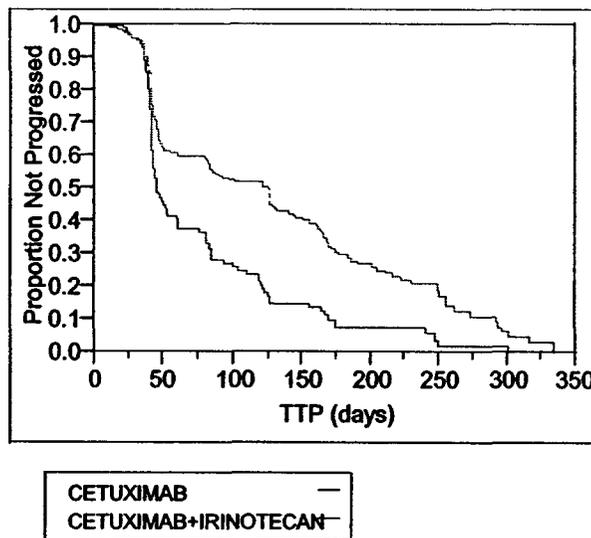
detect statistically significant differences for the secondary analysis populations. Although the protocol was amended to increase the sample size from 225 to 300 to accrue 225 patients for the IRC-PD population with a stricter definition of refractoriness to irinotecan, the actual sample size was 206 patients

Secondary endpoints

Time to Progression

The median TTP in the ITT population was longer in the combination arm than in the monotherapy arm: 4.1 months (95% CI: 2.8, 4.3) vs. 1.5 months (95% CI: 1.4, 2.0). This difference in TTP was statistically significant (Logrank, $p < 0.0001$). The estimated hazard ratio was 0.54 (95% CI: 0.42, 0.71). This indicates a reduction in risk for progression of disease of 46% for a patient in the combination therapy group compared to a patient in the monotherapy group at a given time point. The following reviewer’s Figure 2 presents the Kaplan-Meier plot for TTP (in months) for both treatment groups:

Figure 2 Time to Progression in the ITT population (days)



Summary

Group	N Failed	N Censored	Mean	Std Error
CETUXIMAB	92	19	81.9764	6.77388
CETUXIMAB+IRINOTECAN	152	66	134.389	7.29905
Combined	244	85	116.849	5.53874

Clinical Review Section

Review's comment: the FDA reviewers confirmed the TTP results presented by the applicant. A stratified Logrank analysis to adjust for the effect of the randomization stratification factors also yielded a highly statistically significant result of $p < 0.0001$.

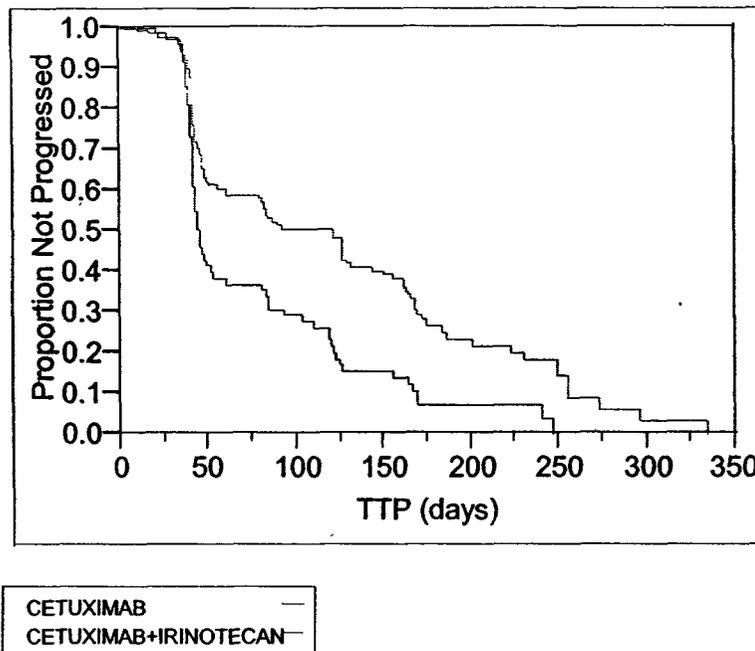
The analysis performed by the FDA reviewers also confirmed the median TTP values in the secondary population. The results of these analyses are summarized in Table 19. Figure 3 shows the Kaplan-Meier curve for time to progression in the IRC-PD population.

Table 19: Time to Progression in Secondary Population

POPULATION	ERBITUX PLUS IRINOTECAN		ERBITUX MONOTHERAPY		HAZARD RATIO (95% CI)	P-VALUE*
	N/N	Median	N/M	Median (months)		
ITT	152/218	4.1	92/111	1.5	0.54 (0.42, 0.71)	< 0.0001
ITT-oxaliplatin	96/135	3.2	61/71	1.5	0.56 (0.40, 0.78)	0.0003
IRC-PD	97/135	4.0	62/71	1.5	0.52 (0.37, 0.73)	0.0001
IRC-PD oxaliplatin	62/84	2.9	43/46	1.5	0.48 (0.31, 0.72)	0.0004
Per protocol	93/132	4.0	60/66	1.5	0.5 (0.36, 0.71)	< 0.0001
IRC-PD oxaliplatin failure	58/80	2.9	42/44	1.5	0.48 (0.31-0.72)	0.0004
IRC-PD 2cycle	95/132	4.0	60/69	1.5	0.52 (0.37, 0.73)	P=0.0001

* P-value based on Logrank test

Figure 3 Time To Progression (IRC-PD Population)



Group	N Failed	N Censored	Mean	Std Error
CETUXIMAB	62	9	80.8651	7.68386
CETUXIMAB+IRINOTECAN	97	38	127.952	8.6718
Combined	159	47	111.513	6.44961

Reviewer’s comment: the reviewer’s analysis confirmed that time to progression was significantly longer in patients who received ERBITUX plus irinotecan in the ITT population and in all subpopulations analyzed.

The following secondary endpoints were analyzed and confirmed by the FDA reviewers:

Duration of Response: The median duration of response in the ITT population was longer in ERBITUX plus irinotecan arm than in the ERBITUX monotherapy arm: 5.7 months (95% CI: 4.2, 7.6) vs. 4.2 months (95% CI: 2.8, 5.5). Results of other secondary populations of interest are summarized in Table 20.

Table 20. Duration of Response in the ITT and secondary population

Population	ERBITUX plus irinotecan Months (CI 95%)	ERBITUX monotherapy months (CI 95%)
ITT	5.7 (4.2, 7.6)	2.2 (2.8, 5.5)
IRC-PD	4.2 (3.8, 7.3)	4.1 (2.8, 5.5)
IRC-PD oxaliplatin failure	5.6 (4.2, 7.3)	4.2 (2.7, 6.5)
IRC-PD 2 cycle	4.2 (3.8, 7.3)	4.1 (2.8, 5.5)

Disease control rates: the disease control rates in all secondary populations were similar to those in the ITT population. Rates in the combination therapy group ranged from 50.4% to 70.7%. Rates in the monotherapy group ranged from 30.4 to 34.8%. The difference in proportions between the two treatment arms ranged from 19.4 to 25.8%. Statistical significance was reached for all populations in favor of the combination therapy arm. Reviewer’s comment: disease control endpoint is a less robust endpoint than objective response since its definition includes stable disease (SD), a category much less precise than CR or PR and of less clear clinical significance.

Investigator assessment of objective response and disease control rates in the ITT population: the objective response rates in the ITT population according to the Investigators’ assessments were similar to the results as assessed by the IRC, i.e., 20.2% vs. 22.9% in the combination therapy group, 13.5% vs. 10.8 in the monotherapy group. The disease control rate according to the investigators’ assessments was higher than that assessed by the IRC, i.e., 62.8% vs. 55.5 % in the combination therapy group, 47.7 vs. 32.4% in the monotherapy group. In the majority of patients (236 patients [71.7%]), there was agreement between the Investigator and IRC assessment of best overall response. In terms of confirmed CR and PR, the IRC found a worse result than the Investigator for 12 patients (including one patients with a change from CR to PR). In 14 patients the IRC found a better results (change from SD to PR). Reviewers comment: analysis of Investigators’ assessments should only be considered supportive.

Time to response: the median time to response estimates in the ITT population were the same in the two treatment arms: combination therapy group 1.4 months (95% CI: 1.3, 2.6), monotherapy group 1.4 months (95% CI: 1.3, 2.7). Similar results were found in the other study populations.

Survival Time: evaluation of survival was based on data collected up until January 31, 2003. 215 (65.3%) of the 329 ITT patients died as of this date (140 in the combination therapy group and 75 in the monotherapy group). The median survival time from randomization in the ITT population was longer in the combination therapy group than in the monotherapy group: 8.6 months, 95% CI of [7.6, 9.6] vs. 6.9 months, 95% CI of [5.6, 9.1]. The difference between the two groups via the Logrank test was not statistically significant (p=0.48). The estimated hazard ratio was 0.91 with associated 95% CI of [0.68, 1.21]. This estimate indicates a slightly reduced risk of death for patients on the combination therapy arm, vs. those on the monotherapy arm at a give time point. Reviewers comment: the trial was not power to detect a difference in survival.

Results of part 2 of the study (as per applicant): 54 patients with PD in the monotherapy group entered part 2 of the study until the cut-off date. One partial remission was observed (1.9%)

Analysis of objective response rate in special subgroup populations

The objective response rate were analyzed in the following special subgroup populations:

Age, Gender, KPS and number of metastatic sites: the age, gender, KPS and number of metastatic sites of the two treatment groups are summarized in Table 21

Table 21. Age, Gender, and KPS Characteristics by Treatment Arm (ITT)

Characteristics	ERBITUX plus irinotecan		ERBITUX monotherapy	
	n/N (%)	95% CI	n/N (%)	95% CI
Age				
< 65 years	36/155 (23.2)	16.8, 30.7	7/78 (9.0)	3.7, 17.6
≥ 65 years	14/63 (22.2)	12.7, 34.5	5/33 (15.2)	5.1, 31.9
Gender				
Men	36/143 (25.2)	18.3, 33.1	10/63 (15.9)	7.9, 27.3
Women	14/75 (18.7)	10.6, 29.3	2/48 (4.2)	0.5, 14.3
KPS				
< 80	4/25 (16.0)	4.5, 36.1	1/15 (6.7)	0.2, 31.9
≥ 80	46/193 (23.8)	18.0, 30.5	11/96 (11.5)	5.9, 19.6
No. Of metastatic sites				
1	30/102 (29.4)	20.8, 39.3	10/62 (16.1)	8.0, 27.7
2	15/78 (19.2)	11.2, 29.7	2/27 (7.4)	0.9, 24.3
≥3	1/9 (11.1)	0.3, 48.2	0/6 (0)	0.0, 45.9

Higher response rates were observed in male patients, patients with higher performance status (KPS ≥80), and patients with a single metastatic site. No significant difference was noted in the response rate in regards to the age group.

EGFr expression on tumor cells: the analysis of the response rate and the EGFr expression factors are shown in Table 22.

Table 22: Response rate and EGFr expression in the ITT population

EGFr expression	ERBITUX plus irinotecan		ERBITUX monotherapy	
	n/N (%)	95% CI	n/N (%)	95% CI
EGFr % positive cells				
0 to ≤10%	15/109 (22.9)	15.4, 32.0	4/56 (7.1)	2.0, 17.3
>10 to ≤20%	4/20 (20.0)	5.7, 43.7	5/16 (31.3)	11.0, 57.7
20 to ≤35%	6/27 (22.2)	8.6, 42.3	0/7 (0.0)	0.0, 41.0
> 35%	15/62 (24.2)	14.2, 36.7	3/32 (9.4)	2.0, 25.0
EGFr staining				
Faint/barely	11/53 (20.8)	10.8, 34.1	1/21 (4.8)	0.1, 23.8
Weak to moderate	22/89 (24.7)	16.2, 35.0	7/55 (12.7)	5.3, 24.5
Strong	17/75 (22.7)	13.8, 33.8	4/34 (11.8)	3.3, 27.5

Reviewer’s comment: in the population analyzed, neither the percentage of EGFr positive cells nor the EGFr staining on the tumor cells correlate with response rate

Prior treatment for colorectal cancer:

Table 23. Response Rate and Prior Treatment for Colorectal Cancer.

Prior therapy	ERBITUX plus irinotecan		ERBITUX monotherapy	
	n/N (%)	95% CI	n/N (%)	95% CI
No. of prior Rx lines				
1	7/14 (17.1)	7.2, 32.1	5/27 (18.5)	6.3, 38.1
2	20/79 (25.3)	16.2, 36.4	5/41 (12.2)	4.1, 26.2
≥3	23/98 (23.5)	15.5, 33.1	2/43 (4.7)	0.6, 15.8
Oxaliplatin				
Yes	30/135 (22.2)	15.5, 30.2	6/71 (8.5)	3.2, 17.5
No	20/83 (24.1)	15.4, 34.7	6/40 (15.0)	5.7, 29.8
Irinotecan schedule				
125 mg/m ² weekly	5/33 (15.2)	5.1, 31.9	4/20 (20.0)	5.7, 43.7
180 mg/m ² every 2 wks	29/124 (23.4)	16.3, 31.8	5/54 (9.3)	3.1, 20.3
350 mg/m ² every 3 weeks	15/57 (26.3)	15.5, 39.7	2/31 (6.5)	0.8, 21.4

Reviewer’s Comment: No significant difference was observed regarding response rate and the number of prior treatment lines, prior oxaliplatin treatment and most recent irinotecan schedule. The reviewer does not agree with the applicant’s assertion that patients who received 125 mg/m² weekly irinotecan had a lower response rate. Due to the low number of patients, the results can be only descriptive.

ERBITUX related dermatologic toxicity: The applicant’s analysis of the response rate and skin toxicity (Section 5.3.5.1.1, table 6.13) is shown in the Table 24.

Table 24: Incidence of Skin Toxicity and Response Rate in the ITT Population

Prior therapy	ERBITUX plus irinotecan		ERBITUX monotherapy	
	n/N (%)	95% CI	n/N (%)	95% CI
Acne-like rash				
None	8/48 (16.7)	7.5, 30.2	2/27 (7.4)	0.9, 24.3
Any	31/170 (24.7)	18.4, 31.9	10/84 (11.9)	5.9, 20.8
Grade 3 or 4	13/22 (58.1)	36.4, 79.3	1/4 (25.0)	0.6, 80.6
Skin reaction				
None	2/32 (6.3)	0.8, 20.8	0/18 (0)	0.0, 18.5
Any	48/186 (25.8)	19.7, 32.7	12/93 (12.9)	6.8, 21.5
Grade 3 or 4	16/29 (55.2)	35.7, 73.6	2/6 (33.3)	4.3, 77.7

Reviewer's Comment: Based on these results, the applicant claims that responses rates are higher in patients with more severe skin reaction (vs. no or less severe reactions). The FDA reviewer does not agree with the applicant's assessment. Results of acneform rash was further examined and presented in Table 25.

Table 25: FDA's Analysis of Severity of Acneform Rash and Tumor Response

	ERBITUX PLUS IRINOTECAN (N=218)		ERBITUX MONOTHERAPY (N=111)	
	Responder N=50 (%)	Non-Responder N=168 (%)	Responder N=12 (%)	Non-Responder N=99 (%)
Acneform rash				
None	8 (16.0)	40 (23.8)	2 (16.6)	25 (25.2)
Grade 1-2	29 (58.0)	119 (70.8)	9 (75.0)	71 (71.7)
Grade 3-4	13 (26.0)	9 (5.3)	1 (8.3)	3 (3.0)

Reviewer's conclusion: While 26% (13/50) of the responders in the combination arm had grade 3-4 toxicity, 58% (29/50) of the responders had mild and 16% (8/50) had no skin toxicity. A similar trend is observed in the monotherapy group. In addition, the sample size in each group is too small to draw any definite conclusion. A relationship between severity of acneform rash and response cannot be established with the available data.

Human Anti-Cetuximab Antibodies (HACA)

HACA was found to be positive in 5/60 patients tested. According to amendment 3, because studies have shown that free cetuximab interferes with HACA detection, 14 patients had serum samples collected 6 weeks after the last dose of ERBITUX. 1/14 patient had positive HACA. 47 patients were selected for determination of HACA based on AEs (fever and chills). Four patients

(402-2, 405-16, 801-6, 906-7) had positive HACA. The time to onset varied from 8 to 96 days. The duration of HACA positivity could not be determined because the last sample collected was positive. For additional results and analysis of HACA, see integrated HACA analysis; section IX, Special Issues Related to Biological Products.

Conclusion

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, 38% of the patients (124/329) had also failed prior therapy with oxaliplatin. Objective tumor response was confirmed in the ITT population (22.9%). Similar response rate was confirmed in the IRC-PD (25.8%) and IRC-PD oxaliplatin refractory population (23.8%). Tumor response was also confirmed for ERBITUX monotherapy ITT population (12.1%) and other populations of interest, 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).

2. Study IMCL CP02-9923

Protocol Title:

“Phase II Study of Anti-Epidermal Growth Factor Receptor (EGFr) Antibody Cetuximab in Combination with Chemotherapy in Patients with Advanced Colorectal Carcinoma”

Study sites: the study was conducted in 27 study centers in the US.

Protocol history:

- The first patient was enrolled on October 8, 1999 and the last patient was out on February 11, 2002.
- The study was amended once, on October 18, 1999. Following are the significant changes to the protocol:
 - The study design was revised to include a treatment arm of 49 patients with stable disease following treatment with irinotecan.
 - The total number of patients was increased from 55 to 110.
 - The population to be studied was modified from recurrent or metastatic to advanced colorectal carcinoma
 - Addition of secondary objectives to determine time to disease progression and tumor EGFr levels
 - KPS required at entry was changed from ≥ 70 % to ≥ 60
 - An exclusion criteria prohibiting therapy for disease between the irinotecan-containing regimen and study entry

Clinical Review Section

- The final study report, dated August 31, 2001 was submitted as the pivotal trial to support the BLA for accelerated approval on August 2001. Due to the serious deficiencies of the study conduct and the report, a refusal-to-file letter was issued on December 24, 2001. In preparation for the BLA resubmission and with FDA guidance, efforts were made by the applicant to retrieve more comprehensive data on the prior irinotecan dosing, dates, response to therapy and imaging documentation, when available. The applicant also performed review of the adverse events, completion of the CRFs and copies of source documents were obtained. Efforts were also made to further refine the data analysis to address issues raised by the FDA in the RTF letter. This resulted in significant amounts of new data in the BLA resubmission as well as correction of prior erroneous information.
- Under FDA guidance, a new Statistical Analysis Plan and a new Independent Review Committee Charter were developed for this submission.

This amended report reflects the data presentation and results according to the new Statistical Analysis Plan and the Independent Review Committee Charter.

Objectives:**Primary objective**

To determine the response rate to cetuximab administered in combination with irinotecan in patients with advanced colorectal carcinoma who were refractory to treatment with an irinotecan-containing regimen

Secondary objectives:

- To determine the time to progression of disease
- To evaluate the safety/adverse event profile of cetuximab in combination with irinotecan
- To assess the quality of life of patients receiving cetuximab in combination with irinotecan
- To determine the level of epidermal growth factor receptor (EGFr) expression in colorectal patients screened
- To determine the rate of survival

Study design

This was a multicenter, open-label, nonrandomized, phase II study of cetuximab in combination with irinotecan therapy. The study was designed to enroll 100 patients with advanced colorectal carcinoma who had stable disease or progressive disease after irinotecan-containing therapy (to yield 49 evaluable patients in each irinotecan response cohort). Patients received an initial cetuximab dose of 400 mg/m² (20 mg test dose on day 1) followed by 250 mg/m² every week in addition to either 350mg/m² of irinotecan every 3 weeks or 125 mg/m² of irinotecan every week for 4 weeks out of the 6-week course.

Study population:**Inclusion criteria:**

- Diagnosis of pathologically-confirmed advanced colorectal carcinoma
- Patients had documented SD (must have received a minimum of 12 weeks of irinotecan therapy) or PD at any time after receiving an irinotecan-containing regimen. Copies of scans were provided to confirm the lack of an objective response to prior therapy.
- The patient had immunohistochemical evidence of EGFr expression ($\geq 1+$)
- Had bidimensionally-measurable advanced colorectal cancer Index lesions must not have been in a previously irradiated portal.
- Karnofsky performance status score ≥ 60
- Signed informed consent
- Age ≥ 18 years.
- Adequate hematologic function: ANC $\geq 1500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, WBC $\geq 3000/\text{mm}^3$, Hb $\geq 9\text{g/dL}$
- Adequate hepatic function: bilirubin ≤ 1.5 x the upper limit of normal and alkaline phosphatase, aspartate transaminases and alanine transaminases levels ≤ 2.5 x the upper limit of normal
- Adequate renal function: serum creatinine level ≤ 1.5 x uln
- The patients had recovered from toxicities of prior treatment
- The patient had been disease-free from a previously treated malignancy for greater than 3 years. Patients with a history of a previous basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix could have been included in the study.
- The patients agreed to use effective contraception if procreative potential existed

Exclusion criteria:

- Patient had received prior murine monoclonal antibody therapy or cetuximab therapy
- The patient had undergone surgery, within 1 month of study entry
- The patient had received irradiation for disease within 2 months of study entry
- The patient had received chemotherapy for colorectal carcinoma since the irinotecan-containing regimen on which the patient demonstrated SD or PD at study entry
- The patient had a history of clinically significant cardiac disease, serious arrhythmia, or significant conduction abnormalities
- The patient had uncontrolled seizure disorder, active neurological disease, \geq grade 2 neuropathy, or meningeal or central nervous system involvement by the tumor
- The patient was pregnant or breastfeeding
- The patient had received any investigational agent within 1 months of study entry

Reviewer's comment:

- *During the pre-BLA meeting, FDA stated that the data on the stable disease population (i.e., patients who had stable disease while receiving an irinotecan containing regimen) could not be used to support licensure. Only patients with documented progressive disease while receiving irinotecan would be analyzed.*
- *The definition of irinotecan-refractoriness was less stringent in this study than the pivotal study EMR 62 202-007. To be eligible, the BOND study required that patients must have failed irinotecan within 30 days of the study entry.*

Treatment Plan

Patients with SD after prior irinotecan response (Cohort 1) and patients with PD after prior irinotecan response (Cohort 2) received cetuximab at a loading dose of 400mg/m² over 120 minutes and weekly cetuximab infusions at a maintenance dose of 250mg/m² over 60 minutes (maximum rate 10 mg/min = 5 mL/min). A test dose of 20 mg was administered over 10 minutes on day 1, prior to the loading dose. Patients were premedicated with 50 mg of i.v. diphenhydramine hydrochloride (or equivalent) prior to the test dose.

Irinotecan was to be administered at the same dosing regimen on which the patient had become refractory to irinotecan therapy. Initial irinotecan regimens for this study were:

- 350mg/m² every 3 weeks (i.e., weeks 1 and 4) or
- 125 mg/m² weekly for 4 weeks followed by 2 weeks of rest.

Irinotecan dose increases were not permitted in this study. The irinotecan infusion was administered 1 hour following the completion of the cetuximab infusion.

Dose modifications and delays:

Toxicity was graded according to the NCI, NCI Common Toxicity Criteria 2.0

Dose modifications and delays for cetuximab and irinotecan follow the same guidelines as described for the protocol EMR 62202-007 (see section C.1.X, page X) and will not be repeated here.

Concomitant Treatment:

Standard oncologic supportive care: sedatives, antibiotics, analgesics, antihistamines, steroids, G-CSF, blood products could be given to assist in the management of complications of the malignancy

Excluded medications and treatments: chemotherapy and radiation therapy. Topical corticosteroids were not recommended for skin adverse events.

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Study evaluations:

The key study procedures are outlined in the Table 26. Patients were to undergo EGFR assessment to determine eligibility. For Quality of Life assessments the FACT-C (version 4.0) questionnaire were applied.

Table 26. Study Flow Chart

Study Procedure	Pre-treatment	Treatment	End of therapy/ Follow up
Medical History	X		
Screening tests	X		
EGFR assessment	X ¹		
Imaging/diagnostic studies	X	X ²	X
Vital signs	X	X ³	
Physical examination	X	X ⁴	X
Hematology profile	X	X ⁴	X
Coagulation profile	X		
Chemistry profile	X	X ⁴	X
CEA assessment	X	X ⁶	X
Quality of life assessment	X	X ⁶	X
Tumor assessment	X	X ²	X
Pharmacology profile		X ⁸	X ⁸
Cetuximab/irinotecan infusions		X ⁹	

- 1) Must be performed prior to all other Pre-therapy evaluation procedures
- 2) Performed at the completion of every 6 week course of therapy
- 3) Vital signs will be evaluated pre, med-post-, and 1 hours post-each cetuximab infusion
- 4) PE and chemistry evaluations every 3 weeks
- 5) Hematology evaluation weekly on treatment days prior to infusion
- 6) CEA assessment will be performed every 6 weeks
- 7) QoL assessment will be performed at the completion of every 6 weeks course of therapy
- 8) PK samples are collected prior to the test dose of cetuximab, prior to the infusion every 6 weeks and four weeks following the completion of cetuximab therapy
- 9) Cetuximab administered weekly, irinotecan administered at the dosage regimen on which the patient became refractory to therapy
- 10) End of therapy evaluations are performed at discontinuation therapy
- 11) Follow up evaluations are performed four weeks after discontinuation of therapy.

Evaluation of Study Data:

Between December 2002 and October 2003, several amendments were submitted to the IND that revised the Statistical Analysis Plan (SAP) and the Independent Review Committee (IRC) charter for this study incorporating guidance from the FDA. These two documents were made as uniform as possible to the EMR62 202-007 study in order to make the data analyses consistent across the trials.

The primary efficacy analysis in this study report is based on the IRC determination. The IRC reviewed the scans from the most recent prior irinotecan therapy as well as on study scans. The IRC assigned patients to one of two groups, PD (irinotecan-refractory) or other/unknown, which

consisted of all remaining patients. The IRC also assigned a date of progression for those patients in the PD group.

The treatment cohort used in the primary analysis of this study consisted of those patients whose IRC prestudy overall progression status was PD and who met the following conditions:

1. The IRC-assigned prestudy progression date was less than or equal to 42 days after the last dose of prior irinotecan therapy
2. The scan assigned as baseline for the prior irinotecan regimen was performed either less than or equal to 6 weeks prior to the first dose of the most recent irinotecan therapy or was performed after the first dose of irinotecan but at least 4 weeks prior to the date of the scan used to assess progression
3. At least one derived cycle of prior irinotecan treatment; for those patients who received less than or equal to one derived cycle, a minimum of four doses of irinotecan for the weekly schedule and a minimum of one dose for the every 3-week schedule (the number of derived cycles, in the context of prior irinotecan, was defined as {stop date of prior irinotecan minus start date of prior irinotecan + 1}/42 for the weekly schedule and {stop date of prior irinotecan minus start date of prior irinotecan + 1}/21 for the every 3-week schedule).

The modified WHO Response Criteria was used to assess tumor response by IRC as in the EMR 606-02-007 study that has been previously described (refer to section xyz)

Efficacy Endpoints:

The primary endpoint was objective response rate in the IRC PD cohort. In addition, a secondary endpoint, disease control rate was calculated, which was defined as (number of SD, PR, and CR patients in the IRC PD cohort)/total number of patients in the IRC PD cohort. A two-sided, Clopper-Pearson exact 95% confidence interval was calculated for each rate.

The secondary efficacy endpoints were: disease control rate, time to progression, time to response, duration of response, duration of disease control, overall survival duration and Investigator-based response rate and quality of life.

Safety endpoints included all worst grade of adverse events, adverse events, the duration of and time until acne-like rash, the worst grade laboratory abnormalities, the duration, cumulative dose, dose intensity, and relative dose intensity of cetuximab, and the reasons for discontinuation from cetuximab.

Data sets analyzed:

The following data sets are analyzed in this study:

All enrolled: all patients for whom informed consent was obtained

All treated: all patients who received at least one dose of study therapy

IRC-PD: treatment cohort assignment based on the IRC

Per protocol: all treated patients who did not have a major violation

An additional subpopulation was included in the FDA analysis, IRC PD 2 cycles, which met the FDA criteria for Fast track product development of cetuximab. IRCPD 2 cycle includes all patients who had received a minimum of 2 cycles of irinotecan-based therapy.

Sample size determination:

The protocol was initially designed to evaluate tumor response in a cohort of patients with PD following treatment with irinotecan and later was revised to include a treatment arm of patients with SD following treatment with irinotecan. For both cohorts, a modified Gehan two-stage design was used to allow early stopping for ineffectiveness after the first stage and to provide a precise estimate of the response. Given a targeted response rate of 15%, 19 patients were to be enrolled into each cohort during the 1st stage, and at least 30 evaluable patients were to be enrolled into each cohort during the second stage. To observe at least 49 evaluable patients in each cohort, it was planned to enroll 55 patients per cohort, 110 patients overall. If none of the first 19 patients responded, enrollment would have been stopped.

Independent Review Committee Charter and Statistical Analysis Plan

As stated in the Protocol History section, in preparation for the BLA resubmission and, in consultation with FDA, a new Statistical Analysis Plan and a new Independent Review Committee Charter were developed for this submission. Data presentation and analysis were made according to the new Statistical Analysis Plan and the Independent Review Committee Charter.

Results

Patient Population

Between October, 1999 and February 2002 and total of 401 patients were screened for EGFr expression. Of the patients 292 patients (73%) had tumors that expressed EGFr (1+ or greater). A total of 139 patients were enrolled in this study (121 in the PD cohort and 18 in the SD cohort). Of the 139 patients, one patient was hospitalized and never received cetuximab treatment. 138 received study treatment: 134 received cetuximab and irinotecan therapy and four patients received cetuximab alone (patient 035603, 060654, 064677 and 066633). These four patients discontinued from the study due to infusion reactions after receiving cetuximab. 83 patients were assigned to the IRC-PD cohort. The patient disposition, as per applicant, is shown in Table 27.

Table 27: Patient disposition, as per applicant, section 9.1, Table 9.1

Patient Status	Number (%) of Patients	
	IRC PD Cohort (N=83)	All enrolled Patients (N=139)
Enrolled	83 (100)	139 (100)
Treated	83 (100)	138 (99.3)
Discontinued	83 (100)	138 (99.3)
Death	4 (4.8)	6 (4.3) ^{2,3}
Adverse Event	7 (8.4)	16 (11.6) ²
Protocol Noncompliance	0 (0.0)	0 (0.0) ²
Withdrew Consent	3 (3.6)	6 (4.3) ²
Progressive Disease	67 (80.7)	106 (76.8)
Other ⁴	2 (2.4)	4 (2.9)
Still on Study	0 (0.0)	0 (0.0)

1. Data from "discontinuation from treatment" case report form
2. N=138
3. PD in four patients, a disease-related complication in one patient (kidney failure), and an intercurrent illness (sepsis and pneumonia)
4. No clinical benefit, elevated CEA level, hospitalization prior to start of treatment and surgery at the completion of course 7

The most common reason for discontinuation from the study was progression of disease. Eight percent of patients in the IRC PD cohort and 12 % of all treated patients discontinued because of adverse events, 4% of patients in the IRC PD cohort and 4% of all treated patients withdrew consent.

Protocol violations:

Major protocol violation was defined as any of the following: no evidence of metastatic colorectal disease at baseline, a lack of measurable disease at baseline, the most recent prestudy irinotecan dose was 25mg/m² less than the first on-study dose for the weekly irinotecan schedule (or < 50mg/m² for an every 3 week irinotecan schedule), and no evidence of positive EGFr expression. Nine patients in the IRCPD cohort (10.8%) and 12 patients in all treated patients population (8.7%) had major violations. All violations were in a single category, i.e., that the most recent prestudy irinotecan dose was lower than the 1st on-study dose.

Reviewer's comment: Nine patients in the IRCPD cohort and 12 patients in the all treated group received doses of irinotecan that were higher than what the patient had failed, a major protocol violation, which places in doubt the efficacy results. These patients will be removed from the efficacy analysis population by the FDA (patient ID # 004-772, 020-649, 041-702, 060-602, 065-697, 065-700, 065-707, 066-632, 066-655).

Eligibility violations: Table 28 summarizes the eligibility violations per applicant and confirmed by the FDA in spot cross check review.

Table 28 - Protocol Eligibility Violations

Criterion violation	Number (%) of patients	
	IRC PD (N=83)	All enrolled (N=139)
Inclusion criterion¹		
- Bidimensionally measurable disease; index lesions not previously irradiated	2 (2.4)	4 (2.9)
- KPS \geq 60	0 (0.0)	1 (0.7)
- Signed informed consent after enrollment	3 (3.6)	4 (2.9)
- Hematologic function	3 (3.6)	6 (4.3)
- Hepatic function	20 (24.1)	36 (25.9)
- Renal function	4 (4.8)	9 (6.5)
Exclusion criterion[*]		
- Prior murine mAb or cetuximab therapy	2 (2.4)	2 (1.4)
- Surgery within 1 month of study entry	1 (1.2)	2 (1.4)
- Chemotherapy for colorectal cancer between irinotecan regimen and enrollment	0 (0.0)	1 (0.7)
- History of clinically significant cardiac disease, arrhythmias, or conduction abnormalities	1 (1.2)	1 (0.7)

* Patient may have had more than one violation

There were 37 eligibility violations in the IRC PD cohort and total 60 instances of violation in all enrolled patients. The most common violation was hepatic function not fulfilled (24% in the IRC PD cohort).

Protocol deviations during the study are shown in Table 29. 35% of the patients in the IRC PD cohort had cetuximab dose discrepancies from the planned dose and 29% had urine analysis missing or incorrect. 28% of the patients in each cohort had on-study irinotecan dose discrepancies and 28% of the patients in the IRC PD cohort had in study diagnostic tests missing or incorrect.

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Table 29 – Protocol deviations during the study

Protocol Deviation	Number (%) of Patients	
	IRC PD (N=83)	All treated (N=138)
Most recent prestudy irinotecan dose was 25 mg/m ² < the 1 st on-study dose for weekly regimen or 50 mg/m ² less than the 1 st on-study dose for every 3 week regimen	15 (18.1)	20 (14.5)
Absent/inappropriate cetuximab treatment alterations due to grade 3/4 adverse events	4 (4.8)	8 (5.8)
Absent/inappropriate irinotecan treatment alterations due to grade 3/4 adverse events	0 (0.0)	1 (0.7)
On-study cetuximab dose discrepancies from planned dose	29 (34.9)	50 (36.2)
On-study irinotecan dose discrepancies from planned dose	23 (27.7)	39 (28.3)
On-study hematology determinations missing/incorrect	8 (9.6)	16 (11.6)
On-study chemistry determinations missing/incorrect	14 (16.9)	26 (18.8)
Urinalysis determinations missing/incorrect	24 (28.9)	43 (31.2)
Diagnostic tests missing/incorrect	23 (27.7)	40 (29.0)
Diphenhydramine hydrochloride administration for test dose missing/incorrect	1 (1.2)	2 (1.4)
Lack of acceptable most recent prior irinotecan dose/schedule: 125 mg/m ² every wk for 4 wks or 350mg/m ² every 3 wks	20 (24.1)	29 (21.0)
Other	6 (7.2)	11 (8.0)

Reviewer’s comment: the large number and the severity of protocol violations and deviations place in question the integrity of the efficacy and safety data derived from this study. Most disconcerting are the large number of on-study cetuximab and irinotecan dose discrepancies from planned dose (36.2% and 28.3% of all patients enrolled did not received the planned dose) and the absent/inappropriate treatment alterations due to severe adverse events.

Patient demographics and baseline characteristics are summarized in Table 30.

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Table 30. Patient Demographics and Baseline Characteristics

Characteristics	IRCPD Cohort (N=83)	All treated patients (N=138)
Gender Male	46 (55.4)	76 (55.1)
Female	37 (44.6)	62 (44.9)
Age (years) median	61	60
Range	26-83	26-83
Race White	69 (83.1)	112 (81.2)
Black	8 (9.6)	14 (10.1)
Asian	2 (2.4)	3 (2.2)
Hispanic	4 (4.8)	7 (5.1)
Other	0 (0)	2 (1.4)
KPS < 80	9 (10.8)	16 (11.6)
≥80	74 (89.2)	122 (88.4)
Site of tumor origin		
Colon	67 (80.7)	114 (82.6)
Rectum	16 (19.3)	24 (17.4)
EGFr status		
1+	40 (48.2)	66 (47.8)
2+	26 (31.3)	48 (34.8)
3+	17 (20.5)	24 (17.4)
Prior therapy		
Chemotherapy	83 (100)	138 (100)
5-Fluorouracil	79 (95.2)	129 (93.5)
oxaliplatin	6 (7.2)	14 (10.1)
Hormonal Therapy	3 (3.6)	5 (3.6)
Radiotherapy	20 (24.1)	29 (21.0)
Most recent irinotecan schedule		
Weekly		
< 100 mg/m ²	8 (9.6)	15 (10.9)
100 to 12 mg/m ²	53 (63.9)	88 (63.8)
125 mg/m ²	6 (7.2)	8 (5.8)
Every 3 weeks		
< 350 mg/m ²	9 (10.8)	13 (9.4)
350mg/m ²	6 (7.2)	9 (6.5)
> 350mg/m ²	0 (0.0)	1 (0.7)
Other		
< 100mg/m ²	0 (0.0)	1 (0.7)
100 to 125 mg/m ²	1 (1.2)	3 (2.2)
> 125 mg/m ²	0 (0.0)	0 (0.0)

Efficacy Results:

Objective tumor response:

Analysis of efficacy endpoints were performed using the Independent Review Committee charter for radiologic assessment of pre-study irinotecan refractoriness and response to on-study treatment. Pre-study and on study scans were submitted by the applicant for review.

The applicant reported a response rate of 13% (95%CI [6.8 to 22.5]) as determined by the IRC. The disease control rate was 53%, with at 95 CI of [41.7 to 64.1]. For all treated patients, the objective response rate was 15%, with a 95 CI of [9.7 to 22.3]. These results are summarized in Table 31.

Table 31: Tumor Response per Applicant (section 10.4.11, Table 10.9)

Tumor Response	Number (%) of patients	
	IRCPD Cohort (N=83)	All treated Patients (N=138)
Best tumor response (IRC)		
Complete response	0 (0)	0 (0.0)
Partial response	11 (13.3)	21 (15.2)
Stable disease	33 (39.8)	63 (45.7)
Progressive disease	29 (34.9)	40 (29.0)
Not evaluable	10 (12.0)	14 (10.1)
Objective response rate (CR+PR) [95%CI]	11/83 (13.3) [6.8 – 22.5]	21/38 (15.2) [9.7-22.3]
Disease Control Rate (CR+PR+SD) [95% CI]	44/83 (53.0) [41.7-64.1]	84/138 (60.9) [52.2-69.1]

Nine patients in the IRCPD cohort (patient ID # 004-772, 020-649, 041-702, 060-602, 065-697, 065-700, 065-707, 066-632, 066-655) were removed from the FDA efficacy analyses (Table 32) due to major protocol violation (the most recent prestudy irinotecan dose was 25mg/m² less than the first on-study dose for the weekly irinotecan schedule or < 50mg/m² for an every 3 week irinotecan schedule), a violation that in the reviewer’s opinion, puts in doubt the “irinotecan refractoriness” of the population . Seventy four patients were included in the IRC-PD per protocol cohort. See Table 32.

An additional subpopulation, IRC PD 2 cycles, was included in the FDA analysis. This population meets the FDA criteria for Fast track product development of cetuximab. IRCPD 2 cycle includes all patients who had received a minimum of 2 cycles of irinotecan-based therapy. Forty-six patients were included in this subpopulation (Table 32).

The FDA imaging reviewers reviewed all scans submitted the application and confirmed both progression following prior irinotecan and tumor responses asserted by the IRC (Appendix A). The response rate in all treated patients was 15.2% (95%CI 9.7, 22.3). The response rate in the

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IRC-PD per protocol population, excluding those with major protocol violation was 12.1 % (95 % CI 5.7, 21.8). The IRCPD 2 cycle response rate was 13.0% (95% CI 4.9, 26.3)

Table 32: Response Rate Analysis by FDA

Best response	IRC-PD N= 83	IRC-PD per protocol N=74 (%)	IRCPD 2 cycles N= 46 (%)	All treated Patients N=138 (%)
CR	0	0	0	0
PR	11 (13.3)	9 (12.1)	6 (13.0)	21 (15.2%)
95% Confidence interval	6.8 – 22.5	5.7 – 21.8	4.9 – 26.3	9.7 to 22.3

Subset analyzes of patients with objective response are shown in Table 33.

Table 33. Subset Analyzes of Patients with Objective Response

Subset	IRCPD N=11 (%)	All treated patients N=21 (%)
Gender		
Male	9 (81)	14 (44)
Female	2 (19)	7 (56)
Age		
< 65 years	3 (27)	10 (47)
≥65 years	8 (73)	11 (53)
KPS		
< 80	2 (19)	3 (14)
≥80	9 (81)	18 (86)
EGFr		
1+	7 (63)	1 (4.7)
2+	2 (19)	7 (33)
3+	2 (19)	3 (14.2)
Irinotecan Schedule		
Weekly	7 (63)	15 (71.4)
Every 3 weeks	4 (37)	6 (28.5)

Reviewer's comment: The subsets are small and unbalanced and do not permit definitive conclusions regarding variables that may be associated with response to cetuximab.

Additional efficacy analysis:

The following secondary analyzes were performed by the applicant. Given the deficiencies of the trial and the small number of patients, definitive conclusions cannot draw.

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1. **Duration of response:** the median duration of response was 5.7 months (95% CI [3.9 to 7.8]) for the patients on the IRC PD cohort and 6.5 months (95% CI of [5.7 to 7.8]) for all treated patients.
2. **Duration of disease control:** the median duration of disease control was 5.4 months (95% confidence interval of [4.2 to 6.8]) for the patients in the IRC PD cohort and 5.5 months (95% CI of [4.4 to 7.4]) for all treated patients.
3. **Median time to response:** the median time to response was 1.3 months (range 1.2 to 5.4 months) for the patients in the IRC PD cohort and 2.6 months (range 1.2 to 5.4 months) for all treated patients.
4. **Time to progression:** the median time to progression was 2.6 months (95CI [1.7 to 3.1]) for patients in the IRC PD cohort and 2.9 months (95% CI of [2.6 to 4.1]) for all treated patients.
5. **Median overall survival:** the median survival was 7.7 months (95% CI of [6.2 to 9.8]) for patients in the IRC PD cohort and 8.4 months (95% CI of [7.2 to 10.3]) for all treated patients.
6. **Quality of Life:** overall QOL showed minor decreases from baseline to the endpoint evaluation for both patients in the IRC PD cohort and all treated patients. The QOL results from this study are non comparative and only exploratory.

Conclusion: This trial had a large number of serious protocol violations and deviations, however these violations do not confound the determination of response rate, after exclusion of ineligible patients. The FDA reviewers confirmed the objective response rate of 15.2% (95% CI 9.7, 22.3) in the all treated population. The response rate was 12.1% (9/74) in the IRC-PD per protocol cohort and 13% (6/42) in the IRC-PD 2 cycles per protocol cohort.

3. Study IMCL CP02-0141

Protocol Title:

“Phase II Study of An Anti-Epidermal Growth Factor Receptor (EGFr) Antibody, Cetuximab, in Patients with Irinotecan-Refractory, Stage IV Colorectal Carcinoma”

Study sites:

The study was conducted in 4 investigational sites in US

Protocol history:

- The protocol was issued on January 21, 2001.
- Date of 1st patient enrolled: April 26, 2001
- Date of last patient randomized: October 9, 2002
- One amendment was made to the protocol prior to the study began.
Significant changes to the protocol were:
 - a. The window of time between receiving an irinotecan-containing regimen and documentation of progressive disease was defined as ≤ 6 months in the inclusion criteria
 - b. The exclusion criterion restricting the use of radiation within 60 days of study entry was changed to within 30 days of study entry.

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- This protocol was submitted with the first BLA by ImClone as a supporting trial for CP02-9923.
- As with IMCL-CP02-9923 trial, in preparation for the BLA resubmission and with FDA guidance, efforts were made by the applicant to retrieve more comprehensive data on the prior irinotecan dosing, dates, response to therapy and imaging documentation, when available. The applicant also performed review of the adverse events, completion of the CRFs and copies of source documents were obtained. Efforts were also made to further refine the data analysis to address issues raised by the FDA in the RTF letter. This resulted in significant amounts of new data in the BLA resubmission as well as correction of prior erroneous information.
- Under FDA guidance, a new Statistical Analysis Plan and a new Independent Review Committee Charter were developed for this submission.

Objectives:**Primary objective**

To determine the response rate of patients to cetuximab with stage IV advanced colorectal carcinoma who were refractory, i.e., had documented progressive disease to treatment with an irinotecan containing regimen

Secondary:

- To collect data on the safety/toxicity profile of cetuximab in patients with stage IV colorectal carcinoma
- To determine the time to progression of disease in patients with stage IV colorectal carcinoma
- To determine the level of EGFR expression of colorectal patients screened

Study design

This was an open-label, uncontrolled, phase II study designed to enroll 40 patients with irinotecan refractory, stage IV colorectal carcinoma.

Patients in this study received cetuximab at an initial dose of 400mg/m² followed by weekly doses of 250mg/m². A 20 mg test dose was administered on day 1 prior to the loading dose. Patients were evaluated for a response after the completion of each 6-week course of therapy. Treatment was terminated in the event of progressive disease or severe toxicity.

Study population**Inclusion Criteria**

- Stage IV (T_{any}, N_{any}, M₁) colorectal cancer with either present or prior histologic or pathologic confirmation of colorectal carcinoma
- Documented progressive disease ≤6 months after receiving an irinotecan-containing regimen
- Bidimensionally measurable metastatic disease

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- Immunohistochemical evidence of EGFr expression (≥ 1). EGFr expression had to be confirmed prior to study entry
- ECOG performance status ≤ 2 at study entry
- Signed informed consent
- ≥ 18 years of age
- Adequate hematologic function, defined as ANC $\geq 1,500/\text{mm}^3$, WBC $\geq 3,500/\text{mm}^3$, a platelet count $\geq 100,000/\text{mm}^3$, and Hb $\geq 9\text{g/dL}$
- Adequate hepatic function, defined as total bilirubin level ≤ 1.5 x the upper limit of normal (ULN) and alkaline phosphatase and AST levels ≤ 5 x uln
- Adequate renal function, with a serum creatinine level ≤ 1.5 x the uln
- Recovered from toxicities of prior treatment, including radiation and chemotherapy
- Disease free from a previously treated malignancy for greater than 3 years (previous basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix were not excluded)
- Agree to use effective contraception if childbearing potential existed.

Exclusion criteria:

- Received prior murine monoclonal antibody therapy or cetuximab therapy
- Received chemotherapy for colorectal carcinoma between the irinotecan-containing regimen on which the patients demonstrated progressive disease and study entry
- Undergone surgery, excluding prior diagnostic biopsy, within 21 days of study entry
- Received irradiation for disease within 30 days of study entry
- Had a history of uncontrolled angina, arrhythmias, or congestive heart failure
- Uncontrolled seizure disorder, active neurological disease, or grade ≥ 2 neuropathy (patients with meningeal or central nervous system involvement by the tumor were eligible)
- Medical or psychiatric condition that constituted an unacceptable risk for participation in this trial, in the judgment of the treating physician
- Pregnant or breastfeeding
- Received any investigational agents within 30 days of study entry.

Treatment Plan:

Patients received cetuximab intravenous infusion at a one-time initial dosage of $400\text{mg}/\text{m}^2$ (over 120 minutes), followed by weekly infusions of $250\text{mg}/\text{m}^2$ (over 60 minutes). The infusion rate did not exceed 10 mg/minute (5mL/minute). Patients received a test dose of 20 mg administered over 10 minutes prior to the initial dose of cetuximab. Patients were premedicated with 50mg i.v. diphenhydramine hydrochloride prior to receiving the test dose of cetuximab.

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Treatment modifications:

Treatment modifications for rash appear to have been implemented in response to a grade 3 acne-like rash as described for EMR-606-02-007 study (Section C.1., page 40). The Investigator was to consider concomitant treatment with topical and/or oral antibiotics, however, topical corticosteroids were not recommended.

Infusion reactions: if a patient experienced a grade 1 or 2 allergic reaction, the infusion rate was decreased. The infusion rate was to remain decreased for subsequent infusions. Patients that experienced a grade 3 or grade 3 allergic reaction were to be discontinued from the study.

Study Schedule:

The schedule of study procedures are summarized on Table 34.

Table 34. Study Schedule

Procedure	Study week								
	Pre-Treatment ¹	1	2	3	4	5	6	End of Therapy	Follow up ²
Medical History/ β HCG test	X								
EGFr assessment	X ³								
ECGO performance score	X								
Physical examination	X ⁵	X			X			X	X
Vital Sign	X	X ⁴	X	X	X	X	X		
Hematology profile	X ⁵	X	X	X	X	X	X	X	X
Serum Chemistry profile	X ⁵	X			X				
Urinalysis	X ⁵	X			X			X	X
CEA		X			X			X	X
ECG/MUGA	X						X	X	
Imaging studies	X ⁸						X ⁸	X ¹⁰	X
Cetuximab infusions		X	X	X	X	X	X		
Cetuximab levels		X		X			X	X	X
Anti-cetuximab antibodies ¹¹		X			X		X	X	X
Dermatological consultation/photographs ¹²		X	X	X	X	X	X	X	X
Survival information									X ¹³

1. Pretreatment evaluations were performed within 2 weeks
2. Follow up evaluations were performed 4 weeks after the end of therapy evaluation
3. tumor EGFr expression was confirmed prior to the start of the study
4. vital signs were evaluated pre, mid-, at the completion of, and 1 hours post each cetuximab infusion
5. the pretreatment data/samples were also considered the week 1 data/sample for course 1 only
6. A CEA assessment was performed during the first week of each course
7. the cardiac profile was performed every 4th treatment course
8. imaging studies were performed within 4 weeks of study entry
9. imaging studies were performed after every treatment course
10. if indicated
11. serum samples were drawn prior to the test dose, and the 4th and 6th infusions; 1 hour following 1st, 4th and 6th infusions in the first course, and prior to and 1 hr post the 1st infusion of each subsequent course of treatment.
12. whenever a grade ≥ 3 acne-like rash occurred and when the toxicity resolved
13. patients were contacted every 3 months.

Efficacy Variables

Between December 2002 and April 2003, amendments were submitted to the IND with revised Statistical Analysis Plan and Independent Review Committee charter, incorporating input and guidance from the FDA. Both the SAP and the IRC charter were made as uniform as possible to the pivotal study, EMR662-02-007, in order to make the data analyses consistent across the trials.

The **primary efficacy endpoint** was response rate, based on the on-study tumor assessment made by the IRC, for patient in the IRC PD cohort. In the original statistical plan, the primary efficacy analysis was to be performed on those patients deemed to have progressive disease by the Investigator.

Secondary efficacy endpoints included disease control rate, time to progression, time to response, duration of response, duration of disease control, overall survival duration, and Investigator-based response rate.

The following **data sets** were used in this study:

All enrolled patients: all patients for whom informed consent was obtained

All treated patients: all patients who received at least one dose of cetuximab

Per protocol patients: all treated patients who did not have a major violation

The cohort used in the primary analyses for this study consisted of those patients whose IRC pre-study overall progression status was PD, i.e. those patients assigned to the PD group, and who met the following conditions:

1. The IRC assigned progression date was less than or equal to 42 days after the last dose of prior irinotecan therapy
2. The scan assigned as baseline for the prior irinotecan regimen was performed either less than or equal to 6 weeks prior to the first dose of the most recent irinotecan therapy or was performed after the 1st dose of the most recent irinotecan therapy, but least 4 weeks prior to the date of the scan used to assess progression
3. At least one derived cycle of prior irinotecan treatment, for those patients who received less than or equal to one derived cycle, a minimum of 4 dose of irinotecan for the weekly schedule and minimum of one dose of the every three week schedule.

Changes to the planned analysis:

This study was submitted as a supporting trial for CP-02-9923 study in the first ERBITUX BLA submission.

As indicated in the Protocol History Section, in preparation for this resubmission, the applicant retrospectively retrieved more comprehensive data on the prior irinotecan therapy, which included, start and stop dates, response to therapy, date of progression, scans, when available documenting disease progression. Efforts were also made to further refine the data analysis to address issues raised by the FDA in the RTF letter. This resulted in significant amounts of new data in the BLA resubmission as well as correction of prior erroneous information.

Results

Study Patients: a total of 140 patients were screened for EGFr expression. Of these 140 patients, 105 (75%) had tumors that expressed EGFr (1+ or greater). A total of 61 patients were enrolled in this study; 57 patients received cetuximab. Four patients decided not to participate in the study prior to receiving cetuximab. Fifty patients (87.1%) had disease progression, 5 patients discontinued due to adverse events; 1 (2%) patient withdrew consent; 1 (2%) died due to disease related complications during the study. Eleven patients were still alive at the time of the data base lock.

Protocol deviations:

Major protocol violation: one patient had no evidence of metastatic colorectal cancer at baseline.

Inclusion/ exclusion eligibility violations: in the all enrolled patient population (N=61), there were 21 instances of eligibility violation. The most common violation (12/21, 19.7%) was that informed consent was signed after study procedures (ECG, MUGA, EGFr determination). One patient became pregnant after being enrolled in the study. The case narrative is summarized here.

Patient #060-1105, a 38-year-old black female, with advanced colon cancer received 1st dose of cetuximab on May 10, 2001. She received five weekly infusions of cetuximab from May 18 through June 15. She experienced grade 1-2 urine abnormality and leucorrhoea on day 43. Miconazole vaginal cream was prescribed on days 43 to 57. The patient was amenorrheic and a positive β HCG was obtained on day 43. The baseline β HCG, performed 13 days prior to the 1st dose of cetuximab, was negative. She elected to undergo termination of the pregnancy, and upon her follow-up visit on day 57; she reported that this had been completed. The patient was removed from the study on day 43.

Protocol deviations: there were 62 instances of protocol deviations. The most common deviation was cetuximab infusion time shorter or longer than specified, poor record keeping for cetuximab infusion time (n=46, 80.7%) and lack of record of skin photos for skin toxicity (n=10, 17.5%).

Reviewer's comment: these protocol violations were minor in nature and did not impact on the efficacy and safety results.

Patient Population:

Primary efficacy analysis population consisted of 28 patients, who fulfilled the criteria for IRC PD as per independent review. There were 57 patients in the All Treated Patient population.

Demographic, baseline and disease characteristics: the all treated population included 35 males and 22 females. The median age of the patient population was 56 years (range of 28 to 80 years). The majority of patients were white (91%). The median baseline ECOG performance status score was 0. The colon was the original site of the tumor in 77% of the patients. The median duration

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of disease was 17.9 months. Fifty-three percent of the patients had an EGFr status of 2+. Liver was the most common and frequent site of index lesions (>60%). One third of the patients (>35%) had more than 3 metastatic sites. More than 95% of the patients failed irinotecan and 5-FU in the all treated population. All patients in the IRC PD cohort had failed both irinotecan and 5-FU. Eight patients (14%) in the All treated population and 5 (17.9%) in the IRCPD cohort received prior oxaliplatin.

Efficacy Analysis:

Per applicant, for patients in the IRC PD cohort the objective response rate was 14% (95% CI: 4.0,32.7); the disease control rate (CR+PR+SD) was 39%, [95% CI: 21.5, 59.4]. For all treated patients, the objective response rate was 9% [95% CI: 2.9, 19.3]. The disease control rate was 46% (95% CI: 32.4, 59.3).

The FDA clinical and imaging reviewers confirmed both progression following prior irinotecan and tumor responses asserted by the IRC. The objective response rate is presented in Table 35.

Table 35 – Objective response rate per FDA

Tumor Response	Number (%) of Patients	
	IRCPD Cohort (N=28)	All treated patients (N=57)
CR	0	0
PR	4 (14.3)	5 (8.8)
Objective Response rate 95% CI	4/28 (14.3) 4.0-32.7	5/57 (8.8) 2.9 –19.3

The demographic, baseline characteristics of the patients who responded to the therapy in the All treated population (N= 5) were as follow: 3 were male and 2 female patients, 3 patients were ≤ 65 years and 2 ≥65 years, 3 patients were white and 2 nonwhite. ECOG was 0 in 3 patients and 2 in 2 patients. Four patients had EGFr status 2+. All five patients had grade 1-2 ERBITUX related skin toxicity.

Other secondary efficacy analysis as per applicant:

For the all treated group, the **time to progression** was 1.4 months [95% CI: 1.3 , 2.8]. The median duration of response was 4.2 months [95% CI: 4.1,4.2]. The median time to response was 1.2 months (range 1.2 to 2.6). For the IRCPD cohort, the time to progression was 1.3 months [95% CI: 1.3,3.2]. The median duration of response was 4.2 months and the median time to response 1.9 months (range 1.2 to 2.6).

Conclusions: study CP-02-0141 was a small, well-conducted clinical trial, in a colorectal cancer population who failed standard therapy. This trial confirms that ERBITUX as a single agent, has activity in this patient population.

D. Efficacy Conclusions

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, 38% of the patients (124/329) had also failed prior therapy with oxaliplatin. There has been no effective therapy found for this patient population.

Objective tumor response was confirmed in the ITT population (22.9%). Similar response rate was confirmed in the IRC-PD (25.8%) and IRC-PD oxaliplatin refractory population (23.8%). Tumor response was also confirmed for ERBITUX monotherapy ITT population (12.1%) and other populations of interest, 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 confirms that ERBITUX alone or in combination with irinotecan can induce responses in this refractory colorectal cancer population.

VII. Integrated Review of Safety**A. Brief Statement of Conclusions**

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 safety database had colorectal cancer. The chemotherapeutic agent most commonly administered 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 blephritis, cheilitis, skin ulcerations and boils were observed, and an unusual adverse event, paronychia 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, 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 an influence of gender, age or race on cetuximab-induced adverse events.

B. Description of Patient Exposure

Extent of exposure to cetuximab was characterized by duration (weeks), number of infusions, cumulative dose (mg/m^2), dose intensity ($\text{mg}/\text{m}^2/\text{week}$), number of dose reductions, and number and length of dose delays. Factors effecting exposure included the following:

1. Removal of Patients from Therapy or Assessment

Conditions for discontinuation from cetuximab therapy prior to the completion of the required regimen included: protocol noncompliance, disease progression prior to completing a course of therapy, a cetuximab-related grade 4 adverse event, more than two consecutive infusions held for an intercurrent event, or a fourth occurrence of a grade 3 cetuximab-related skin adverse event, withdrawal of consent.

2. Choice of dose regimen

PK modeling from Phase I studies indicated that a $500 \text{ mg}/\text{m}^2$ initial dose of cetuximab followed by weekly doses of $250 \text{ mg}/\text{m}^2$ would maintain steady-state levels near the K_m , however the occurrence of a grade 3 acne-like rash in 2/6 patients treated at the 500 dose resulted in the trial regimen of $400 \text{ mg}/\text{m}^2$ and weekly doses of $250 \text{ mg}/\text{m}^2$. Infusions were administered over a period of one hour (maximum infusion rate of 5 mL/minute).

3. Treatment alterations

a. Cetuximab

In the event of grade 1 or 2 allergic reaction, cetuximab infusion time could be increased (to a maximum of 4 hours). If this did not effectively control the reaction, therapy could be withdrawn. Any grade 3 or 4 allergic reaction called for discontinuing cetuximab.

If a patient experienced a grade 3 skin toxicity, cetuximab therapy could be interrupted. Therapy could be subsequently decreased (first to 250 mg/m² then to 150 mg/m²) or discontinued.

Cetuximab also was to be discontinued in patients who experienced any Grade 4 cetuximab-related toxicity.

b. Irinotecan

Irinotecan was administered either weekly at a dose of 125 mg/m² for 4 weeks followed by 2 weeks of rest or at a dose of 350 mg/m² every 3 weeks. Dose modifications in accordance with the irinotecan package insert were allowed for adverse events such as diarrhea, mucositis, neutropenia or thrombocytopenia.

Table 36: Patients Exposure to Cetuximab

	Colorectal Carcinoma		Other Indications	
	Cetuximab + Irinotecan (N=354)	Monotherapy (N=279)	Cetuximab + Chemo (N=224)	Monotherapy (N=54)
<u>Total duration of Cetuximab (weeks)</u>				
Median	13.6	7.3	12.9	9.0
Range	1.0 - 86.0	1.0 - 67.0	1.0 - 82.0	1.0 - 74.3
<u>Number of Cetuximab infusions per patient</u>				
Median	12.0	7.0	12.0	8.5
Range	1.0 - 84.0	1.0 - 63.0	1.0 - 73.0	1.0 - 71.0
1-6 infusions	122 (34.5%)	131 (47.0%)	61 (27.2%)	10 (18.5%)
7-48 infusions	226 (63.8%)	147 (52.7%)	153 (68.3%)	43 (79.6%)
>48 infusions	6 (1.7%)	1 (0.4%)	10 (4.5%)	1 (1.9%)

Reviewer Comment: The decreased total duration of treatment and decreased median doses in the Cetuximab monotherapy arm is consistent with its decreased efficacy compared to the cetuximab + irinotecan arm.

C. Methods and Specific Findings of Safety Review

1. Methods
 - a. Data analysis

The format of the Integrated Summary of Safety (ISS) for cetuximab was discussed at the pre-BLA meeting between the applicant and FDA. FDA agreed that safety data from patients in the Phase 2 trials (n=932) would be compiled separately from Phase I patient data (n=191). Within the Phase 2 dataset, subsets pertaining to trials in colorectal cancer (CRC) versus other indications were created separately for review. In compliance with the pre-BLA agreement (June 5, 2003), an amendment was submitted to the BLA on September 15, 2003 containing safety summary of IMCL CP02-0144 (Table 6, A Phase II Multicenter Study of ERBITUX in Patients with Metastatic Colorectal Carcinoma) for the first 111 patients enrolled (Safety data provided through March 31, 2003). Standard review files for safety assessment (e.g., adverse event incidence) were compiled for colorectal and non-colorectal indications from the Phase 2 dataset, but several analyses (e.g., time to onset of skin reaction) were performed by the applicant only for the colorectal studies.

Quality Assurance assessment of CRF data into SAS Reviewer data sets: A 100% check of all adverse event data for responders in colorectal cancer studies EMR62202-007, CP02-9923 and CP02-0141 was conducted. A similar review for 10% of the non-responders from these studies was also conducted. Spot checks were made for quality of transportation of CRF data to reviewer data sets for the non-CRC Phase 2 studies as well. The following SAS datasets were utilized for this aspect of the review:

- EMR 62202-007: LAB_a.xpt, LAB_b.xpt, adr.xpt, conmed.xpt, define.pdf, dose.xpt, patient.xpt
- CP02-9923: lab.xpt, adr.xpt, conmed.xpt, define.pdf, dose.xpt, patient.xp
- CP02-0141: lab.xpt, adr.xpt, conmed.xpt, define.pdf, dose.xpt, patient.xpt

There was a > 99% accuracy of data transposed to the SAS dataset with very minor discrepancies.

Quality Assurance assessment of correct populating of safety summary tables from SAS dataset information: Random spot checks were made for various table values in the Integrated Safety Summary Adverse Event table summaries for the Phase 2 trial dataset. Each value checked in the tables matched exactly the incidence as derived by the reviewer from the SAS dataset. Thus it was determined that the applicant's values in incidence tables in both the ISS and the proposed labeling adequately reflected trial results.

Although most ISS tables comprised verbatim COSTART terms for presentation of adverse events, the applicant combined related terms in selected analyses to better determine incidences of events that might otherwise be described by a variety of COSTART terms. The applicant proposed the following concatenation of COSTART terms to characterize specific adverse events:

- Hypersensitivity Reaction: Allergic reaction, anaphylactoid reaction
- Acne-like Rash: Acne, Maculopapular rash, Pustular rash, Rash

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- **Diarrhea:** Diarrhea, Bloody diarrhea, “Nausea, vomiting and diarrhea”
- **Fatigue/Asthenia/Lethargy/Malaise:** Asthenia, malaise, somnolence
- **Mucositis/Stomatitis:** Aphthous stomatitis, gingivitis, glossitis, mouth ulceration, mucous membrane disorder, stomatitis, ulcerative stomatitis

After review of the submitted data, it was the opinion of the FDA clinical reviewers that, although most composite groupings were appropriate, both hypersensitivity (infusion) reactions and certain skin toxicities were not adequately represented by the applicant’s concatenated terms. Thus the following terms were concatenated in the FDA determination of adverse events rates in certain tables (e.g., SAE table, AE table to be used in product label) for the following adverse events:

- **Infusion reaction:** Allergic reaction, anaphylactoid reaction, Grade 3 or 4 chills, fever or dyspnea, occurring within 24 hours of first dose, not otherwise designated as either anaphylactoid or allergic reaction
- **Acneform rash:** acne, maculopapular rash, pustular rash, rash, exfoliative dermatitis, dry skin

b. Adverse Events

Safety evaluations consisted of reported adverse events (AEs) [active inquiry at each patient visit], physical examination findings, vital sign measurements, and clinical laboratory evaluations. Safety evaluations were performed throughout the study, and AEs were followed until their resolution. Adverse events were defined as (1) all unfavorable changes in general condition, (2) all subjective or objective symptoms, (3) all concomitant diseases or accidents, and (4) all clinically relevant changes in chemical laboratory parameters. Causal relationship was rated as unrelated, possible, probable or definite. Severity was assessed according to the toxicity criteria defined in the NCI Common Toxicity Criteria version 2.0.

All adverse events were recorded in the case report forms and presented in the SAS datasets submitted with the BLA. When compiled in AE incidence tables, events were summarized by worst severity per patient.

c. Laboratory safety variables

Determination of standard hematology and biochemistry variables and urinalysis were performed at the study sites. Blood and urine samples for these tests were taken before infusion of the study medication. Samples were measured at screening, at each visit, and at end-of-study.

Laboratory results were classified by grade according to NCI-CTC Version 2.0. The last available measurement before cetuximab administration was used as baseline measurement. The worst on-study grades after the first dose of

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cetuximab were summarized, and only patients with post-baseline laboratory values were included in the analyses.

d. Other safety variables

- **Vital signs**
Vital signs were measured at screening, at each weekly visit, and at end-of-study. They were taken before, during, immediately after, and one-hour after cetuximab infusion. Mean, minimum and maximum changes in each parameter were tabulated for each infusion.
- **Physical examination**
Physical examination parameters were also measured at screening, at each weekly visit, and at end-of-study. Only clinically significant, abnormal findings were reported by noting the finding as an adverse event.
- **ECG**
ECG recordings were measured at screening and at end-of-study.
- **Karnofsky Performance Score**
Karnofsky Performance Score was measured at screening, every 6 weeks, and at end-of-study.

2. Specific Findings

Table 37: Overview of Adverse Events

	Colorectal Carcinoma		Other Indications	
	Cetux + Irino (N=354)	Monotherapy (N=279)	Cetux + Chemo (N=224)	Monotherapy (N=54)
Number (%) Patients with:				
Any AE (1)	354 (100)	279 (100)	223 (99.6)	54 (100)
Any grade 3 / 4 AE	266 (75.1)	149 (53.4)	186 (83.0)	27 (50.0)
Any serious AE	160 (45.2)	93(33.3)	126 (56.3)	16 (29.6)
AE leading to discontinuation (2)	86 (24.3)	23 (8.2)	42 (18.8)	6 (11.1)
(1) Adverse events with relationship to any study agent classified as Definite, Probable, Possible or Missing				
(2) Adverse events with "Cetuximab Action Taken" or "Chemotherapy Action Taken" classified as "Discontinued"				

Reviewer Comment: Nearly all patients experienced an adverse event during the trials. Treatment with cetuximab in combination with chemotherapy (irinotecan in colorectal cancer studies and other chemotherapy agents in non-CRC studies) appeared to result in a higher likelihood of severe and serious adverse event

a. Deaths

Table 38: Deaths Within 30 days of End-of-Treatment with Cetuximab, or Within 60 Days of Start of Cetuximab Treatment

	Colorectal carcinoma		Other Indications	
	Cetux + Irino (N=354)	Monotherapy (N=279)	Cetux + Chemo (N=224)	Monotherapy (N=54)
<u>Number of patients who died within 30 days of last dose of Cetuximab</u>	50 (14.1)	52 (18.6)	44 (19.6)	2 (3.7)
<u>Cause of Death</u>				
Adverse event	0	4 (1.4) ¹	0	0
Disease progression	36 (10.2)	39 (14.0)	24 (10.7)	2 (3.7)
Disease complication	7 (2.0)	4 (1.4)	13 (5.8)	0
Related to chemo	1 (0.3)	0	0	0
Related to Cetuximab	0	1 (0.4) ²	0	0
Intercurrent illness	3 (0.8)	3 (1.1)	4 (1.8)	0
Not reported	1 (0.3)	0	0	0
Unknown	2 (0.6)	1 (0.4)	3 (1.3)	0
<u>Number of patients who died within 60 days of first dose of Cetuximab</u>	31 (8.8)	38 (13.6)	26 (11.6)	3 (5.6)
<u>Cause of Death</u>				
Adverse event	0	2 (0.7)	0	0
Disease progression	23 (6.5)	29 (10.4)	14 (6.3)	3 (5.6)
Disease complication	4 (1.1)	3 (1.1)	7 (3.1)	0
Related to chemo	1 (0.3)	0	0	0
Related to Cetuximab	0	0	0	0
Intercurrent illness	1 (0.3)	2 (0.7)	3 (1.3)	0
Not reported	1 (0.3)	1 (0.4)	0	0
Unknown	1 (0.3)	1 (0.4)	2 (0.9)	0

Source: Table 3.7, Amended ISS, page 71

¹ Applicant assessment in ISS: 5 (1.9)

² Applicant assessment in ISS: 0

Reviewer Comment: The applicant's assessment was that no deaths were related to cetuximab. FDA's analysis differs and concludes that one of the deaths from the ISS dataset relevant to the table above was related to receipt of cetuximab (Patient CP02-0144-019-1078, death secondary to cetuximab-induced interstitial pneumonitis with non-cardiogenic pulmonary edema). In

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addition, one other death not reflected in the table above (occurred greater than 30 days after discontinuation of cetuximab), was determined to be related to cetuximab therapy (fatal progression of pulmonary fibrosis) [see following Section c (2), Serious Adverse Events / Pulmonary Toxicity].

c. Serious Adverse Events

Table 39: Incidence of SAEs that Occurred in > 1% of Any Treatment Group Within the Phase 2 Safety Population

	Colorectal carcinoma		Other Indications	
	Cetux + Irino (N=354)	Monotherapy (N=279)	Cetux + Chemo (N=224)	Monotherapy (N=54)
Pts. with any SAE (%)	160 (45.2)	93 (33.3)	126 (56.3)	16 (29.6)
Pts. with SAE (%) (1):				
<u>Body as a Whole</u>				
Carcinoma	23 (6.5)	4 (1.4)	24 (10.7)	0
Fever	22 (6.2)	10 (3.6)	7 (3.1)	0
Infusion reaction (2)	13 (3.7)	12 (4.3)	ND	ND
Asthenia	15 (4.2)	9 (3.2)	3 (1.3)	1 (1.9)
Sepsis	11 (3.1)	7 (2.5)	7 (3.1)	0
Abdominal pain	9 (2.5)	6 (2.2)	4 (1.8)	1 (1.9)
Anaphylactoid reaction	6 (1.7)	1 (0.4)	4 (1.8)	0
Pain	5 (1.4)	5 (1.8)	5 (2.2)	0
Ascites	3 (0.8)	6 (2.2)	2 (0.9)	0
Chills	3 (0.8)	0	0	1 (1.9)
Infection	3 (0.8)	1 (0.4)	5 (2.2)	0
Allergic reaction	2 (0.6)	5 (1.8)	4 (1.8)	2 (3.7)
Back pain	2 (0.6)	0	3 (1.3)	2 (3.7)
Death	1 (0.3)	0	3 (1.3)	0
Disease progression	0	0	0	1 (1.9)
Injection site reaction	0	3 (1.1)	0	0
<u>Cardiovascular system</u>				
Deep thrombophlebitis	4 (1.1)	2 (0.7)	4 (1.8)	0
Syncope	4 (1.1)	0	1 (0.4)	1 (1.9)
Thrombosis	4 (1.1)	1 (0.4)	0	0
Hypotension	3 (0.8)	2 (0.7)	5 (2.2)	0
Heart failure	1 (0.3)	1 (0.4)	0	1 (1.9)
Myocardial infarct	1 (0.3)	1 (0.4)	1 (0.4)	1 (1.9)

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Atrial fibrillation	0	3 (1.1)	3 (1.3)	1 (1.9)
Hemorrhage	0	0	6 (2.7)	0
<u>Digestive System</u>				
Diarrhea	22 (6.2)	0	4 (1.8)	0
Intestinal obstruction	14 (4.0)	17 (6.1)	7 (3.1)	0
Vomiting	14 (4.0)	2 (0.7)	8 (3.6)	1 (1.9)
Nausea	7 (2.0)	1 (0.4)	3 (1.3)	0
Gastrointestinal d/o	4 (1.1)	1 (0.4)	1 (0.4)	0
Jaundice	4 (1.1)	1 (0.4)	2 (0.9)	0
GI hemorrhage	3 (0.8)	1 (0.4)	5 (2.2)	0
Anorexia	2 (0.6)	4 (1.4)	2 (0.9)	0
<u>Hemic / Lymph System</u>				
Leukopenia	13 (3.7)	0	2 (0.9)	0
Anemia	1 (0.3)	3 (1.1)	3 (1.3)	1 (1.9)
<u>Metab / Nutritional d/o</u>				
Dehydration	16 (4.5)	6 (2.2)	22 (9.8)	0
Bilirubinemia	6 (1.7)	2 (0.7)	0	0
<u>Musculoskeletal System</u>				
Osteomyelitis	0	0	1 (0.4)	1 (1.9)
<u>Nervous System</u>				
Convulsion	0	2 (0.7)	4 (1.8)	0
<u>Respiratory System</u>				
Pneumonia	8 (2.3)	5 (1.8)	10 (4.5)	0
Pleural effusion	4 (1.1)	6 (2.2)	0	0
Dyspnea	1 (0.3)	8 (2.9)	4 (1.8)	1 (1.9)
Pulmonary embolus	1 (0.3)	5 (1.8)	3 (1.3)	0
Apnea	0	3 (1.1)	6 (2.7)	0
Aspiration pneumonia	0	0	4 (1.8)	0
Lung disorder	0	1 (0.4)	5 (2.2)	0
<u>Skin and Appendages</u>				
Dry skin	0	0	0	1 (1.9)
<u>Urogenital System</u>				
Kidney failure	5 (1.4)	1 (0.4)	2 (0.9)	0
Hydronephrosis	4 (1.1)	0	0	0
UTI	4 (1.1)	1 (0.4)	0	0
Acute kidney failure	3 (0.8)	2 (0.7)	3 (1.3)	0
Hematuria	1 (0.3)	1 (0.4)	0	1 (1.9)

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

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(2) Infusion reaction SAE case definition: Anaphylactoid designated as an SAE, Allergic reaction designated as an SAE; Grade 3 or 4 chills, fever or dyspnea, occurring within 24 hours of first dose, not otherwise designated as either anaphylactoid or allergic reaction, and which also was noted in the CRF as an SAE.

- *Reviewer Comment: In an effort to determine the most relevant SAEs to include in the product label for cetuximab, in addition to the review of SAEs collated by event (table above), per patient specific SAEs were also reviewed for the colorectal cancer subgroup in the submission (Appendix 3.4, pages 717- 748). In discussion with Dr. Keegan, Director, Division of Therapeutic Oncology Products, specific SAEs repeatedly emerged as difficult to dismiss as being related solely to the patient disease process. Since the clinical trials were not designed to clearly distinguish SAEs causally related to receipt of cetuximab, it was decided to apply conservative judgment to the relatedness of events. The outcome of these discussions was the decision to highlight the following SAEs in the product label cetuximab + irinotecan arm: Diarrhea, fever, dehydration, infusion reaction, sepsis, kidney failure, skin events, interstitial lung disease*
- *Cetuximab monotherapy arm: Fever, infusion reaction, dyspnea, sepsis, pulmonary embolus, dehydration, skin events, interstitial lung disease*

Of primary concern were infusion reactions and pulmonary toxicity. These serious events associated with receipt of cetuximab were further investigated to determine appropriate labeling language for the events:

1) Infusion Reaction

Infusion reactions are not an unexpected consequence of monoclonal antibody therapy in many patients. Nineteen % of the patients who received ERBITUX plus irinotecan and 25% of the patients who received ERBITUX monotherapy had infusion reactions occurring after cetuximab infusion despite protocol-directed pre-treatment of all patients with antihistamine therapy. In addition, it became evident that many cetuximab-related infusion reactions had been under-reported by the applicant in the ISS submission. The applicant elected to categorize infusion reactions as “Hypersensitivity Reactions”, and to only include the COSTART terms “allergic reaction” and “anaphylactic reaction” in the compilation of infusion-related reactions.

The FDA review team felt it was necessary to change and expand the adverse events in this category to better advise physicians and patients of events to anticipate and prepare for, especially preceding the first dose of product.

Accordingly, FDA created a case-definition of “Infusion Reaction”, and applied the definition to a re-compilation of this category of event. The infusion reaction category thus combined the aforementioned COSTART terms “allergic reaction” and “anaphylactic reaction”, but also added any

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of the following events that occurred within one day of initial infusion of cetuximab: chills, fever, dyspnea. Although this case definition potentially missed collecting some events in subsequent dosing with cetuximab, it was thought that events such as chills, fever, etc. further into the study would be too non-specific to be able to definitively relate to the product.

The Infusion Reaction incidence was calculated in preparing the SAE table (Table 39) for this review, and also in preparation of the adverse event incidence table to appear in the product label. The applicant presentation of “allergic reaction” and “anaphylactic reaction” is furnished in other tables in the ISS review, since the intention of some sections were relative COSTART term comparisons across all Phase 2 groups, and not a setting for the use of composite terms derived by either the applicant or FDA.

As described in the table above, infusion reactions that resulted in a serious adverse event report occurred in 3.7% and 4.3% of patients receiving cetuximab + irinotecan and cetuximab monotherapy, respectively. Nearly 90% of these reactions occurred at the time of first infusion of cetuximab, despite the required pre-treatment of the patients with oral antihistamines.

During the clinical development program for cetuximab, no deaths due to infusion reaction occurred. However, during the BLA review period, the applicant notified FDA of a report of a patient death in an ongoing Phase 3b clinical trial taking place in Europe. The patient (#501/0012) was a 58-year old Caucasian male with no known history of allergies who was diagnosed with epidermoid carcinoma of the tongue. Following surgical resection, the cancer recurred on three occasions and was treated unsuccessfully with radiation and platinum-based therapy. One week prior to entry into cetuximab study EMR 62202-016, he was evaluated for oral bleeding, and lab results showed concomitant increased fibrinogen. On the day before first infusion, the patient had a performance status of 70% , BP 113/79, HR 99 and temperature 36.2°C. On the day of first infusion, he was premedicated with i.v. dexchlorpheniramine maleate, 5 mg, prior to a test dose of cetuximab. His vital signs at the start of the test dose were: BP 130.80, HR 88. Thirty minutes after the test dose, the patient received the initial dose of cetuximab over a 2-hour infusion. His vital signs were BP 148/80 and HR 90 at the start of the infusion, and BP 110/70 and HR 110 at the end of infusion. Ten minutes after the infusion was completed, the patient developed dyspnea and stridor due to edema of the glottis. He received i.v. hydrocortisone 100 mg , epinephrine 1mL of 1:1000 s.c. and oxygen 50%, but the patient did not respond. The patient subsequently died of cardiac arrest, and the cause of death was reported to

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be glottic edema secondary to anaphylactic reaction. The investigator noted the event as definitely related to cetuximab infusion.

a) Infusion Reaction Analyses

1] Discontinuation of the initial practice of a cetuximab test dose

Because of the potential for allergic reaction, patients in the initial clinical studies of cetuximab received a test infusion prior to the initial dose of cetuximab. The test dosage was a 10 mL (20 mg) infusion administered over 10 minutes followed by an observation period of 30 minutes, whereupon patients (in the absence of an AE), received the remainder of their dose. All patients were premedicated with an antihistamine (50 mg i.v. diphenhydramine hydrochloride) prior to receiving the test dose. If a patient experienced a grade 1 through 3 allergic reactions, the duration of the infusion could be increased (to a maximum of 4 hours) for subsequent infusions. If this was not effective, removal from the study was to have been considered.

During the later phases of the clinical development program, the test dose was discontinued prior to first infusion of the product. Upon submission of the BLA, no explanation by the applicant was provided regarding the rationale for the discontinuation of this practice. Upon request by FDA for clarification of the utility of the test dose, the applicant provided analyses of outcome data for patients who did or did not receive the test infusion vis-à-vis its ability to predict significant infusion reactions. The applicant asserted, and FDA agreed, that the data indicated that administration of the test dose was not predictive of subsequent significant infusion reaction to Cetuximab, and further agreed that the test dose would not be recommended in the product label for cetuximab.

2] Infusion rate change for Grade 1 / 2 Infusion Reaction

Language in the proposed labeling for cetuximab included recommendations that, if a patient were to develop a Grade 1 or 2 infusion reaction, that the infusion rate should be halved. However, the applicant did not provide analyses from the clinical trial data set to substantiate these dose modification recommendations.

Subsequent to conversation during the review period between FDA and the applicant, the applicant provided data and analyses that, although limited in quantity, indicated that a decrease in infusion rate did indeed improve the patient's condition, and that in subsequent dosing, infusing at the reduced rate resulted in no recurrences of severe infusion reactions.

b) Pulmonary Toxicity

In one of the clinical study reports in support of the BLA submission (EMR 62202-007), the applicant had pointed out the absence of cases of interstitial pneumonitis secondary to receipt of Cetuximab therapy relative to the safety concerns raised by this event associated with receipt of a drug agent targeting the EGF pathway, gefitinib (Iressa).

However, once the full BLA ISS was compiled, two documented cases of interstitial pneumonitis related to cetuximab were reported.

In the first case (Patient CP02-0144-019-1078 [trial in colorectal cancer]), the patient was a 58-year-old Caucasian male with a history of metastatic (liver, bone) colon cancer. His disease progressed despite irinotecan, 5FU/leucovorin, and although he had brief response to oxaliplatin/5FU/Leucovorin/Bevacizumab, the disease continued to progress (pulmonary metastases). The patient received palliative XRT for thoracolumbar spine and pelvis metastases, and entered hospice care. Upon being informed of the Cetuximab clinical trials in metastatic CRC, however, he enrolled into Study CP02-0144, and was randomized to the Cetuximab monotherapy arm. He received 6 weeks of treatment, and began to show clinical response. Chest CT showed decrease in lung metastases, but also mixed interstitial alveolar opacification – this finding was initially attributed to the XRT. The patient received 3 additional treatments, during which time he was evaluated for development of bilateral rib pain, dyspnea at rest and exertion. The chest X-ray was negative for metastases, but it showed bilateral diffuse interstitial infiltrates. The cardiac work-up was non-contributory. Chest CT demonstrated ground glass opacification, with decrease in size of pulmonary disease. The radiologist differential diagnosis was drug toxicity vs. bronchiolitis obliterans with organizing pneumonia vs. diffuse interstitial pneumonitis and pulmonary edema.

The patient subsequently developed respiratory failure, leading to mechanical ventilation and chest tube placement. A lung biopsy showed no bacterial growth or fungus. The patient briefly responded to steroids and was extubated. However, within a week, the patient relapsed and went into respiratory failure. A chest X-ray showed increasing edema, infiltrates, and possible worsening of pulmonary metastases. The patient expired shortly thereafter. The investigator considered the respirator failure secondary to diffuse alveolar damage probably related to cetuximab.

The second case of interstitial lung disease was from a patient (EMR-62202-001-0600-0003) in a clinical trial of cetuximab in head and neck

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squamous cell carcinoma. The patient, a 68-year-old Caucasian male, received cetuximab monotherapy. Except for treatment in week 3 (transfusion for pre-existing anemia), his course was uneventful. By week 11 the patient had developed progressive fatigue with fever. Labs showed a serum CRP of 156 mg/L (normal is <10) and hemoglobin 9.2 g%. A chest X-ray revealed interstitial changes in the lungs, and a CT scan confirmed interstitial pneumonitis. A bronchoalveolar lavage was normal, with no pathogens identified. The event resolved gradually, and CRP decreased to near normal. The investigator considered the interstitial pneumonitis event possibly related to cetuximab.

At the same time that the ILD cases above were being reviewed, it was noted by FDA reviewers that the cetuximab monotherapy group, especially those in the colorectal cancer studies, had a relatively high incidence of severe (Grade 3 / 4) dyspnea (7.2%) compared to the cetuximab + irinotecan arm (2.3%). Severe dyspnea was observed in the CRC monotherapy group despite a higher incidence of pulmonary metastases in the cetuximab + irinotecan combination therapy group (33% compared to 26% in the monotherapy arm). In addition, several cases of pulmonary effusion developed in concert with cetuximab administration. Since pulmonary effusion is not typically observed secondary to colon cancer lung metastatic spread, this finding in concert with the other findings added to concerns about the possible involvement/contribution of cetuximab to the pulmonary events.

Based on these concerns, during the BLA review period, the applicant was asked to provide additional safety information on all cases involving Grade 4 dyspnea that did not appear to have an allergic/anaphylactic origin, and also information regarding two cases of worsening of pulmonary fibrosis (worsening of pulmonary fibrosis was a specific finding in the gefitinib safety database, and is a part of the labeled Warnings for gefitinib). Extensive narratives on the twenty-three patients of interest were subsequently provided by the applicant and reviewed.

In the analysis provided by the applicant, a total of four patients, including the two acknowledged cases of ILD (above), and the two patients who experienced a worsening of their pulmonary fibrosis, were judged by the applicant to possibly be due to cetuximab administration. The FDA opinion is that the events were due to cetuximab administration, and that the product label should reflect this potentially life-threatening risk secondary to use of the product.

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d. Dropouts and Other Significant Adverse Events

1) Discontinuations

Table 40: Incidence of Discontinuations that Occurred in > 1% of Any Treatment Group Within the Phase 2 Safety Population

	Colorectal carcinoma		Other Indications	
	Cetux + Irino (N=354)	Monotherapy (N=279)	Cetux + Chemo (N=224)	Monotherapy (N=54)
<u>Pts. w/any AE (1) Leading to d/c of Study Agent</u>	86 (24.3)	23 (8.2)	42 (18.8)	6 (11.1)
<u>Body as a Whole</u>				
Carcinoma	18 (5.1)	2 (0.7)	15 (6.7)	0
Asthenia	16 (4.5)	6 (2.2)	2 (0.9)	1 (1.9)
Fever	4 (1.1)	1 (0.4)	0	0
Anaphylactoid reaction	6 (1.7)	1 (0.4)	4 (1.8)	0
Abdominal pain	1 (0.3)	4 (1.4)	0	0
Allergic reaction	1 (0.3)	4 (1.4)	3 (1.3)	2 (3.7)
<u>CV System</u>				
Myocardial infarct	1 (0.3)	0	1 (0.4)	1 (1.9)
<u>Digestive System</u>				
Diarrhea	13 (3.7)	0	0	0
Nausea	4 (1.1)	0	0	0
<u>Metab / Nutritional d/o</u>				
Bilirubinemia	4 (1.1)	0	0	0
<u>Musculoskeletal System</u>				
Myasthenia	0	0	0	1 (1.9)
<u>Nervous System</u>				
Hypesthesia	0	0	0	1 (1.9)
Paralysis	0	0	0	1 (1.9)
<u>Respiratory System</u>				
Pneumonia	2 (0.6)	1 (0.4)	0	0
Dyspnea	1 (0.3)	4 (1.4)	0	0
Lung disorder	1 (0.3)	1 (0.4)	2 (0.9)	0
<u>Skin and Appendages</u>				
Rash	5 (1.4)	0	0	0
Acne	4 (1.1)	0	0	0

Source: Amended ISS, Table S.3.5A, pages 184 - 195

(1) AE is any grade

2) Other Significant Adverse Events

a) Nail disorder

In 13% of patients treated with cetuximab, paronychia and other nail disorders occurred. The inflammation/infection of the nail beds most often occurred in the thumb and great toe, were rarely severe (0.5%) and were most often successfully treated with topical measures.

b) Lack of cardiac toxicity

Reviewer Comment: Although it is unusual to mention negative findings in an ISS review, because of the cardiac toxicity thought to be associated with disruption of the HER-2 pathway (e.g., Herceptin associated cardiac toxicity), it was considered important to indicate that cetuximab did not appear to elicit any remarkable cardiovascular system toxicity.

c) Significant events occurring in Cetuximab + Chemotherapy population

In general, patients in the merged "Other Indications / Cetuximab + Chemotherapy" group (n=224) had an incidence of serious adverse events that was similar to the Cetuximab + Irinotecan group (as part of the colorectal cancer merged group). Exceptions were (1) hemorrhage (Cetux+Chemo=2.7%, Cetux+Irino=0%) and (2) dehydration (Cetux+Chemo=9.8%, Cetux+Irino=4.5%).

Similarly, patients in the merged "Other Indications / Cetuximab monotherapy" group (n=54) had an incidence of adverse events that was similar to the Cetuximab monotherapy group (as part of the colorectal cancer merged group). Exceptions were (1) Digestive system disorders (Monotherapy in CRC=11.1%, Monotherapy in non-CRC=1.9%) and (2) Respiratory system disorders (Monotherapy in CRC=9.0%, Monotherapy in non-CRC=1.9%).

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e. Common Adverse Events

Table 41. Adverse Events with an Incidence of $\geq 10\%$

	Colorectal carcinoma		Other Indications	
	Cetux + Irino (N=354)	Monotherapy (N=279)	Cetux + Chemo (N=224)	Monotherapy (N=54)
Patients (%) with AE: (1)				
<u>Body as a Whole</u>				
Asthenia	252 (71.2)	132 (47.3)	147 (65.6)	23 (42.6)
Abdominal pain	160 (45.2)	71 (25.4)	65 (29.0)	3 (5.6)
Fever	121 (34.2)	92 (33.0)	67 (29.9)	21 (38.9)
Pain	80 (22.6)	52 (18.6)	84 (37.5)	7 (13.0)
Back pain	56 (15.8)	30 (10.8)	38 (17.0)	7 (13.0)
Infection	56 (15.8)	31 (11.1)	41 (18.3)	7 (13.0)
Headache	50 (14.1)	70 (25.1)	42 (18.8)	17 (31.5)
Chills	40 (11.3)	31 (11.1)	34 (15.2)	10 (18.5)
Carcinoma	25 (7.1)	5 (1.8)	24 (10.7)	2 (3.7)
Chest pain	20 (5.6)	13 (4.7)	18 (8.0)	7 (13.0)
Flu Syndrome	15 (4.2)	13 (4.7)	5 (2.2)	6 (11.1)
Mucous membrane d/o	15 (4.2)	7 (2.5)	32 (14.3)	4 (7.4)
Allergic reaction	10 (2.8)	17 (6.1)	17 (7.6)	7 (13.0)
Face edema	8 (2.3)	2 (0.7)	34 (15.2)	1 (1.9)
Flank pain	8 (2.3)	1 (0.4)	5 (2.2)	6 (11.1)
<u>Cardiovascular System</u>				
Hypotension	19 (5.4)	3 (1.1)	33 (14.7)	2 (3.7)
<u>Digestive System</u>				
Diarrhea	254 (71.8)	77 (27.6)	83 (37.1)	9 (16.7)
Nausea	194 (54.8)	80 (28.7)	126 (56.3)	12 (22.2)
Vomiting	145 (41.0)	70 (25.1)	95 (42.4)	8 (14.8)
Anorexia	128 (36.2)	69 (24.7)	85 (37.9)	5 (9.3)
Constipation	105 (29.7)	79 (28.3)	75 (33.5)	11 (20.4)
Stomatitis	91 (25.7)	32 (11.5)	40 (17.9)	6 (11.1)
Dyspepsia	48 (13.6)	19 (6.8)	20 (8.9)	5 (9.3)
Dysphagia	8 (2.3)	4 91.40	26 (11.6)	0
<u>Hemic / Lymphatic System</u>				
Leukopenia	87 (24.6)	1 (0.4)	69 (30.8)	1 91.9)
Anemia	58 (16.4)	27 (9.7)	70 (31.3)	12 (22.2)
Thrombocytopenia	8 (2.3)	1 (0.4)	30 (13.4)	0

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<u>Metabolic/Nutritional D/o</u>				
Weight loss	76 (21.5)	25 (9.0)	85 (37.9)	0
Peripheral edema	55 (15.5)	27 (9.7)	47 (21.0)	4 (7.4)
Dehydration	53 (15.0)	26 (9.3)	53 (23.7)	1 (1.9)
Hypokalemia	26 (7.3)	13 (4.7)	31 (13.8)	2 (3.7)
Hyperglycemia	21 (5.9)	3 (1.1)	15 (6.7)	18 (33.3)
Edema	18 (5.1)	17 (6.1)	27 (12.1)	1 (1.9)
Hypomagnesemia	10 (2.8)	3 (1.1)	28 (12.5)	1 (1.9)
Healing abnormal	4 (1.1)	0	28 (12.5)	0
BUN increased	1 (0.3)	0	1 (0.4)	7 (13.0)
<u>Nervous System</u>				
Insomnia	42 (11.9)	29 (10.4)	32 (14.3)	2 (3.7)
Depression	37 (10.5)	24 (8.6)	26 (11.6)	2 (3.7)
Anxiety	31 (8.8)	12 (4.3)	30 (13.4)	1 (1.9)
Dizziness	30 (8.5)	14 (5.0)	32 (14.3)	4 (7.4)
<u>Respiratory System</u>				
Dyspnea	80 (22.6)	55 (19.7)	57 (25.4)	16 (29.6)
Cough increased	70 (19.8)	27 (9.7)	51 (22.8)	11 (20.4)
Rhinitis	29 (8.2)	15 (5.4)	23 (10.3)	6 (11.1)
Lung disorder	12 (3.4)	2 (0.7)	28 (12.5)	1 (1.9)
<u>Skin and Appendages</u>				
Rash	189 (53.4)	69 (24.7)	75 (33.5)	24 (44.4)
Acne	133 (37.6)	172 (61.6)	124 (55.4)	31 (57.4)
Dry skin	105 (29.7)	72 (25.8)	78 (34.8)	11 (20.4)
Alopecia	76 (21.5)	13 (4.7)	47 (21.0)	1 (1.9)
Skin disorder	54 (15.3)	13 (4.7)	31 (13.8)	2 (3.7)
Nail disorder	44 (12.4)	46 (16.5)	29 (12.9)	7 (13.0)
Pruritis	37 (10.5)	27 (9.7)	21 (9.4)	4 (7.4)
Skin ulcer	14 (4.0)	5 (1.8)	23 (10.3)	0
<u>Special Senses</u>				
Conjunctivitis	51 (14.4)	20 (7.2)	19 (8.5)	2 (3.7)

Source: Table 3.2; Amended ISS pages 52-57

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