CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125084/103

Trade Name: Erbitux

Generic Name: cetuximab

Sponsor: ImClone Systems, Inc.

Approval Date: October 2, 2007

Indications: As a single agent in patients with EGFR-expressing, metastatic colorectal cancer after failure of both irinotecan and oxaliplatin-based regimens.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125084/103

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125084/103

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125084/103

OCT 0 2 2007

ImClone Systems, Incorporated
Attention: Cheryl Anderson
Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Anderson:

Your request to supplement your biologics license application for cetuximab to expand the colorectal cancer indication to include cetuximab as a single agent in patients with EGFR-expressing, metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens, has been approved.

We approved your biologic license application for the use of cetuximab monotherapy for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy, under the regulations of 21 CFR 601 Subpart E for accelerated approval of biological products for serious or life-threatening illnesses. The data provided in this supplement verify the clinical benefit of cetuximab as monotherapy.

Please note that you have not verified the clinical benefit of cetuximab in combination with chemotherapy. Specifically, your approval for cetuximab, in combination with irinotecan, for treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy, which was also approved under the regulations of 21 CFR 601 Subpart E, requires verification of clinical benefit, either through data to be submitted to BL STN 125084/115 or through additional studies.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies until December 31, 2007.

We acknowledge your written commitments as described in your letters of September 25 and 28, 2007, as outlined below:

Postmarketing Study Commitments subject to reporting requirements of 21 CFR 601.70.

1. To conduct a study to evaluate the impact of cetuximab on QTc as discussed in ICH E14. The protocol will be submitted by March 31, 2008, patient accrual will be completed by September 30, 2009, the study will be completed by January 29, 2010, and the final study report, including revised labeling, if applicable, will be submitted by June 30, 2010.

2. To submit data sets for primary study data, narrative summaries for all serious adverse events in both treatment arms, and a complete set of case report forms for all patients who died within 30 days of receiving study drug and all patients who discontinued treatment prematurely for study CA225006. These data should include determination of the secondary endpoints of progression-free survival and overall response rate. This information will be submitted as an amendment [redacted].

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125084. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration

Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm) for further information.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 125084/103". In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125084/103

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125084/103

JUN 01 2007

ImClone Systems, Incorporated
Attention: Cheryl Anderson
Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Anderson:

This letter is in regard to your supplement to your biologics license application (BLA) for Cetuximab submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplement dated March 30, 2007, to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your supplement today. The user fee goal date is October 2, 2007. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before June 15, 2007.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 796-2320.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Erbitux® safely and effectively. See full prescribing information for Erbitux®.

Erbitux® (cetuximab)
Solution for intravenous use
Initial U.S. Approval: 2004

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

See full prescribing information for complete boxed warning.

- **Serious infusion reactions, some fatal, occurred in approximately 3% of patients. (5.1)**
- **Cardiopulmonary arrest and/or sudden death occurred in 2% of patients receiving Erbitux® in combination with radiation therapy. (5.2, 5.6)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Colorectal Cancer (1.2) 10/2007

----------INDICATIONS AND USAGE----------

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. (1.1, 14.1)
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. (1.1, 14.1)

Colorectal Cancer

- As a single agent, EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens. (1.2, 14.2)
- In combination with irinotecan, EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Approval is based on objective response rate; no data are available demonstrating an improvement in increased survival (1.2, 14.2)

----------DOSAGE AND ADMINISTRATION----------

- Premedicate with an H_1 antagonist. (2.3)
- Administer 400 mg/m^2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m^2 weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux® one week prior to initiation of radiation therapy. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grade 3-4 infusion reactions. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneform rash. Reduce dose for recurrent, severe rash. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- 100 mg/50 mL, single-use vial (3)
- 200 mg/100 mL, single-use vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- **Infusion Reactions:** Immediately stop and permanently discontinue Erbitux® for serious infusion reactions. Monitor patients following infusion. (5.1)
- **Cardiopulmonary Arrest:** Closely monitor serum electrolytes during and after Erbitux®. (5.2, 5.6)
- **Pulmonary Toxicity:** Interrupt therapy for acute onset or worsening of pulmonary symptoms. (5.3)
- **Dermatologic Toxicity:** Limit sun exposure. Monitor for inflammatory or infectious sequelae. (2.4, 5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥ 25%) are: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy:** Administer Erbitux® to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers:** Discontinue nursing during and for 60 days following treatment with Erbitux®. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions: Serious infusion reactions occurred with the administration of Erbitux® in approximately 3% of patients in clinical trials, with fatal outcome reported in less than 1 in 1000. [See *Warnings and Precautions (5.1)* and *Adverse Reactions (6).*] Immediately interrupt and permanently discontinue Erbitux® infusion for serious infusion reactions. [See *Warnings and Precautions (5.1)* and *Dosage and Administration (2.4).*]

Cardiopulmonary Arrest: Cardiopulmonary arrest and/or sudden death occurred in 2% of 208 patients with squamous cell carcinoma of the head and neck treated with radiation therapy and Erbitux®. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux®. [See *Warnings and Precautions (5.2, 5.6).*]

1 INDICATIONS AND USAGE

1.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Erbitux® is indicated in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck. [See *Clinical Studies (14.1).*]

Erbitux®, as a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed. [See *Clinical Studies (14.1).*]

1.2 Colorectal Cancer

Erbitux®, as a single agent, is indicated for the treatment of EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. Erbitux®, as a single agent, is also indicated for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens. [See *Clinical Studies (14.2)* and *Warnings and Precautions (5.7).*]

Erbitux®, in combination with irinotecan, is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. The effectiveness of Erbitux® in combination with irinotecan is based on objective response rates. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Erbitux® in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal carcinoma. [See *Clinical Studies (14.2)* and *Warnings and Precautions (5.7)*.]

2 DOSAGE AND ADMINISTRATION

2.1 Squamous Cell Carcinoma of the Head and Neck

Erbitux® in combination with radiation therapy:

- The recommended initial dose is 400 mg/m^2 administered one week prior to initiation of a course of radiation therapy as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).

- The recommended subsequent weekly dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of radiation therapy (6–7 weeks). Complete Erbitux® administration 1 hour prior to radiation therapy.

Erbitux® monotherapy:

- The recommended initial dose is 400 mg/m^2 administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).

- The recommended subsequent weekly dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.2 Colorectal Cancer

- The recommended initial dose, either as monotherapy or in combination with irinotecan, is 400 mg/m^2 administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).

- The recommended subsequent weekly dose, either as monotherapy or in combination with irinotecan, is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.3 Recommended Premedication

Premedicate with an H_1 antagonist (eg, 50 mg of diphenhydramine) intravenously 30–60 minutes prior to the first dose; premedication should be administered for subsequent Erbitux® doses based upon clinical judgment and presence/severity of prior infusion reactions.

2.4 Dose Modifications

Infusion Reactions

Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grade 3–4 infusion reactions.

Immediately and permanently discontinue Erbitux® for serious infusion reactions, requiring medical intervention and/or hospitalization. [See *Warnings and Precautions (5.1)*.]

Dermatologic Toxicity

Recommended dose modifications for severe (NCI-CTC Grade 3 or 4) acneform rash are specified in Table 1. [See *Warnings and Precautions (5.4)*.]

Table 1: Erbitux® Dose Modification Guidelines for Rash

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

2.5 Preparation for Administration

Do not administer Erbitux® as an intravenous push or bolus.

Administer via infusion pump or syringe pump. Do not exceed an infusion rate of 10 mg/min.

Administer through a low protein binding 0.22-micrometer in-line filter.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, cetuximab particulates. **Do not shake or dilute.**

3 DOSAGE FORMS AND STRENGTHS

100 mg/50 mL, single-use vial

200 mg/100 mL, single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of Erbitux® included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, and/or cardiac arrest. Severe (NCI CTC Grade 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in clinical trials, with fatal outcome in 1 patient.

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Monitor patients for 1 hour following Erbitux® infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine,

corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

Immediately and permanently discontinue Erbitux® in patients with serious infusion reactions. [See *Boxed Warning* and *Dosage and Administration (2.4)*.]

5.2 Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and Erbitux® as compared to none of 212 patients treated with radiation therapy alone in a randomized, controlled trial in patients with SCCHN. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of Erbitux®. One patient with no prior history of coronary artery disease died one day after the last dose of Erbitux®. Carefully consider use of Erbitux® in combination with radiation therapy in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux®. [See *Boxed Warning* and *Warnings and Precautions (5.6)*.]

5.3 Pulmonary Toxicity

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving Erbitux® in clinical trials. Interrupt Erbitux® for acute onset or worsening of pulmonary symptoms. Permanently discontinue Erbitux® for confirmed ILD.

5.4 Dermatologic Toxicity

Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychial inflammation, and infectious sequelae (for example *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, cheilitis) occurred in patients receiving Erbitux® therapy. Acneform rash occurred in 76–-88% of 1373 patients receiving Erbitux® in clinical trials. Severe acneform rash occurred in 1–17 % of patients.

Acneform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event

continued beyond 28 days. Monitor patients receiving Erbitux® for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during Erbitux®. [See *Dose Modifications (2.4)*.]

5.5 Use of Erbitux® in Combination With Radiation and Cisplatin

The safety of Erbitux® in combination with radiation therapy and cisplatin has not been established. Death and serious cardiotoxicity were observed in a single-arm trial with Erbitux®, radiation therapy, and cisplatin (100 mg/m^2) in patients with locally advanced SCCHN. Two of 21 patients died, one as a result of pneumonia and one of an unknown cause. Four patients discontinued treatment due to adverse events. Two of these discontinuations were due to cardiac events.

5.6 Hypomagnesemia and Electrolyte Abnormalities

In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients (199/365) receiving Erbitux® and was severe (NCI-CTC Grade 3 and 4) in 6–17%. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of Erbitux®. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of Erbitux®. Replete electrolytes as necessary.

5.7 Epidermal Growth Factor Receptor (EGFR) Expression and Response

Because expression of EGFR has been detected in nearly all SCCHN tumor specimens, patients enrolled in the head and neck cancer clinical studies were not required to have immunohistochemical evidence of EGFR tumor expression prior to study entry.

Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR tumor expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak-to-moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Infusion reactions [See *Boxed Warning* and *Warnings and Precautions (5.1).*]
- Cardiopulmonary arrest [See *Boxed Warning* and *Warnings and Precautions (5.2).*]
- Pulmonary toxicity [See *Warnings and Precautions (5.3).*]
- Dermatologic toxicity [See *Warnings and Precautions (5.4).*]
- Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions (5.6).*]

The most common adverse reactions with Erbitux® (incidence ≥ 25%) are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The most serious adverse reactions with Erbitux® are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

Across all studies, Erbitux® was discontinued in 3–10% of patients because of adverse reactions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Erbitux® in 1373 patients with colorectal cancer or SCCHN in randomized phase 3 (Studies 1 and 3) or phase 2 (Studies 2 and 4) trials treated at the recommended dose and schedule for a median of 7 to 14 weeks. [See *Clinical Studies (14).*]

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of patients; infusion reactions were fatal in 1 patient.

Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients.

Renal: Renal failure occurred in 1% of patients with colorectal cancer.

Squamous Cell Carcinoma of the Head and Neck

Table 2 contains selected adverse events in 420 patients receiving radiation therapy either alone or with Erbitux® for locally or regionally advanced SCCHN in Study 1. Erbitux® was administered at the recommended dose and schedule (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 8 infusions (range 1–11).

Table 2: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

Body System Preferred Term	Erbitux® plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia	56	4	49	5
Fever[1]	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction[2]	15	3	2	0
Infection	13	1	9	1
Chills[1]	16	0	5	0
Digestive				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8

Table 2: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

Body System Preferred Term	Erbitux® plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Respiratory				
Pharyngitis	26	3	19	4
Skin/Appendages				
Acneform Rash[3]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[1] Includes cases also reported as infusion reaction.

[2] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever", or "dyspnea".

[3] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

The incidence and severity of mucositis, stomatitis, and xerostomia were similar in both arms of the study.

Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in Erbitux® in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%). The incidence of Grade 3 or 4 late radiation toxicities was similar between the radiation therapy alone and the Erbitux® plus radiation treatment groups.

Colorectal Cancer

Table 3 contains selected adverse events in 562 patients receiving best supportive care (BSC) alone or with Erbitux® monotherapy for metastatic colorectal cancer in Study 3.

208 Erbitux® was administered at the recommended dose and schedule (400 mg/m^2 initial
209 dose, followed by 250 mg/m^2 weekly).

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux® Monotherapy

	Erbitux® plus BSC (n=288)		BSC alone (n=274)	
Body System Preferred Term	**Any Grades[2]**	**Grades 3 and 4**	**Any Grades**	**Grades 3 and 4**
	% of Patients			
Dermatology				
Rash/Desquamation	89	12	16	<1
Dry Skin	49	0	11	0
Pruritus	40	2	8	0
Other-Dermatology	27	1	6	1
Nail Changes	21	0	4	0
Body as a Whole				
Fatigue	89	33	76	26
Fever	30	1	18	<1
Infusion Reactions[3]	20	5		
Rigors, Chills	13	<1	4	0
Pain				
Abdominal Pain	59	14	52	16
Pain-Other	51	16	34	7
Headache	33	4	11	0
Bone Pain	15	3	7	2
Pulmonary				
Dyspnea	48	16	43	12
Cough	29	2	19	1
Gastrointestinal				
Constipation	46	4	38	5
Diarrhea	39	2	20	2
Vomiting	37	6	29	6
Stomatitis	25	1	10	<1
Other-Gastrointestinal	23	10	18	8
Mouth Dryness	11	0	4	0
Infection				
Infection without neutropenia	35	13	17	6

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux® Monotherapy

	Erbitux® plus BSC (n=288)		BSC alone (n=274)	
Body System Preferred Term	**Any Grades[2]**	**Grades 3 and 4**	**Any Grades**	**Grades 3 and 4**
	% of Patients			
Neurology				
Insomnia	30	1	15	1
Confusion	15	6	9	2
Anxiety	14	2	8	1
Depression	13	1	6	<1

[1] Adverse reactions occurring more frequently in Erbitux® treated patients compared with controls.

[2] Adverse events were graded using the NCI CTC, V 2.0.

[3] Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion related.

BSC = best supportive care

The most frequently reported adverse events in 354 patients treated with Erbitux® plus irinotecan in clinical trials were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common Grade 3/4 adverse events included diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneform rash (14%).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an ELISA assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving Erbitux® has not been adequately determined. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of 1001) of evaluable patients without apparent effect on the safety or antitumor activity of Erbitux®.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay

methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Erbitux® with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

A drug interaction study was performed in which Erbitux® was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between Erbitux® and irinotecan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with cetuximab. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore, cetuximab has the potential to be transmitted from the mother to the developing fetus. It is not known whether Erbitux® can cause fetal harm when administered to a pregnant woman or whether Erbitux® can affect reproductive capacity. There are no adequate and well-controlled studies of Erbitux® in pregnant women. Erbitux® should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of Erbitux® treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

8.3 Nursing Mothers

It is not known whether Erbitux® is secreted in human milk. IgG antibodies, such as Erbitux®, can be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Erbitux®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If nursing is

interrupted, based on the mean half-life of cetuximab [see *Clinical Pharmacology (12.3)*], nursing should not be resumed earlier than 60 days following the last dose of Erbitux®.

8.4 Pediatric Use

The safety and effectiveness of Erbitux® in pediatric patients have not been established. The pharmacokinetics of cetuximab have not been studied in pediatric populations.

8.5 Geriatric Use

Of the 1062 patients who received Erbitux® with irinotecan or Erbitux® monotherapy in five studies of advanced colorectal cancer, 363 patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Clinical studies of Erbitux® conducted in patients with head and neck cancer did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 208 patients with head and neck cancer who received Erbitux® with radiation therapy, 45 patients were 65 years of age or older.

10 OVERDOSAGE

The maximum single dose of Erbitux® administered is 1000 mg/m^2 in one patient. No adverse events were reported for this patient.

11 DESCRIPTION

Erbitux® (cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian (murine myeloma) cell culture.

Erbitux® is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Erbitux® is supplied at a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use vials. Cetuximab is formulated in a preservative-free solution containing 8.48 mg/mL

sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha. *In vitro* assays and *in vivo* animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. *In vitro*, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

12.3 Pharmacokinetics

Erbitux® administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m^2.

Following the recommended dose regimen (400 mg/m^2 initial dose; 250 mg/m^2 weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with SCCHN and those with colorectal cancer.

Based on a population pharmacokinetic analysis, female patients with colorectal cancer had a 25% lower intrinsic clearance of cetuximab than male patients. Qualitatively similar, but smaller gender differences in cetuximab clearance were observed in patients with SCCHN. The gender differences in clearance do not necessitate any alteration of dosing because of a similar safety profile.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test cetuximab for carcinogenic potential, and no mutagenic or clastogenic potential of cetuximab was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. Menstrual cyclicity was impaired in female cynomolgus monkeys receiving weekly doses of 0.4 to 4 times the human dose of cetuximab (based on total body surface area). Cetuximab-treated animals exhibited increased incidences of irregular or absent cycles, as compared to control animals. These effects were initially noted beginning week 25 of cetuximab treatment and continued through the 6-week recovery period. In this same study, there were no effects of cetuximab treatment on measured male fertility parameters (ie, serum testosterone levels and analysis of sperm counts, viability, and motility) as compared to control male monkeys. It is not known if cetuximab can impair fertility in humans.

13.2 Animal Pharmacology and/or Toxicology

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of

the animals at the highest dose level beginning after approximately 13 weeks of treatment.

14 CLINICAL STUDIES

14.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Study 1 was a randomized, multicenter, controlled trial of 424 patients with locally or regionally advanced SCCHN. Patients with Stage III/IV SCCHN of the oropharynx, hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either Erbitux® plus radiation therapy or radiation therapy alone. Stratification factors were Karnofsky Performance Status (60–80 versus 90–100), nodal stage (N0 versus N+), tumor stage (T1–3 versus T4 using American Joint Committee on Cancer 1998 staging criteria), and radiation therapy fractionation (concomitant boost versus once-daily versus twice-daily). Radiation therapy was administered for 6–7 weeks as once daily, twice daily, or concomitant boost. Erbitux® was administered as a 400 mg/m^2 initial dose beginning one week prior to initiation of radiation therapy, followed by 250 mg/m^2 weekly administered 1 hour prior to radiation therapy for the duration of radiation therapy (6–7 weeks).

Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were Caucasian, and 90% had baseline Karnofsky Performance Status ≥80. There were 258 patients enrolled in US sites (61%). Sixty percent of patients had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

The main outcome measure of this trial was duration of locoregional control. Overall survival was also assessed. Results are presented in Table 4.

Table 4: Study 1: Clinical Efficacy in Locoregionally Advanced SCCHN

	Erbitux® + Radiation (n=211)	Radiation Alone (n=213)	Hazard Ratio (95% CI[a])	Stratified Log-rank p-value
Locoregional control				
Median duration (months)	24.4	14.9	0.68 (0.52–0.89)	0.005
Overall survival				
Median duration (months)	49.0	29.3	0.74 (0.57–0.97)	0.03

[a] CI = confidence interval

Study 2 was a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN. All patients had documented disease progression within 30 days of a platinum-based chemotherapy regimen. Patients received a 20-mg test dose of Erbitux® on Day 1, followed by a 400-mg/m^2 initial dose, and 250 mg/m^2 weekly until disease progression or unacceptable toxicity.

The median age was 57 years, 82% were male, 100% Caucasian, and 62% had a Karnofsky Performance Status of ≥80.

The objective response rate was 13% (95% confidence interval 7%–21%). Median duration of response was 5.8 months (range 1.2–5.8 months).

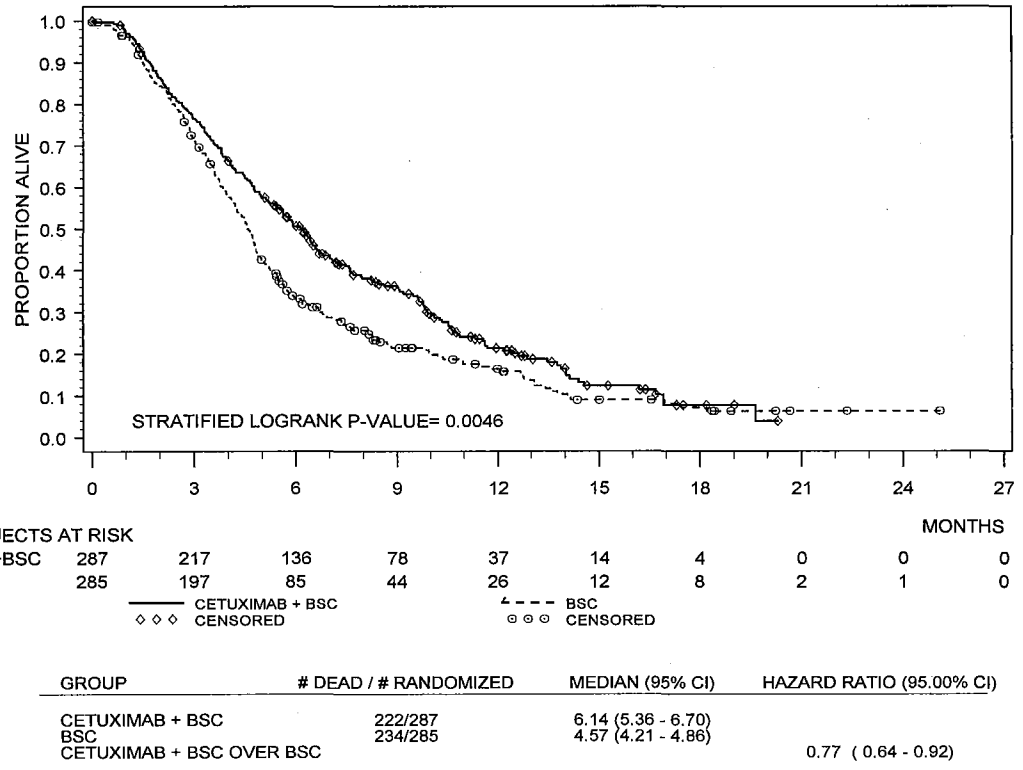
14.2 Colorectal Cancer

Study 3 was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal cancer. Patients were randomized (1:1) to receive either Erbitux® plus best supportive care (BSC) or BSC alone. Erbitux® was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity.

Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were Caucasian, and 77% had baseline ECOG Performance Status of 0–1. All patients were to have received and progressed on prior therapy including an irinotecan-containing regimen and an oxaliplatin-containing regimen.

The main outcome measure of the study was overall survival. The results are presented in Figure 1.

Figure 1: Kaplan Meier Curve for Overall Survival in Patients with Metastatic Colorectal Cancer



GROUP	# DEAD / # RANDOMIZED	MEDIAN (95% CI)	HAZARD RATIO (95.00% CI)
CETUXIMAB + BSC	222/287	6.14 (5.36 - 6.70)	
BSC	234/285	4.57 (4.21 - 4.86)	
CETUXIMAB + BSC OVER BSC			0.77 (0.64 - 0.92)

Study 4 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent metatstatic colorectal cancer. Patients were randomized (2:1) to receive either Erbitux® plus irinotecan (218 patients) or Erbitux® monotherapy (111 patients). Erbitux® was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. In the Erbitux® plus irinotecan arm, irinotecan was added to Erbitux® using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly times four doses every 6 weeks. Of the 329 patients, the median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline Karnofsky Performance Status ≥80. Approximately two-thirds had previously failed oxaliplatin treatment.

The efficacy of Erbitux® plus irinotecan or Erbitux® monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In patients receiving Erbitux® plus irinotecan, the objective response rate was 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months, and median time to progression was 4.1 months. In patients receiving Erbitux® monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%), median duration of response was 4.2 months, and median time to progression was 1.5 months. Similar response rates were observed in the pre-defined subsets in both the combination arm and monotherapy arm of the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

Erbitux® (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, preservative-free, injectable liquid.

NDC 66733-948-23 100 mg/50 mL, single-use vial, individually packaged in a carton

NDC 66733-958-23 200 mg/100 mL, single-use vial, individually packaged in a carton

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased particulate formation may occur at temperatures at or below 0° C. This product contains no preservatives. Preparations of Erbitux® in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To report signs and symptoms of infusion reactions such as fever, chills, or breathing problems.

- Of the potential risks of using Erbitux® during pregnancy or nursing and of the need to use adequate contraception in both males and females during and for 6 months following the last dose of Erbitux® therapy.
- That nursing is not recommended during, and for 2 months following the last dose of Erbitux® therapy.
- To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months following the last dose of Erbitux®.

Erbitux® is a registered trademark of ImClone Systems Incorporated.

Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876
Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125084/103

MEDICAL REVIEW

Division Director Decisional Review

Date	October 2, 2007
From	Patricia Keegan, M.D. Director, Div of Biologic Oncology Products
Subject	Division Director Decisional Review
NDA/BLA # Supp #	BL STN 125084.103
Proprietary / USAN names	Erbitux Cetuximab
Dosage forms / strength	Solution for intravenous infusion/ (b) (4)
Proposed Indication(s)	Erbitux, as a single agent, is indicated for EGFR-expressing metastatic colorectal carcinoma (b) (4) The effectiveness of Erbitux, in combination with irinotecan, is based on objective response rates…The effectiveness of Erbitux as a single agent as a single agent (b) (4) (b) (4)
Action:	Approval

1. Introduction to Review

The application contains the results of a single, randomized, open-label, multinational, 572-patient study conducted by the National Cancer Institute of Canada (NCIC) Clinical Trials Group, entitled "CO.17 (the study is also referred to by the applicant under the study number "CA225025" and the latter designation will be used throughout this memo and in the medical officer's review). The CA225025 study compared the impact of single agent Erbitux to best supportive care in patients with EGFR-expressing metastatic colorectal cancer, that had progressed on or following both irinotecan- and oxaliplatin-containing regimens. This study demonstrated a clinically relevant and highly significant improvement in overall survival, as well as longer progression-free survival and higher overall response rates for patients randomized to receive Erbitux according to the currently approved dose and schedule. The application also contained clinical study reports from three single arm trials (CP02-0144, CA225041, and CA225045) of single agent Erbitux, intended to provide additional safety information.

The primary efficacy study, CA225025, verified the clinical benefit which was predicted by durable objective tumor responses in historically-controlled studies of single agent Erbitux that supported the accelerated approval in Feb. 2004. Although this approval action is based on data from a single trial, this is sufficient because the primary endpoint, impact on survival, is both clinically important and the effect has been robustly demonstrated with consistent effects across all relevant subgroups. The findings of this single trial (CA225025) are further supported clinically important and highly significant effects on key secondary endpoints of progression-free survival and overall tumor response rates. Based on FDA field inspection of two of the largest accruing sites, the reported data are reliable and accurate. The NCIC also reviewed radiologic studies supporting objective tumor responses; although not fully independent, this review provides additional weight to the investigator-reported results for response.

In addition, while the clinical study reports for the single arm studies contributed relatively little information characterizing the risks of Erbitux due both to the summary nature of the results as well as the study designs, the primary efficacy study (CA225025) has both sufficient size and acceptable design to characterize safety.

(b) (4)

(b) (4)

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

On February 12, 2004, cetuximab was granted accelerated approval under 21 CFR 601 Subpart E for the following two indications:

- "ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy ."
- "Erbitux, administered as a single-agent, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy."

The original approval was based primarily on a single, open-label, multicenter, parallel group study that enrolled 329 patients with EGFR-expressing metastatic colorectal cancer whose disease progressed while receiving (irinotecan-refractory) or following completion of an adequate course of irinotecan, or were unable to tolerate irinotecan. All patients were also required to have had received prior fluoropyrimidines. Oxaliplatin was available under accelerated approval when the study was initiated and approximately two-thirds of patients had cancer that also progressed on or following oxaliplatin. The primary objective of the study was demonstrate durable objective tumor response rates (ORR) of ≥10% in patients receiving cetuximab alone and that the combination of irinotecan plus irinotecan yielded higher response rates than those receiving single agent cetuximab. Patient records, including radiologic studies, were reviewed by an independent committee to both verify refractoriness to irinotecan and to determine the presence and duration of objective tumor responses. The surrogate endpoint for clinical benefit was durable ORR, as determined by an endpoint-review committee masked to treatment assignment and investigator ORR determination. The results of this study demonstrated an ORR of 11% (95% CI: 6%, 18%) with a median duration of 4.2 months in patients receiving single agent cetuximab and ORR of 23% (95% CI 18%, 29%) with a median duration of response of 5.7 months in patients receiving irinotecan plus cetuximab.

Verification of clinical benefit (improvement in overall survival) was to be obtained in the following two studies, as required postmarketing commitments (PMCs):

- CA225006 (EPIC), "A Phase III Randomized, Open-label, Multicenter Study of Irinotecan and Cetuximab versus Irinotecan as Second-line Treatment in Patients with Metastatic, EGFR-positive Colorectal Carcinoma."

- CA225014, "A phase III, randomized, Multicenter Study of Cetuximab, Oxaliplatin, 5-FU, and Leucovorin versus Oxaliplatin, 5-FU, and Leucovorin in Patients with Previously Treated Metastatic EGFR-Positive Colorectal Carcinoma."

Study CA225014 (also referred to as the EXPLORE trial) was terminated prematurely due to slow accrual rates after 102 of the planned 1100 patients had been accrued. Study CA225006 (also referred to as the EPIC trial) completed accrual in 2006, with analysis of study results in the fall of 2006.

On June 2, 2006, ImClone Systems, Inc. submitted a request to discuss submission of an efficacy supplement containing the results of (b) (4) CA225025, (b) (4) At the time of the meeting request, the results of the (b) (4) were not available. FDA provided preliminary draft comments,

requesting that the CA225025 (b) (4) protocols and associated documents be submitted to the US IND for FDA review and that the meeting be rescheduled when the study results were available.

On December 13, 2006 a meeting was held between ImClone Systems Inc and the Division of Biologic Oncology Products, CDER for the agency to discuss studies CA225025 (b) (4) and the PMC pertaining to CA225006. The salient points of that meeting were:

- If determined to be well conducted, the summary results of CA225025 could be used to verify the clinical benefit of Erbitux as a single agent in EGFR-expressing, metastatic colorectal cancer.

- Based on the results of CA225006, which demonstrated no evidence of improved survival, the clinical benefit of Erbitux when given in combination with irinotecan has not been verified and data from additional studies should be submitted.

- (b) (4)

On March 30, 2007, BL STN 125084.103 was submitted

(b) (4)

3. **CMC/Microbiology/Device**
   There were no manufacturing changes regarding the commercial product and no microbiology findings provided in this application.

4. **Nonclinical Pharmacology/Toxicology**
   The clinical dose and schedule of Erbitux and the patient population studied under this supplement are the same as those supporting the original approval. The nonclinical pharmacology/toxicology data provided in the original application are sufficient to support this labeling expansion. No additional nonclinical studies were provided, nor were any requested in support of this efficacy supplement.

5. **Clinical Pharmacology/Biopharmaceutics**
   The clinical dose and schedule of Erbitux and the patient population studied under this supplement are the same as those supporting the original approval. The clinical pharmacology data provided in the original application are sufficient to support this labeling expansion. No additional nonclinical studies were provided in the supplement. However, due to the publication of ICH E14 and given the higher incidence of sudden

deaths in patients with advanced head and neck cancer receiving Erbitux plus irradiation compared to those receiving irradiation alone, a post-marketing study was requested to evaluate the impact of Erbitux on the QTc interval. The applicant has agreed to conduct a QTc study in patients as a post-marketing commitment to this application.

6. **Clinical/Statistical** (See medical and statistical reviews by Kevin Shannon, M.D. and Kyung Yul Lee, Ph.D. for additional detail)

6.1. General Discussion

As noted under the discussion of the regulatory history, the CA225025 study reviewed under this application was not intended to verify clinical benefit and the acceptability of CA225025 for this purpose was not conducted until the study was completed, when the protocol was submitted to the US IND. The Agency's considerations for accepting the study results in support of a labeling expansion were the study design elements (large sample size, primary endpoint of overall survival) and quality of the study conduct (conducted by an experienced cooperative group, good data quality as determined by the DSI audit and upon review of the primary study results). (b) (4)

The findings of CA225025, however, are sufficiently compelling to support, as displayed in the following table. While the results of progression-free survival were not independently confirmed, the radiologic studies and patient records for all patients with an objective tumor response were evaluated centrally by the NCIC Clinical Trials Group..

Study CA225025 Trial Results

	Erbitux plus BSC (n=287)	BSC (n=285)
Median Overall Survival (months)	6.14	4.75
Hazard Ratio (95% CI)	0.77 (0.64, 0.92)	
Log-rank test	0.0048	
Progression-free Survival (months)	1.91	1.84
Hazard Ratio (95% CI)	0.68 (0.57, 0.81)	
Log-rank test	<0.0001	
Sensitivity Analysis* for Progression-free Survival (months)	1.9	1.8
Hazard Ratio (95% CI)	0.58 (0.49, 0.69)	
Log-rank test	<0.0001	
Overall response rate	6.6 %	0
Response duration (months)	5.5	N/A

* patients censored at initiation of non-study specified anti-cancer chemotherapy

(b) (4)

(b) (4)

(b) (4)

6.2. Efficacy

6.2.1. Dose identification/selection and limitations

The efficacy study utilized the currently approved dose and schedule.

Unlike studies supporting earlier approvals, the CA225025 study did not utilize a test dose prior to initiation of the recommended dose. The adverse reaction profile in this study is similar to that observed with initial accelerated approval study and further support the findings of smaller studies showing that that there is no increase in the incidence or severity of infusion reactions when the test dose is omitted.

[1] Goldberg RM, Hecht JR. Randomized phase III trial of cetuximab plus irinotecan vs irinotecan alone for metastatic colon cancer in patients who have failed prior oxaliplatin-based therapy: The EPIC trial. Highlights Newsletter from AACR; April 30, 2007; p5.

The dosing regimen in one of the supporting safety studies (CA225045) is of interest because the CA225045 study investigates both the safety and activity of a dosing regimen in which the dose is escalated to achieve NCI CTC ≥ grade 2 acneiform rash. This regimen directly tests the hypothesis that has been widely accepted by the medical community based on post-hoc exploratory analyses, correlating skin rash to clinical activity (i.e., objective tumor response). The CA225045 study design resulted in higher relative and cumulative dose intensity as compared to the CA225025 study; data are shown in the table below.

Cetuximab Exposure in Pharmacodynamically- and Conventionally-dosed Studies (CA225045 and CA225006)

	CA225006 (n=288)	CA225045 (n=110)
Median cumulative dose (mg/m^2)	2156	3009
Median cumulative dose intensity (mg/m^2/week)	247	295
Median duration of treatment (weeks)	8	9

(b) (4)

(b) (4)

Based on the outcome of overall response rate and response duration, a treatment strategy intended to dose to moderate dermatologic toxicity does not appear to be more active than the current recommended dosing strategy. The

applicant has (b) (4)

6.2.2. Phase 3/essential clinical studies, including design and analytic features
The study was a multinational, randomized, open-label study; because the primary endpoint of overall survival is objective (as opposed to disease progression or tumor response, which can be influenced by investigator bias), an independent endpoint review committee was not required. The analysis of the primary endpoint, using the stratified log-rank test, was acceptable. While the analysis excluded study center (a stratification variable for randomization), this was acceptable because the large number of centers would create many small or unfilled cells. An exploratory analysis in which both ECOG performance status and region were considered also demonstrated highly significant effects on survival.

The results of this single study demonstrated a highly significant and, given the overall short survival of this population, clinically important increase in overall survival [HR 0.77 (95% CI: 0.64, 0.92), p=0.0048 stratified log-rank test] with median overall survival of 6.1 months and 4.6 months in the cetuximab and BSC arms, respectively. The study also demonstrated improvement in investigator-determined progression-free survival (

6.2.3. Other efficacy studies
The labeling expansion is based on a single efficacy study. Considerations based on the results of other studies are discussed in section 6.1 above.

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions
There was no disagreement between primary and secondary reviewers either in the clinical and statistical teams regarding interpretation of the study results or in the recommendations regarding approval.

6.2.5. Pediatric use/PREA waivers/deferrals
The applicant has agreed to conduct a study to assess pharmacokinetics, activity and tolerability in pediatric patients with EGFR-expressing tumors under the original approval. No additional studies are considered necessary at this time.

6.2.6. Notable issues
Issues relating to the efficacy of Erbitux when administered in combination with other agents are discussed in Section 6.1

Issues regarding optimal dosing are discussed under section 6.21

The other notable issue that remains to be addressed, is the relationship of EGFR tumor expression, as detected by current immunohistochemical means, to efficacy. The CA225025 study screened 1243 subjects for eligilibity. 21%

of these patients were excluded for lack of detectable EGFR tumor expression. Of the 752 patients registered and randomized on CA225025, EGFR staining intensity (1-3+) and percentage of tumor cells staining for EGFR were assessed by a central laboratories for all but 54 patients. These 54 patients' tumor specimens were assessed by a different lab which confirmed EGFR expression but did not document staining intensity or proportion of cells staining. An exploratory analysis of the primary endpoint was conducted in subgroups defined by EGFR staining intensity in tumor.

Table 1. Median Overall Survival (in months) by EGFR Intensity

EGFR Intensity	Cetuximab+BSC (n) N=260	BSC (n) N=260	Hazard Ratio (95% CI)
1+	6.24 (170)	4.76 (158)	0.83 (0.61, 1.14)
2+	5.65 (75)	4.47 (81)	0.71 (0.50, 1.01)
3+	6.34 (15)	3.61 (21)	0.63 (0.29, 1.37)

(table reproduced from Dr. Shannon's medical review)

Given the small numbers in each subgroup and lack of randomization for this parameter, conclusions cannot be drawn regarding a relationship. However, unlike other studies where no relationship has been observed even in exploratory analysis, the hazard ratio decreases as the level of intensity increases. This relationship should be explored in further studies, specifically in a study designed to directly test this relationship through prospective randomization, in which the intensity of EGFR staining is a stratification variable.

6.3. Safety (for detailed discussion refer to medical review by Kevin Shannon, M.D.)

6.3.1. General safety considerations

Clinical safety data supporting the original approval also supports the proposed labeling extension. Of note, this is the first large randomized trial isolating the safety and efficacy of Erbitux in patients with metastatic colorectal cancer. Therefore, although safety data from the CA225006 trial provides primary safety information on only an additional 288 patients, the information is important in further characterizing the adverse drug reaction profile iin the background of the disease setting.

The applicant provided summary information in the form of clinical study reports and tabular line listings from three additional studies; electronic patient-level data were not provided for FDA analysis. Electronic datasets containing patient level safety data were not requested for these three studies because each of limitations in study design. All three studies were single-arm, open-label studies. Patient-level data for CP02-0144 were already reviewed for 252 of the 374 total patients enrolled, under the efficacy supplement BL STN 125084.1.

The data from CA225041 were obtained in an expanded access trial with no monitoring or auditing of information collected. The data from CA225045 were obtained using an unapproved dosing regimen and thus were unlikely to be directly applicable to the regimen used in this study.

The summary safety information contained in the clinical study reports and the primary data from CA225006 were reviewed for evidence of new safety signals. No new safety signals were identified.

6.3.2. Safety findings from submitted clinical trials

The adverse reaction profile from CA225025 was similar to prior studies both in colorectal cancer patients and patients with head and neck cancer, with the exception of infusion reactions, as discussed in the next paragraph.. Because of the study design and internal control, the results of CA225025 provide better data regarding the toxicity of Erbitux in the context of the underlying disease.

The only novel observation regarding safety was the number of patients with severe and serious infusion reactions occurring beyond the first week of infusion (7 of the 13 cases were reported beyond the first week of infusion). This is not consistent with prior observations that 90% of severe infusion reactions occur with the first infusion. Dr. Shannon reviewed data for all reported cases; one of the late events appeared to be dermatologic toxicity (facial rash) that occurred several days after infusion. In an additional 2 cases of "late" infusion reactions, the patients had experienced infusion reactions previously but not of the same severity. Of those patients who were rechallenged, there was one positive rechallenge and the remainder successfully completed subsequent infusions. The incidence and clinical significance of infusion reactions occurring after one or more previous uncomplicated infusions should be investigated in future studies.

6.3.3. Safety update

No additional safety signals were identified in post-submission safety update amendments to BL STN 125084.103.

6.3.4. Immunogenicity

On July 13, 2007, the applicant submitted a cover letter regarding the 120-day safety report. The cover letter stated that, as of the March 6, 2007 data cut-off for the efficacy supplement, there were no unexpected deaths, no serious adverse events, and no events of special interest (hypomagnesemia, infusion reactions, cardiac events) reported in clinical studies or post-marketing experience.

6.3.5. Special safety concerns

No new safety signals were identified. Because of the imbalance in sudden deaths observed in a randomized, controlled trial of Erbitux for head and neck cancer, and in the absence of data demonstrating that Erbitux cannot mediate

such effects, the applicant was asked to conduct a study to assess the effects of Erbitux on the correct QT interval (QTc study).

Adverse reactions of Erbitux that were observed in this supplement and which need to be monitored in future studies include dermatologic toxicity, infusion reactions, and hypomagnesemia.

6.3.6. Discussion of primary and secondary reviewers' comments and conclusions
The medical officer did not identify new safety signals and determined that the currently described risks are acceptable when weighed against the modest survival advantage demonstrated in CA225006.

6.3.7. Notable issues: none.

6.4. Clinical Microbiology

Evaluation of clinical microbiology was not conducted nor was it relevant to the review of this efficacy supplement.

7. Advisory Committee Meeting

An advisory committee meeting was not convened to discuss the findings of this efficacy supplement.

8. Risk Minimization Action Plan

The applicant did not submit a risk minimization action plan with this supplement. Neither the review team nor the Division felt that such a plan was required for this product.

9. Other Regulatory Issues

There were no unusual regulatory issues associated with this application other than the decision to convert only a portion of the accelerated approval indications to regular approval. This issue is discussed in sections 2 and 6 of this memo. Specifically, there were no concerns regarding the application's data integrity nor issues regarding exclusivity or patent infringement.

10. Financial Disclosure

A small number of investigators failed to respond regarding financial conflicts despite due diligence efforts by the applicant to collect such information. Because of the small percentage of total study subjects enrolled at any individual site, the ability of impropriety or erroneous data from one or a limited number sites to affect the overall conclusions is considered negligible.

11. Labeling (See additional reviews by Ms. Sharon Sickafuse [RPM] Carole Broadnax [DDMAC], and Iris Massuci [SEALD])

11.1. Proprietary name:
No concerns regarding the proprietary name were identified either by this Division or the consultants from the Office of Surveillance and Epidemiology.

11.2. Physician labeling
Product labeling was extensively reformatted in order to comply with the Physician labeling Rule. The following significant revisions to the applicant's proposed labeling were also made by FDA and accepted by the applicant.

- (b) (4)

- Boxed Warnings: The information in the Boxed Warnings sections was revised to incorporate only the most critical elements with references to the Warnings sections for additional information. This resulted in deletion only of redundant information. (b) (4)

- Dosage and Administration: The information in this section was revised to increase white space and for brevity. Dose modifications clarified for consistency with clinical protocol recommendations, in which Erbitux was to be discontinued only for specified, serious infusion reactions and not for all CTC NCI Grade 3 or 4 events (e.g., fever or chills).

- Warnings and Precautions:

  - All subsections in Warnings and Precautions were revised for brevity and to highlight only the most important information.

  - (b) (4)

  - (b) (4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

12. DSI Audits (See detailed review by Lloyd Johnson, Pharm.D.)
The Division of Scientific Integrity conducted a field inspection of two of the largest accruing sites, enrolling 41 and 34 patients, respectively. The field inspectors audited all study records for subjects enrolled at each of these sites. The inspectional findings were classified as no action indicated (NAI) and the results from these sites were deemed reliable and acceptable.

13. Conclusions and Recommendations

13.1. Regulatory action:

This application will be approved with the final draft labeling of October 2, 2007. The review team members unanimously recommended approval. Two post-marketing commitments were requested and agreed upon; the first to evaluate product safety with regard to the impact of Erbitux on QT interval, as discussed in ICH E14. The second was to provide the primary study results for the PMC study CA225006; once review of these data are completed, additional discussions with the applicant will be pursued regarding the indication for Erbitux in combination with irinotecan for metastatic colorectal cancer, which remains under accelerated approval. The applicant will either need to conduct additional studies or withdraw the indication. Evaluation of the results of CA225006 may help inform the design of additional studies.

13.2. Safety concerns to be followed postmarketing

No new safety concerns have been identified. In discussions with the applicant, the Agency recommends continued efforts to identify patients at risk for and optimal dosing strategies to decrease the risks of serious infusion reactions and demrmatologic toxicities in ongoing and future studies.

13.3. Risk Minimization Action Plan, if any

The applicant did not propose a risk minimization action plan and the review team did not request or identify the need for such a plan at this time.

13.4. Postmarketing studies

13.4.1. Required studies:

One required PMC (under 21 CFR 601.40) has been terminated (b) (4)

(b) (4)

(b) (4)

13.4.2. Commitments (PMCs)

The applicant has agreed to FDA's request to conduct a study to evaluation the impact of Erbitux on the QT interval (QTc study) in accordance with the principles described in ICH E14. This is requested as part of the routine characterization of product safety and because of an increased incidence in sudden deaths observed in a randomized controlled trial of patients with head and neck cancer receiving Erbitux plus radiotherapy, as compared to the radiotherapy alone control arm.

13.4.3. Other agreements: None

13.5. Summary of reviewers' comments

The members of the review team and consultants have recommended approval of this application.

13.6. Comments to be conveyed to the applicant: None.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

CLINICAL REVIEW

Application Type:	sBLA
Submission Number:	[redacted]
Submission Code:	[redacted]
Letter Date:	March 30, 2007
Stamp Date:	April 2, 2007
PDUFA Goal Date:	[redacted]
Reviewer Name:	Kevin Shannon, M.D., Medical Officer
Through:	Patricia Keegan, M.D., Acting Team Leader
Review Completion Date:	October 1, 2007
Established Name:	Cetuximab
Trade Name:	Erbitux
Therapeutic Class:	Epidermal growth factor receptor antagonist
Applicant:	ImClone Systems Incorporated
Priority Designation:	Priority
Formulation:	Intravenous
Dosing Regimen:	Cetuximab 400mg/m^2 IV week 1, then 250mg/m^2 IV weekly
Indication:	As a single agent, cetuximab is indicated for the treatment of EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. Cetuximab, as a single agent, is also indicated for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens.
Intended Population:	Patients with metastatic colorectal cancer progressing on or following irinotecan- and oxaliplatin-based regimens

Kevin Shannon 10/2/07

Patricia Keegan 10-2-2007

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1. EXECUTIVE SUMMARY

This clinical review is a based primarily on the analyses of efficacy and safety information from the randomized, two-arm, open-label, multinational trial, CA225025. The results of CA225025 were submitted to expand product labeling for cetuximab for the following proposed indication:

(b) (4)

There were 572 patients enrolled and randomized, of these, 288 patients received cetuximab 400mg/m^2 IV initial dose then 250mg/m^2 IV weekly. The study was 2 ½ years in duration with overall survival (OS) as the primary endpoint. Patients treated with cetuximab had a significant improvement in OS (6.1 months, 95% CI 5.4, 6.7) compared to those who received best supportive care (4.6 months, 95% CI 4.2, 4.9) with a stratified log-rank p-value of 0.0048. Considering the advanced disease status of the patient population, toxicities were acceptable and consistent with those already described in current labeling.

1.1 Recommendation on Regulatory Action

It is the recommendation of this reviewer to approve the BLA efficacy supplement STN125084.103 for the use of Erbitux at the recommended dose for third-line treatment to prolong survival in patients with metastatic colorectal cancer, which (b) (4) on irinotecan- and oxaliplatin-containing chemotherapy regimens. Modifications, as contained herein, to the Sponsor's proposed label are reviewed.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No Risk Management programs or activities are recommended.

1.2.2 Required Phase 4 Commitments

The required Phase 4 commitments are needed under PREA. This supplement is not an accelerated approval.

1.2.3 Other Phase 4 Requests

Two post-marketing commitments were requested by the Agency:

- To conduct a study to evaluate the impact of Erbitux on prolongation of the QTc-

interval according to principles discussed in ICH E14. The Applicant has agreed to submit the protocol by March 31, 2008; patient accrual will be completed by September 30, 2009; the study will be completed by January 29, 2010; and the final study report, including revised labeling, if applicable, will be submitted by June, 2010.

- To submit data sets for primary study data, narrative summaries for all serious adverse events in both treatment arms, and a complete set of case report forms for all patients who died within 30 days of receiving study drug and all patients who discontinued treatment prematurely for study CA225006. These data should include determination of the secondary endpoints of progression-free survival and overall response rate. (b) (4)

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The submission contains results from one efficacy and safety trial. The trial was conducted by the (b) (4) National Cancer Institute of Canada, and supported by Bristol-Myers Squibb, a corporate partner of ImClone Systems in the development of Erbitux.

Other pertinent clinical data sources were used as follows:

1) The reviewer also assessed the summary data provided in this supplement (BL STN 125084.103). Final Clinical Study Reports (CSRs) of 3 single arm studies enrolling a total of 1,198 patients are also included with this submission (Table 1). Interim results of Trial CP02-0144 have been previously reviewed under BL STN 125084.1. No primary data is provided for any of these studies, which are to be considered as secondary data sources accompanying this supplement.

Table 1. Additional CSRs in sBLA STN 125084/103

CA225041	Anti-epidermal Growth Factor Antibody, Cetuximab, in Patients with Stage IV Colorectal Carcinoma who Failed All Standard Therapy: an Access Protocol	742
CA225045	An Exploratory Pharmacogenomic Study of Erbitux Monotherapy in Patients with Metastatic Colorectal Carcinoma	110
CP02-0144*	A Phase II Multicenter Study of Erbitux in Patients with Metastatic Colorectal Carcinoma	346
*Interim data previously reviewed by Dr. Lee Pai-Scherf, STN 125084/1		

The review also considered prior safety experience from the following sources:

2) Information from the initial application (BL STN 125084.0) which contained a full report (i.e., electronic datasets, case report forms (CRFs), and narrative summaries for serious adverse events) for the results of three uncontrolled studies (two single-arm

studies of Erbitux monotherapy and Erbitux plus irinotecan, and one, parallel-arm, study that randomized patients to either Erbitux monotherapy or Erbitux plus irinotecan) in previously treated, EGFR-expressing metastatic colorectal cancer.

3) Information from the interim, detailed safety results (i.e., datasets, CRFs, CRTs) of 252 patients enrolled in an ongoing study, Study CP-02-0144, provided in support of a manufacturing change (BL STN 125084.1).

The safety datasets for these submission contained safety data from development program for Erbitux for a total of 354 patients who received Erbitux in combination with irinotecan and 420 patients who received Erbitux monotherapy.

4) Information from a CBE labeling supplement (BL STN 125084.30) which contained interim safety data from three clinical studies (including CA225025), characterizing the incidence and severity of hypomagnesemia, hypocalcemia, and hypokalemia in randomized, controlled trials.

1.3.2 Efficacy

This application provides results of a single phase 3, multicenter, randomized trial (CA225025) in 572 patients that was designed to assess the impact of treatment with cetuximab on overall survival (OS). The study was initiated in August 2003 and completed on March 6, 2006. Efficacy was evaluated in patients with EGFR-expressing, metastatic colorectal cancer who had failed all prior therapies including an irinotecan-containing and an oxaliplatin-containing regimen. Patients were randomized in a 1:1 fashion to either best supportive care (BSC) or cetuximab in addition to BSC. Stratification factors were by center (Australia, New Zealand and Singapore region and 30 Canadian sites) and by ECOG PS (0 or 1 versus 2). There was no blinding. The cetuximab arm patients were administered cetuximab weekly with an initial dose of 400 mg/m^2 intravenous (IV) infusion followed by weekly doses of 250 mg/m^2 IV infusion until disease progression or unacceptable toxicity.

The primary endpoint was OS; secondary endpoints included time-to-progression (TTP – same as progression-free survival (PFS)) and objective response rate (OR). The duration of response was computed for patients whose best response was either a complete response (CR) or a partial response (PR). It was defined as the number of months from when the measurement criteria were first met for a CR or PR until the first date of progressive disease or death. Tumor response was assessed by the investigator every 8 weeks using RECIST criteria and confirmed by reassessment within 4 to 6 weeks.

OS was prolonged by 1.5 months in the cetuximab arm compared to the BSC-only arm. This difference was statistically significant. See Table 2 on the following page.

Table 2. Summary of Efficacy, Primary Endpoint, Trial CA225025

Overall Survival	Cetuximab + Best Supportive Care N = 287	Best Supportive Care N = 285
Median duration (95% CI), months	6.1 (5.4, 6.7)	4.6 (4.2, 4.9)
Stratified log-rank p value (stratified by ECOG PS)	0.0048	
Hazard ratio	0.766	
95% CI	0.637, 0.921	

It is to be noted that secondary endpoints are based on investigator determinations and not based on an endpoint-review committee masked to treatment arm. The stratified log rank test of PFS was also statistically significant for patients randomized to the cetuximab arm compared to the BSC arm ($p<0.0001$) with 1.91 months and 1.84 months of median PFS duration. This difference translates into only ~ 2 days.

Another secondary endpoint, objective response rate revealed 6.6% PRs based on 19 patients in the cetuximab arm and none in the BSC arm. There were no CRs in either arm. The median duration of the 19 PR patients was 5.5 months (95% CI 4.0 – 10.2).

1.3.3 Safety

The safety profile emerging from this trial for single-agent cetuximab was generally consistent with the labeled reactions already described.

The most common adverse events reported in trial CA225025 for cetuximab were skin toxicities (including rash, dry skin, pruritis, and nail changes), fatigue, infusions reactions, diarrhea, stomatitis, infections and insomnia. The most common laboratory abnormality associated with cetuximab therapy was hypomagnesemia. Of these common adverse events, only infusion reactions and rash led to discontinuation of therapy due to intolerable toxicity.

The most common categories of SAEs, which were more frequent in the cetuximab arm, were infection, fever, pain-other (mostly musculoskeletal symptoms), fatigue, dehydration, and tachyarrhythmias.

Two deaths occurred while on cetuximab (patients AUXA0253 and CAVA0021) as detailed in Section 7.1.1 which cannot be definitely excluded from causal linkage to cetuximab.

In summary, no new safety concerns were found during trial CA225025.

1.3.4 Dosing Regimen and Administration

The studies submitted used the Package Insert recommended dose of cetuximab of 400mg/m^2 initial dose followed by 250mg/m^2 IV weekly.

1.3.5 Drug-Drug Interactions

No drug interaction studies were conducted.

1.3.6 Special Populations

Effects of Age: There was estimated benefit for the cetuximab treatment effect based on overall survival (OS) hazard ratios in both age groups (Table 3). A total of 287 patients were randomized to receive cetuximab. 177 subjects were <65 years. Improvement in OS was seen in this age group, although the confidence interval is broad, and contains unity.

Effects of Gender: In study CA225025, there were 368 male patients and 204 female patients who received Erbitux. Improvement in OS was statistically significant among female subjects treatment with Erbitux. Similar to the subgroup analysis by age, the male population demonstrated an improved OS with Erbitux treatment; however, the CI is wide.

Effects of Race: The study population of CA225025 reflects the populations of the Canadian and Australian census. Insufficient numbers of non-Caucasian subjects were enrolled to permit subgroup analysis.

Table 3. Subgroup Analysis for OS by Age, Gender, Race

Subgroup	Median Months		Hazard Ratio (95% CI)
	Cetuximab+BSC (n) N = 287	BSC (n) N = 285	
Age			
<65	6.14 (177)	4.57 (158)	0.80 (0.62, 1.01)
≥65	5.91 (110)	4.53 (127)	0.71 (0.53, 0.95)
Gender			
Male	6.51 (186)	4.76 (182)	0.80 (0.64, 1.01)
Female	5.52 (101)	4.21 (103)	0.67 (0.49, 0.91)
Race			
White	6.14 (258)	4.53 (250)	0.79 (0.65, 0.96)
Other	4.80 (26)	4.99 (33)	0.84 (0.43, 1.66)

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Cetuximab (Erbitux) is a chimeric EGFR antibody, which binds with high specificity and affinity to the extra cellular domain of the human EGF receptor. Cetuximab blocks activation of EGFR, resulting in inhibition of cell proliferation and other cellular functions. Non-clinical studies have shown that cetuximab affects many EGFR-mediated processes, such as regulation of the cell cycle, apoptosis, angiogenesis, tumor metastasis and DNA repair mechanisms.

This submission is an efficacy supplement. For more detailed product information, please refer to the original BLA (125084/0) review submitted on August 14, 2003 and supplemental BLA (125084/1) submitted on February 17, 2004.

Established (USAN) Name:	Cetuximab
Trade Name:	Erbitux
Pharmacological Category:	Epidermal growth factor receptor antagonist
Drug Class:	Chimeric mouse/human monoclonal antibody
Route of Administration:	Intravenous
Dose and Regimen:	Cetuximab 400mg/m^2 loading dose IV infusion over 120 minutes, followed by weekly 250mg/m^2 infusions over 60 minutes.
Proposed indication:	Treatment of patients with EGFR-expressing metastatic colorectal cancer (b) (4) following, or who were not suitable candidates to receive irinotecan- or oxaliplatin-based chemotherapy

2.2 Currently Available Treatment for Indications

Colorectal carcinoma is the third most common cancer after prostate and lung cancer in men and after breast and lung cancer in women. It is estimated that in 2007 there will be approximately 153,700 new cases of colorectal carcinoma in the United States and approximately 52,200 deaths. Colorectal carcinoma accounts for approximately 10% of cancer-related mortality in the United States.[1] The primary therapy for colorectal cancer is surgical resection. Almost 50% of cases recur after initial surgery and 10-15% of patients have metastatic disease at presentation. Almost 50% of the cases will recur after initial surgery; in addition, 10-15% of the patients will already have metastatic disease at the time of presentation. The 5-year survival rate for patients with metastatic colorectal cancer is 5%.[1]

Following are the FDA approved Drugs for use in third-line treatment of metastatic colorectal cancer:

- Cetuximab (Erbitux)
- Panitumumab (Vectibix)

Both Erbitux and Vectibix were granted accelerated approval.

Erbitux was granted accelerated approval, under CFR§601.41 Subpart E, on Feb. 12, 2004. The assessment of benefit in the original license application was based on the surrogate endpoint of objective response, as determined by a review panel masked to treatment and to investigator-determined outcomes, in populations (irinotecan-refractory and irinotecan-intolerant) who have no effective alternative therapy available to them. The data were obtained

[1] Jemal A, Siegel R, Ward E, *et al.* Cancer Statistics, 2007. CA Cancer J Clin 2007; 57(1): 43-66.

from one primary efficacy trial, EMR-62 202-007 and two supportive studies (IMCL-CP02-9923 and IMCL-CP02-0141) for efficacy evaluation.

- EMR-62 202-007 is a multi-center, phase 2, open-label study. Patients with EGFR-expressing, metastatic colorectal cancers are randomized in a 2:1 ratio, to treatment with cetuximab plus irinotecan or to cetuximab alone. The study enrolled 329 patients and was conducted in Europe.

- IMCL-CP02-9923 is a multi-center, single arm trial of cetuximab plus irinotecan in patients with irinotecan refractory metastatic colorectal cancer. The study enrolled 139 patients and was conducted in the U.S.A.

- IMCL-CP02-0141 is a multicenter, single arm trial of cetuximab alone in patients with EGFR-expressing recurrent or metastatic colorectal cancer, who had progressive disease after irinotecan. The study enrolled 61 patients and was also conducted in the U.S.A.

An Independent Radiographic Review Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients (Table 4). Efficacy was evaluated in all randomized patients (ITT) and in several pre-specified sub-populations, including two key populations:

- IRC-PD, defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with ERBITUX and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy

- IRC-PD oxaliplatin failure defined as IRC-PD patients who had previously been treated and had progressive disease or were intolerant to oxaliplatin therapy.

Table 4. FDA Analysis of Objective Response Rates

POPULATION	ERBITUX PLUS IRINOTECAN		ERBITUX MONOTHERAPY	
	N/N	%	N	%
Intent-to-treat (ITT)	50/218	**22.9**	12/111	**10.8**
IRC-PD	34/132	**25.8**	10/69	**14.5**
IRC-PD Oxaliplatin failure	19/80	**23.8**	5/44	**11.4**

Vectibix was granted accelerated approval, under CFR§601.41 Subpart E, on September 27, 2006. The effectiveness of Vectibix was established in a single, randomized, open-label trial which evaluated in an open-label, multi-center, randomized (1:1) study conducted in Europe, which enrolled a total of 463 patients. Patients were required to have progressed on or following treatment with a regimen(s) containing a fluoropyrimidine, oxaliplatin, and irinotecan; this was confirmed by an independent review committee (IRC) for 75% of the patients. In addition, all patients were required to have EGFR expression defined as at least 1+ membrane staining in tumor cells by the

DakoCytomation EGFR pharmDx® test kit.

The primary objective of the trial was progression-free survival, with secondary endpoints of estimation of objective response rate, response duration, overall survival and toxicity profile. The primary analyses of progression-free survival (PFS), objective response, and response duration were based on events confirmed by the independent review committee (IRC) composed of a panel of radiologists and a medical oncologist who were masked to treatment assignment.

Based upon IRC determination of disease progression, a statistically significant prolongation in PFS was observed in patients receiving Vectibix compared to those receiving BSC alone ($p<0.001$, stratified log-rank test) . The mean PFS was 96 days (13.8 weeks) in the Vectibix arm and 60 days (8.5 weeks) in the BSC arm. There were 19 partial responses identified by the IRC in patients randomized to Vectibix for an overall response of 8% (95% CI: 5.0%, 12.6%). No patient in the control arm had an objective response identified by the IRC. The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks).

There was no difference in overall survival observed between the study arms. Of the 232 patients randomized to BSC, 75% of patients crossed over to receive Vectibix following investigator determination of disease progression; the median time to cross over was 8.4 weeks (0.3–26.4 weeks).

The regimen of 5-fluorouracil and leucovorin was the standard treatment for patients with advanced colorectal cancer in the early 1990s. In June 1996, irinotecan received accelerated approval for the treatment of recurrent or progressive colorectal carcinoma following 5-FU therapy. Approval was based on objective tumor response documented in 12.5% of the 304 patients treated with irinotecan in three phase II studies. Conversion to regular approval was granted in October 1998, based on two large, randomized phase 3 studies that showed evidence of a survival advantage.

In August 2002, oxaliplatin in combination with 5-FU/LV received accelerated approval for the treatment of metastatic colorectal patients who recurred or progressed after 5-FU/LV and irinotecan therapy. Later, oxaliplatin in combination with infusional 5-FU/LV received approval for the initial treatment of advanced colorectal cancer on January 9, 2004. Safety and efficacy were demonstrated in one multi-center, randomized controlled clinical trial.

2.3 Availability of Proposed Active Ingredient in the United States

Currently, cetuximab is FDA approved for use in combination with irinotecan for the treatment of patients with EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Also, cetuximab is indicated for use as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

In addition, cetuximab, in combination with radiotherapy, is indicated for the treatment of

locally or regionally advanced squamous cell carcinoma of the head and neck region.

2.4 Important Issues with Pharmacologically Related Products

Panitumumab (Vectibix) is a fully human monoclonal antibody that is also directed against EGFR. Similar to the side effect profile of Erbitux, the most common premarketing adverse events seen with Vectibix monotherapy were skin rash, hypomagnesemia, paronychia, fatigue, abdominal pain and diarrhea. The most serious adverse events were pulmonary fibrosis, dermatologic toxicity complicated by infection and death, infusion reactions, abdominal pain, nausea and diarrhea.

On March 22, 2007, Amgen[2] announced the decision to discontinue Vectibix treatment in the PACCE trial, a trial evaluating the addition of Vectibix to standard chemotherapy and Avastin (bevacizumab) for the treatment of first-line metastatic colorectal cancer (mCRC). This decision was based on a preliminary review of data from a pre-planned interim efficacy analysis scheduled after the first 231 events (death or disease progression). This analysis revealed a statistically significant difference in progression-free survival in favor of the control arm. An unplanned analysis of overall survival also demonstrated a statistically significant difference favoring the control arm. A review of the interim analysis showed an increased incidence of grade 3 severe events of diarrhea, dehydration and infections in the Vectibix-treated patients. In addition, an increased incidence of pulmonary embolism was observed in patients who received Vectibix compared with those who did not (4 percent and 2 percent, respectively). One (<1 percent) fatal event of pulmonary embolism occurred in a patient receiving Vectibix.

Because Erbitux is a related molecular entity (monoclonal antibody) directed against the same target (EGFR), the safety and efficacy of adding Cetuximab to standard chemotherapy, the findings of the PACCE trial should be considered relevant background information in evaluating the safety and effectiveness of this product class. As reported in the EPIC trial (CA225006), Cetuximab, when added to irinotecan, failed to improve OS over irinotecan alone in the second-line treatment of mCRC.[3] Patients in the Erbitux plus irinotecan arm experienced more adverse events, including diarrhea, fatigue, rash, and infusion reactions than those receiving irinotecan alone. Superiority of cetuximab administered in combination with chemotherapy over chemotherapy alone, in terms of OS is yet to be proven.

2.5 Presubmission Regulatory Activity

- IND 5804 for Cetuximab was filed on October 18, 1994.

[2] http://wwwext.amgen.com/media/media_pr_detail.jsp?year=2007&releaseID=977186
[3] Goldberg RM, Hecht JR. Randomized phase III trial of cetuximab plus irinotecan versus irinotecan alone for metastatic colon cancer in patients who have failed prior oxaliplatin-based therapy: The EPIC trial. Highlights Newsletter from AACR; April 30, 2007; p4-7.

- On February 12, 2004 Cetuximab was granted accelerated approval for metastatic colorectal cancer in combination with irinotecan for patients refractory to irinotecan-based chemotherapy and as a single-agent in patients intolerant to irinotecan, based on the surrogate endpoint of durable objective responses in patients with an unmet medical need. Approval was contingent upon verification of clinical benefit (improvement in overall survival) in the following studies, as required postmarketing commitments (PMCs):
  - CA225006 (EPIC), "A Phase III Randomized, Open-label, Multicenter Study of Irinotecan and Cetuximab versus Irinotecan as Second-line Treatment in Patients with Metastatic, EGFR-positive Colorectal Carcinoma."
  - (b) (4) , "A Phase III, randomized, Multicenter Study of Cetuximab, Oxaliplatin, 5-FU, and Leucovorin versus Oxaliplatin, 5-FU, and Leucovorin in Patients with Previously Treated Metastatic EGFR-Positive Colorectal Carcinoma."

- On December 13, 2006 a meeting was held between ImClone Systems Inc. and the Division of Biologic Oncology Products, CDER for the agency to discuss studies CA225025 (b) (4) and the PMC pertaining to CA225006.

Table 5. Confirmatory Trials for Cetuximab

	EXPLORE, CA225014	EPIC, CA225006
Phase, Design	III, randomized 1:1	III, randomized 1:1
Accrual Goals	1100	1300
Treatment	Cetuximab + FOLFOX	Cetuximab + Irinotecan
Control	FOLFOX	Irinotecan
1° Endpoint	OS	OS
Outcome	Closed prematurely; no conclusions can be drawn regarding efficacy	No effect on OS demonstrated

- The first study, EXPLORE (CA225014), was a randomized study of FOLFOX +/- cetuximab for first-line treatment of mCRC. Post-approval, accrual to EXPLORE was poor, and the trial was closed after only 102 patients of a planned 1100 were enrolled.

- The second study, EPIC (CA225006), was a randomized study of irinotecan +/- cetuximab in a second-line treatment of metastatic colorectal cancer. The study completed accrual and was analyzed in April 2007. Overall survival, the primary endpoint, was not significantly different between the study arms (Table 6). Investigators postulated that crossover of almost half (47%) of patients in the irinotecan-only arm to cetuximab confounded the efficacy analysis.[4]

[4] Goldberg RM, Hecht JR. Randomized phase III trial of cetuximab plus irinotecan vs irinotecan alone for metastatic colon cancer in patients who have failed prior oxaliplatin-based therapy: The EPIC trial. Highlights Newsletter from AACR; April 30, 2007; p5.

Table 6. EPIC (CA225006) Reported Trial Results

Regimen	N	Primary Endpoint	Key Secondary efficacy endpoints	
		Median Overall Survival (months)	Response Rate	Median PFS (months)
Irinotecan	629	9.99	4%	2.56
Cetuximab + Irinotecan	638	10.71	16%	3.98

- In June 2006, ImClone requested a Type C meeting to discuss submission of the continued development program for Erbitux in the metastatic colorectal cancer and their intent to utilize the results of CA225025. The meeting was cancelled by ImClone upon receipt of FDA's draft responses on August 31, 2006, which contained FDA's responses to ImClone's questions and FDA's requests for additional information. FDA noted that the CA225025 trial was not conducted under the US IND and was first identified as part of the development program in June 2006. In response to the August 31, 2006 communication, the clinical protocol for CA225025 was submitted in Oct. 2006.

- On December 13, 2006 a meeting was held between ImClone Systems Inc and the Division of Biologic Oncology Products, CDER for the agency to discuss the results of studies CA225025 (b) (4) and the PMC pertaining to CA225006.

Excerpts from meeting on cetuximab – December 13, 2006

1. *In light of the statistically significant effect on overall survival with Erbitux in the refractory metastatic colorectal cancer patient population enrolled into study CA225025, does FDA agree that the submission of a study report for this study could satisfy the requirement for a demonstration of clinical benefit with Erbitux treatment in the setting of metastatic colorectal cancer and that the study could therefore be considered to address the relevant post-marketing commitment leading to approval of Erbitux for colorectal cancer?*

   FDA Response:
   Results from the CA225025 study would support regular approval for the use of Erbitux monotherapy as third line therapy for metastatic colorectal cancer.

   (b) (4)

   Discussion: (b) (4) s

   Results from CA225025 would (b) (4) support conversion to regular approval of Erbitux administered as a single agent. (b) (4)

(b) (4)

FDA asked for an update on the status of the CRYSTAL study. The CRYSTAL study is a Phase 3 study of Erbitux plus FOLFIRI vs. FOLFIRI alone in patients with previously untreated colorectal cancer. The primary endpoint is progression-free survival (PFS) as determined by an independent review committee. The trial is powered to examine overall survival. ImClone stated that this trial is almost completed and asked if a positive PFS result from the CRYSTAL study would support conversion of Erbitux plus chemotherapy to regular approval. Dr. Pai-Scherf stated that this matter will be the subject of further internal discussion and the decision will be communicated to ImClone at a later time.

FDA recommended that ImClone submit a meeting request to discuss the results of the CRYSTAL study. (b) (4)

(b) (4)

2. *The CA225025 study provides important new information on the efficacy of Erbitux as monotherapy in patients whose disease had progressed after both oxaliplatin and irinotecan containing therapies. Does FDA agree that the data from this study could form the basis for an efficacy supplement?*

FDA Response:

We note that the CA225025 protocol was first submitted to the FDA on October 16, 2006, after results of the study had been analyzed. Assuming that the FDA determines that CA225025 is a well designed and well conducted study, yes.

Discussion: ImClone stated that the protocol and analysis plan for the CA225025 study were submitted prior to the data lock and data analysis. ImClone plans to submit a sBLA for this study by the end of March 2007. FDA asked that ImClone submit a proposed Table of Contents for the proposed sBLA as soon as possible.

In response to FDA questions, regarding the CA225005 study, ImClone stated that the study was conducted in New Zealand, Canada, and Australia. Both arms of the trial had equal data collection. They also collected data on duration of response, subsequent therapy after progression, and the number of cross-overs and will include this data in the sBLA. In addition to CA225005, the sBLA will contain supporting data from the following single arm, Phase 2 monotherapy studies:

Study 045 (n=110) safety and efficacy data will be submitted
Study 041 (n=742) limited safety data will be submitted
Study 0144 (n=346) safety and efficacy data will be submitted

3. *If the answer to question #2 is positive, would the FDA agree that the following claim could be supported by data from study CA225025:*

(b) (4)

FDA Response:

Data from study CA225025 could support the following claim:

(b) (4)

2.6 Other Relevant Background Information

As of May 9, 2007 cetuximab in combination with irinotecan is approved in 63 countries outside the United States for the treatment of patients with metastatic colorectal cancer and in 23 countries outside the United States as a single agent in patients with metastatic colorectal cancer, which has progressed after irinotecan. Cetuximab in combination with radiation therapy is approved in 54 countries outside the United States for treatment of patients with locally/regionally advanced SCCHN. Cetuximab as a single agent is approved in 13 countries outside the United States for use in patients with recurrent/metastatic SCCHN after platinum failure.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

With this efficacy supplement, no changes to the product have been made by the sponsor. The product has been reviewed and previously found acceptable by the FDA.

3.2 Animal Pharmacology/Toxicology

No animal pharmacology toxicology studies were submitted with this efficacy supplement.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary data submitted by ImClone Systems Inc. were based on the single randomized clinical study (trial CA225025), sponsored by the (b) (4) conducted in Canada, Australia, New Zealand and Singapore. Primary data sets in electronic format, the final Clinical Study Report, and all patient Case Report Forms (CRFs) and case narratives for those patients who died, discontinued due to adverse events or who experienced a serious adverse event other than disease progression from this study were submitted.

For trials CA225041, CA225045, and CP02-0144, safety data are available only from the final CSRs, which are included with this supplement. ImClone was the sponsor of CP02-0144, conducted by 40 investigators in the US and Belgium. Bristol-Myers Squibb was the sponsor for studies CA225041 and CA225045.

(b) (4)

4.2 Tables of Clinical Studies

The studies described in this submission are delineated in Table 7. Data sets are submitted with this supplement only for CA225025. Final Clinical Study Reports with the Sponsor's summaries for safety are provided for remaining three studies.

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Table 7. Table of Clinical Studies

Study	Title	No. of Patients
	Efficacy and Safety data	
CA225025	A Phase III Randomized Study of Cetuximab and Best Supportive Care (BSC) versus BSC in Patients with Pretreated metastatic EGFR-positive Colorectal Carcinoma	572 (287/285)
	Final Clinical Study Reports	
CA225041	Anti-epidermal Growth Factor Antibody, Cetuximab, in Patients with Stage IV Colorectal Carcinoma who Failed All Standard Therapy: an Access Protocol	742
CA225045	An Exploratory Pharmacogenomic Study of Erbitux Monotherapy in Patients with Metastatic Colorectal Carcinoma	110
CP02-0144	A Phase II Multicenter Study of Erbitux in Patients with Metastatic Colorectal Carcinoma	346*

*Interim results of the first 252 patients in Study CP02-0144 reviewed under BL STN 125084/1.

4.3 Review Strategy

The clinical review was primarily focused on the efficacy and safety data submitted for the randomized trial CA225025 because complete information including patient level data were provided in an electronic format. Additional data (in the form of final CSRs) from the three single arm studies were reviewed, however due to lack of patient-level primary data, reliance on such studies was limited to summary safety results. Summary information regarding efficacy from Study CA225006 were considered in the evaluation of this supplement. (b) (4) The assessment of this data was limited because patient-level data were not provided electronically.

4.4 Data Quality and Integrity

The protocol amendments and subject informed consent received approval by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to initiation of study at the site. CRFs were completed by site personnel and were reviewed, signed, and dated by an investigator or subinvestigator. Data were entered and stored in the NCIC database. At the time of the database lock, the NCIC transferred the datasets to BMS for the analysis. Representatives of NCIC CTG, AGITG, and BMS or their designees visited all study site locations periodically to assess the data, quality and study integrity. In addition, the study was evaluated by BMS internal auditors and Health Canada inspectors. The NCIC CTG Data Safety Monitoring Committee, an independent group of experts, reviewed the safety data every 6 months throughout the study.

The Division of Scientific Investigation (DSI) was asked to audit selected investigational sites to assess data quality and integrity. Goals of the inspections were to verify that the clinical trial was well conducted and that the data submitted by the clinical investigators could be used in support of approval of the application. Sites were selected on the basis of larger enrollment. See Table 8.

Table 8. Sites Selected for Inspection by DSI

Site # (Name, Address, Phone number)	Protocol #	Number of Subjects	Indication
Site #013 Derek Jonker Ottawa Regional Cancer Centre 503 Smyth Road Ottawa, Ontario Canada K1H 1C4 613-737-7700 X-6029	CA225-025	34	metastatic colorectal cancer
Site #029 Malcolm Moore Princess Margaret Hospital University Health Network 610 University Avenue Toronto, Ontario Canada M5G 2M9 416-946-2263	CA225-025	41	metastatic colorectal cancer

The field inspectors audited all study records for subjects enrolled at each of these sites. As stated in Dr. J. Lloyd Johnson's investigation, "there were no reported limitations of inspection. It appeared that sufficient documentation to assure that all study subjects audited did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements. In summary, the submitted data from the sites inspected appeared acceptable" (see Appendix 5), and no action was indicated for either inspection site.

4.5 Compliance with Good Clinical Practices

The applicant asserted that all studies were performed in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50. Further, the studies were conducted in accordance with the ethical principles in the Declaration of Helsinki. The protocols, amendments, and subject informed consent received appropriate approval by the Institutional Review Board/Independent Ethics Committee prior to initiation of study at the site.

4.6 Financial Disclosures

ImClone submitted a completed FDA Form 3454, certifying the financial interests and arrangements of clinical investigators (Appendix 10.6). For Study CA225025, a list of all 61 clinical investigators with potentially disclosable information was provided. Of the 57 responding investigators, none reported arrangement or financial interests to disclose. Four investigators provided no responses, despite diligent Sponsor efforts (see Table 9, copied from Sponsor's submission). None of these four investigators registered patients or participated as a principal investigator, which suggests a lack of potential bias. Yet, no information is provided regarding the numbers of randomized patients who may have received direct medical by these 4 investigators.

Table 9. Outstanding Financial Disclosures, Protocol CA225025

Investigator Name (Principal Investigator name bolded)	Protocol/Site Number	Participated as Principal Investigator (Yes/No)	Patients Enrolled at the Site	Patients Enrolled by the Individual	Comments/Status
(b) (6)		NO	(b) (6)	NO	In ESF there is a File Note: Site replied that D(b) (6) is a (b) (6) and that th(b) (6) don't sign financial disclosures as they are considered consultants.
		NO		NO	In ESF there is a File Note: Dr(b) (6) ceased employment with cente(b) (6) 5. Letter and form sent to D(b) (6)'s forwarding address 10/02/2005. No reply from Dr.(b) (6) regarding this matter. 08/03/2006.
		NO		NO	In ESF there is a File Note: On 4/18/2005 NCIC CTG sent a memo to all investigators advising them to complete the new financial disclosure form. On 01/19/2006 responses were reviewed. Multiple email and phone contacts were made in an attempt to obtain all outstanding documents. On 05/15/2006(b) (6) e advised to complete a note to file. As of 08/11/2006, updated financial disclosures were not received for D(b) (6).
		NO		NO	In ESF there is a File Note: On 4/18/2005 NCIC CTG sent a memo to all investigators advising them to complete the new financial disclosure form. On 01/19/2006 responses were reviewed. Multiple email and phone contacts were made in an attempt to obtain all outstanding documents. On 05/15/2006(b) (6) ce advised to complete a note to file. As of 08/11/2006, updated financial disclosures were not received for Dr(b) (6).

In addition, there were 66 other investigators who participated in studies CA225041, CA225045, and CP02-0144. Three of these investigators (in CA225041 and CA225045) provided disclosable information, and four others provided no responses. Because these three single arm studies were not submitted to support labeling changes for indication, investigator bias based on financial influence will not impact efficacy analysis. Therefore, I do not believe potential study bias (within trials CA225041, CA225045, and CP02-0144) can have any impact on efficacy and safety claims that support the changes to the current cetuximab label.

5. CLINICAL PHARMACOLOGY

Pharmacokinetic and pharmacodynamic studies were not conducted during the clinical studies in this sBLA.

5.1 Pharmacokinetics

Pharmacokinetic and pharmacodynamic studies were not conducted during the clinical studies in this sBLA. Although the clinical protocol for Study CA225041 was amended to collect pharmacokinetic data in patients enrolled in US sites with renal and/or hepatic impairment, the study report states that such data were collected only for a single patient.

5.2 Pharmacodynamics

Pharmacokinetic and pharmacodynamic studies were not conducted during the clinical studies in this sBLA.

5.3 Exposure-Response Relationships

Study CA225025 was not designed to assess exposure-response relationships. Study CA225045 was designed to assess such affects however only summary data were provided, FDA review of such data were therefore limited in scope.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The current indication for use of cetuximab in colorectal cancer is as follows:

> Cetuximab, in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Cetuximab administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

Approval is sought for cetuximab for the following indication, (copied from Applicant's submitted proposed label):

(b) (4)

6.1.1 Methods

Efficacy review is focused on data submitted for study CA225025, because no data sets

were provided for the other 3 studies. In CA225025, the primary endpoint, overall survival, was compared between best supportive care and cetuximab plus best supportive care treatment groups.

The sponsor performed a sensitivity analysis for PFS by considering patients who received other anti-cancer chemotherapy as PFS events. In addition to the Applicant's SAP, Dr. Kyung Lee performed OS sensitivity analyses by (1) excluding patients who had protocol violations, and (2) using patients lost to follow-up. Primary and secondary endpoint results were not significantly different in these analyses.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for Study CA225025 was duration of survival. Overall survival (OS) is an accepted direct measure of benefit, and has the advantages of being easily and precisely measured. The ImClone statistical analysis plan included progression-free survival and objective response rate as secondary efficacy endpoints.

In addition, there were secondary objectives comparing quality of life (QOL), health utilization, and economic evaluation between study arms. No primary data were provided for these endpoints. Also note, the instrument to collect QOL information has not been prospectively validated. No labeling claims were proposed for these endpoints.

6.1.3 Study Design

Study CA225025 Protocol Title: "A Phase III Randomized Study of Cetuximab (Erbitux) and Best Supportive Care versus Best Supportive Care in Patients with Pretreated Metastatic Epidermal Growth Factor Receptor (EGFR)-Positive Colorectal Carcinoma"

Study sites: The study was conducted at 58 sites in Canada, Australia and New Zealand.

Study period: Study initiation date: August 28, 2003
Study completion date: March 6, 2006

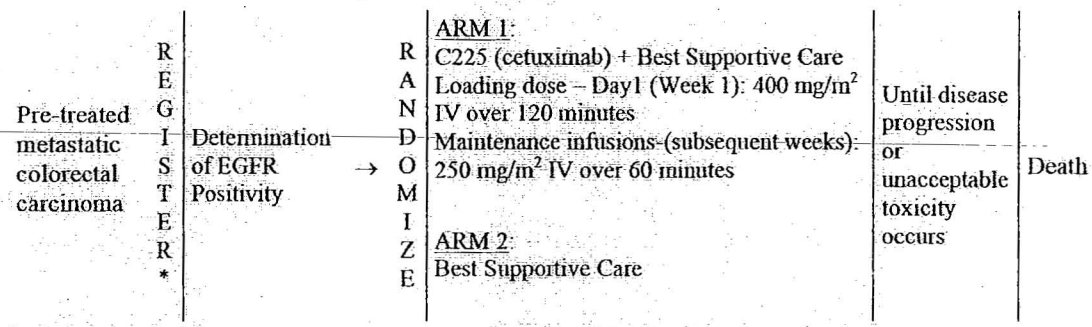
Objectives:
Primary: To assess whether cetuximab plus best supportive care (BSC) improves overall survival (OS) compared with BSC alone as third line therapy in subjects with metastatic colorectal cancer.

Secondary: To assess time to progression (TTP), objective response and safety of patients treated with cetuximab plus BSC compared with BSC alone as third line therapy in subjects with metastatic colorectal cancer.

Study design: This was a multi-centre, prospective, open-label, randomized phase III trial of cetuximab plus best supportive care (BSC) versus best supportive care alone (where BSC is defined as those measures designed to provide palliation of symptoms and improve quality of life as much as possible) in patients with pre-treated metastatic EGFR-positive colorectal carcinoma. Patients were stratified by

ECOG performance status (0 or 1 versus 2) and by center. The overall study design is summarized in Figure 1.

Figure 1. Design of Trial CA225025



* prior to submission to the reference laboratory of representative slides of the diagnostic tumour tissue for EGFR testing

Study population:

Inclusion criteria:

- EGFR positivity of representative samples of diagnostic tumor tissue by immunohistochemistry, performed by reference laboratory.
- Received a prior thymidylate synthase inhibitor for adjuvant and/or metastatic disease, which may have been given in combination with oxaliplatin or irinotecan.
- Received and failed an irinotecan (CPT-11)-containing regimen (single-agent or in combination) for treatment of metastatic disease, OR relapsed within 6 months of completion of an irinotecan-containing adjuvant therapy, OR have documented unsuitability for an irinotecan-containing regimen. Failure was defined as either progression of disease (clinical or radiologic) or intolerance to the irinotecan-containing regimen.
- Received and failed an oxaliplatin-containing regimen (single-agent or in combination) for treatment of metastatic disease, OR relapsed within 6 months of completion of an oxaliplatin-containing adjuvant therapy OR have documented unsuitability for an oxaliplatin-containing regimen. Failure was defined as either progression of disease (clinical or radiological) or intolerance to the oxaliplatin-containing regimen.
- Measurable or evaluable disease.
- The only remaining standard available therapy as recommended by the Investigator was best supportive care.
- Adequately recovered from recent surgery, chemotherapy and/or radiation therapy. At least 4 weeks must have elapsed from major surgery, prior chemotherapy, and prior treatment with an investigational agent or prior radiation therapy.
- ECOG performance status of 0, 1 or 2.
- Imaging investigations including chest x-ray and CT/MRI of abdomen/pelvis or other scans as necessary to document all sites of disease done within 28 days prior to randomization.
- ECG done within 28 days prior to randomization.
- Hematology done within 14 days prior to randomization and with initial values

within the ranges specified: absolute granulocyte count > 1.5 x 10^9/L, platelets > 75 x 10^9/L, hemoglobin > 80 g/L

- Biochemistry done within 14 days prior to randomization and with initial values within the ranges specified: total bilirubin < 2.5 x upper limit of normal (ULN), ALT < 5.0 x ULN, AST < 5.0 x ULN, serum creatinine < 1.5 x ULN
- Age > 16 years.
- Women of child bearing potential must have a negative serum or urine pregnancy test within 72 hours prior to randomization.
- Patient consent
- Protocol treatment was to begin within 2 working days of patient randomization.
- No concurrent enrollment in a clinical study.

Exclusion criteria:

- History of other malignancies.
- Women who are pregnant or breastfeeding.
- Any active pathological condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy.
- Any condition (e.g. psychological, geographical, etc.) that would not permit compliance with the protocol.
- History of uncontrolled angina, arrhythmias, cardiomyopathy, congestive heart failure, or documented myocardial infarction within the 6 months preceding registration
- Symptomatic metastases in the central nervous system.
- Prior cetuximab or other therapy which targets the epidermal growth factor receptor pathway (for example, Tarceva or Iressa).
- Prior murine monoclonal antibody therapy (for example, Edrecolomab).
- Severe restrictive lung disease or radiological pulmonary findings of interstitial lung disease on the baseline chest x-ray
- Receipt of an experimental therapeutic agent within the past 30 days.

Randomization: Eligible patients were randomized in a ratio of 1:1 to receive cetuximab plus BSC or BSC alone. Randomizations were performed centrally by the NCIC CTG for Canadian sites and by AGITG for all other sites. At the time of randomization, confirmation of EGFR positivity from a reference laboratory was required.

Treatment plan: All patients received best supportive care (BSC defined as those measures designed to provide palliation of symptoms and improve quality of life). Permitted interventions included medications such as antibiotics, analgesics, antihistamines, steroids, G-CSF, erythropoietin, procedures (e.g., paracentesis, thoracentesis), or blood products. Cetuximab was administered weekly until there was evidence of progressive disease or unacceptable toxicity.

Table 10. Treatments per Arm

Arm	Agent(s)	Dose	Route	Duration	Schedule
1	Cetuximab	400 mg/m^2 250 mg/m^2	IV	120 min 60 min	day 1 weekly
2	Best supportive care	N/A	N/A	N/A	N/A
• The infusion rate of cetuximab should never exceed 10 mg/minute (5 mL/min). • BSA should be recalculated prior to every 4th dose and /or if there is a weight change of >5%.					

Premedication (Arm 1): All patients were premedicated with anti-histamine (50 mg diphenhydramine or equivalent IV antihistamine) 30-60 minutes prior to cetuximab dose. Premedication was mandatory prior to all doses of cetuximab, although may be reduced beyond the tenth week of therapy at the investigator's discretion.

Dose modification and delay: Cetuximab was to be interrupted, delayed, or dose reduced for toxicities. Dose adjustments were made according to the greatest grade of toxicity, using the NCI Common Toxicity Criteria Version 2.0. Dose reductions due to unacceptable toxicity are defined in Table 11. Definitions of unacceptable toxicities are further clarified in Tables 11, 12, and 13.

Table 11. Dose Reduction Scheme

Starting Dose	First Dose Reduction Level	Second Dose Reduction Level
Loading dose (day1) of 400 mg/m^2 Maintenance infusions - weekly dose of 250 mg/m^2	weekly dose of 200 mg/m^2	weekly dose of 150 mg/m^2

There will be no dose level reductions below a weekly dose of 150 mg/m^2. Cetuximab dose reductions were *permanent*; there were no re-escalations of dose.

Following dose delays, patients may be resumed if: 1) they have not had a toxicity requiring that they be discontinued from cetuximab therapy 2) treatment-related toxicity has resolved to baseline or to Grade 0 – 1 (except Grade 2 alopecia or fatigue, acne-like rash, or paronychia). 3) Cetuximab has not been omitted for more than four consecutive infusions.

Non-hematologic Toxicity (Arm 1): Guidelines for dose modification for non-hematological toxicity (with the exception of acne-like rash and allergic reaction/hypersensitivity) may be found in Appendix 10.7. Dose alterations for dermatologic toxicities are summarized in Appendix 10.8. Dose alterations for hypersensitivity/infusional toxicities are summarized in Appendix 10.9.

Study schedule: Study schedules reproduced from the original protocol may be found in Appendices 10.3 and 10.4.
Comment: Toxicity assessments were done weekly in the cetuximab arm compared to monthly in the BSC arm. This schedule difference could potentially lead to reporting bias.

Statistical considerations (copied from protocol): Overall survival, the primary endpoint of this study, was defined as the time from randomization to the time of death from any cause. Patients who were alive at the time of the final analysis or who became lost to follow-up were to be censored at their last contact date. Patients were analyzed in the arms to which they are allocated regardless of whether they receive the assigned treatment (intention-to-treat). The survival experience of patients in both treatment groups were described by the Kaplan-Meier method. A stratified log-rank test adjusting for the following stratification factors (ECOG performance status (0 or 1 versus 2)) was used as the primary method to compare the overall survival between arms. All patients who have at least one objective tumor assessment after baseline will be considered evaluable for response. RECIST criteria were used for tumor response evaluation. Response duration was measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented or death occurs.

For safety analyses, patients will be evaluable for toxicity from the time of their first treatment with cetuximab. Adverse events and other symptoms will be graded according to the NCI CTCAE Version 2.0. A Fisher's exact test will be used as needed to compare toxicities between arms.

Time to progression (TTP) was defined as the time from randomization to the first observation of disease progression or death due to any cause. If a patient had progressed or died at the time of final analysis, TTP was censored on the date of the last disease assessment. All analyses for survival were performed for TTP, using similar methodology. The objective response rate was estimated as the proportion of response evaluable patients that met the criteria of partial or complete response. A Cochran-Mantel-Haenszel test adjusting the ECOG performance status (0 or 1 versus 2) at the time of randomization was used to compare the objective response rates between arms.

Sample Size and Duration of Study: The 1-year survival of the patients treated by BSC was estimated to be 16.2% for the 75% patients with ECOG performance status (PS) 0 or 1 and 7.9% for the 25% patients with ECOG PS 2. The overall 1-year survival for all the patients on the BSC arm of this trial was estimated to be 14.1%. To have 90% power to detect a hazards ratio of 1.36 between two treatment arms, which corresponds to 9.6% improvement in 1-year survival with the addition of cetuximab for all the patients (and respectively 10% for patients with PS 0 or 1 and 7.6% for patients with PS 2), using a two-sided 5% level test, 445 deaths should occur before the final analysis. Therefore, the total sample size for this study was estimated to be 500 (250/arm).

Amendments to protocol: Important modifications from amendments to the protocol are summarized in Table 12 on the following page.

Table 12. Amendments to Protocol CA225025

Version	Date	Modifications
0	April 2, 2003	Original protocol
1	June 12, 2003	• numerous typographical errors and ambiguities corrected
2	July 29, 2003	• eligibility criteria clarified: no concurrent clinical study participation allowed • pulmonary function tests (spirometry) required at baseline and progression • central radiology review is to be blind to study group assignment
3	May 17, 2004	• increase in eligibility thresholds for ALT, AST and bilirubin • remove requirements for assessment of pulmonary function at baseline and throughout the study for all patients • cessation of immunogenicity testing • change in frequency of pregnancy testing in women of child-bearing potential from weekly to monthly • permit pre-randomization CT/MRI scan of chest in place of CXR • addition of delayed drug fever adverse event classification and dose adjustment actions • update the list of study contacts • change of central laboratory undertaking EGFR testing • include specific recommendation regarding sun exposure
4	Feb 1, 2005	• updates to the informed consent, EGFR screening and tissue banking consent

6.1.4 Efficacy Findings

A total of 1243 subjects were allowed to register (enroll) to this study. Some patients (still on prior antineoplastic therapy regimens) registered months prior to randomization. Of the registered patients, 262 (21%) were found to have EGFR negative tumors upon central review, and were thus excluded from randomization. Ultimately, 572 subjects were randomized in 1:1 ratio. The efficacy population (for ITT analysis) is comprised of 287 patients randomized to the cetuximab arm and 285 patients randomized to BSC. The submission does not detail the reasons for exclusion from randomization of the other 409 registered patients. Figure 4 illustrates the disposition and treatment of randomized patients.

The randomized ITT population in CA225025 was fairly balanced between arms with respect to metastatic sites, prior chemotherapy and number of prior chemotherapeutic regimens (Table 13 on the following page).

Table 13. Trial CA225025 Patient Characteristics

	Erbitux + BSC (%)* n = 287	BSC (%) n = 285	Total (%) n = 572
Metastatic sites			
Liver	75	77	76
Lung	45	43	44
Lymph nodes	31	25	28
Abdomen	8	8	8
Prior chemotherapy			
5-FU or equivalent	100	100	100
oxaliplatin	97.9	97.5	97.7
irinotecan	96.5	95.8	96.2
Prior chemo regimens			
1	0.7	1.4	1.0
2	17	18	17
3	38	38	38
4	30	25	28
5 or more	14	17	16

Histopathology was centrally reviewed, and EGFR expression was also well-balanced between the study arms (Table 14). The DakoCytomation EGFR pharmDx™ test kit was used to assay samples.

Table 14. EGFR Expression Intensity, Trial CA225025

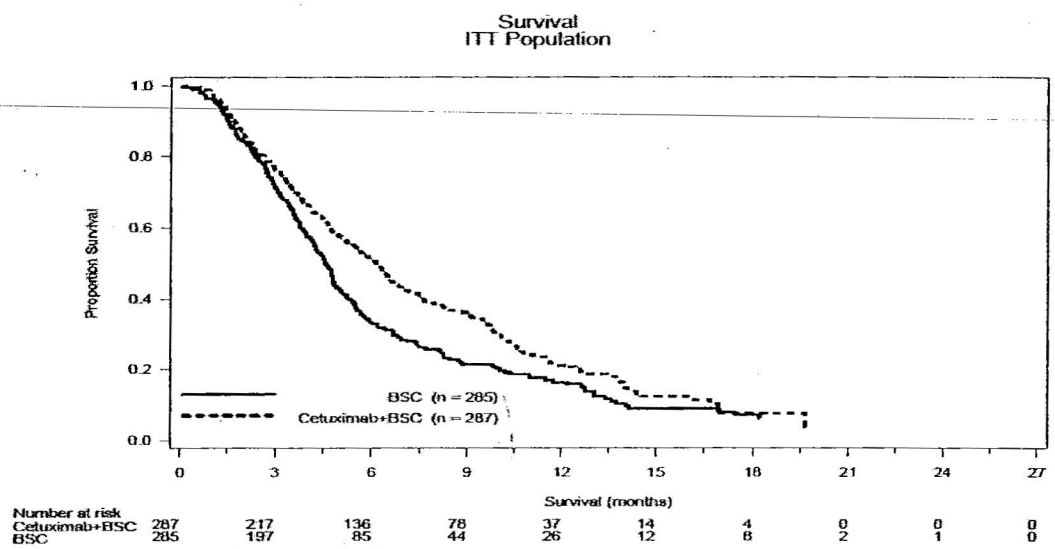
Maximum Staining Intensity	Erbitux + BSC (%) n = 287	BSC (%) n = 285	Total (%) n = 572
Missing	9.4	8.8	9.1
Weak (1+)	59.2	55.4	57.3
Moderate (2+)	26.1	28.4	27.3
Strong (3+)	5.2	7.4	6.3

Of note, approximately 9% of patient samples have missing staining intensity information. The Applicant has stated that BMS originally contracted with (b) (4) to perform the EGFR testing. After (b) (4), BMS then contracted with (b) (4) to assume testing, following the same methods and criteria previously used by (b) (4) for data consistency. Unfortunately, BMS experienced performance issues with (b) (4). Specifically, it was noted that staining intensity had not been documented on the form used to collect results, although EGFR positivity had been confirmed. BMS could not get resolution of this missing data issue. Thus, BMS changed to yet another facility, (b) (4), to complete the EGFR testing. The samples from 54 patients who have missing EGFR staining intensity were all tested by (b) (4), who did not document the data on the form.

Cetuximab plus best supportive care (BSC) demonstrated superior overall survival (OS) when compared with BSC in study CA225025 (p=.0048 by stratified log-rank test, using stratification factors of center and ECOG PS). Median duration of overall survival was

6.14 months (95% CI: 5.36, 6.70) for the cetuximab arm and 4.57 (95% CI: 4.21, 4.86) months for the BSC arm. The hazard ratio was 0.77(95% CI: 0.64, 0.92).

Figure 2. Kaplan-Meier Curve for Overall Survival



Of the 1243 patients registered for potential randomization, 262 (21%) were found to have EGRF negative tumors. EGFR expression was not correlated with efficacy in subgroup analysis, although the number of specimens with 3+ staining was low, possibly impacting statistical findings. Fifty-four subjects had missing EGFR staining intensity as described above.

Table 15. Overall Survival (in months) by EGFR Intensity

EGFR Intensity	Cetuximab+BSC (n) N=260	BSC (n) N=260	Hazard Ratio (95% CI)
1+	6.24 (170)	4.76 (158)	0.83 (0.61, 1.14)
2+	5.65 (75)	4.47 (81)	0.71 (0.50, 1.01)
3+	6.34 (15)	3.61 (21)	0.63 (0.29, 1.37)

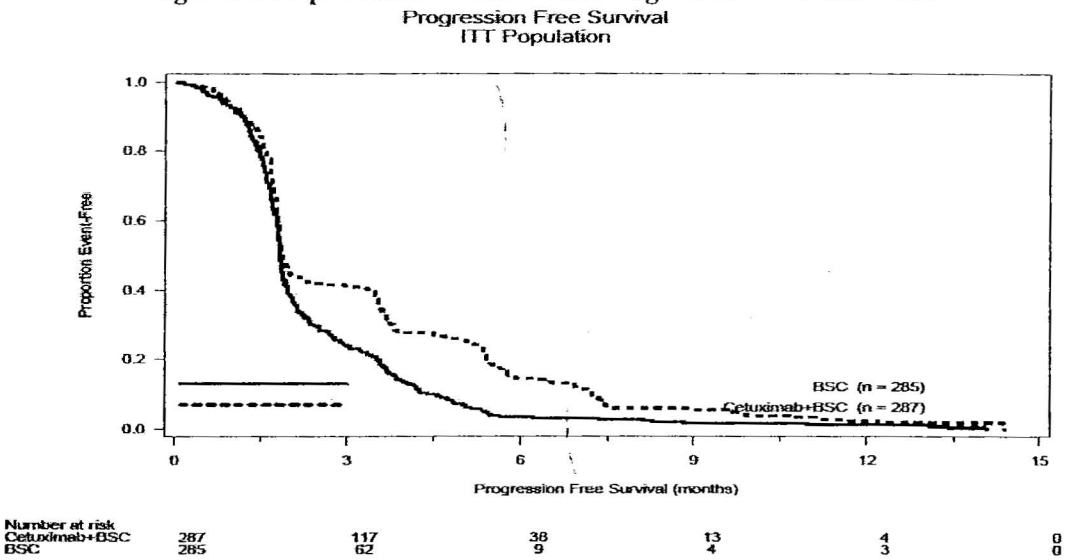
The cetuximab arm also demonstrated superior PFS over BSC ($p<0.0001$ by stratified log-rank test)). The median duration of PFS was not *clinically* relevant between groups: 1.91 months (95% CI: 1.84, 2.07) for cetuximab versus 1.84 months (95% CI: 1.81, 1.91) for BSC, a difference of 0.07 months (~2 days). The hazard ratio was 0.68 (95% CI 0.57, 0.81).

The Applicant performed a sensitivity analysis for PFS, subsequently confirmed by Dr. Kyung Lee, in which patients were censored at the time of alternative therapies taken prior to progression. This analysis still reveals a significant difference in PFS between arms (Table 16). The hazard ratio of cetuximab+BSC to BSC alone was 0.58 (95% CI: 0.49, 0.69) and stratified log rank P-value was highly statically significant.

Table 16. PFS Sensitivity Analysis

	Cetuximab + BSC N = 287	BSC N = 285
Number of patients with PFS event	273 (95.1%)	270 (94.7%)
Number of patients without PFS event	14 (4.9%)	15 (5.3%)
Median duration of PFS in months (95% CI)	1.9 (1.8, 2.1)	1.8 (1.8, 1.8)
Hazard Radio (95% CI)	0.58 (0.49, 0.69)	
Stratified P-value (log-rank test)	< 0.0001	

Figure 3. Kaplan-Meier Curve for Progression-Free Survival



The objective response rate was 6.6% (all partial responses) in the cetuximab arm. There were no complete or partial responses in the BSC arm.

Please see the Statistical Review and Evaluation by Dr. Kyung Lee for a detailed evaluation of efficacy findings.

6.1.6 Efficacy Conclusions

Study CA225025 is a randomized phase 3 clinical study conducted in patients with metastatic colorectal cancer who had failed both irinotecan- and oxaliplatin-containing regimens. There has been no therapy which has shown improved OS in this patient population. The findings of CA225025 provide positive results for use of cetuximab in this heavily pretreated population, although the improvement in median OS is a modest 6 weeks.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety profile for Erbitux was reviewed and described in detail in the original BLA application, STN 125084/0. The studies reviewed in the original BLA were three trials which included 168 patients who received cetuximab monotherapy and 356 patients who received cetuximab in combination with irinotecan. The most common toxicities described with the original BLA included acneform-rash and infusion reactions. Subsequently, hypomagnesemia was evaluated as another common side effect and reviewed in the supplement STN125084/30.

The analysis herein is based on the data in the efficacy supplement STN 125084/103. Data sets were provided only for the randomized trial, CA225025. The safety data set of this trial is comprised of 288 patients who received cetuximab and 274 patients in the best supportive care (BSC) arm. A total of 1243 subjects registered (enrolled) to this study. Some patients (still on prior antineoplastic therapy regimens) registered months prior to randomization. Of the registered patients, 262 (21%) were found to have EGFR negative tumors upon central review, and were thus excluded from randomization. Ultimately, 572 subjects were randomized in 1:1 ratio. The submission does not detail the reasons for exclusion from randomization of the other 409 registered patients. Figure 4 illustrates the disposition and treatment of randomized patients.

All randomized patients (287 in cetuximab and 285 in BSC arms) represent the total efficacy population for intent to treat analysis.

The safety data set is comprised of all treated patients. On the cetuximab arm, treated patients are defined as those who received at least one dose of cetuximab. Four patients randomized to cetuximab received no treatment (and were deleted from the safety data set) and 5 subjects randomized to BSC received at least one dose of cetuximab on study (and were moved from the BSC to the cetuximab safety data set). Of 285 patients randomized to BSC, 6 did not return for the first follow-up visit, and were deleted from the safety data set.

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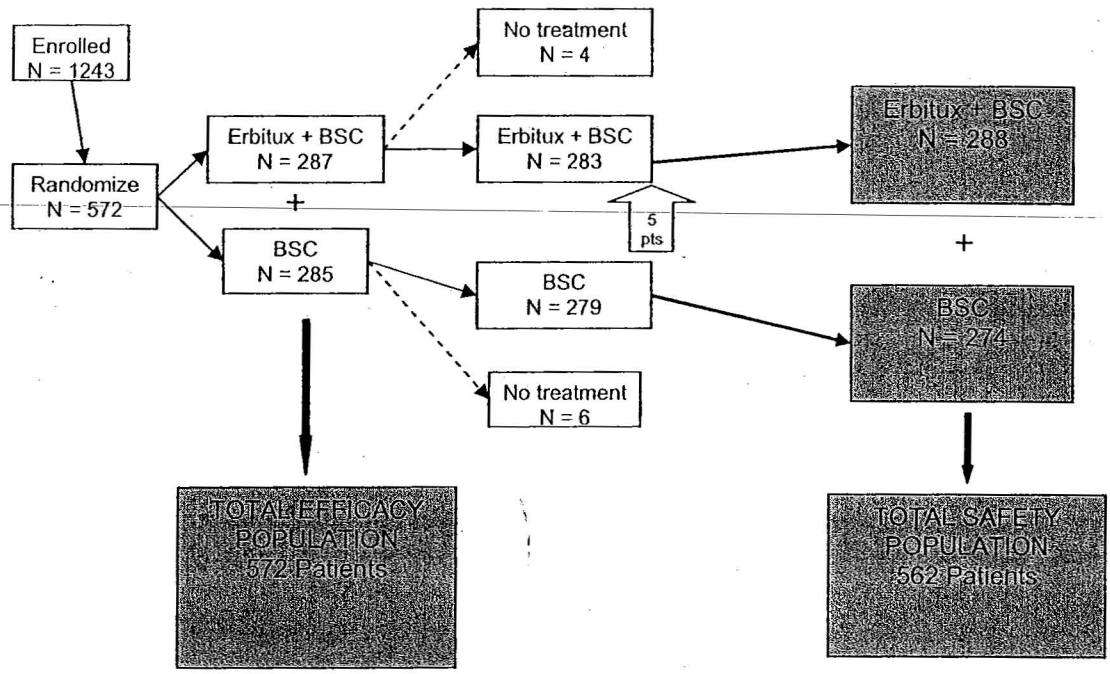
Figure 4. Disposition and Treatment of Patients in Trial CA225025



In trial CA225025, 288 subjects received cetuximab as monotherapy for metastatic colorectal carcinoma (mCRC). The safety review of these treated subjects portrays an adverse event profile of cetuximab which is quite similar to what is already known and reported about this agent. Please see Table 17 for an overview of adverse events in this study.

Table 17. Overall Incidence of Adverse Events (AEs), Trial CA225025

	Cetuximab+BSC N = 288 n (%)	**BSC N = 274 n (%)**
Any AE	287 (99.7)	251 (91.6)
Grade 3 – 4 AEs	171 (59.4)	139 (50.7)
Any SAE	127 (44.1)	92 (33.6)
AEs resulting in death	67 (23.3)	28 (10.2)*
AE resulting in discontinuation of cetuximab	11 (3.8)	Not applicable

*Deaths reviewed in Section 7.1.1

7.1.1 Deaths

Case reports for all patients who died either on study or within 30 days of the last dose of cetuximab administration were reviewed. There are only two patients whose cause of death is attributed differently between applicant and this reviewer.

Table 18 summarizes deaths in all subjects in the cetuximab arm within 30 days of last cetuximab dose.

Table 18. Deaths within 30 days of Last Cetuximab Dose

All treated subjects, N = 288 (Cetuximab + BSC)		
Cause of Death	**Applicant n (%)**	**Reviewer n (%)**
Progressive mCRC	58 (20.1)	56 (19.4)
Suspected PE	1 (0.3)*	1 (0.3)
Gram negative sepsis	0	1 (0.3)**
Non-malignant bowel process	0	1 (0.3)***
TOTAL Deaths within 30 days of last cetuximab	59 (20.5)	59 (20.5)

*AUXA0253; **CAVA0021; ***AUXA0247

Selected Case Histories and Analyses:

*AUXA0253

66yo F with mCRC previously treated with 5FU, oxaliplatin, and irinotecan-containing regimens has h/o pulmonary emboli (diagnosed April 2004) and was continuing on daily anticoagulant therapy (both warfarin and enoxaparin.) She was randomized to cetuximab arm on November 29, 2004 and received her fifth dose of cetuximab on January 12, 2005. Baseline magnesium was WNL at 0.71 mmol/L (0.65-1.30). Subsequently, magnesium declined to 0.56 on Dec 22, 2004. She did not apparently receive magnesium supplements. On (b) (6), the patient was observed by her family to have sudden onset dyspnea, collapsed, and died at home. Resuscitative efforts were unsuccessful. Autopsy was not performed, and unconfirmed pulmonary embolus was the suspected cause of death.
COMMENT: Based on the patient's past history of pulmonary emboli and the available data, the Investigator and Sponsor's assessment pulmonary emboli as the proximal cause of death is reasonable. However, a causal link between thromboemboli and cetuximab cannot be excluded.

**CAVA0021

50yoM with colon CA with extensive metastatic deposits in right abdomen, pelvis and liver was randomized on Apr 15, 2005. He received infusions of Erbitux on April 18, April 25, May 2, 2005, after which he left on a cruise on May 4, 2005. It appears that cultures obtained on May 2, 2005 (prior to his departure on cruise) subsequently became positive for Klebsiella. He received appropriate care onboard ship, was subsequently hospitalized, but had rapid decline with septic parameters. He expired on (b) (6). His extremely rapid decline just days after leaving on a cruise indicates the proximal cause of death to be more likely due to Gram negative sepsis rather than progressive colon carcinoma.
COMMENT: Infectious events are noted to be more common in the cetuximab arm of this and other controlled studies. A causal link between this patient's Gram negative sepsis and cetuximab cannot be excluded.

***AUXA0247

72yoF with mCRC was randomized on September 14, 2004, received Erbitux 9/16/04 – 10/7/04, developed abdominal pain and was admitted to the hospital on (b) (6) with bowel obstruction. Initial evaluation of abdominal CT (b) (6) was interpreted as "bowel obstruction secondary to colorectal cancer. She was discharged to the palliative care unit for end of life care and died on (b) (6) The formal CT reading clearly

confirms SBO, however the cause is likely "due to the right Spigelian hernia." Dilated bowel lead into the hernia, with a compressed loop more distally. Neoplastic disease was noted to have been progressive; however the proximal cause of death is likely related to hi-grade SBO and strangulation of bowel loop, with subsequent intra-abdominal catastrophe. Spigelian hernias carry very high risk of bowel strangulation, necrosis, and perforation if not promptly corrected by surgical reduction.

Deaths up to data cut-off:
Up to the time of the data cut-off, March 6, 2007, there were 224 deaths in the Cetuximab plus BSC arm including those that occurred during long-term follow-up. A total of 227 deaths occurred among patients randomized to the BSC-alone arm, as summarized in Table 19. Prior to disease progression, 5 patients in the BSC arm were treated with cetuximab and 16 others received other approved antineoplastic agents (Xeloda, Avastin, others). After evidence of progression, an additional 19 (6.7%) of subjects in the BSC arm received cetuximab.
Comment: Because a large number of subjects randomized to the BSC arm subsequently received cetuximab and other antineoplastic therapies, a direct comparison between study arms is confounded.

Table 19. All Deaths up to Data Cut-Off

Cause of death (per Applicants)	Cetuximab+BSC (N = 288)	BSC (N = 274)
Disease Progression	219	225
Septicemia, UTI	1	0
mCRC and non-protocol treatment complication	1	0
Unconfirmed PE	1	0
Other condition or circumstance	2	2
Toxicity from protocol treatment	0	0
TOTAL Deaths up to data cut-off	224 (77.8%)	227 (82.8%)

As indicated in Table 19 above, the Applicant attributed 219 deaths to progressive disease in the Cetuximab arm. Fifty-nine of these occurred during the study or within 30 days of the last dose of cetuximab, and 160 additional deaths occurred thereafter. Except for the 2 cases detailed above (CAVA0021 and AUXA0247), progressive disease is a plausible explanation for the deaths in the study population.

There is little evidence that cetuximab contributed to mortality. Individual CRFs of patients who died while receiving Erbitux and for a period of 30 days after the last dose of Erbitux were reviewed. As displayed in Table 19, the causes of death were almost entirely related to progressive disease. No excess mortality from cetuximab is apparent.

7.1.2 Other Serious Adverse Events

Section 8.3 (analysis of SAEs) in the final CSR for trial CA225025 contains an inaccurate

statement regarding SAE collection. SAEs were in fact collected for both study arms, but were analyzed only for the cetuximab arm by the Applicant. A serious adverse event was defined as any event regardless of assessment causality that is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, is a persistent or significant disability, or results in a congenital anomaly/birth defect.

The adverse event categories were not very granular for some entries (such as infection). This reviewer, therefore, assessed SAEs by first collecting them by toxicity description (which contained the most granular information in the provided data sets), then summarizing them within toxicity by patient and by maximum grade per toxicity for each treatment group. Various grades of the same toxicity description for each patient were counted as only one report. The analysis below of SAE data excludes events that antedate the first dose of cetuximab and includes only those SAEs during cetuximab treatment and for a follow-up interval of 30 days. These SAE reports, for toxicities reported 4 or more times, are presented in Table 20.

Table 20. Reports of Serious Adverse Events

Serious Adverse Event	Cetuximab + BSC N = 288 patients 351 SAE reports	BSC N = 274 patients 311 SAE reports
	number of reports	number of reports
Infection	31	20
Pain – other	23	11
Fever	21	13
Dyspnea	20	16
Nausea	17	15
Vomiting	17	20
Fatigue	14	7
Abdominal Pain	14	22
Bowel obstruction	12	14
Tachyarrhythmia	11	1
Confusion	11	7
Rigors/Chills	11	2
Infusion reactions	10	0
Dehydration	9	8
Jaundice/hyperbilirubinemia	8	6
Thrombosis/embolism	7	9
Anxiety, agitation, aggression, mood changes	7	0
Anorexia	5	4
Diarrhea	4	6
Cough	4	6
Rash/Pruritis	4	1
Hypomagnesemia	4	0

The most common categories of SAEs, which were more frequent in the cetuximab arm, were infection, pain-other, fever, and fatigue. "Pain-other" was generally referred to musculoskeletal pain, bone pain, non-cardiac chest pain, but excluded abdominal pain. Of note, there were 11 reports of tachyarrhythmias in the cetuximab group and only 1 in BSC.

Ten SAE infusion reactions (described variously as allergic, anaphylactic, hypersensitivity, or bronchospastic reactions, in addition to one case of hives) were reported. Interestingly, anxiety/agitation/aggression was reported only in the cetuximab-treated arm.

To better delineate the types of infections which were reported as SAEs, the SAE infections from Table 20 were further evaluated and are shown in Table 21. Because of the method of data collection, many infections (9 in the cetuximab arm and 5 in the BSC arm) are not further specified. There were more SAE cellulitis infections reported in the cetuximab group. Given the limitations of the collected data, no single anatomic site or body system appears to explain the disparity between overall incidences of infections between the arms.

Table 21. SAE Infection Reports

Infection description	Cetuximab 31 reports	BSC 20 reports
Respiratory	6	7
UTI/urosepsis	5	2
Cellulitis	4	0
Sepsis	2	2
Catheter-related	1	0
Cholangitis	1	0
Renal fungus	1	0
Wound/post-op	1	1
Zoster	1	0
Thrush	0	1
Peritonitis	0	1
Perirectal abscess	0	1
Infection-unspecified	9	5
TOTAL	47	17

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Adverse events leading to discontinuation of cetuximab were reported by 11/288 (3.8%) of subjects in the cetuximab+BSC group. The Applicant assessed these AEs to be treatment-related in 8/288 (2.8%) of subjects. The most common treatment-related AE leading to discontinuation of cetuximab was hypersensitivity reaction (infusion reaction) (5 subjects, 1.7%). Other AEs leading to discontinuation of cetuximab included rash/desquamation, petechiae/purpura, and headache (1 subject each). See Table 22 for a list of all patients who discontinued study therapy because of AE. Brief narratives are included for these 11 subjects.

Comments:

- *As discussed above in Section 7.1.1, the relatedness of cetuximab to the possible thromboembolic event experienced by subject AUXA025 cannot be ruled out.*
- *Patient CAMP0049 discontinued therapy because of an infection. Infections are more frequent in the cetuximab arm, and causal linkage between infection and cetuximab is*

not excluded.

- *Therefore, cetuximab may possibly be related to AEs that resulted in therapy discontinuation in 10/288 (3.5%) of subjects.*

Table 22. AEs Leading to Study Withdrawal

Cetuximab plus BSC				
ID	Age/sex	Cetuximab Dose #	AE	Grade
AUXA0145	60M	1	Acute spinal cord compression from met*	4
AUXA0253	66F	3	Thromboembolism, dypnea*	5
AUXA0270	57M	14	Hypersensitivity reaction: dyspnea	4
AUXA0374	76M	1	Rash/desquamation	3
AUXA0437	37F	4	Hypersensitivity reaction: chills, rigors	2
CAAJ0003	55M	4	Hypersensitivity reaction: chills, rigors	3
CAKO0054	54M	2	Hypersensitivity reaction: dyspnea	4
CAMP0043	62M	1	Hypersensitivity reaction: dyspnea	3
CAMP0049	64M	25	Infection (positive blood cultures)*	3
CASS0003	54M	6	Petechiae/purpura	3
CATW0043	55M	1	Headache	4

*Per Sponsor: unlikely related to treatment therapy.

Histories of Subjects Discontinuing Cetuximab due to AEs:
Patient AUXA0145 developed LBP, lower extremity weakness and paresthesias approximately 2 weeks after receiving his loading dose of Cetuximab. He was found to have spinal cord compression at the T4 level, requiring decompressive laminectomy. He received no further study therapy, although the AE was unlikely related to study treatment.

Patient AUXA0253 had a prior h/o PE and was on continued lovenox and coumadin. Her family reports that she had sudden onset of dyspnea at home and collapsed. Resuscitative efforts were unsuccessful and she died at home. No autopsy was performed, but the presumptive cause of death is pulmonary embolism.

Patient AUXA0270 was a 57 year old man randomized to cetuximab and best supportive care experienced an allergic/hypersensitivity reaction to his 14th cetuximab infusion. The patient had chills, fever, tachycardia, hypertension, dyspnea and bronchospasm. The patient received ventolin, hydrocortisone, phenergan and morphine and the symptoms resolved the same day. Events were definitely related to protocol therapy. No further cetuximab was given. He died a month later from progressive metastatic disease.

Patient AUXA0270 was a 76 year old male who developed a grade 3 rash after his loading dose of cetuximab. No further narrative description is provided. He died of disease progression 7 months later.

Patient AUXA0437 was a 37 year old female randomized to Cetuximab and best supportive care complained of chest tightness halfway through week 4 infusion of Cetuximab and experienced rigors and sweating. The infusion was ceased and oxygen was given via a mask and the chest tightness resolved. Pethidine IV was also administered. The events are definitely related to the protocol therapy and the patient recovered from all

events.

CAAJ003 was a 55 year old male who had grade 3 chills and rigors during infusions on weeks 3 and 4. Thus, he discontinued therapy. He had progressive disease, developed brain mets and died a month after his last cetuximab dose.

CAKO0054 was a 54 year old man who came to clinic to receive his second cetuximab infusion. After a small amount of cetuximab was administered, the patient experienced flushing, dyspnea, hypotension and nausea. The patient lost consciousness and was placed in Trendelenburg's position. The patient's pulse and respiration became very shallow. Epinephrine was administered and he regained consciousness and began to retch again and complained of back pain. A few hives were identified. The patient was placed on oxygen and transferred to the ICU for observation. Events were definitely related to protocol therapy.

CAMP0043 was a 62 year old male patient who discontinued cetuximab after developing a grade 3 rash after the initial dose. He went on to palliative care at home and expired one month later.

CAMP0049 was a 64 year old male patient randomized to cetuximab and best supportive care was assessed by the co-PI on 2005-Dec-12. The patient's condition was clinically deteriorating. He was referred to palliative care. He had elevated WBC, no fever, decreased hemoglobin and positive blood cultures for gram positive cocci. The patient was instructed to go to local emergency department for IV antibiotics, blood transfusion and palliative care management. The cetuximab infusions were interrupted.

CASS0003 was a 54 year old male patient randomized to cetuximab and best supportive care presented to clinic for cetuximab infusion. After one week he developed grade 3 rash that is still ongoing. Patient's hemoglobin dropped from 91 to 52 g/L and he has soft tissue bruising on the left hand/arm and the right leg. Patient denies any trauma to either area. Further work-up demonstrated a factor VIII coagulation defect. Patient was treated with FFP, Vitamin K, PRBC support and was discharged home on prednisone. Events of petechiae/purpura considered possibly related to protocol therapy. Relation of other events: Rash – definitely related, anemia – unlikely related, RBC transfusion – unrelated

CATW0043 was a 55 year old male patient randomized to cetuximab and best supportive care developed a grade 4 headache after receiving his first dose of cetuximab. He was seen in emergency and was treated with morphine and gravol. He only had minor relief and was seen again on (b) (6) at the (b) (4) where he was given a repeat dose of morphine and gravol. A CT scan of the head on (b) (6) did not show any evidence of brain metastasis. The patient was discharged home with morphine and continued the medication until 2005-May-20 after which he switched to codeine tablets. His headache was grade 2/3 on 2005-May-21. The event is possibly related to protocol therapy.

Cetuximab-related toxicities resulted in discontinuation of drug in 8 (2.8%) subjects as

assessed by the Applicant. Causal relationship between infectious and thrombotic events and cetuximab cannot be definitely excluded. Therefore, this reviewer believes it more accurate to state that cetuximab-related toxicities possibly/definitely resulted in discontinuation of drug in 10 (3.5%) of subjects. The most common reported side effect related to discontinuation was infusion reaction.

7.1.3.3 Other significant adverse events

Skin toxicity

Table 23 below lists the dermatologic toxicities experienced by patients in CA225025. Rash/desquamation was reported in 93.7% of subjects receiving cetuximab+BSC with 13.9% of those subjects reporting a worst grade of Grade 3; no subjects were reported to have Grade 4 or 5 dermatologic toxicity. Events were reported as SAEs in 3 subjects on cetuximab+BSC and led to discontinuation in 1 subject (AUXA0374).

Table 23. Dermatologic Toxicity

	Cetuximab + BSC (N = 288)		BSC Alone (N = 274)	
Toxicity	**Any grade**	**Grade 3***	**Any grade**	**Grade 3***
ANY Dermatology	270 (94)	40 (14)	97 (35)	3 (1)*
Rash/desquamation	253 (88)	34 (12)	36 (12)	1 (<1)
Dry Skin	138 (48)	0	33 (12)	0
Pruritis	115 (40)	7 (2)	23 (8)	0
Other-skin	75 (26)	2 (1)	8 (3)	2 (<1)
Nail changes	60 (21)	0	12 (4)	0
*There were no grade 4 skin toxicities.				

As expected, skin toxicity is far greater in the Cetuximab arm in all subcategories studied; however in only one case did rash/desquamation lead to discontinuation of study treatment.

Infusional toxicity

(b) (4)

In study CA225025, infusion reaction was defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever", or dyspnea.

In study CA225025, the Applicant made an attempt to control for the variability of reporting and capturing of infusion-associated adverse events through the use of a specific adverse event page in the case report form on which all infusion related adverse events were to be captured. However, the Applicant noted upon review of the safety data from CA225025 that the specific adverse event page may not have captured all terms potentially associated with infusion reactions. Thus, the Applicant conducted an additional review of the data and included all terms from the specific CRF page plus all "fever", "chills", "chills and fever" and "dyspnea" occurring on day 1 of cetuximab. This was an attempt to remain consistent with the composite AE term from existing labeling. Adverse events considered to be a symptom of an infusion-related hypersensitivity reaction (HSR) were summarized under the CTC category, HSRs. At least 1 AE of HSR was reported by 20.1% of the

cetuximab-treated subjects (see Table 24), and resulted in discontinuation of treatment in 5 subjects.

Thirteen subjects (4.5%) reported a worst grade 3-4 infusion reaction. In this reviewer's opinion, one patient (CAKN0001) did not experience an infusion reaction, as her angioedema, rash, and perioral paresthesias occurred 7 days *after* her 18th infusion. She may indeed have experienced a delayed drug reaction, but not an infusion reaction.

Despite grade 3-4 toxicities, 8 subjects continued treatments, violating protocol requirements. Interestingly, of the 8 subjects who experienced grade 3-4 infusion reactions (mostly grade 3-4 dyspnea) yet were rechallenged with cetuximab, 7 patients had no recurrent HSR per review of patient narratives. These 7 patients received multiple additional doses (range 3 – 9). The eighth rechallenged patient (AUXA0270) experienced a grade 4 infusion reaction with his 13th dose; his symptoms resolved with treatment, and he was restarted on cetuximab a week later and had recurrent grade 3 bronchospasm and grade 4 dyspnea. Symptoms again resolved with treatment, but further cetuximab was not given. Of all 13 patients with reported grade 3-4 HSR, 6 were during or after their initial infusions, 7 had prior infusions (range 2 – 18).

Table 24. Infusion (Hypersensitivity) Reactions

Cetuximab + BSC, N = 288, in > 1% patients		
	Any Grade n (%)	**Grade 3/4 n (%)**
Any HSR	58 (20.1)	13 (4.5)
Drug fever	23 (8.0)	0
Chills, rigors	19 (6.6)	0
Dyspnea	8 (2.8)	8 (2.8)
Other	9 (3.1)	3 (1.0)
Tachycardia	7 (2.4)	1 (0.3)
Bronchospasm	5 (1.7)	2 (0.7)
Chest tightness	5 (1.7)	2 (0.7)
Swelling	6 (2.1)	1 (0.3)
Urticaria	6 (2.1)	1 (0.3)
Hypotension	4 (1.4)	1 (0.3)
Flushing	4 (1.4)	0
Rash	4 (1.4)	0

Cardiovascular toxicity

Regardless of the attribution, cardiovascular events were reported for 39.2% of subjects on cetuximab+BSC and 32.5% of subjects on BSC. The most common cardiovascular AE in both groups was edema (30.9% cetuximab+BSC, 26.6% BSC), considered as severe (grade 3 – 4) in 5.2% of patients in the cetuximab+BSC group and 5.8% in the BSC group. The interpretation of edema is, however, confounded by the nature and symptoms from the underlying disease.

The second most common cardiac AE was sinus tachycardia, reported in 5.9% of subjects on cetuximab+BSC and 2.2% of subjects on BSC; tachycardia was often reported in the

context of an infusion reaction. Supraventricular arrhythmia was reported in 4 subjects (1.4%) on cetuximab+BSC and 1 subject on BSC (0.4%). The 4 cases for cetuximab+BSC-treated subjects were severe. However, it is unlikely the symptoms are related to cetuximab as they were reported more than 2 months after cetuximab was discontinued for disease progression for 3 subjects and 2 weeks later for 1 subject.

Table 25. Cardiovascular AEs, > 1% patients

	Cetuximab + BSC, N = 288		BSC, N=274	
	Any grade n (%)	**Grades 3/4 n (%)**	**Any grade n (%)**	**Grades 3/4 n (%)**
Any Cardiovascular	113 (39.2)	28 (9.7)	89 (32.5)	32 (11.7)
Edema	89 (30.9)	15 (5.2)	73 (26.6)	16 (5.8)
Thromboembolism	11 (3.8)	8 (2.8)	14 (5.1)	14 (5.1)
Sinus tachycardia	17 (5.9)	1 (0.3)	6 (2.2)	1 (0.4)
Hypotension	7 (2.4)	3 (1.0)	4 (1.5)	2 (0.7)
Other	8 (2.8)	0	1 (0.4)	1 (0.4)
Supraventricular arrhythmia	4 (1.4)	4 (1.4)	1 (0.4)	0
Hypertension	4 (1.4)	1 (0.3)	3 (1.1)	1 (0.4)

Comment: In the CSR, the Applicant asserts that no cases of sudden death, fatal MI, or cardiopulmonary arrest were reported during treatment with cetuximab. However, as described in Deaths, Section 7.1.1, AUXA0253 died suddenly at home 6 days after her fifth dose of cetuximab. Pulmonary embolus is the suspected cause of death. Relatedness to cetuximab is possible.

Infections

Infections were captured with use of the CTCAE version 2.0 term "Infection without Neutropenia". The toxicity data set contains a potentially more descriptive variable called "TOX_DESC" or toxicity description, which sometimes contain more specific information from the case report forms. Unfortunately, for many line listings, the TOX_DESC reiterates the CTCAE term "Infection without Neutropenia" or more simply, "Infection." Thus, data for infectious toxicities was captured in a non-granular fashion, which limits investigation to discern the reason for the infection incidence rate difference between the treatment arms (Table 26).

Table 26. Incidence of Infections without Neutropenia by Grade and Arm by Highest Grade Toxicity per Patient

	TOTAL	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cetuximab + BSC (N = 288)	101 (35.1%)	26	36	36	2	1
BSC (N = 274)	46 (16.8%)	11	19	15	0	1

As can be seen in Table 26, the incidence of infections is approximately twice as frequent in the cetuximab-treated group, and Grades 1 through 3 events are largely responsible for this difference.

During the entire study, 444 infectious events were reported, 314 in the cetuximab group and 130 in the BSC group. As can be seen in Table 27 below, further details to characterize these events were given for only a minority of infections.

Table 27. Listing of All Infectious Events

Toxicity Description	Cetuximab + BSC 314 total reports	BSC 130 total reports
Infection not further specified*	271 (86.3)	110 (84.6)
Pneumonia/pulmonary/respiratory/chest	15 (4.1)	11 (8.5)
UTI/urinary sepsis/urosepsis	9 (2.9)	3 (2.3)
Catheter-associated	4 (1.3)	0
Cellulitis	4 (1.3)	0
Sepsis/Septicemia	3 (1.0)	2 (1.5)
Right foot	2 (0.6)	0
Abdominal cellulitis	1 (0.3)	0
Cholangitis	1 (0.3)	0
Gram Negative Sepsis	1 (0.3)	0
Herpes Zoster	1 (0.3)	0
Renal fungal	1 (0.3)	0
Wound infection	1 (0.3)	0
Oral thrush, cold sore	0	3 (2.3)
Post-op	0	1 (0.8)
Total Infectious Events	314 (100%)	130 (100%)
*Includes descriptions "infec w/o neutropenia, infection, infection w/o neutron, infection without ne, infection without neutropenia"		

Because of the limited descriptive information, a detailed analysis of the type of infections is not possible using the datasets from the Applicants. Possibilities for the disparity in the incidence rate of infections between the treatment arms may be speculated to include the following:

- Cetuximab itself causes or predisposes toward infections by unknown mechanism, possibly due to increased cellulitis from dermatologic side effects
- Administration of cetuximab causes or predisposes toward infections, possibly due to catheter use, increased number of medical procedures, increased visits to a medical facility, other iatrogenic events
- Ascertainment bias has led to the disparity in the incidence rate of infections as patients in the cetuximab arm were seen and evaluated for symptoms weekly in contrast to BSC subjects, who were evaluated monthly.

Unfortunately, this study was not designed and data were not collected in detailed-enough fashion to permit further explanation of this disparity in infections.

7.1.4 Other Search Strategies

Not applicable to this drug which is commonly used in the oncology community and has a well-known side effect profile.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse event data were collected on Case report forms (CRFs), were very specific to elicit signs and symptoms related to the integument, hypersensitivity reactions, and GI toxicities. Additional adverse events (fever, fatigue, headache and dyspnea) were also individually listed. All other toxicities were to be written by the clinician and noted on CRFs under a heading, "other".

Adverse events were coded using the descriptions and grading scales found in the NCI CTCAE Version 2.0. Data were recorded at each site on CRFs provided by the cooperative group NCIC. As can be seen in the Patient Evaluation Flow Sheet for each arm of the study (Appendices 10.3 and 10.4), subjects in the cetuximab arm were seen *weekly* for treatment, vital sign assessments and toxicity evaluations. In contrast, subjects in the BSC arm were evaluated only once *monthly* for toxicities. This design difference may have resulted in ascertainment bias in the determination of adverse event incidence rates.

Primary data source collection was done on forms which contained a checklist, with particular detail given for skin toxicity and hypersensitivity reactions. Records of adverse events are found in two datasets, CO17_TOX and CO17AER. The CO17_TOX set contains adverse events recorded at baseline, on treatment, at off-treatment follow-up visits, and for the period between the last visit and death. The CO17AER set contains all adverse event data deemed as serious by an NCIC review. There was no pooling of SAE and AE records in the original submission; therefore no one dataset contained all AE records. A complete dataset was subsequently requested and presented by the applicant. Furthermore, only data from study CA225025 was submitted, so there was no pooling of data from other trials.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Verbatim terms from the investigator were not collected, so there is no way to assess the accuracy of data collection from patients' clinical charts. Adverse event data were collected and coded according to the CTCAE, version 2.0. Data were provided to us as SAS transport files, allowing manipulation with SAS and JMP programs. There are no pooled data, and hence there is no integrated safety set.

As noted above, some symptoms are well detailed (cutaneous reactions, infusion reactions), whereas other symptoms may be more "lumped" (infections).

(b) (4)

(b) (4)

7.1.5.3 Incidence of common adverse events

Because of the nature of the patient population in this study, here was a high rate of background or baseline symptoms, which could be attributable to the underlying disease process. Thus, a comparison between the two groups allows the best opportunity to assess drug-related adverse effects. The most common adverse events (all grades) occurring in the cetuximab-treated group that were at least 10% more frequently reported than in the BSC arm were fatigue, dermatologic toxicities (rash, desquamation, dry skin, pruritis, nail changes, stomatitis), pain-other, headache, diarrhea, infection, fever, and insomnia. Infusion reactions, which were reported with an incidence of 20.1%, were recorded only for patients receiving cetuximab. Please see Table 28 in Section 7.1.5.4.

Grades 3 and 4 reactions which were at least 5% more frequent in the cetuximab arm compared to the BSC arm were fatigue, dermatologic toxicities, pain-other, and infection (Table 28).

The term "pain-other" contained entries almost exclusively for musculoskeletal pains, with back pain being the most common description.

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7.1.5.4 Common adverse event tables

Table 28. Incidence of Common Adverse Events

	Cetuximab + BSC N = 288				BSC N = 274			
	All Grades		Grade 3 and 4		All Grades		Grades 3 and 4	
Adverse Event	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Fatigue*	257	89.2	96	33.3	207	75.5	72	26.3
Rash/desquamation*	255	88.5	34	11.8	44	16.1	1	0.4
Anorexia	193	67.0	24	8.3	177	64.6	16	5.8
Abdominal pain	169	58.7	41	14.2	143	52.2	43	15.7
Nausea	164	56.9	17	5.9	131	47.8	16	5.8
Pain-Other	146	50.7	45	15.6	92	33.6	20	7.3
Dry skin	141	49.0	0	0.0	30	10.9	0	0.0
Dyspnea	139	48.3	46	16.0	119	43.4	33	12.0
Constipation	132	45.8	10	3.5	103	37.6	14	5.1
Pruritus	116	40.3	7	2.4	23	8.4	0	0.0
Diarrhea	112	38.9	7	2.4	55	20.1	5	1.8
Neuropathy-sensory	111	38.5	5	1.7	99	36.1	5	1.8
Vomiting	107	37.2	17	5.9	80	29.2	15	5.5
Infection	101	35.1	38	13.2	46	16.8	15	5.5
Headache	95	33.0	11	3.8	29	10.6	0	0.0
Edema	89	30.9	15	5.2	73	26.6	16	5.8
Fever	85	29.5	4	1.4	48	17.5	1	0.4
Insomnia	85	29.5	2	0.7	41	15.0	2	0.7
Cough	84	29.2	5	1.7	52	19.0	3	1.1
Other-skin	79	27.4	2	0.7	16	5.8	2	0.7
Stomatitis	73	25.3	2	0.7	26	9.5	1	0.4
Other-GI	65	22.6	28	9.7	49	17.9	23	8.4
Nail changes	61	21.2	0	0.0	10	3.6	0	0.0
Infusion reactions	58	20.1	13	4.5	N/A	N/A	N/A	N/A
Confusion	43	14.9	16	5.6	25	9.1	6	2.2
Bone pain	42	14.6	9	3.1	19	6.9	4	1.5
Anxiety	41	14.2	6	2.1	23	8.4	2	0.7
Dyspepsia/heartburn	41	14.2	2	0.7	39	14.2	1	0.4
Depression	38	13.2	2	0.7	16	5.8	1	0.4
Rigors, chills	38	13.2	1	0.3	11	4.0	0	0.0
Mouth dryness	31	10.8	0	0.0	12	4.4	0	0.0
Dizziness	29	10.1	3	1.0	19	6.9	2	0.7

7.1.5.5 Identifying common and drug-related adverse events

The most common adverse events which can be probably or definitely due to cetuximab (based on a comparison between the two treatment groups) include dermatologic toxicities, infusion reactions. Although a cause and effect mechanism is not apparent from this study, non-abdominal pain was reported more frequently by subjects receiving cetuximab. It is conceivable that monoclonal antibody therapy could result in non-specific systemic symptoms of myalgias and arthralgias. Fatigue was also more frequent in patients receiving

cetuximab, however the background incidence of fatigue in this patient population was quite high (75% of patients in BSC reported fatigue). Laboratory abnormalities will be discussed later in section 7.1.7.

7.1.6 Less Common Adverse Events

The incidence of less common, potentially serious events is shown in Table 29.

Table 29. Less Common Adverse Events

	Cetuximab + BSC N = 288				BSC N = 274			
	All Grades		Grade 3 and 4		All Grades		Grades 3 and 4	
Adverse Event	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Dehydration	27	9.4	12	4.2	15	5.5	1	0.4
Sinus tachycardia	17	5.9	1	0.3	6	2.2	1	0.4
Depressed conscious.	14	4.9	5	1.7	5	1.8	0	0.0
Thrombosis/embolism	11	3.8	8	2.8	14	5.1	14	5.1
Hallucinations	10	3.5	10	3.5	4	1.5	4	1.5
Supraventric. arrhyth.	4	1.4	4	1.4	1	0.4	0	0.0
Hypertension	3	1.0	0	0.0	0	0.0	0	0.0

Cardiac tachyarrhythmias (combination of sinus tachycardia and supraventricular arrhythmias) are reported in 7.3% (2% grade 3 and 4) of patients receiving cetuximab and in 2.6% (0.4%) of patients in the BSC arm. During the study, tachycardia was also reported in the context of an allergic or infusion reaction. The table above does not include tachyarrhythmias which occur in the context of an infusion reaction.

Of note, no cases of sudden death, fatal MI, or cardiopulmonary arrest were reported during treatment with cetuximab.

Dehydration of any grade occurred in 27 patients receiving cetuximab and is 15 patients on BSC. Diarrhea is reported with greater frequency in patients receiving cetuximab; thus, one possible explanation of the greater occurrence of dehydration in those receiving cetuximab may be as a result of diarrhea.

Thomboembolic events were infrequent and were more numerous in the BSC arm. This would suggest thrombosis is a risk associated with this patient population and disease process, rather than the therapy rendered.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In study CA225025, complete blood counts, serum chemistries (including magnesium), creatinine and liver function tests were to be collected in all patients monthly during the study. Some data are missing, and it is not clear if these missing data in the CRT are due to

lack of recordation or lack of evaluation (i.e., lack of patient testing). The percentages reported in the laboratory summary tables are based on the total number of subjects in each treatment group who had laboratory evaluations performed, not the total number of subjects randomized to each treatment group.

Baseline WBC, ANC, hemoglobin and platelet means, medians, and ranges were calculated. No clinically important differences in baseline values were found between the two treatment groups.

Although hypomagnesemia was not identified as a significant issue at the time of approval, in March, 2005, it came to FDA's attention that hypomagnesemia was associated with cetuximab treatment. Data related to cetuximab-associated hypomagnesemia (and other electrolyte abnormalities) was evaluated by Dr. Lee Pai-Scherf in labeling supplement review STN 125084.30. Because of this prior finding, electrolytes including magnesium, calcium and potassium were collected monthly during trial CA225025. Serum creatinines were similarly collected, but recordation errors made review of the primary data impossible.

The incidence of Grades 1 through 4 hematology and chemistry toxicity in CA225025 was analyzed. Worst-grade per subject values were determined and compared between treatment groups.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory assessments of serum chemistries, including magnesium and calcium levels, complete blood counts, and urinalysis, were collected at protocol-specified time points in study CA225025 (Appendices 10.2 and 10.3). The investigators were instructed that any laboratory test result that meets the criteria for an SAE, led to withdrawal from the study, was associated with sequelae, or is associated with a clinical diagnosis must be recorded as adverse events.

Drug-control comparisons were limited to evaluation of differences between the cetuximab and BSC arms of trial CA225025.

7.1.7.3 Standard analyses and explorations of laboratory data

The incidence of Grades 1 through 4 laboratory values in study CA225025 was analyzed. Severity was graded according to the NCIC CTCAE Version 2.0. For the cetuximab-treated subjects, all lab evaluations were included for analysis including those obtained on or after the first infusion and not more than 30 days after the last date of infusion. For the BSC-treated arm, all reported lab values excluding those obtained at baseline were included in analysis.

Incidence of clinically significant hematologic toxicities did not vary between study arms

(Table 30). Grade 1/2 anemias, most likely the result of the underlying neoplastic disease process, were the most frequent CBC abnormalities, occurring in both groups of patients.

Table 30. Incidence of Hematologic AEs

	Cetuximab + BSC N = 288		BSC N = 274	
	n	%	n	%
ANEMIA				
Grade 1	131	45.5	120	43.8
Grade 2	47	16.3	60	21.9
Grade 3	8	2.8	19	6.9
Grade 4	1	0.3	6	2.2
LEUKOPENIA				
Grade 1	16	5.6	7	2.6
Grade 2	3	1.0	6	2.2
Grade 3	0	0	1	0.4
Grade 4	0	0	1	0.4
NEUTROPENIA				
Grade 1	9	3.1	4	1.5
Grade 2	3	1.0	2	0.7
Grade 3	0	0	3	1.0
Grade 4	0	0	2	0.7
THROMBOCYTOPENIA				
Grade 1	41	14.2	28	10.2
Grade 2	3	1.0	1	0.4
Grade 3	1	1.8	2	0.7
Grade 4	1	0.7	1	0.4

As has been previously reported, hypomagnesemia of all grades is more frequently reported in the cetuximab arm. Most cases (32%) are of grade 1 severity, a small proportion of subjects had grade 3 (2.4%) or grade 4 (2.8%) abnormalities. However, no subject discontinued therapy due to hypomagnesemia, nor was any clinical symptom or sign during the study attributable to low magnesium values.

Mild hypocalcemia and hypokalemia were roughly equally common in both study groups. There were no clinically significant differences in potassium or calcium abnormalities between groups (see Table 31 on the next page).

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Table 31. Incidence of Chemistry AEs

	Cetuximab + BSC N = 288		BSC N = 274	
	n	%	n	%
HYPOMAGNESEMIA				
Grade 1	93	32.3	29	10.6
Grade 2	28	9.7	1	0.4
Grade 3	7	2.4	0	0
Grade 4	8	2.8	0	0
HYPOKALEMIA				
Grade 1	47	16.3	33	12.0
Grade 2	0	0	0	0
Grade 3	5	1.7	7	2.6
Grade 4	2	0.7	1	0.4
HYPOCALCEMIA				
Grade 1	89	30.1	78	28.5
Grade 2	19	6.6	16	5.8
Grade 3	4	1.4	2	0.7
Grade 4	0	0	0	0

There were no significant differences found in laboratory values for AST, ALT, LDH, alkaline phosphatase, total bilirubin, sodium, and glucose. The primary dataset with serum creatinine values could not be analyzed as they were captured with uncertain unit assignments. This error could not be subsequently rectified by the Applicant. No patient was reported to require dialysis.

7.1.7.5 Special assessments

No other special assessments were conducted

7.1.8 Vital Signs

The submission did not contain a dataset that would permit comparative analysis of vital signs.

7.1.9 Electrocardiograms

No EKG data are provided with this submission.

7.1.10 Immunogenicity

Serial samples to collect baseline and post-treatment anti-cetuximab antibodies were not collected in CA225025. The immunogenicity profile of cetuximab has been adequately characterized in prior studies.

7.1.11 Human Carcinogenicity

None requested. Human carcinogenicity studies are generally not required for products indicated for treatment of metastatic cancer.

7.1.12 Special Safety Studies

No special safety studies were performed or requested.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Cetuximab is a drug that has no expected abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

There are no pregnancy or lactation studies of cetuximab. The population of patients for whom cetuximab is indicated have advanced metastatic colorectal cancer. For these terminally ill patients, the benefit of therapy in terms of overall survival is generally considered to outweigh the potential reproductive risks.

7.1.15 Assessment of Effect on Growth

There is no information on the use of this drug in children. The indication supported by this application occurs almost exclusively in adults.

7.1.16 Overdose Experience

Clinical Trial Reports:

There was no report of overdose in the sBLA application. In response to FDA request, the sponsor performed a review of clinical trials using the MedDRA HLT term "overdoses." Search results revealed a total of 7 reports from clinical trials which met this search parameter. Three were reported from the US. A breakdown of these reports follows:

- One patient received 1000 mg/m2 loading dose due to an error of drug preparation. No AE was reported.
- One patient was receiving a loading dose at 7 mg/m2 higher than 400 mg/m2 due to incorrect calculation of BSA. This patient did not complete the full dose due to an infusion reaction.
- One patient received a weekly dose at 381 mg/m2 instead of 250 mg/m2; no AE was reported.
- Four patients received 2 or more loading doses instead of one. One patient experienced stomatitis, asthenia and infection. A second patient reported febrile neutropenia and stomatitis. The remaining two patients did not experience any AEs.

Postmarketing Reports:

A total of 16 spontaneous reports were retrieved from the database which met the same MedDRA search criteria. Fourteen were reported from the US. Of these 16 reports, none describe a patient who received cetuximab at a dose higher than 400 mg/m2. Most of the reports describe an episode of medication error rather than true overdose, including more than one loading dose, higher than planned weekly dose, infusion rate higher than 5 ml/min, test dose administered via IVP rather than syringe pump. The adverse reactions attached to these 16 reports are as follows: Infusion reactions (5), skin lesions (4), other (2).

7.1.17 Postmarketing Experience

PLEASE NOTE: THE FOLLOWING TWO PARAGRAPHS CONTAIN COMMERCIAL CONFIDENTIAL INFORMATION FROM THE APPLICANT AND MUST BE REDACTED PRIOR TO PUBLIC POSTING.

Based on information provided in the existing PSURs which covered the period from December 1, 2003 to November 30, 2006, the total number of patients enrolled in cetuximab clinical trials was (b) (4). This number was derived from the clinical trials sponsored by BMS, ImClone and Merck for all indications. The total number of cases with at least one drug-related SAE reported from worldwide clinical trials sources during the same period is (b) (4).

The estimated number of patients receiving commercial cetuximab treatment during the same PSUR period is (b) (4) This estimation is based on the commercial vials sold during the PSUR period in worldwide markets. The total number of cases with at least one SAE reported from worldwide Postmarketing spontaneous or literature source during the same period is 1,192.

PLEASE NOTE: THE ABOVE TWO PARAGRAPHS CONTAIN COMMERCIAL CONFIDENTIAL INFORMATION FROM THE APPLICANT AND MUST BE REDACTED PRIOR TO PUBLIC POSTING.

Hypomagnesemia was identified as a cetuximab-related adverse reaction in the postmarketing setting. The USPI was updated to include this information in September 2005.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

This submission provides efficacy and safety data for review of Trial CA225025, a phase 3 randomized study of cetuximab and best supportive care (BSC) compared to BSC alone in patients with pretreated metastatic EGFR-positive CRC. 572 patients were randomized in 1:1 fashion, 287 patients to the cetuximab arm and 285 to BSC, as seem in Figure 4. The submission contains a full study report related to safety, case report form, and electronic data sets.

7.2.1.3 Extent of exposure (dose/duration)

During Trial CA225025, the median duration of cetuximab therapy was 8 weeks (range 1 to 60) with a median cumulative dose of 2,156 mg/m2 (rage 391 to 15,216 mg). Most subjects (75%) received >90% of their planned weekly doses Table 32. The submission did not contain data that would permit analysis to determine median number of doses (infusions) of cetuximab.

Table 32. Erbitux Exposure during CA225025 Trial

Cetuximab + BSC, N = 288	
Median duration of therapy	8 weeks (range 1 – 60)
Median cumulative dose	2,156 mg/m2 (391 – 15, 216)
Relative Dose Intensity = dose given/planned weekly dose	
>90%	216 subjects (75%)
>80-90%	33 subjects (12%)
>60-80%	18 subjects (5%)
<60%	10 subjects (3%)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Secondary clinical data sources are listed in Table 33 on the following page.

Table 33. Secondary Data Sources of Erbitux in Metastatic Colorectal Cancer

Study	Title	No. of Patients
Efficacy and Safety data		
CA225006	Randomized Phase 3 Trial of Cetuximab plus Irinotecan versus Irinotecan Alone for Metastatic Colon Cancer in Patients who have Failed Prior Oxaliplatin-Based Therapy: The EPIC Trial	1298 (648/650)
IMCL CP02-9923*	Cetuximab plus Irinotecan in Irinotecan-refractory Metastatic Colorectal Cancer	138
IMCL CP02-0141*	Cetuximab Monotherapy in Metastatic Colorectal Cancer	61
EMR-62 202-007*	Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-refractory Metastatic Colorectal Cancer	329 (111/218)
CA225041	Anti-epidermal Growth Factor Antibody, Cetuximab, in Patients with Stage IV Colorectal Carcinoma who Failed All Standard Therapy: an Access Protocol	742
CA225045	An Exploratory Pharmacogenomic Study of Erbitux Monotherapy in Patients with Metastatic Colorectal Carcinoma	110
CP02-0144**	A Phase II Multicenter Study of Erbitux in Patients with Metastatic Colorectal Carcinoma	346
*Previously reviewed by Dr. Lee Pai-Scherf, STN 125084/0 **Previously reviewed by Dr. Lee Pai-Scherf, STN 125084/1		

Several studies have been previously submitted and reviewed under BLA 125084 as noted in the table. A literature report from the American Association for Cancer Research has reported the EPIC trial results showed no difference in OS between the study arms.[5] However, almost half of patients in the irinotecan-only arm went on to receive cetuximab post-study, thus confounding the results. Patients in the combination group experienced more grade 3/4 diarrhea, fatigue, rash, infusion reactions and hypomagnesemia. (b) (4)

7.2.2.1 Other studies

There are no other studies.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of patients had exposure to the drug to provide safety information, with the following limitations:

- Inadequate numbers of non-white patients were enrolled in CA225025 to draw specific conclusions regarding this subpopulation.

[5] Goldberg RM, Hecht JR. Randomized phase III trial of cetuximab plus irinotecan vs irinotecan alone for metastatic colon cancer in patients who have failed prior oxaliplatin-based therapy: The EPIC trial. Highlights Newsletter from AACR; April 30, 2007; 4-7.

- Data collection was insufficiently detailed to fully investigate the increased incidence of infections seen in the cetuximab arm.
- No data on QTc interval prolongation have been provided. This is requested as a postmarketing commitment.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable to this efficacy supplement.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing in CA225025 was inadequate to capture detailed information on infectious events. Also, serum creatinine results were collected with errors in unit values, making the results useless for analysis.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No drug-drug interactions were conducted or necessary during CA225025.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of data was inadequate for detailed investigation of cetuximab results on serum creatinine and infectious events. However, the lack of data and errors in data collection do not appear to substantially affect FDA's analyses or change the study results.

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions or safety updates and none were required for the indication sought with this efficacy supplement.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most common adverse events reported for cetuximab were skin toxicities (including rash, dry skin, pruritis, and nail changes), fatigue, infusions reactions, diarrhea, stomatitis, infections and insomnia. The most common laboratory abnormality associated with cetuximab therapy is hypomagnesemia. Of these common adverse events, only infusion reactions and rash led to discontinuation of therapy due to intolerable toxicity.

As detailed elsewhere in this review (Sections 7.1.2, 7.1.3.3, 7.2.5), collection of data for infectious events was limited and not sufficiently detailed to permit in-depth analyses. For example, a potentially useful clinical question to resolve is to determine if the increased

incidence of infections with cetuximab therapy has organ or body system focality.

Deaths in this patient population were expected and common. Two deaths occurred while on cetuximab (patients AUXA0253 and CAVA0021) as detailed in Section 7.1.1 which cannot be reasonably or definitely excluded from causal linkage to cetuximab.

Adverse events associated with cetuximab were generally consistent with the labeled reactions described for single-agent cetuximab.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen used in CA225025 was the current labeled dose which is commonly used in clinical practice[6]: 400 mg/m^2 IV initial dose, followed by 250 mg/m^2 IV weekly until disease progression or intolerable toxicity occurs.

8.2 Drug-Drug Interactions

No drug-drug interaction studies were conducted in this monotherapy study.

8.3 Special Populations

This efficacy supplement contained no specific studies to evaluate dosing based on race, gender, age or major organ impairment. Subgroup analyses based on race, gender and age were conducted and the results are present in section 1.3.6. No data from Trial CA225025 suggested that dosing should be modified based on demographic characteristics.

8.4 Pediatrics

A "Phase I Study of Erbitux in Pediatric Subjects with Refractory Solid Tumors: Characterization of Serum Pharmacokinetics, Safety, and Efficacy of Cetuximab when Combined with Irinotecan" is ongoing as part of the post-marketing commitment for cetuximab.

The indication supported by this application is a rare occurrence in patients less than 18 years old. No additional pediatric studies will be requested for the indication of colorectal carcinoma.

[6] Chu E, DeVita VT, *Physicians' Cancer Chemotherapy Drug Manual 2007*, Jones and Bartlett Publishers.

8.5 Advisory Committee Meeting

No Advisory Committee meeting related to this application was held or is planned. The application was straightforward, with a statistically significant improvement in overall survival. No new safety issues were identified.

8.6 Literature Review

The Applicant performed an extensive literature review and submitted an extensive reference section with this application as part of the sBLA. FDA has reviewed the submitted references, which were a mixture of efficacy and safety information. Literature references for Erbitux safety and efficacy were not utilized as a basis for recommendations in this review.

8.7 Postmarketing Risk Management Plan

The application did not submit a plan for risk management. No new safety concerns were identified during evaluation of this supplement that would require a postmarketing risk management plan.

8.8 Other Relevant Materials

Other materials were studied, including prior clinical reviews by Dr. Lee Pai-Scherf for the original cetuximab approval, supplements STN 125084.1, STN 125084.30, and the safety section from the head and neck cancer indication (STN 125084.46). The specific issue of sudden death, observed during trial CP02-9815 (STN 125084.46), was a concern that was evaluated during the course of this review by reviewing all provided CRFs for patients who died in the current submission.

9. OVERALL ASSESSMENT

9.1 Conclusions

Cetuximab monotherapy provided a statistically significant improvement in overall survival when compared to best supportive care in patients with EGFR-expressing colorectal carcinoma who have progressed on both oxaliplatin- and irinotecan-containing chemotherapy regimens. The safety profile is acceptable and consistent with prior characterization of clinical side effects.

9.2 Recommendation on Regulatory Action

Approval is recommended for the following indication: Erbitux (b) (4) is indicated

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk management activity will be primarily handled by pharmacovigilance and ongoing postmarketing reports of safety information.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

Two post-marketing commitments were requested by the Agency:

- A study to evaluate the impact of Erbitux on prolongation of the QTc-interval according to principles discussed in ICH E14. The Applicant has agreed to conduct this study and to provide projected milestones, including date of protocol submission, protocol completion, final study report submission, and submission of a labeling supplement, in appropriate, to include results of the QTc study.
- The primary study results, in electronic datasets, for Study CA225006. This data will be submitted as an amendment (b) (4)

9.4 Labeling Review

Implementation of the Physician's Labeling Rule (21 CRF 201.57) required extensive format and content changes to the label. A copy of the original proposed label is attached as an appendix. There were labeling negotiations with the Applicant, and the final version of the label is also attached.

The following points highlight the changes made to the Package Insert (see section 10.2 for more detailed line-by-line review):

INDICATIONS AND USAGE
Colorectal Cancer

- Revised the section to include modified indication for use of Erbitux as monotherapy for treatment mCRC in third line setting (after both irinotecan- and oxaliplatin-containing chemotherapy regimens)

Preparation for Administration

- Made section more concise for clarity

Dosage Forms and Strengths

- Added newly available 200mg/100ml formulation

ADVERSE REACTIONS
Clinical Trials Experience

(b) (4)

Overdosage

- Updated information

CLINICAL STUDIES
Colorectal Cancer

- (b) (4)

9.5 Comments to Applicant

No additional comments to the applicant were provided.

10. APPENDICES

10.1 Review of Individual Study Reports

CA225025 was the only new study with supporting datasets reviewed for this application. This review discusses the data from this study at length. FDA reviews of legacy study reports were also reviewed (STN 125084.0, STN 125084.1, STN 125084.30, STN 125084.46).

10.2 Line-by-Line Labeling Review

Substantive changes are summarized in section 9.4. FDA has recommended the following major changes in the content of the originally proposed label:

Overall changes in the content of most sections, including the elimination of some sections, were made pursuant to the Physician's Labeling Rule (21 CRF 201.57).

(b) (4)

(b) (4)

34 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

10.2.2 Most Recent Text of Erbitux Label (10/1/07)

After labeling meetings with Applicant

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Erbitux® safely and effectively. See full prescribing information for Erbitux®.

Erbitux® (cetuximab)
Solution for intravenous use
Initial U.S. Approval: 2004

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST
See full prescribing information for complete boxed warning.
- **Serious infusion reactions, some fatal, occurred in approximately 3% of patients. (5.1)**
- **Cardiopulmonary arrest and/or sudden death occurred in 2% of patients receiving Erbitux® in combination with radiation therapy. (5.2, 5.6)**

----------RECENT MAJOR CHANGES----------
Indications and Usage, Colorectal Cancer (1.2) 10/2007

----------INDICATIONS AND USAGE----------
Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer
- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. (1.1, 14.1)
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. (1.1, 14.1)

Colorectal Cancer
- As a single agent, EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens. (1.2, 14.2)
- In combination with irinotecan, EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Approval is based on objective response rate; no data are available demonstrating an improvement in increased survival (1.2, 14.2)

----------DOSAGE AND ADMINISTRATION----------
- Premedicate with an H_1 antagonist. (2.3)
- Administer 400 mg/m^2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m^2 weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux® one week prior to initiation of radiation therapy. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grade 3-4 infusion reactions. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneform rash. Reduce dose for recurrent, severe rash. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
- 100 mg/50 mL, single-use vial (3)
- 200 mg/100 mL, single-use vial (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- **Infusion Reactions:** Immediately stop and permanently discontinue Erbitux® for serious infusion reactions. Monitor patients following infusion. (5.1)
- **Cardiopulmonary Arrest:** Closely monitor serum electrolytes during and after Erbitux®. (5.2, 5.6)
- **Pulmonary Toxicity:** Interrupt therapy for acute onset or worsening of pulmonary symptoms. (5.3)
- **Dermatologic Toxicity:** Limit sun exposure. Monitor for inflammatory or infectious sequelae. (2.4, 5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥ 25%) are: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- **Pregnancy:** Administer Erbitux® to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers:** Discontinue nursing during and for 60 days following treatment with Erbitux®. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions: Serious infusion reactions occurred with the administration of Erbitux® in approximately 3% of patients in clinical trials, with fatal outcome reported in less than 1 in 1000. [See *Warnings and Precautions (5.1)* and *Adverse Reactions (6).*] Immediately interrupt and permanently discontinue Erbitux® infusion for serious infusion reactions. [See *Warnings and Precautions (5.1)* and *Dosage and Administration (2.4).*]

Cardiopulmonary Arrest: Cardiopulmonary arrest and/or sudden death occurred in 2% of 208 patients with squamous cell carcinoma of the head and neck treated with radiation therapy and Erbitux®. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux®. [See *Warnings and Precautions (5.2, 5.6).*]

1 INDICATIONS AND USAGE

1.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Erbitux® is indicated in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck. [See *Clinical Studies (14.1).*]

Erbitux®, as a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed. [See *Clinical Studies (14.1).*]

1.2 Colorectal Cancer

Erbitux®, as a single agent, is indicated for the treatment of EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. Erbitux®, as a single agent, is also indicated for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens. [See *Clinical Studies (14.2)* and *Warnings and Precautions (5.7).*]

Erbitux®, in combination with irinotecan, is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. The effectiveness of Erbitux® in combination with irinotecan is based on objective response rates. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Erbitux® in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal carcinoma. [See *Clinical Studies (14.2)* and *Warnings and Precautions (5.7).*]

2 DOSAGE AND ADMINISTRATION

2.1 Squamous Cell Carcinoma of the Head and Neck

Erbitux® in combination with radiation therapy:

- The recommended initial dose is 400 mg/m^2 administered one week prior to initiation of a course of radiation therapy as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).
- The recommended subsequent weekly dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of radiation therapy (6–7 weeks). Complete Erbitux® administration 1 hour prior to radiation therapy.

Erbitux® monotherapy:

- The recommended initial dose is 400 mg/m^2 administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).
- The recommended subsequent weekly dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.2 Colorectal Cancer

- The recommended initial dose, either as monotherapy or in combination with irinotecan, is 400 mg/m^2 administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).

- The recommended subsequent weekly dose, either as monotherapy or in combination with irinotecan, is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.3 Recommended Premedication

Premedicate with an H_1 antagonist (eg, 50 mg of diphenhydramine) intravenously 30–60 minutes prior to the first dose; premedication should be administered for subsequent Erbitux® doses based upon clinical judgment and presence/severity of prior infusion reactions.

2.4 Dose Modifications

Infusion Reactions

Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grade 3–4 infusion reactions.

Immediately and permanently discontinue Erbitux® for serious infusion reactions, requiring medical intervention and/or hospitalization. [See *Warnings and Precautions (5.1)*.]

Dermatologic Toxicity

Recommended dose modifications for severe (NCI-CTC Grade 3 or 4) acneform rash are specified in Table 1. [See *Warnings and Precautions (5.4)*.]

Table 1: Erbitux® Dose Modification Guidelines for Rash

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

2.5 Preparation for Administration

Do not administer Erbitux® as an intravenous push or bolus.

Administer via infusion pump or syringe pump. Do not exceed an infusion rate of 10 mg/min.

Administer through a low protein binding 0.22-micrometer in-line filter.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, cetuximab particulates. **Do not shake or dilute.**

3 DOSAGE FORMS AND STRENGTHS

100 mg/50 mL, single-use vial

200 mg/100 mL, single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of Erbitux® included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, and/or cardiac arrest. Severe (NCI CTC Grade 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in clinical trials, with fatal outcome in 1 patient.

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Monitor patients for 1 hour following Erbitux® infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine,

corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

Immediately and permanently discontinue Erbitux® in patients with serious infusion reactions. [See *Boxed Warning* and *Dosage and Administration (2.4)*.]

5.2 Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and Erbitux® as compared to none of 212 patients treated with radiation therapy alone in a randomized, controlled trial in patients with SCCHN. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of Erbitux®. One patient with no prior history of coronary artery disease died one day after the last dose of Erbitux®. Carefully consider use of Erbitux® in combination with radiation therapy in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux®. [See *Boxed Warning* and *Warnings and Precautions (5.6)*.]

5.3 Pulmonary Toxicity

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving Erbitux® in clinical trials. Interrupt Erbitux® for acute onset or worsening of pulmonary symptoms. Permanently discontinue Erbitux® for confirmed ILD.

5.4 Dermatologic Toxicity

Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychial inflammation, and infectious sequelae (for example *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, cheilitis) occurred in patients receiving Erbitux® therapy. Acneform rash occurred in 76–88% of 1373 patients receiving Erbitux® in clinical trials. Severe acneform rash occurred in 1–17 % of patients.

Acneform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event

continued beyond 28 days. Monitor patients receiving Erbitux® for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during Erbitux®. [See *Dose Modifications (2.4)*.]

5.5 Use of Erbitux® in Combination With Radiation and Cisplatin

The safety of Erbitux® in combination with radiation therapy and cisplatin has not been established. Death and serious cardiotoxicity were observed in a single-arm trial with Erbitux®, radiation therapy, and cisplatin (100 mg/m^2) in patients with locally advanced SCCHN. Two of 21 patients died, one as a result of pneumonia and one of an unknown cause. Four patients discontinued treatment due to adverse events. Two of these discontinuations were due to cardiac events.

5.6 Hypomagnesemia and Electrolyte Abnormalities

In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients (199/365) receiving Erbitux® and was severe (NCI-CTC Grade 3 and 4) in 6–17%. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of Erbitux®. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of Erbitux®. Replete electrolytes as necessary.

5.7 Epidermal Growth Factor Receptor (EGFR) Expression and Response

Because expression of EGFR has been detected in nearly all SCCHN tumor specimens, patients enrolled in the head and neck cancer clinical studies were not required to have immunohistochemical evidence of EGFR tumor expression prior to study entry.

Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR tumor expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak-to-moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Infusion reactions [See *Boxed Warning* and *Warnings and Precautions (5.1).*]
- Cardiopulmonary arrest [See *Boxed Warning* and *Warnings and Precautions (5.2).*]
- Pulmonary toxicity [See *Warnings and Precautions (5.3).*]
- Dermatologic toxicity [See *Warnings and Precautions (5.4).*]
- Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions (5.6).*]

The most common adverse reactions with Erbitux® (incidence ≥ 25%) are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The most serious adverse reactions with Erbitux® are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

Across all studies, Erbitux® was discontinued in 3–10% of patients because of adverse reactions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Erbitux® in 1373 patients with colorectal cancer or SCCHN in randomized phase 3 (Studies 1 and 3) or phase 2 (Studies 2 and 4) trials treated at the recommended dose and schedule for a median of 7 to 14 weeks. [See *Clinical Studies (14).*]

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of patients; infusion reactions were fatal in 1 patient.

Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients.

Renal: Renal failure occurred in 1% of patients with colorectal cancer.

Squamous Cell Carcinoma of the Head and Neck

Table 2 contains selected adverse events in 420 patients receiving radiation therapy either alone or with Erbitux® for locally or regionally advanced SCCHN in Study 1. Erbitux® was administered at the recommended dose and schedule (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 8 infusions (range 1–11).

Table 2: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

	Erbitux® plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
Body System Preferred Term	**Grades 1–4**	**Grades 3 and 4**	**Grades 1–4**	**Grades 3 and 4**
	% of Patients			
Body as a Whole				
Asthenia	56	4	49	5
Fever[1]	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction[2]	15	3	2	0
Infection	13	1	9	1
Chills[1]	16	0	5	0
Digestive				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8

Table 2: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

Body System Preferred Term	Erbitux® plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Respiratory				
Pharyngitis	26	3	19	4
Skin/Appendages				
Acneform Rash[3]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[1] Includes cases also reported as infusion reaction.

[2] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever", or "dyspnea".

[3] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

The incidence and severity of mucositis, stomatitis, and xerostomia were similar in both arms of the study.

Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in Erbitux® in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%). The incidence of Grade 3 or 4 late radiation toxicities was similar between the radiation therapy alone and the Erbitux® plus radiation treatment groups.

Colorectal Cancer

Table 3 contains selected adverse events in 562 patients receiving best supportive care (BSC) alone or with Erbitux® monotherapy for metastatic colorectal cancer in Study 3.

208 Erbitux® was administered at the recommended dose and schedule (400 mg/m^2 initial
209 dose, followed by 250 mg/m^2 weekly).

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux® Monotherapy

	Erbitux® plus BSC (n=288)		BSC alone (n=274)	
Body System Preferred Term	**Any Grades[2]**	**Grades 3 and 4**	**Any Grades**	**Grades 3 and 4**
	% of Patients			
Dermatology				
Rash/Desquamation	89	12	16	<1
Dry Skin	49	0	11	0
Pruritus	40	2	8	0
Other-Dermatology	27	1	6	1
Nail Changes	21	0	4	0
Body as a Whole				
Fatigue	89	33	76	26
Fever	30	1	18	<1
Infusion Reactions[3]	20	5		
Rigors, Chills	13	<1	4	0
Pain				
Abdominal Pain	59	14	52	16
Pain-Other	51	16	34	7
Headache	33	4	11	0
Bone Pain	15	3	7	2
Pulmonary				
Dyspnea	48	16	43	12
Cough	29	2	19	1
Gastrointestinal				
Constipation	46	4	38	5
Diarrhea	39	2	20	2
Vomiting	37	6	29	6
Stomatitis	25	1	10	<1
Other-Gastrointestinal	23	10	18	8
Mouth Dryness	11	0	4	0
Infection				
Infection without neutropenia	35	13	17	6

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux® Monotherapy

	Erbitux® plus BSC (n=288)		BSC alone (n=274)	
Body System	Any Grades[2]	Grades 3 and 4	Any Grades	Grades 3 and 4
Preferred Term	% of Patients			
Neurology				
Insomnia	30	1	15	1
Confusion	15	6	9	2
Anxiety	14	2	8	1
Depression	13	1	6	<1

[1] Adverse reactions occurring more frequently in Erbitux® treated patients compared with controls.

[2] Adverse events were graded using the NCI CTC, V 2.0.

[3] Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion related.

BSC = best supportive care

The most frequently reported adverse events in 354 patients treated with Erbitux® plus irinotecan in clinical trials were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common Grade 3/4 adverse events included diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneform rash (14%).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an ELISA assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving Erbitux® has not been adequately determined. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of 1001) of evaluable patients without apparent effect on the safety or antitumor activity of Erbitux®.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay

methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Erbitux® with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

A drug interaction study was performed in which Erbitux® was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between Erbitux® and irinotecan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with cetuximab. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore, cetuximab has the potential to be transmitted from the mother to the developing fetus. It is not known whether Erbitux® can cause fetal harm when administered to a pregnant woman or whether Erbitux® can affect reproductive capacity. There are no adequate and well-controlled studies of Erbitux® in pregnant women. Erbitux® should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of Erbitux® treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

8.3 Nursing Mothers

It is not known whether Erbitux® is secreted in human milk. IgG antibodies, such as Erbitux®, can be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Erbitux®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If nursing is

interrupted, based on the mean half-life of cetuximab [see *Clinical Pharmacology (12.3)*], nursing should not be resumed earlier than 60 days following the last dose of Erbitux®.

8.4 Pediatric Use

The safety and effectiveness of Erbitux® in pediatric patients have not been established. The pharmacokinetics of cetuximab have not been studied in pediatric populations.

8.5 Geriatric Use

Of the 1062 patients who received Erbitux® with irinotecan or Erbitux® monotherapy in five studies of advanced colorectal cancer, 363 patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Clinical studies of Erbitux® conducted in patients with head and neck cancer did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 208 patients with head and neck cancer who received Erbitux® with radiation therapy, 45 patients were 65 years of age or older.

10 OVERDOSAGE

The maximum single dose of Erbitux® administered is 1000 mg/m^2 in one patient. No adverse events were reported for this patient.

11 DESCRIPTION

Erbitux® (cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian (murine myeloma) cell culture.

Erbitux® is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Erbitux® is supplied at a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use vials. Cetuximab is formulated in a preservative-free solution containing 8.48 mg/mL

sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha. *In vitro* assays and *in vivo* animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. *In vitro*, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

12.3 Pharmacokinetics

Erbitux® administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m^2.

Following the recommended dose regimen (400 mg/m^2 initial dose; 250 mg/m^2 weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with SCCHN and those with colorectal cancer.

Based on a population pharmacokinetic analysis, female patients with colorectal cancer had a 25% lower intrinsic clearance of cetuximab than male patients. Qualitatively similar, but smaller gender differences in cetuximab clearance were observed in patients with SCCHN. The gender differences in clearance do not necessitate any alteration of dosing because of a similar safety profile.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test cetuximab for carcinogenic potential, and no mutagenic or clastogenic potential of cetuximab was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. Menstrual cyclicity was impaired in female cynomolgus monkeys receiving weekly doses of 0.4 to 4 times the human dose of cetuximab (based on total body surface area). Cetuximab-treated animals exhibited increased incidences of irregular or absent cycles, as compared to control animals. These effects were initially noted beginning week 25 of cetuximab treatment and continued through the 6-week recovery period. In this same study, there were no effects of cetuximab treatment on measured male fertility parameters (ie, serum testosterone levels and analysis of sperm counts, viability, and motility) as compared to control male monkeys. It is not known if cetuximab can impair fertility in humans.

13.2 Animal Pharmacology and/or Toxicology

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of

the animals at the highest dose level beginning after approximately 13 weeks of treatment.

14 CLINICAL STUDIES

14.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Study 1 was a randomized, multicenter, controlled trial of 424 patients with locally or regionally advanced SCCHN. Patients with Stage III/IV SCCHN of the oropharynx, hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either Erbitux® plus radiation therapy or radiation therapy alone. Stratification factors were Karnofsky Performance Status (60–80 versus 90–100), nodal stage (N0 versus N+), tumor stage (T1–3 versus T4 using American Joint Committee on Cancer 1998 staging criteria), and radiation therapy fractionation (concomitant boost versus once-daily versus twice-daily). Radiation therapy was administered for 6–7 weeks as once daily, twice daily, or concomitant boost. Erbitux® was administered as a 400 mg/m^2 initial dose beginning one week prior to initiation of radiation therapy, followed by 250 mg/m^2 weekly administered 1 hour prior to radiation therapy for the duration of radiation therapy (6–7 weeks).

Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were Caucasian, and 90% had baseline Karnofsky Performance Status ≥80. There were 258 patients enrolled in US sites (61%). Sixty percent of patients had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

The main outcome measure of this trial was duration of locoregional control. Overall survival was also assessed. Results are presented in Table 4.

Table 4: Study 1: Clinical Efficacy in Locoregionally Advanced SCCHN

	Erbitux® + Radiation (n=211)	Radiation Alone (n=213)	Hazard Ratio (95% CI[a])	Stratified Log-rank p-value
Locoregional control				
Median duration (months)	24.4	14.9	0.68 (0.52–0.89)	0.005
Overall survival				
Median duration (months)	49.0	29.3	0.74 (0.57–0.97)	0.03

[a] CI = confidence interval

Study 2 was a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN. All patients had documented disease progression within 30 days of a platinum-based chemotherapy regimen. Patients received a 20-mg test dose of Erbitux® on Day 1, followed by a 400-mg/m^2 initial dose, and 250 mg/m^2 weekly until disease progression or unacceptable toxicity.

The median age was 57 years, 82% were male, 100% Caucasian, and 62% had a Karnofsky Performance Status of ≥80.

The objective response rate was 13% (95% confidence interval 7%–21%). Median duration of response was 5.8 months (range 1.2–5.8 months).

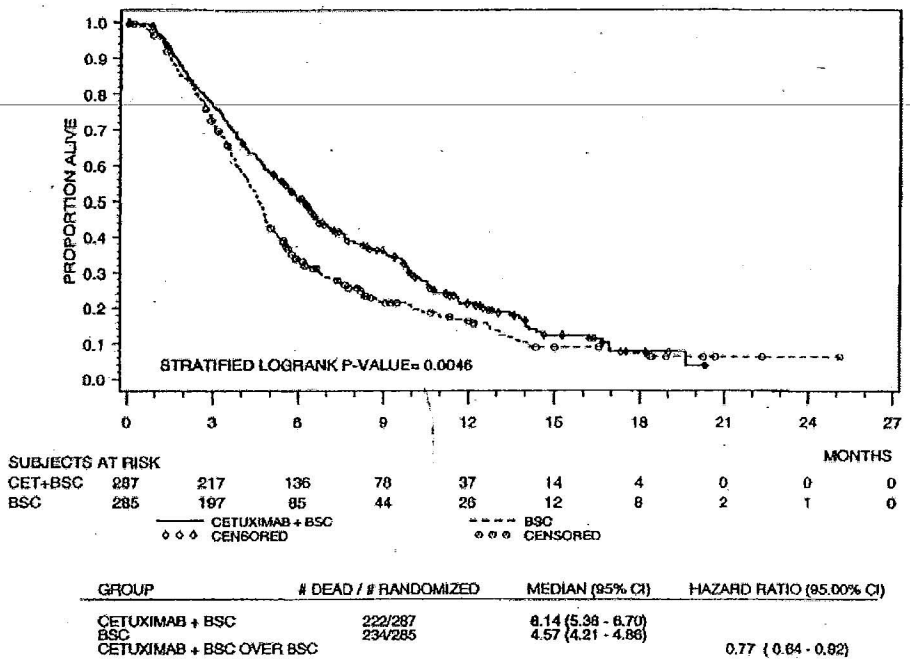
14.2 Colorectal Cancer

Study 3 was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal cancer. Patients were randomized (1:1) to receive either Erbitux® plus best supportive care (BSC) or BSC alone. Erbitux® was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity.

Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were Caucasian, and 77% had baseline ECOG Performance Status of 0–1. All patients were to have received and progressed on prior therapy including an irinotecan-containing regimen and an oxaliplatin-containing regimen.

389 The main outcome measure of the study was overall survival. The results are presented in
390 Figure 1.

391 **Figure 1:** **Kaplan Meier Curve for Overall Survival in Patients with**
392 **Metastatic Colorectal Cancer**



GROUP	# DEAD / # RANDOMIZED	MEDIAN (95% CI)	HAZARD RATIO (95.00% CI)
CETUXIMAB + BSC	222/287	8.14 (5.36 - 8.70)	
BSC	234/285	4.57 (4.21 - 4.86)	
CETUXIMAB + BSC OVER BSC			0.77 (0.64 - 0.92)

393

394 Study 4 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing
395 recurrent metatstatic colorectal cancer. Patients were randomized (2:1) to receive either
396 Erbitux® plus irinotecan (218 patients) or Erbitux® monotherapy (111 patients). Erbitux®
397 was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m^2 weekly until
398 disease progression or unacceptable toxicity. In the Erbitux® plus irinotecan arm,
399 irinotecan was added to Erbitux® using the same dose and schedule for irinotecan as the
400 patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every
401 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly times four doses every 6
402 weeks. Of the 329 patients, the median age was 59 years, 63% were male, 98% were
403 Caucasian, and 88% had baseline Karnofsky Performance Status ≥80. Approximately
404 two-thirds had previously failed oxaliplatin treatment.

The efficacy of Erbitux® plus irinotecan or Erbitux® monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In patients receiving Erbitux® plus irinotecan, the objective response rate was 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months, and median time to progression was 4.1 months. In patients receiving Erbitux® monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%), median duration of response was 4.2 months, and median time to progression was 1.5 months. Similar response rates were observed in the pre-defined subsets in both the combination arm and monotherapy arm of the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

Erbitux® (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, preservative-free, injectable liquid.

NDC 66733-948-23 100 mg/50 mL, single-use vial, individually packaged in a carton

NDC 66733-958-23 200 mg/100 mL, single-use vial, individually packaged in a carton

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased particulate formation may occur at temperatures at or below 0° C. This product contains no preservatives. Preparations of Erbitux® in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

17 PATIENT COUNSELING INFORMATION

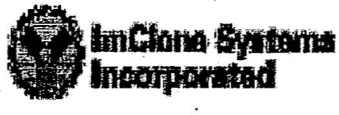
Advise patients:

- To report signs and symptoms of infusion reactions such as fever, chills, or breathing problems.

- Of the potential risks of using Erbitux® during pregnancy or nursing and of the need to use adequate contraception in both males and females during and for 6 months following the last dose of Erbitux® therapy.
- That nursing is not recommended during, and for 2 months following the last dose of Erbitux® therapy.
- To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months following the last dose of Erbitux®.

Erbitux® is a registered trademark of ImClone Systems Incorporated.

Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876
Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543



10.3 Patient Evaluation Flow Sheet – Cetuximab Arm

Investigations		Timing from Randomization
Physical Examination	• Assessment of vital signs[1]	Weekly
	• Physical examination • Weight + ECOG Performance status	every 4 weeks
Hematology	• CBC + differential • Platelet count	
Biochemistry	• Creatinine • Total bilirubin • AST + ALT + Alk Phos	
	• LDH • Sodium, Potassium, Calcium, Magnesium, Glucose	
Economics	• Resource Utilization Assessment	
Cardiac assessment	• ECG	at 16 weeks and at the end of cetuximab therapy, unless within 6 weeks of each other
Radiology & Imaging	• Chest x-ray (PA and lateral)	As clinically indicated
	• CT/MRI scan as per baseline assessment	every 8 weeks + at end of cetuximab therapy if indicated[2]
Other Investigations	• Serum or urine pregnancy test[3]	monthly[3]
Toxicity[4]	• Toxicity evaluation	weekly
Quality of Life	• EORTC QLQ-C30	at 4, 8, 16 and 24 weeks[5]
Health Utilities	• Health Utilities Index (HUI3)	

1. Vital sign measurements will be obtained before, in the middle, at the completion of and 1 hour after cetuximab infusion.
2. Standard tumour measurement procedures will be followed to assess response to therapy. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Radiologists should be blinded to study group assignment. For patients considered to have demonstrated response or prolonged stable disease (CR, PR or SD – see section 10.2), all radiological images (CT/MRI scans in CD format or copied film format, and/or CXR copies) used to characterize identified and reported lesions at baseline and during follow-up will be requested by NCIC central office for central radiology review. It is strongly suggested that investigators consider collecting this information prospectively wherever possible.
3. In women of childbearing potential only a negative pregnancy test must be demonstrated monthly and 4 weeks after the administration of the final dose of cetuximab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.
4. Toxicities will be graded according to the NCI Common Toxicity Criteria Version 2.0 (see Appendix V).
5. EORTC QLQ-C30 and HUI3 to be completed in clinic.

10.4 Patient Evaluation Flow Sheet – Best Supportive Care Arm

Arm 2 – Patients Randomized to Receive Best Supportive Care

Required Investigations	Prestudy	*Weekly	Every 4 weeks	Every 8 weeks	Week 4, 8, 16 and 24	16 weeks
History and Physical						
history[1], physical exam, height, weight	x		x			
ECOG performance status						
clinical tumour measurement[2]						
Hematology						
CBC + differential, platelet count	x		x			
Biochemistry						
creatinine, total bilirubin, AST, ALT, Alk Phos, LDH	x		x			
Radiology						
chest x-ray (CT/MRI)[3]	x[3]	as clinically indicated				
CT/MRI scan of index lesion[4]	x			x[4]		
Other Investigations						
ECG[5]	x					x[5]
serum or urine pregnancy test[6]	x[6]					
post-progression follow-up[7]			x[7]			
EGFR testing[8]	x[8]					
Toxicity						
Toxicity assessments[9]	x		x[9]			
Quality of Life						
EORTC QLQ-C30[10]	x				x[10]	
Resource Utilization						
Health Utilities Index (HUI3)[10]	x				x[10]	
Resource Utilization Assessment			x			

1 Medical history must include date of diagnosis including histological documentation of malignancy, prior anticancer therapy and prior date(s) of disease progression. Note: Documentation of progression or intolerance must be submitted as described in section 10.2.

2 Not required after disease progression has been documented.

3 Where chest x-ray is suspicious for or reveals metastatic disease a CT/MRI scan of the chest must also be performed.

4 Standard tumour measurement procedures will be followed to assess response to therapy. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. A response must be confirmed by tumour reassessment preferable 4 weeks and not more than 6 weeks after the initial evaluation demonstrating a response. CT scan will be conducted at the end of therapy if progression has not yet been demonstrated. For patients considered to have demonstrated response or prolonged stable disease (CR, PR or SD – see section 10.2), all radiological images (CT/MRI scans in CD format or copied film format, and/or CXR copies) used to characterize identified and reported lesions at baseline and during follow-up will be requested by NCIC CTG central office for central radiotherapy review. It is strongly suggested that investigators consider collecting this information prospectively wherever possible.

5 At 16 weeks.

6 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. Should be repeated 4 weeks after end of cetuximab therapy.

7 For post-progression patients not regularly attending clinic (e.g. ECOG PS 4 or hospitalized for end of life care), follow-up may be by telephone.

8 No patient may be randomized until confirmation that representative samples of diagnostic tumour tissue exhibited positive EGFR immunohistochemistry in reference laboratory. Since only EGFR positive patients will be included in the trial, completion of IHC is a critical pre-randomization requirement (see section 13.2).

9 Toxicities will be graded according to the NCI Common Toxicity Criteria Version 2.0 (see Appendix V)

10 EORTC QLQ-C30 and HUI3 to be completed in clinic or patient contacted to complete at home if no longer attending clinic unless deterioration to ECOG PS 4 or hospitalization for end of life care (see Appendix VI and Appendix VII).

10.5 Consultative Review: Division of Scientific Integrity

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 4, 2007

TO: Sharon Sickafuse Regulatory Project Manager, OND/OODP/DBOP
Kevin Shannon, M.D., Medical Officer, OND/OODP/DBOP
Jeff Summers, M.D., Team Leader, OND/OODP/DBOP

THROUGH: Leslie Ball, M.D., Branch Chief, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

FROM: J. Lloyd Johnson, Pharm.D., Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: STN BL 125084/103

APPLICANT: ImClone Systems, Incorporated and Bristol-Myers Squibb Company

DRUG: Erbitux® (cetuximab)

CHEMICAL CLASSIFICATION: 6P (New Indication; Priority Review)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Use as a single agent in the treatment of EGFR-expressing, metastatic colorectal carcinoma

CONSULTATION REQUEST DATE: March 31, 2007

GOAL DATE TO PROVIDE CLINICAL INSPECTION SUMMARY: September 7, 2007

ACTION GOAL DATE: September 19, 2007

I. BACKGROUND

Imclone Systems Inc., submitted a sBLA for Cetuximab (ERBITUX®) an Epidermal growth factor receptor (EGFR) blocker initially approved as combination therapy with irinotecan for the treatment of EGFR-expressing, metastatic colorectal cancer (CRC) in patients who are refractory to irinotecan-based chemotherapy and as a single agent in patients who are intolerant to irinotecan-based chemotherapy. The sponsor is now seeking to expand the single agent indication to include the use cetuximab as monotherapy in the treatment of patients with

EGFR-expressing, metastatic CRC who failed all available standard chemotherapy treatment options.

The initial approval was based on data from the Phase II studies. In this BLA supplement, data from a Phase III study, CA225-025, was submitted in support of the single agent expanded treatment indication in EGFR-expressing, metastatic CRC patients.

The sponsor claims that based on data submitted in Study CA225-025, data is now available from a randomized Phase 3 trial that demonstrate significantly improved survival and confirms the efficacy of single-agent cetuximab in subjects with EGFR-expressing metastatic CRC who have failed all available chemotherapeutic agents, including an irinotecan-containing regimen and an oxaliplatin-containing regimen, for whom no standard anti-cancertherapy is available.

Study CA225-025 was the primary focus of the bioresearch monitoring clinical investigator inspections conducted for this BLA supplement submission. The purpose of the inspections was to validate data submitted in support of BLA 125084/103.

II. RESULTS (by site):

Investigators:

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECTN DATE	EIR-REC'VD	FIELD CLASS.
Derek Jonker , M.D. (Site #013)	Ottawa, Onterio	Canada	Study CA 225-025	August 13 – 17, 2007	Pending	NAI
Malcom Moore, M.D. (Site #029)	Toronto, Onterio	Canada	Study CA225-025	August 20 – 24, 2007	Pending	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations from regulations. Data unreliable

Pending = Inspection/Report not completed
Investigators:

Study Protocol:

CA225-025: A Phase 3, Randomized Study of Cetuximab (Erbitux™, C225) and Best Supportive Care vs. Best Supportive Care in Patients with Pretreated Metastatic Epidermal Growth Factor Receptor (EGFR)- Positive Colorectal Carcinoma.

Page 3 - Clinical Inspection Summary/BLA STN 125084/103

Basis for site selection: DBOP (Division of Biologic Oncology Products) selected two study sites for inspection because of their relatively high subject numbers and considered essential for the approval of the application. No single site drove the study results. DBOP did not identify any specific problems with the study data or specific areas to emphasize during the inspections.

(1) Derek Jonker (Study 225-025) (Site #013) (34 Subjects)
Ottawa Regional Cancer Centre
503 Smyth Road
Ottawa, Onterio
Canada K1H 1C4

Inspection dates: August 13 – 17, 2007.
Methodology: Inspection assignments were issued to the field office.

a. What was inspected
Records of 34 subjects randomized in the study were reviewed.

b. Limitations of inspection: none

General observations/commentary: NOL-DO Field Investigator, Patricia Smith, reported by e-mail that a comprehensive audit of the study records was conducted; source documents were compared with data listings and case report forms. Protocol eligibility criteria, randomization and efficacy end points including response rates, progression date/tumor assessment date, and best response records were reviewed and verified. Adverse events, serious adverse event, deaths, informed consent documents, and drug accountability records were also verified. Overall, the study records were found to be in good shape with good oversight and good source documentation for CRF entries. No deviations/discrepancies from the data listings were observed. NOL-DO is currently preparing the EIR for submission to DSI for evaluation and final classification.

The preliminary inspection results noted above are based on communication from the field investigator. Further review and evaluation of the observations will be made when the EIR and exhibits are submitted. An inspection summary addendum will be generated if conditions change upon receipt and review of the EIR.

Recommendation: Data from this site are acceptable. Preliminary review does not indicate any serious deviations or findings that would impact the validity or reliability of the submitted data

(2) Malcolm Moore (Study 225-025) (Site #029) (41 Subjects)
Princess Margaret Hospital
University Health Network
610 University Avenue
Toronto, Onterio

Inspection dates: August 20 - 27, 2007.
Methodology: Inspection assignments were issued to the field office.

a. What was inspected
The study records of 41 subjects enrolled in the study were audited.

b. Limitations of inspection: none.

c. General observations/commentary: Field Investigator, Patricia Smith, also conducted the inspection of this study site. A similar data audit at this site was conducted. Source documents were compared with data listings and case report forms for protocol eligibility criteria, randomization dates, efficacy study end points including response rates, progression date/tumor assessment date, best response etc. Adverse events, serious adverse event, deaths, informed consent documents, and drug accountability records were reviewed. In general, the study records were also found to be well organized. There were no deviations or discrepancy findings observed. The inspection report (EIR) is being prepared for DSI evaluation and final classification.

The preliminary inspection results noted above are based on communication from the field investigator. Further review and evaluation of the observations will be made when the EIR and exhibits are submitted. An inspection summary addendum will be generated if conditions change upon receipt and review of the EIR.

Recommendation: Data from this site are acceptable. Preliminary review does not indicate any serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the two study sites inspected, it appears that sufficient documentation to assure that all study subjects audited did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

Follow-up action: An inspection summary addendum will be generated if conclusions changes significantly upon receipt and review of the EIRs and evidence exhibits from ATL-DO.

J. Lloyd Johnson, Pharm.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

Page 5 - Clinical Inspection Summary/BLA STN 125084/103

CONCURRENCE:

Supervisory comments:

Joseph J. Saleweski for 9-5-07
Leslie Ball, M.D.
Branch Chief, Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

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DBOP/RPM (Sharon Sickafuse)

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10.6 FDA Form 3454 from Applicant

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Ana Stancic	Senior Vice President, Finance
FIRM / ORGANIZATION	
ImClone Systems Incorporated	
SIGNATURE Ana Stancic	**DATE** 3/23/07

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (4/06) Approved 1.0

financial.pdf

10.7 Non-hematologic Toxicity Dose Modification Scheme

CTC Grade	Action
1	No change
2	Delay until ≤ grade 1 at discretion of Investigator. For nail change (payonychia) reduce 1 dose level.
3	Delay until ≤ grade 2, then resume at one reduced dose level
4	Discontinue patient from any additional cetuximab treatment.

10.8 Dermatologic Toxicity Dose Modification Scheme

Grade	CTC Version 2.0 Description	Guidelines for management	Action
1	Macular or papular eruption or erythema without associated symptoms.	No intervention.	Maintain dose.
2	Macular or papular eruption or erythema with pruritis or other associated symptoms covering < 50% of body surface or localized desquamation or other lesions covering < 50% of body surface area.		
3	Symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥ 50% of the body surface area	Hold cetuximab for up to four consecutive weeks, assessing weekly. Consider concomitant treatment with topical and/or oral antibiotics; topical corticosteroids are not recommended.	Resume treatment when ≤ grade 2. With 1st occurrence use same dose, 2nd occurrence reduce one dose level, 3rd occurrence reduce an additional dose level. On the 4th occurrence discontinue cetuximab. Patient is taken off protocol treatment.
4	Generalized exfoliative dermatitis or ulcerative dermatitis.	Discontinue cetuximab. Consider concomitant treatment with topical and/or oral antibiotics; topical corticosteroids are not recommended.	Patient is taken off protocol treatment.

10.9 Hypersensitivity Reactions Dose Modification Scheme

CTC Grade	CTC Version 2.0 Description	Guidelines for management	Action
1	Transient rash, drug fever <38°C	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.	Maintain 50% reduction in infusion rate.
2	Urticaria, drug fever ≥ 38°C, and/or asymptomatic bronchospasm	Stop cetuximab infusion. Administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.	1st occurrence: Maintain 50% reduction in infusion rate. 2nd occurrence: A patient who experiences a second hypersensitivity reaction ≥ grade 2 in severity under slower infusion rate should have the infusion stopped and should be taken off protocol treatment.
1 or 2	Delayed drug fever (starting after cetuximab infusion)	Maintain cetuximab dose and infusion rate.	Consideration should be given to administration of acetaminophen or a nonsteroidal anti-inflammatory (NSAID) prior to the subsequent cetuximab infusion, if not otherwise contraindicated in subjects. Dose and schedule of these agents is entirely at the investigator's discretion.
3	Symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related oedema/angioedema	Stop the cetuximab infusion immediately and disconnect infusion tubing from the patient. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Telephone/fax NCIC CTG and BMS or telephone/fax AGITG as a serious adverse event (see section 11.5)	Patient taken off protocol treatment.
4	Anaphylaxis		

REFERENCES

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125084/103

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Transitional Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125084/103
Drug Name:	Cetuximab
Indication(s):	Refractory Metastatic Colorectal Cancer
Applicant:	Bristol-Myers Squibb and ImClone
Date(s):	Date Submitted: March 30, 2007 PDUFA due date: October 2, 2007
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Kyung Yul Lee, Ph.D.
Concurring Reviewers:	Mark Rothmann, Ph. D. Aloka Chakravarty, Ph.D.
Medical Division:	Division of Biologic Oncology Products
Clinical Team:	Kevin Shannon, M.D., Clinical reviewer Jeffrey Summers, M.D., Clinical team leader
Project Manager:	Sharon Sickafuse

Keywords: Refractory Metastatic Colorectal Cancer, Best Care Support, Stratified log-rank test, Cox proportional hazards regression

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1. EXECUTIVE SUMMARY

BLA supplement 125084/103 was designed to investigate the effect of cetuximab (Erbitux™) on overall survival (OS) in patients with advanced epidermal growth factor receptor (EGFR) expressing colorectal cancer (CRC) who have failed all chemotherapy and for whom no standard anti-cancer therapy was available. Results of the Phase III trial, Study CA225025 is included in this supplement.

1.1 Conclusions and Recommendations

The cetuximab plus best supportive care arm (cetuximab+BSC) demonstrated superior overall survival (OS) when compared with the best supportive care arm (BSC) for study CA225025 (p=0.0048). Median overall survival was 6.14 months for the cetuximab plus BSC arm and 4.57 months for the BSC arm alone with a difference of 1.57 months. These results were consistent with results of sensitivity analyses conducted by the sponsor and this reviewer. See Section 3.1.3 for the further detail.

The secondary endpoint of progression-free survival demonstrated superiority in the cetuximab plus BSC arm when compared with the BSC arm alone ($p<0.0001$). The median duration of PFS was 1.91 months for cetuximab plus BSC arm and 1.84 months for BSC arm with a difference of 0.07 months (~2 days). For objective response rate, there were no complete or partial responses in the BSC arm patients. The objective response rate is 6.6 because 19 patients out of 286 patients (6.6%) reported partial responses only in the cetuximab+BSC arm.

This study supports that the addition of cetuximab administered weekly with initial dose of 400 mg/m² intravenous (IV) infusion and weekly maintenance dose of 250 mg/m² IV infusion to BSC improves the overall survival in patients with advanced epidermal growth factor receptor (EGFR) expressing metastatic colorectal cancer who are refractory to irinotecan-based chemotherapy in combination with irinotecan and as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients whose disease has progressed following, or who were not suitable candidates to receive, irinotecan- and oxaliplatin-based chemotherapy.

1.2 Brief Overview of Clinical Studies

Study CA225025 is a multi-center, prospective, open-label, randomized Phase 3 trial of Cetuximab +BSC versus BSC alone in patients with previously treated metastatic, EGFR-expressing colorectal cancer. The sponsor's proposed indication is that cetuximab (Erbitux™) is for use as a single agent for the treatment of metastatic colorectal cancer (b) (4) following, oxaliplatin- and irinotecan containing chemotherapy regimens (third-line indication).

The cetuximab arm patients administered cetuximab weekly with initial dose of 400 mg/m² intravenous (IV) infusion and weekly maintenance dose of 250 mg/m² IV infusion until disease progressed, or until other conditions including unacceptable toxicity, symptomatic disease

progression, and need for standard radiation treatment for index lesions, led to discontinuation from protocol treatment. From August 28, 2003 to August 26, 2005, 1243 enrolled patients were tested EGFR expression. A total of 572 eligible patients were randomized for the study after checking EGFR expression; 274 patients to receive cetuximab+BSC and 285 patients to receive BSC by one to one ratio.

The stratification factors were Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 versus 2 and centers. There were total 58 centers, 30 centers in Canada and 28 centers in Australia, New Zealand, and Singapore. In the randomization procedure, Australia, New Zealand, and Singapore were considered as one region, but not for Canada centers. In Canada centers, the enrolled patients less than equal to 5 patients were 12 centers out of 30 Canada centers.

The primary efficacy endpoint was the overall survival and the major secondary efficacy endpoints were the progression-free survival (PFS) and the overall response rate (OR).

1.3 Statistical Issues and Findings

The primary efficacy results of the overall survival and one of major secondary efficacy results of PFS demonstrated statistically significantly longer duration on the cetuximab+BSC compared with the BSC arm. The cetuximab+BSC arm patients demonstrated objective responses but not for the BSC arm patients. In addition, the results of sponsor's sensitivity analyses and reviewer's sensitivity analyses were robust. However, there are statistical issues and these issues are summarized below.

- The estimated differences in median overall survival and median progression-free survival between the two arms were 1.57 months and 0.07 months, respectively.

- In the randomization procedure, the sponsor used ECOG Performance score 0 or 1 versus 2 and centers with 30 centers in Canada and one region of 28 Australia, New Zealand, and Singapore centers for stratification factors. There were less than or equal to 5 patients in the 12 Canada centers out of 30 Canada centers. Only ECOG PS score 0 or 1 versus 2 was used as a stratification factor in the efficacy analyses. However, the efficacy results adjusted using stratification factors as region (Canada versus Non-Canada) and ECOG score PS 0 versus ≥ 1 were very similar.

- There was little estimated benefit or a negative estimated benefit for the cetuximab treatment effect based on overall survival hazard ratios in three subgroups. For LDH level $\leq$ UNL and ECOG score 2 at baseline, the hazard ratios were 0.99 and 0.92. The subgroup sample size of LDH $\leq$UNL was 71 and 63 for cetuximab+BSC and BSC arms, respectively. The sample size of ECOG score 2 was 67 for both of the cetuximab+BSC and the BSC arms. For previously used chemotherapy drug class less than or equal to 2 at baseline, the hazard ratio was 1.18, but the subgroup sample size was only 15 and 13 patients, for the cetuximab+BSC arm and the BSC arm, respectively.

2. INTRODUCTION

2.1 Overview

The cetuximab is currently indicated in combination with irinotecan use for the treatment of EGFR-expressing colorectal cancer in patients who are refractory to irinotecan-based chemotherapy and as a single agent for the treatment of EGFR-expressing colorectal in patients who are intolerant to irinotecan-based chemotherapy.

The sponsor proposed new indication as cetuximab to be for use as a single agent for the treatment of metastatic colorectal cancer (b) (4) following, oxaliplatin- and irinotecan containing chemotherapy regimens.

The primary objective was to examine the effect of cetuximab on overall survival in patients with advanced epidermal growth factor receptor (EGFR)-expressing colorectal cancer who had failed all chemotherapy recommended by their oncologist (including an irinotecan-containing regimen and an oxaliplatin-containing regimen), and for whom no standard anti-cancer therapy was available.

The secondary objectives are to compare the progression-free survival (PFS), objective response rate (OR), safety profile evaluation, quality of life, health utilization and an economic evaluation in patients with pre-treated metastatic, EGFR-expressing, colorectal carcinoma treated with cetuximab plus BSC to BSC only.

A total of 1243 patients were enrolled to this study as early as the time of prior chemotherapy. There were often several months the time between enrollment and randomization because patients were enrolled as the time of prior chemotherapy. After testing EGFR expression and checking of all other eligibility criteria, 572 patients out of 1243 patients were randomized; 287 patients to cetuximab+BSC arm and 285 patients to BSC arm over 2 years in 30 centers of Canada and 28 centers in Australia, New Zealand, and Singapore. In the randomization procedure, Australia, New Zealand, and Singapore were considered as one region. The first patient was randomized on August 28, 2003 and the last patient was randomized on August 26, 2005.

2.2 Data Sources

The sponsor provided datasets electronically, the location of datasets is \\cbsap58\M\EDR Submissions\2007 BLA\DCC60004598\roadmap.pdf.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

The study design was a multicenter, prospective, open-label, randomized Phase 3 trial of cetuximab+BSC versus BSC alone in patients with pre-treated metastatic, EGFR-expressing CRC.

The stratification factors were

- Center (Australia, New Zealand and Singapore region and 30 Canada centers)
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 or 1 versus 2)

Among total of 1243 enrolled patients, after testing EGFR expression and checking of all other eligibility criteria such as patients with $\geq$ 16 years old, had metastatic EGFR-expressive colorectal cancer, ECOG performance status of 0-2, and had received and failed all other standard recommended therapies, 572 patients were randomized (287 patients to cetuximab+BSC, 285 patients to BSC) over a period of 2 years (28-Aug-2003 to 26-Aug-2005) in 30 centers in Canada and in 28 centers in Australia, New Zealand, and Singapore. Dynamic randomization was used for randomization procedure between two treatment arms considering Australia, New Zealand, and Singapore centers as one region.

For patients randomized to receive cetuximab, the initial cetuximab dose (Week 1) was an intravenous (IV) infusion of 400 mg/m^2, administered over 120 minutes and IV infusions of 250 mg/m^2, administered over 60 minutes was followed by weekly maintenance.

The study protocol was amended four times on June 12, 2003, July 29, 2003, May 17, 2004 and February 1, 2005 after patient enrollment. A change that may affect the efficacy evaluation in subsequent amendments was that the denominator of response rates (a complete or partial response) had changed from response evaluable patients to intent-to-treat patients.

In addition, the following analyses were included:

- An analysis of overall survival based on an unstratified log-rank test and a sensitivity analysis using lost to follow-up patients
- Sensitivity analyses for PFS using patients receiving other anti-cancer chemotherapy as censored
- Summary of the number of patients who received prior chemotherapy: TS inhibitors and irinotecan-, and oxaliplatin-based regimens by setting (neoadjuvant, adjuvant, or metastatic)
- Overall survival subgroup analyses based on patients receiving adjuvant or palliative radiotherapy and patients receiving TS inhibitors in the adjuvant setting

3.1.2 Endpoints

The primary efficacy endpoint is overall survival which was defined as the time from randomization to the time of death due to any cause. Patients who were alive at the time of OS analysis or who had been lost to follow-up were censored at their last contact date. Survival was evaluated every 4 weeks post-progression.

The secondary endpoints are time to progression (same as progression-free-survival (PFS)) and response rate (OR). PFS is defined per protocol as the time from randomization to progressive disease or death due to any cause. For PFS, patients who had not progressed or died at the time of analysis or who were lost to follow-up were censored at the date of their last disease assessment. Patients who did not have any post-baseline disease assessments were censored at the randomization date.

The duration of overall response which was computed for patients whose best response was either a complete response (CR) or a partial response (PR). It was defined as the number of months from when the measurement criteria were first met for a CR or PR, whichever is recorded first, until the first date of progressive disease or death. A patient who neither progresses nor dies was censored at the date of their last tumor assessment.

Tumor response was scored on the basis of measurable and evaluable criteria and classified by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Imaging studies of measurable and evaluable tumors were conducted pre-treatment, every 8 weeks during treatment and at post-treatment visits unless a patient discontinued for disease progression. The same method of assessment was used to identify and report each lesion at baseline and each reassessment. A response was confirmed by reassessment no less than 4 to 6 weeks after the initial evaluation demonstrating a response.

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

Among the 572 intent-to-treat patients, 287 patients were assigned to cetuximab+BSC and 285 patients were assigned to BSC. The sponsor defined major protocol deviations based on treatment with cetuximab after episode of greater than common toxicity criteria (CTC) Grade 2 and treatment with another anti-cancer therapy while on study. Table 1 summarizes the major protocol deviations.

Table 1: Major Protocol Deviations

Deviations	Cetuximab+BSC (N=287)	BSC (N=285)
Continuation despite Grade 3/4 Infusion Reaction	9 (3.1%)	0
Received concurrent anticancer therapy	4 (1.4%)	45 (15.8%)

There were total 58 patients in the major protocol violation criteria, 13 (4.5%) in the cetuximab+BSC arm and 45 (15.8%) in the BSC arm.

The discontinuation of study therapy is summarized in Table 2.

Table 2 : Reason Off-Treatment - All Treated Patients

	CETUXIMAB+BSC N = 288
Total patients off treatment	271 (94.1)
Progressive disease	205 (75.6)
Intercurrent illness	5 (1.8)
Symptomatic progression	27 (10.0)
Toxicity to protocol therapy	9 (3.3)
Patient refusal	10 (3.7)
Death	12 (4.4)
Other	3 (1.1)

The progressive disease was the major reason for discontinuation in the cetuximab+BSC group. Nine patients discontinued for treatment-related toxicities (5 for HSRs, 1 for rash/desquamation, 1 for petechiae/purpura, 1 for headache, and 1 for hypomagnesemia). Demographic characteristics at baseline are summarized in Table 3.

Table 3: Demographic Characteristics at Baseline- All Randomized Patients

	Number of Patients (%) CETUXIMAB+BSC N = 287	BSC N = 285	Total N = 572
Gender (Number of Patients [%])			
Female	101(35.19)	103(36.14)	204(35.66)
Male	186(64.81)	182(63.86)	368(64.34)
Race (Number of Patients [%])			
White	258(89.90)	250(87.72)	508(88.81)
Black of African or Caribbean Heritage	5(1.74)	4(1.40)	9(1.57)
Black/Asian	0	1(0.35)	1(0.17)
Asian	20(6.97)	25(8.77)	45(7.87)
American Indian or Alaska Native	0	2(0.70)	2(0.35)
Not Reported	1(0.35)	0	1(0.17)
Unknown	3(1.05)	3(1.05)	6(1.05)
Age (years)			
N	287	285	572
Median	62.98	63.59	63.17
Min - Max	28.60-88.07	28.73-85.93	28.60-88.07
Age Group			
<65	177(61.67)	158(55.44)	335(58.57)
>=65	110(38.33)	127(44.56)	237(41.43)
ECOG Performance Status			
0	72(25.09)	64(22.46)	136(23.78)
1	148(51.57)	154(54.04)	302(52.80)
2	67(23.34)	67(23.51)	134(23.43)
BSA (m**2)			
N	287	285	572
Median	1.83	1.84	
Min - Max	1.30-2.46	1.31-2.50	1.30-2.50

The cetuximab+BSC and BSC groups were comparable for demographic characteristics at baseline. The study population was primarily male (64.3%), white (88.8%), ranged in age from 29 to 88 years with median age of 63.2 years, and only 23.4% had ECOG score 2.

Disease characteristics at baseline are summarized in Table 4.

Table 4: Disease Characteristics at Baseline

	Number of Patients (%)		
	CETUXIMAB+BSC N = 287	BSC N = 285	Total N = 572
Type of Malignancy			
Colon only	171 (59.6)	161 (56.5)	332 (58.0)
Rectum only	63 (22.0)	70 (24.6)	133 (23.3)
Colon and rectum	53 (18.5)	54 (18.9)	107 (18.7)
First Histological Diagnosis to Randomization (months)			
Median	27.4	26.6	26.9
Min - Max	-6.4 - 188.1	0.4 - 181.2	-6.4 - 188.1
Histology			
Adeno-carcinoma	287 (100.0)	284 (99.6)	571 (99.8)
Missing/Unknown	0	1 (0.4)	1 (0.2)
Intensity (Complete Membrane),			
Missing	30 (10.5)	24 (8.4)	54 (9.4)
Weak(1+)	168 (58.5)	158 (55.4)	326 (57.0)
Moderate(2+)	74 (25.8)	81 (28.4)	155 (27.1)
Strong(3+)	15 (5.2)	21 (7.4)	36 (6.3)
Unknown	0	1 (0.4)	1 (0.2)
Type of prior chemotherapy(1)			
At least one Adjuvant	108 (37.6)	103 (36.1)	211 (36.9)
At least one Neo-Adjuvant	9 (3.1)	13 (4.6)	22 (3.8)
At least one Metastatic	286 (99.7)	283 (99.3)	569 (99.5)
Number of prior chemotherapy regimens			
1	2 (0.7)	4 (1.4)	6 (1.0)
2	48 (16.7)	50 (17.5)	98 (17.1)
3	109 (38.0)	108 (37.9)	217 (37.9)
4	87 (30.3)	72 (25.3)	159 (27.8)
5	28 (9.8)	35 (12.3)	63 (11.0)
6	9 (3.1)	10 (3.5)	19 (3.3)
7	3 (1.0)	5 (1.8)	8 (1.4)
8	1 (0.3)	1 (0.4)	2 (0.3)
Prior irinotecan containing regimen			
No	10 (3.5)	12 (4.2)	22 (3.8)
Yes	277 (96.5)	273 (95.8)	550 (96.2)
Prior oxaliplatin containing regimen			
No	6 (2.1)	7 (2.5)	13 (2.3)
Yes	281 (97.9)	278 (97.5)	559 (97.7)

Any Prior Radiotherapy			
No	184 (64.1)	186 (65.3)	370 (64.7)
Yes	103 (35.9)	99 (34.7)	202 (35.3)
Adjuvant	40 (13.9)	34 (11.9)	74 (12.9)
Palliative	55 (19.2)	54 (18.9)	109 (19.1)
Adjuvant and Palliative	8 (2.8)	11 (3.9)	19 (3.3)

There were no big differences in the disease characteristics at baseline between the two arms.

3.1.4 Statistical Methodologies

Sample size determination

In the original protocol, the sample size of 500 was calculated to accrue over 20 months with an additional 8 months follow-up by assuming to detect a hazards ratio of 1.36 between two arms, which corresponds to 9.6% improvement in 1-year survival with the addition of cetuximab for all patients and respectively 10% for patients with ECOG performance status (PS) 0 or 1 and 7.6% for patients with PS 2, using a two-sided 5% level test. The number of 445 events was calculated using 1-year survival of the patients treated by the best supportive care (BSC) is estimated to be improved 16.2% for the 75% patients with PS 0 or 1 patients and 7.9% for the 25% patients with PS 2. The overall 1-year survival for all the patients on the BSC arm of this trial would be 14.1%.

Statistical methods

The primary analyses of all efficacy endpoints were performed using 572 patients (intent-to-treat) which are all randomized patients. All treated 563 patients were used for the safety population.

The primary efficacy endpoint OS and secondary endpoint PFS were analyzed using a two-sided stratified log-rank test with ECOG PS score (0-1 versus 2) at randomization as a stratification factor. In addition, two-sided unstratified log-rank tests were used. The median durations of OS and PFS were estimated using the Kaplan-Meier methods. Stratified Cox regression models were used to estimate the hazard ratio of OS and PFS with ECOG PS score (0-1 versus 2) as a stratification factor.

The sponsor proposed to perform a sensitivity analysis for OS by modifying the definition of censoring for patients who were lost follow-up.

3.1.5 Results and Conclusions

Sponsor's Primary Efficacy Results

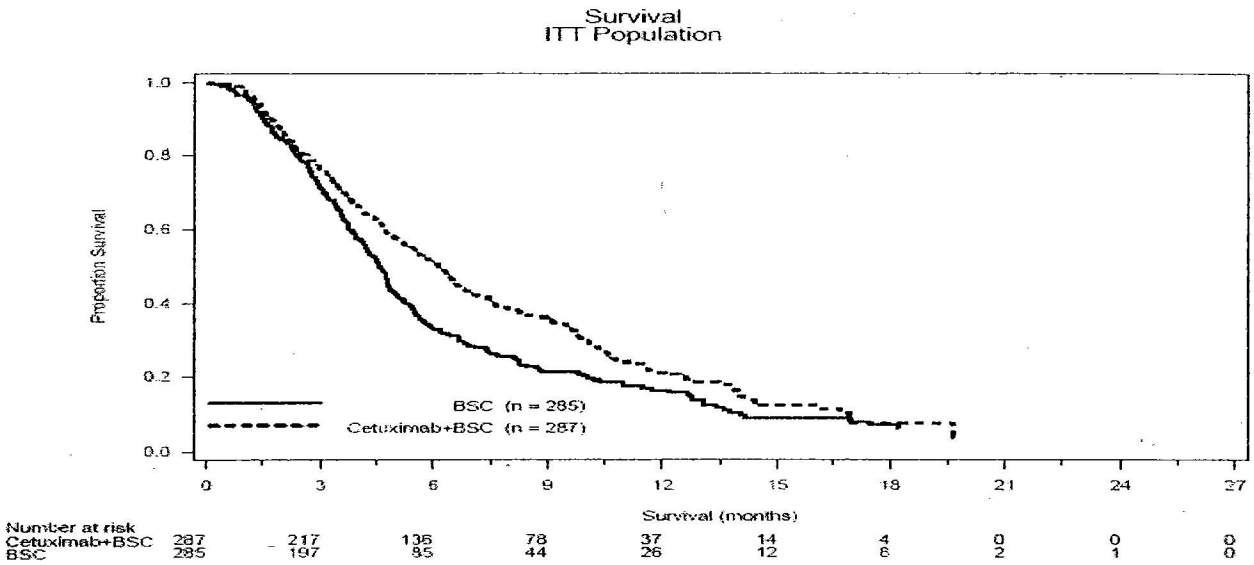
The primary efficacy endpoint of overall survival (OS) is summarized in Table 5.

Table 5: The Primary Endpoint of Overall Survival Analysis Results

Overall Survival	CETUXIMAB+BSC N = 287	BSC N = 285
Number of Patients With OS Event	222 (77.4%)	234 (82.1%)
Number of Patients Without OS Event	65 (22.7%)	51 (17.9%)
Median Duration of OS months(95% CI)	6.14 (5.36, 6.70)	4.57 (4.21, 4.86)
Mean Duration (SE)	7.63 (0.35)	6.22 (0.31)
Minimum, Maximum (@)	0.13, 19.6	0.03, 18.2
Hazard Ratio (95% CI)	0.77 (0.64, 0.92)	
P-Value (Log-Rank Test) With Stratification factor	0.0048	

The cetuximab+BSC arm demonstrated superior overall survival as compared with that of BSC arm. The estimated difference in overall survival between the two arms is small; the median durations of survival was 6.14 months and 4.57 months, for cetuximab+BSC arm and BSC, respectively. The hazard ratio of cetuximab+BSC to BSC alone was 0.77.

Figure 1: Kaplan-Meier Curve for Overall Survival



The Sponsor proposed to perform a sensitivity analysis for overall survival by using lost to follow-up patients as censored. However, in the overall survival analysis, 4 patients out of 116 censored patients were lost to follow-up with two patients in each arm. No sensitivity analysis for OS based on modified definition of censoring for the lost to follow-up was performed.

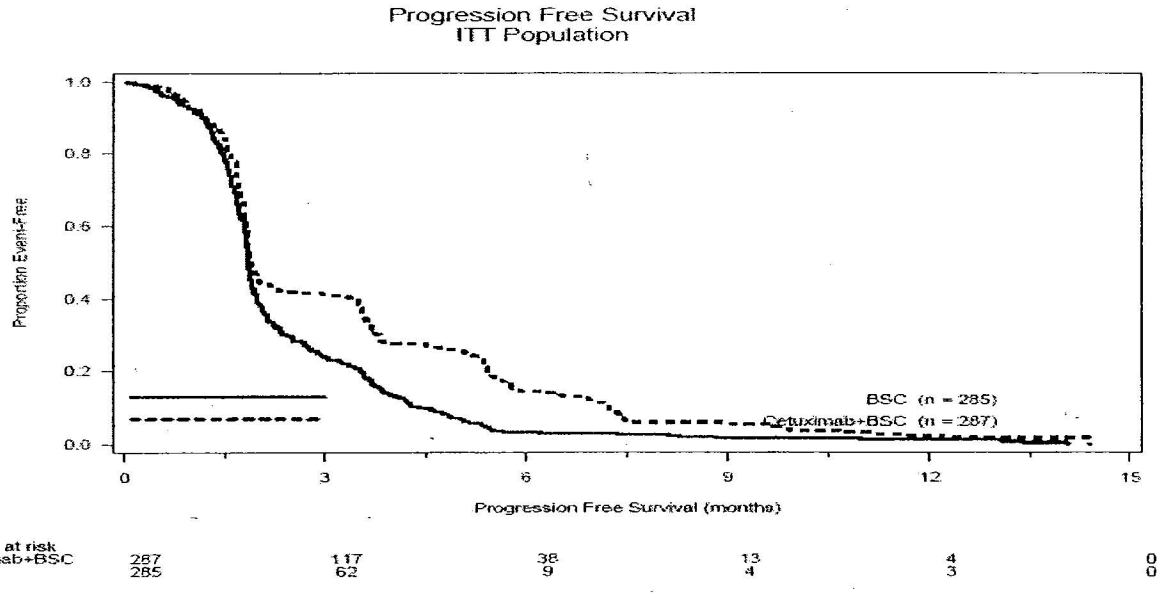
The secondary efficacy endpoint of progression-free survival analysis results are summarized in Table 6.

Table 6: Progression-Free Survival (PFS) Analysis Results

Progression Free Survival	CETUXIMAB+BSC N = 287	BSC N = 285
Number of Patients With PFS Event	273 (95.1%)	269 (94.4%)
Number of Patients Without PFS Event	14 (4.9%)	16 (5.6%)
Median Duration of PFS months (95% CI)	1.91 (1.84, 2.07)	1.84 (1.81, 1.91)
Mean Duration (SE)	3.43 (0.17)	2.48 (0.12)
Minimum, Maximum (@)	0.13, 14.4	0.03, 14.1
Hazard Ratio (95% CI)	0.68 (0.57, 0.81)	
P-Value (Log-Rank Test) With Stratification factor	<0.0001	

The stratified log rank test of PFS was statistically significant for patients randomized to the cetuximab+BSC arm compared to the BSC arm (stratified log-rank $p < 0.0001$) with 1.91 months and 1.84 months of median PFS duration. The hazard ratio of cetuximab+BSC to BSC alone was 0.68 (95% CI: 0.57, 0.80).

Figure 2: Kaplan-Meier Curve for Progression-Free Survival



Tumor measurements were scheduled to be done every 8 weeks from randomization per protocol. The average duration between scans was 54 days both for cetuximab+BSC and BSC arms based on the actual target lesion data.

The sponsor performed the sensitivity analysis for PFS by considering patients who received other anti-cancer chemotherapy as PFS events. Table 7 summarizes the results of the sensitivity analysis.

Table 7: PFS Sensitivity Analysis Results

Progression Free Survival	CETUXIMAB+BSC N = 287	BSC N = 285
Number of Patients With PFS Event	273 (95.1%)	270 (94.7%)
Number of Patients Without PFS Event	14 (4.9%)	15 (5.3%)
Median Duration of PFS months (95% CI)	1.9 (1.8, 2.1)	1.8 (1.8, 1.8)
Hazard Ratio (95% CI)	0.58 (0.49, 0.69)	
P-Value (Log-Rank Test)		
- With Stratification factor	<0.0001	

The hazard ratio of cetuximab+BSC to BSC alone was 0.58 (95% CI: 0.49, 0.69) and stratified log rank test was statistically significant.

The objective response was one of the major secondary efficacy endpoints. The results of objective response are summarized in Table 8.

Table 8: Objective Response Based on Best Response

	Cetuximab+BSC N=287 N (%)	BSC N=285 N (%)
PR	19 (6.6)	0
SD	84 (29.3)	29 (10.2)
PD	133 (46.3)	155 (54.4)
Not evaluable	35 (12.2)	98 (34.3)
Unknown	16 (5.6)	3 (1.1)
Objective Response Rate (CR or PR)[95% CI]	19 (6.6) [4.0-10.2]	0
Median Duration	5.5 months	

There were no complete response patients either in cetuximab+BSC arm or BSC arm. There were no partial response patients in the BSC arm. The objective response rate was 6.6 % based on 19 partial response patients in the cetuximab+BSC arm. The median duration of 19 partial response patients in the cetuximab+BSC arm was 5.5 months.

Reviewer Comment:

The sponsor did not specify how adjustments would be made for multiplicity to guarantee an overall 2-sided 0.05 level for the tests of key secondary efficacy endpoints of progression-free or the objective response rate to include in the labeling in the protocol.

Reviewer's Efficacy Analyses

This reviewer checked the proportional assumption for OS and PFS using plots of the log-log survival versus the log (survival time). The log-log plots for OS and PFS exhibited parallel patterns. The reviewer agrees with the sponsor's conclusion that the proportional assumption was appropriate.

This reviewer examined the time to censoring difference between the two arms by reversing the time to death. The median follow-up time was 12.8 months for cetuximab+BSC arm and 14.4 months for BSC arm. The hazard ratio was 1.07 after adjusting for center and ECOG PS scores.

Center was one of the stratification factors in the randomization procedure. The randomization stratification was used with 30 centers of Canada and Australia, New Zealand, and Singapore as one region. The sponsor analyzed efficacy analyses using a stratification factor of ECOG performance scores 0 or 1 versus 2. This reviewer analyzed the Cox regression for OS and PFS adjusting region Canada versus Australia, New Zealand, and Singapore as Non-Canada region and ECOG score 0 vs. ≥1 as stratification factors. The hazard ratio for OS was 0.76 (0.63, 0.92 with p=0.0041 and the PFS hazard ratio of cetuximab+BSC to BSC was 0.68 (0.57, 0.81) with p <0.0001. The results were almost the same with that of the sponsor.

Table 9: OS and PFS Analysis Results by Canada versus Non-Canada

	Median Months (n)		HR(95%CI)
	Cetuximab+BSC N=287	BSC N=285	
OS			
All Events	6.14 (222)	4.57 (234)	0.77 (0.64, 0.92)
Canada	6.31 (118)	4.73 (128)	0.80 (0.62, 1.03)
Non-Canada	6.14 (104)	4.47 (106)	0.73 (0.55, 0.96)
PFS			
All Events	1.91 (273)	1.84 (269)	0.68 (0.57, 0.81)
Canada	1.94 (153)	1.81 (152)	0.61 (0.48, 0.77)
Non-Canada	1.84 (120)	1.97 (117)	0.79 (0.61, 1.02)

There were no big differences in median survival duration between the two arms across Canada and Non-Canada sites. The OS hazard ratios of cetuximab+BSC to BSC were 0.80 and 0.73, for Canada and Non-Canada sites, respectively. The PFS hazard ratio of cetuximab+BSC to BSC for Canada site (0.61) was smaller than that of Non-Canada site (0.79).

Figure 3: Kaplan-Meier Curve for OS by Canada Site vs. Non-Canada Site

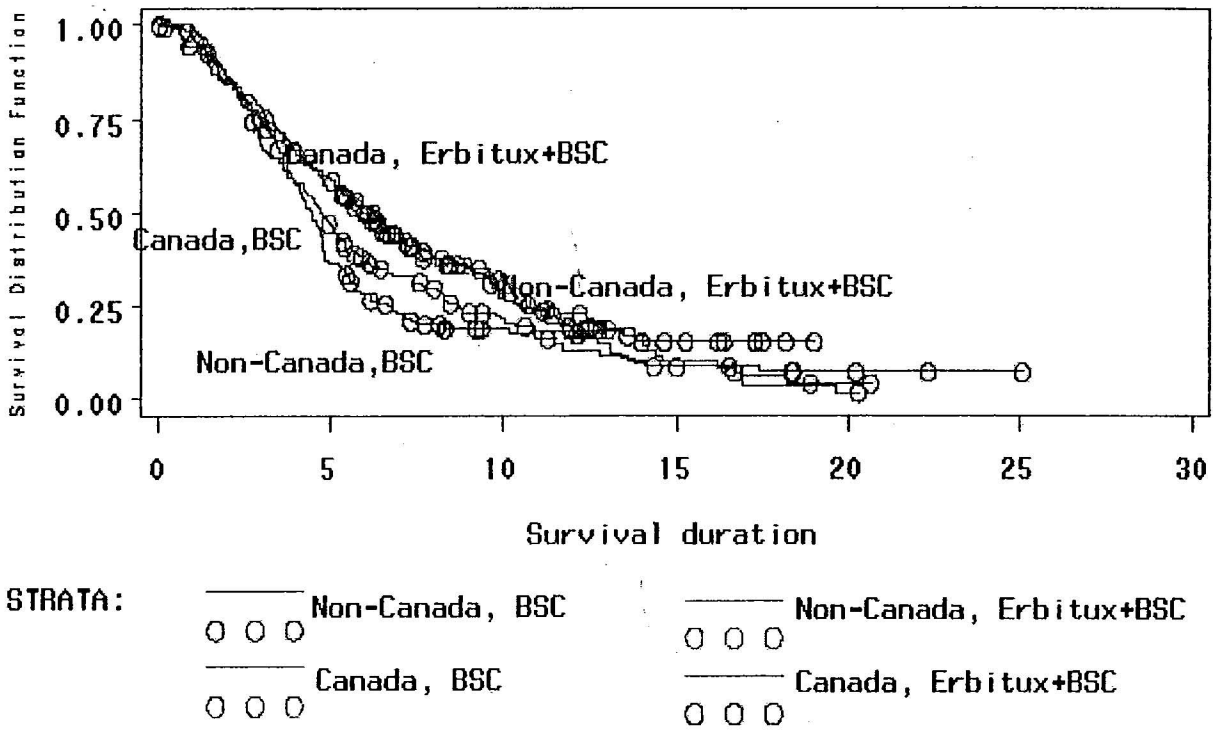
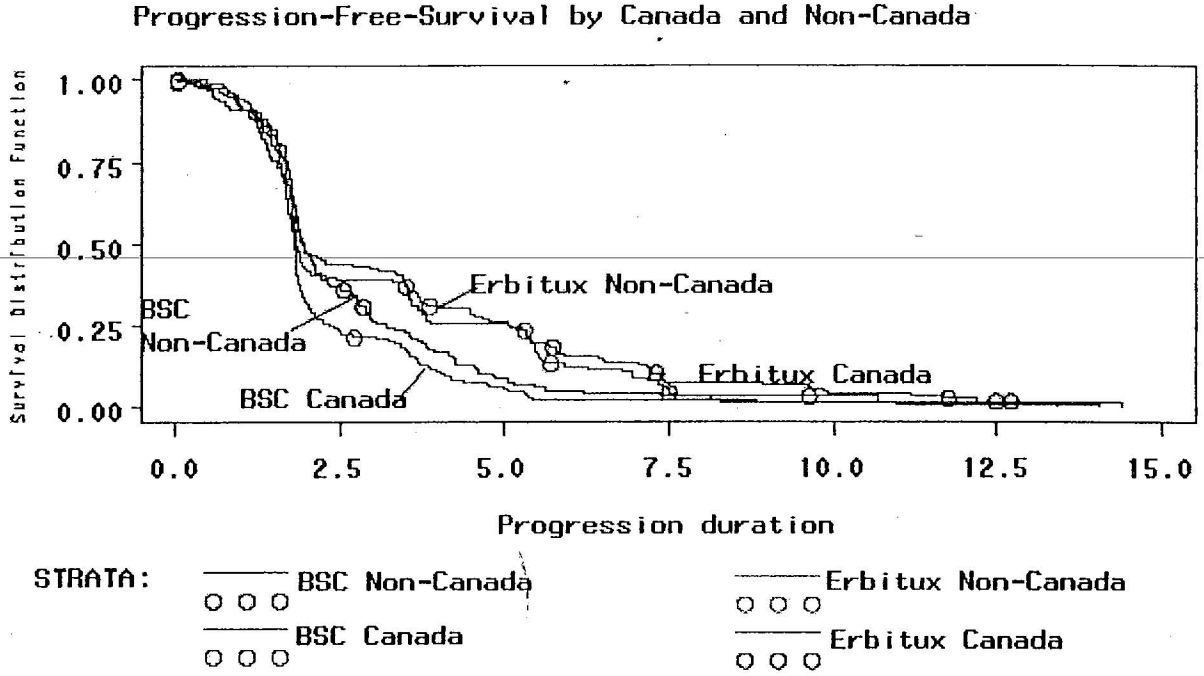


Figure 4: Kaplan-Meier Curve for PFS by Canada Site vs. Non-Canada Site



Conclusions

The primary endpoint of overall survival (OS) was statistically significantly longer among patients in the cetuximab+BSC arm as compared to that of BSC arm ($p=0.0048$). The median durations of survival were 6.14 months and 4.57 months in the cetuximab + BSC arm and BSC arm respectively by adjusting a stratification factor of ECOG score 0-1 versus 2. The reviewer's OS sensitivity analysis by excluding protocol violation patients and a sensitivity analysis using stratification factors, Canada site versus Non-Canada site and ECOG score 0-1 versus 2 provided similar results for the overall survival.

The secondary endpoints of progression-free survival (PFS) was statistically significantly longer among patients in the cetuximab+BSC as compared to that of BSC arm ($p<0.0001$). The sponsor's sensitivity analysis by modifying patients received other anti-cancer chemotherapy as PFS event patients provided similar results.

The results of OS and PFS analyses by Canada site versus Non-Canada site showed similar median durations and hazard ratios.

The objective response rate based on complete response or partial response was 6.6 in the cetuximab+BSC arm and neither CR nor PR response for the BSC arm.

3.2 Evaluation of Safety

For a summary of the evaluation of safety refer the review by Dr. Kevin Shannon.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The subgroup analyses of OS for gender, age, ECOG score, and center are summarized in Table 10.

Table 10: Gender, Age, ECOG Score and Center Subgroup Analyses for OS

Subgroup	Median Months		Hazard Ratio (95% CI)
	Cetuximab+BSC (n) N=287	BSC (n) N=285	
Gender			
Male	6.51 (186)	4.76 (182)	0.80 (0.64, 1.01)
Female	5.52 (101)	4.21 (103)	0.67 (0.49, 0.91)
Age			
<65	6.14 (177)	4.57 (158)	0.80 (0.62, 1.01)
≥65	5.91 (110)	4.53 (127)	0.71 (0.53, 0.95)
Race			
White	6.14 (258)	4.53 (250)	0.79 (0.65, 0.96)
Other	4.80 (26)	4.99 (33)	0.84 (0.43, 1.66)
ECOG Score			
0-1	7.10 (220)	4.96 (218)	0.72 (0.58, 0.89)
2	3.38 (67)	2.96 (67)	0.92 (0.64, 1.32)
ECOG score			
0	7.62 (72)	6.18 (64)	0.74 (0.51, 1.10)
≥ 1	5.42 (215)	4.21 (221)	0.77 (0.62, 0.95)
Region			
Non-Canada	6.14 (125)	4.47 (127)	0.75 (0.57, 0.98)
Canada	6.31 (162)	4.73 (158)	0.78 (0.61, 1.00)

The HRs were adjusted by ECOG score 0 versus ≥1 and region Canada versus Non-Canada. The HRs for ECOG score were adjusted by region. The HRs for region was adjusted by region.

Overall, hazard ratios were similar between the two arms except gender, ECOG score 0 or 1 versus 2. Hazard ratio of the ECOG PS score 2 at baseline was 0.92 as compared with the ECOG score 0 or 1 hazard ratio of 0.72. The hazard ratio for female was smaller than that of male.

4.2 Other Special/Subgroup Populations

Other subgroups, baseline characteristics at baseline are summarized in Table 11.

Table 11: Subgroup Analyses for OS

Subgroup	Median Months		Hazard Ratio (95% CI)
	Cetuximab+BSC (n) N=287	BSC (n) N=285	
Primary Tumor Sites			
Colon	6.14 (224)	4.53 (215)	0.75 (0.61, 0.92)
Rectum	6.14 (63)	5.26 (70)	0.84 (0.56, 1.25)
Hemoglobin			
Grade 0	9.10 (104)	5.55 (87)	0.76 (0.54, 1.08)
Grade ≥1	4.76 (183)	3.98 (198)	0.78 (0.63, 0.97)
LDH			
≤ UNL	8.25 (71)	8.28 (63)	0.99 (0.64, 1.53)
> UNL	5.52 (200)	4.21 (210)	0.72 (0.58, 0.89)
Liver Metastases			
No	8.25 (57)	5.72 (52)	0.78 (0.49, 1.26)
Yes	5.62 (230)	4.30 (233)	0.76 (0.62, 0.93)
ALK			
≤ UNL	9.20 (89)	7.10 (70)	0.78 (0.53, 1.15)
> UNL	5.03 (196)	4.14 (213)	0.78 (0.63, 0.97)
Previous Chemo Drug Class			
≤ 2	6.44 (15)	4.80 (13)	1.18 (0.46, 3.01)
> 2	6.14 (272)	4.57 (272)	0.75 (0.62, 0.91)
Number of regimens			
≤ 3	5.78 (162)	4.47 (159)	0.83 (0.64, 1.07)
> 3	7.49 (123)	4.80 (128)	0.68 (0.51, 0.90)
Disease Site			
≤ 2	9.20 (124)	5.45 (122)	0.66 (0.49, 0.89)
> 2	4.57 (163)	3.98 (163)	0.88 (0.70, 1.12)
TS Inhibitor			
Adjuvant only	5.91 (106)	4.99 (102)	0.83 (0.61, 1.14)
No adjuvant	6.34 (181)	4.27 (183)	0.71 (0.56, 0.89)
EGFR			
1	6.24 (170)	4.76 (158)	0.80 (0.63, 1.02)
≥1	5.65 (90)	4.27 (102)	0.73 (0.53, 1.01)

The HRs were adjusted by ECOG score 0 versus ≥1 and region Canada versus Non-Canada
For some characteristics total numbers of patients in the arm are different from 287 or 285 due to missing or unknown baseline values.

The subgroup analyses of EGFR intensity and EGFR percent for OS are summarized in Table 12.

Table 12: EGFR Subgroup Analyses for OS

	Cetuximab+BSC (n) N=260	BSC (n) N=260	Hazard Ratio (95%CI)
EGFR Intensity			
1	6.24 (170)	4.76 (158)	0.80 (0.63, 1.02)
2	5.65 (75)	4.47 (81)	0.71 (0.50, 1.02)
3	6.34 (15)	3.61 (21)	0.63 (0.29, 1.37)
EGFR Percent			
1-25%	6.24 (124)	4.50 (110)	0.81 (0.61, 1.08)
26-50%	6.70 (68)	4.21 (84)	0.59 (0.41, 0.86)
>50%	4.93 (68)	4.80 (66)	0.95 (0.65, 1.38)

The HRs were adjusted by ECOG score 0 versus ≥1 and region Canada versus Non-Canada.

The patients who reported rash events during the study are summarized by treatment arm. The patients who reported yes for rash/desquamation variable in the toxicity file were used as having rash events.

Table 13: Reported Rash Events by Grade-Safety Population

	Cetuximab+BSC (n) N=286	BSC (n) N=277	P-value
Rash			<0.0001*
No	33	230	
Grade			
≤ 2	19 (57.6%)	187 (81.3%)	
≥ 3	14 (42.4%)	43 (18.7%)	
Yes	253	47	
Grade			
≤ 2	199 (78.7%)	40 (85.1%)	
≥ 3	54 (21.3%)	7 (14.9%)	
Median reported rash events	12	0	
Mean reported rash events	14.8	0.9	

The p-value for Cochran-Mantel-Haenszel test

In the 286 cetuximab+BSC arm patients, 253 patients (88.5%) reported at least one rash event and 33 patients (11.5%) didn't report any rash event. In the 277 BSC arm, only 47 patients (17%) reported at least one rash event and 230 patients (83.0%) reported no rash event. Among 253 patients who reported at least one rash events, 199 patients (78.7%) were Grade less than or equal to 2 and 54 patients (21.3%) were Grade greater than or equal to 3 in the cetuximab+BSC

arm. Among 47 patients who reported at least one rash event, 40 patients (85.1%) were Grade less than or equal to 2 and 7 patients (14.9%) were grade greater than or equal to 3. The median number of reported rash evens was 12 for the cetuximab+BSC arm and 0 for the BSC arm, respectively. The mean number of reported rash events was 14.8 for the cetuximab+BSC arm and 0.9 for the BSC arm. The reported rash events between the two arms were statistically significantly different across grade by Cochran-Mantel-Haenszel test.

This reviewed used a Cox proportional hazards regression using a presence of rash as a time dependent covariate to examine how the risk of rash is related to overall survival. The p-value for the time dependent covariate of a presence of rash was 0.0010. This provides that a presence of rash event was increased over time. The hazard ratio cetuximab +BSC over BSC was 1.42 (p=0.0136) after adjusting for a rash presence as a time dependent covariate.

The rash events were very high in the cetuximab+BSC arm as compared with BSC arm based on the toxicity data. Among 286 cetuximab treated arm patients, 253 patients (88.5%) reported rash events, while 47 patients out of 277 BSC arm patients reported rash events. The median number of reported rash events from the cetuximab arm was 12 and 0 for BSC arm. The presence of rash events was increased over time.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary efficacy results of the overall survival and one of the major secondary efficacy results of PFS demonstrated statistically significantly longer median duration on the cetuximab+BSC arm compared with that of the BSC arm. The cetuximab+BSC arm patients demonstrated objective responses but not for the BSC arm patients. In addition, sponsor's sensitivity analyses and this reviewer's sensitivity analyses provided similar results. The statistical issues are summarized below.

- The estimated differences in median overall survival and median progression-free survival between the two arms were 1.57 months and 0.07 months, respectively.

- In the randomization procedure, the sponsor used ECOG Performance score 0 or 1 versus 2 and centers with 30 centers in Canada and one region of 28 Australia, New Zealand, and Singapore centers for stratification factors. There were less than equal to 5 patients in the 12 Canada centers out of 30 Canada centers. Only ECOG PS score 0 or 1 versus 2 was used as a stratification factor in the efficacy analyses. However, the efficacy results adjusted using stratification factors as region (Canada versus Non-Canada) and ECOG score PS 0 versus $\geq$ 1 were very similar.

- There was little estimated benefit or a negative estimated benefit for the cetuximab treatment effect based on overall survival hazard ratios in three subgroups. For LDH level $\leq$ UNL and ECOG score 2 at baseline, the hazard ratios were 0.99 and 0.92. The subgroup sample size

of LDH ≤UNL was 71 and 63 for cetuximab+BSC and BSC arms, respectively. The sample size of ECOG score 2 was 67 for both of the cetuximab+BSC and the BSC arms. For previously used chemotherapy drug class less than or equal to 2 at baseline, the hazard ratio was 1.18, but the subgroup sample size was only 15 and 13 patients, for the cetuximab+BSC arm and the BSC arm, respectively.

5.2 Conclusions and Recommendations

The cetuximab plus best care supportive arm (cetuximab+BSC) demonstrated superior overall survival (OS) when compared with the best supportive care arm (BSC) for study CA225025 (p=0.0048). The median duration of OS was 6.14 months for cetuximab plus BSC arm and 4.57 months for BSC arm alone. Similar results were provided from the sensitivity analyses conducted by the sponsor and this reviewer. See Section 3.1.3 for further details.

The secondary endpoint of progression-free survival demonstrated superiority in the cetuximab plus BSC arm when compared with the BSC arm alone (p<0.0001). The median duration of PFS was 1.91 months for cetuximab plus BSC arm and 1.84 months for BSC arm with a difference of 0.07 months (~2 days). For objective response rate, there were no complete or partial responses in the BSC arm patients. The objective response rate is 6.6 because 19 patients out of 286 patients (6.6%) reported partial responses only in the cetuximab+BSC arm.

This study supports that the administration of cetuximab weekly with initial dose of 400 mg/m² intravenous (IV) infusion and weekly maintenance dose of 250 mg/m² IV infusion plus BSC to patients with advanced epidermal growth factor receptor (EGFR) expressing colorectal cancer who have failed all chemotherapy and for whom no standard anti-cancer therapy was available improves the overall survival as compared to patients in the BSC arm.

SIGNATURES/DISTRIBUTION LIST (Optional)

Primary Statistical Reviewer: Kyung Yul Lee, Ph.D. Kyung Yul Lee
Date: 9/20/2007

Concurring Reviewer(s):

Statistical Team Leader: Mark Rothmann, Ph.D. Mark Rothmann 9-20-07

Statistical Staff Director: Aloka Chakravarty, Ph.D. Aloka Chakravarty 9/20/07

cc:
HFD-107/ Ms. Sharon Sickafuse
HFD-107/Dr. Kevin Shannon
HFD-107/Dr. Jeff Summers
HFD-107/Dr. Joseph Gootenberg
HFD-711/Dr. Mark Rothmann
HFD-711/Dr. Aloka Chakravarty
HFD-700/Ms. Lillian Patrician
HFD-700/Dr. Edward Nevius

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125084/103

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : STN 125084/103 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A

FDA Received Date: 4-2-07 **Action Date:** 10-2-07

HFM _____ **Product and Proprietary names/dosage form:** Cetuximab (Erbitux) 100 mg, 200 mg

Applicant: ImClone Systems, Inc. **Therapeutic Class:** N/A

Indication(s) previously approved:

Squamous cell carcinoma of the head and neck.

EGFR-expressing metastatic colorectal carcinoma.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Monotherapy for treatment of EGFR-expressing, previously treated, recurrent, metastatic colorectal cancer

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☑ **No: Please check all that apply:** ☐ **Partial Waiver** ☑ **Deferred** ☐ **Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.** 1	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** 18	**Tanner Stage**____

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☑ Adult studies ready for approval
☐ Formulation needed
Other:_____

Date studies are due (mm/dd/yy): 12-31-07

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:

Sharon Sickafuse 9-25-07
Regulatory Project Manager

cc: **NDA/BLA #**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03;revised 8-10-04 for RMS/BLA use)

ImClone Systems Incorporated

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

Targeted Oncology®

Debarment Certification

ImClone Systems Incorporated hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Cheryl Anderson
Vice President, Regulatory Affairs
ImClone Systems Incorporated

3/9/07
Date

LICENSING ACTION RECOMMENDATION
(Required for all BLA supplements without a Completion Package)

Applicant: ImClone Systems, Incorporated BLA #: 125084/103

Product (established and proprietary names): Cetuximab (Erbitux)

Indication / Requested change: To expand the colorectal cancer indication to include Cetuximab as a single agent in patients with EGFR-expressing, metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens.

RECOMMENDED ACTION

X Approval: ☐ Refusal to File: ☐ Denial of application / supplement:

RECOMMENDATION BASIS
(Select all that apply)

☐ Refusal to File Memo
☐ Denial of Application/Supplement Memo

X Approval Action - Discipline Reviews
☐ Approval Action - 2° Review
X Approval Action - 3° Review

X Review of labeling
- X Package Insert – Content
- ☐ Package Insert – SPL Data Elements
- X Package Insert - PLR Format
- ☐ Patient Package Insert
- ☐ Medication Guide
- ☐ Container / Carton (OBP review)

☐ DMPQ Establishment inspections completed

X DSI BiMo inspections completed

☐ OBP Review of Protocols for lot no.(s) _____

☐ OBP Review of Test Results for lot no.(s) _____

X Review of Environmental Assessment
☐ FONSI included X Categorical Exclusion

CLEARANCE – FDA PRODUCT RELEASE
Required for Non-Specified Products Only

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REGULATORY REVIEW

X Compliance status checked - Acceptable

☐ Compliance status checked – Hold (Requires justification for approval action)

☐ Compliance status check not required **(CBE Labeling supplements ONLY)**

Regulatory Project Manager (RPM) Sharon Sickafuse Date: 10-2-07

Chief, Project Management (CPMS) Karen O. Jones Date: 10-2-07

FINAL CLEARANCE

Cross-Discipline Team Leader (if assigned) _____ Date: _____

Responsible Division Director Patricia Keegan Date: 10-2-2007

Form: LARM (CDER – 10/2006)

Jones, Karen

From: Jones, Karen
Sent: Monday, October 01, 2007 9:21 AM
To: 'Cheryl.Anderson@imclone.com'
Cc: Sickafuse, Sharon; Keegan, Patricia
Subject: Draft labeling for STN 125084/103

Importance: High

Attachments: Cetuximab PI_9-28-07 FDA revisions.doc

Cetuximab
_9-28-07 FDA revis.

Hello Cheryl,

On behalf of Sharon Sickafuse, attached is draft labeling for the STN 125084/103 supplement that we want you to have in hand prior to the 10:30 telephone call this morning between FDA and ImClone regarding the labeling for this supplement. In addition to the changes noted in the labeling, we will also request that ImClone (b) (4) ; we will discuss this at 10:30 am.

Please send a response email to Sharon Sickafuse (cc me and Patricia Keegan) confirming your receipt of this email.

Thank you.

Karen D. Jones
Chief, Project Management Staff
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
301-796-1377; fax 301-796-9849

Tracking:

Recipient	Read
'Cheryl.Anderson@imclone.com'	
Sickafuse, Sharon	
Keegan, Patricia	Read: 10/1/2007 9:33 AM

24 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Wednesday, September 26, 2007 2:24 PM
To: 'anderson.cheryl@imclone.com'; 'lynch.deborah@imclone.com'
Subject: request for 2nd PMC

Please submit, as a post marketing,commitment, data sets for primary study data, narrative summaries for all serious adverse events in both treatment arms, and a complete set of case report forms for all patients who died within 30 days of study drug and (b) (4) These data should include determination of the secondary endpoints of progression-free survival, overall response rates, and response durations by the independent endpoint review committee. This information will be submitted (b) (4) by _____.

MEMORANDUM

To: **Sharon Sickafuse**
Division of Biologic Oncology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **September 26, 2007**

Re: **Comments on draft labeling for Erbitux (cetuximab)**
BLA 125084/103

We have reviewed the proposed label for Erbitux (FDA version dated 9/21/07 and the sponsor's response of 9/26/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- Please consider if the boxed warning discussions of infusion reactions and cardiopulmonary arrest should be revised slightly so that the box alerts the reader to the risk, but then the detailed discussion, including clinical recommendations, would appear in the corresponding section of Warnings and Precautions. In general, boxed warnings give brief, concise summaries of the risks to alert the reader to their existence. As currently written, the boxed warning in the Full Prescribing Information (FPI) gives more detailed information than the discussions under 5.1 and 5.2. We suggest that the FPI boxed warning have one or two sentences on each of the two topics, and that the detailed data and clinical recommendations appear under Warnings and Precautions. Some corresponding changes may be needed for the boxed warning in Highlights if changes are made in the FPI. This change would also avoid the awkward bullet for "Cardiopulmonary arrest" in Highlights, which says nothing other than "See boxed warning."

- Please use a lower case "c" for each use of "cetuximab" throughout the label as is done for established names for drugs.

- Throughout the label, doses are often expressed using a dash between the dose and the units (e.g., 400-mg). A recent joint effort of the Institute for Safe Medication Practices and FDA aims to reduce potential medication errors by avoiding abbreviations, symbols, and dose designations known to be commonly misinterpreted. One recommendation is to use only a space between the number and the units (e.g., 400 mg) to avoid misreading of doses. Please revise throughout the label.

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Tuesday, September 25, 2007 4:26 PM
To: 'anderson.cheryl@imclone.com'; 'lynch.deborah@imclone.com'
Subject: FW: Questions for Imclone

Dr. Keegan has the following questions:

From: Keegan, Patricia
Sent: Tuesday, September 25, 2007 1:08 PM
To: Sickafuse, Sharon
Cc: Shannon, Kevin
Subject: Questions for Imclone

I have a couple of questions for Imclone regarding the 125084.103 supplement

1) Do we have an answer about regarding the missing EGFR data- it was implied that data are missing as a result of change in central laboratory site for EGFR testing during the trial. Just need more details on this.

2) Is there an analysis of the incidence (overall and Gr 3-4) of infusion reactions by treatment cycle? If so, idenfity the location of this analysis in the supplement. If not, can Imclone provide this?

3) Were CRFs submitted for all 14 patients who experienced NCI CTC gr 3-4 infusion reactions (HSRs) or only for those who actually discontinued treatment per-protocol? Please provide the patient ID number for each of these 14 patients.

4) Were CRFs submitted for all patients who experienced NCI CTC gr 3-4 cutaneous toxicity or only for those who actually discontinued treatment per-protocol? Please provide the patient ID number for each of these patients.

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Biologic Oncology Products

Application Number: STN 125084/103 9-24-07

Name of Drug: Erbitux (Cetuximab) 100 mg, 200 mg

Applicant: ImClone Systems, Inc.

Material Reviewed:

Submission Date(s): April 12, 2007

Receipt Date(s): April 13, 2007

Submission Date of Structure Product Labeling (SPL): April 12, 2007

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the proposed labeling:

(b) (4)

[redacted]

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Recommendations

Comments conveyed to ImClone on September 21, 2007.

Sharon Sickafuse 9-21-07

Sharon Sickafuse, M.S.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Karen Jones 9/24/07

Karen Jones
Chief, Project Management Staff

Drafted: SKS/8-10-07, 8-16-07, 9-21-07
Revised/Initialed:
Finalized:
Filename: N:DBOP/Sickafuse/Cetuximab/efficacy supplements/STN 125084_91/labeling review.doc
CSO LABELING REVIEW OF PLR FORMAT

Sickafuse, Sharon

om: Ferguson, Shirnette D
nt: Monday, September 24, 2007 9:23 AM
To: Sickafuse, Sharon; CDER-TB-EER
Subject: RE: request for compliance check for STN 125084/103

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the TFRB compliance check below. There are no pending or ongoing compliance actions to prevent approval of STN 125084/103.

Manufacturer	Inspection Date	Classification	Profile
ImClone Systems	6/4-6/8/2007	NAI	BTP
Lonza Biologics	1/8-1/12/2007	NAI	TRP

(b) (4)

Shirnette Ferguson

From: Sickafuse, Sharon
Sent: Friday, September 21, 2007 11:39 AM
To: CDER-TB-EER
Subject: FW: request for compliance check for STN 125084/103

Can I please receive an update on the status of this request? We plan to approve this supplement on October 2nd. Thanks

---

From: Sickafuse, Sharon
Sent: Tuesday, September 04, 2007 6:27 PM
To: CDER-TB-EER
Subject: request for compliance check for STN 125084/103

Please perform a compliance check for the following sBLA:

Sponsor: ImClone Systems, Inc.

Product: Cetuximab (Erbitux)

License #: 1695

Purpose of sBLA: Submit data from confirmatory study of Cetuximab monotherapy for colorectal cancer to convert from accelerated approval to full approval for this indication.

Action due date: October 2, 2007

Cetuximab is manufactured at the following facilities:

Drug Substance Manufacture:

ImClone Systems, Incorporated
33 ImClone Drive
Branchburg, NJ 08876
Contact: Cheryl Anderson, 908-541-8060
Establishment number: 3002889358

Lonza Biologics, Incorporated
101 International Drive
Pease International Tradeport
Portsmouth, NH 03801
Contact: Kim Keyser, 603-610-4613
Establishment number: 3001451441

(b) (4)

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Friday, September 21, 2007 3:22 PM
To: 'anderson.cheryl@imclone.com'; 'lynch.deborah@imclone.com'
Subject: Cetuximab PI

Attachments: Erbitux PLR label 9-21-07.doc

Good Afternoon,

Attached are FDA's proposed revisions to the Cetuximab PI. Please note that most of the sections have been revised due to the PLR requirements. Our promotional labeling and PLR experts may have additional changes, but I don't expect them to be major.

In order for us to meet the action goal date of October 2nd, I need to receive by COB Tuesday, September 25th any items that you want to discuss or change.

I would greatly appreciate it if you could let me know that you've received this. Thanks

Erbitux PLR label 9-21-07.doc ...

21 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Sickafuse, Sharon

From: Shannon, Kevin
Sent: Friday, September 21, 2007 9:48 AM
To: Sickafuse, Sharon
Subject: FW: SAEs

FYI

From: Shannon, Kevin
Sent: Thursday, September 20, 2007 1:19 PM
To: 'Deborah.Lynch@imclone.com'
Subject: SAEs

Hi Deb:

I am getting very different numbers (especially infection) when I run SAEs. I have excluded baseline SAEs. My analysis includes a comparison with the BSC arm which was not provided in the final CSR. FYI, I will include this Table in my review. I don't believe it impacts the label in any way. If you or your team have any comments, please let me know. Thanks,

Kev

Table 23. Incidence of Serious Adverse Events reported for > 4 patients

Serious Adverse Event	Cetuximab + BSC N = 288		BSC N = 274	
	n	%	n	%
Infection	38	13.2	14	5.1
Fever	28	9.7	12	4.4
Abdominal Pain	24	8.3	29	10.6
Vomiting	23	8.0	20	7.3
Pain – other	20	6.9	6	2.2
Dypnea	20	6.9	15	5.5
Fatigue	20	6.9	9	3.3
Nausea	18	6.3	15	5.5
Dehydration	16	5.6	8	2.9
Jaundice/hyperbilirubinemia	13	4.5	6	2.2
Tachyarrhythmias	10	3.5	1	0.4
Confusion	10	3.5	6	2.2
Edema	10	3.5	5	1.8
Anorexia	8	2.8	5	1.8
Anemia	8	2.8	8	2.8
Infusion reactions	7	2.4	0	0
Rigors/Chills	7	2.4	2	0.7
Allergic Reaction	7	2.4	0	0
Thrombosis/embolism	7	2.4	9	3.3
Diarrhea	6	2.1	6	2.2
GI bleeding	6	2.1	10	3.6
Constipation	5	1.7	8	2.9
Cough	5	1.7	6	2.2
Falls	5	1.7	0	0
Anxiety	4	1.4	0	0
Hypomagnesemia	4	1.4	0	0
Urinary Retention	4	1.4	1	0.4

Sickafuse, Sharon

om: Shannon, Kevin
ent: Friday, September 21, 2007 9:48 AM
To: Sickafuse, Sharon
Subject: (b) (4)

FYI

From: Shannon, Kevin
Sent: Thursday, September 20, 2007 12:18 PM
To: 'Deborah.Lynch@imclone.com'
Subject: (b) (4)

Hi Deb:

(b) (4)

Thanks very much,
kevin

**Division of Drug Marketing,
Advertising, and Communications**

Internal Consult

****Pre-decisional Agency Information****

To: Sharon Sickafuse, Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Division of Drug Marketing, Advertising and Communications, CDER

Date: September 21, 2007

Re: **Erbitux (Cetuximab)**
STN BL 125084/403
Comments on draft labeling

In response to your Request for Consultation dated April 23, 2007, we have reviewed ImClone's draft labeling (working copy sent by electronic mail on September 18, 2007) for Erbitux and offer the following comments.

ImClone has submitted a supplemental BLA for conversion from accelerated approval to full approval for the metastatic colorectal cancer single agent indication.

(b) (4)

[redacted]

___2____ Page (s) Withheld

____ Trade Secret / Confidential (b4)

_✓_ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

MINUTES OF A TELECONFERENCE
sBLA STN 125084/103

Date:	September 21, 2007
Time:	1300 – 1335 hours
For FDA:	Kevin Shannon, M.D.
For ImClone:	Cheryl Anderson - Regulatory Affairs
	Hagop Youssoufian, MD - Clinical Research
	Michael Szarek - Biostatistics
	Deb Lynch - Regulatory
For BMS:	Fred Frullo - Regulatory
	Judy Dechamplain - Biostatistics
	Damon Owens - Commercial
	Jamie Fava - Labeling
	Nancy Gustafson - Biostatistics
	Anna Labrosciano - Clinical Project Manager

A teleconference was held with members of ImClone and BMS to discuss several issues regarding their efficacy supplement.

1. It was clarified that datasets were provided only for study CA225025.
2. As datasets were not provided for the other studies, there is no Integrated Summary of Safety.
3. The data cut-off date was March 6, 2006.
4. Dr. Shannon inquired about the missing EGFR data in Table S.3.2 of the final CSR. Specifically 54 patients had missing EGFR intensity data and 1 had unknown data. ImClone/BMS was certain that all patients had to be EGFR-positive prior to randomization, however, the Sponsors had no explanation for the missing data. They agreed to investigate and offer an explanation.
5. ImClone/BMS confirmed the language that approximately 3% of patients receiving Erbitux experienced (b) (4) reactions (CTCAE grade 3/4 reactions).
6. SAE data were extensively discussed. BMS/ImClone asserted they saw no need in the final CSR to provide comparator arm data in the SAE table, since no drug therapy was given in the best supportive care (BSC) arm. The data in the Sponsor's analysis show lower numbers than Dr. Shannon because Dr. Shannon did not use a cut-off date after patients had discontinued Erbitux. The sponsors indicated that it was not possible in the current SAE dataset to determine when disease progression occurred for BSC patients.

Sickafuse, Sharon

om: Sickafuse, Sharon
nt: Thursday, September 20, 2007 1:10 PM
o: 'anderson.cheryl@imclone.com'; 'lynch.deborah@imclone.com'
Subject: STN 125084/103 - request for a PMC

Good Afternoon,

DBOP is requesting a PMC to conduct a study to evaluate the impact of Erbitux on QTc (corrected QT interval) as discussed in ICH E14. Please submit a letter as an amendment to the supplement with your commitment to conduct such a study including the following milestone dates: date of submission of the study protocol to the IND, date for completion of patient accrual, date for completion of the study and date of submission of the final study report including revised labeling, if applicable. I would also appreciate receiving the letter as an email attachment. Thanks

Sickafuse, Sharon

From: Shannon, Kevin
Sent: Wednesday, September 19, 2007 5:26 PM
To: Sickafuse, Sharon
Subject: FW: Erbitux question

Hi Sharon, here was my most recent question to ImClone.
kevin

From: Shannon, Kevin
Sent: Tuesday, September 18, 2007 11:30 AM
To: 'Deborah.Lynch@imclone.com'
Subject: Erbitux question

STN 125084/103

Hi Deb:

Are you able to please supply answers (approximations) to the following question?

As of a recent date, how many patients have received Erbitux (in trials vs. commercially available Erbi).
How many total SAEs have been reported?

Thanks,
kevin

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Tuesday, September 11, 2007 2:23 PM
To: 'lynch.deborah@imclone.com'; 'anderson.cheryl@imclone.com'
Subject: Cetuximab PI - questions

STN 125084/103

Good Afternoon,

My team has the following questions regarding the package insert (line numbers refer to your version with changes marked):

1. Line (b) (4) Please confirm that in the clinical studies, the infusion rate was reduced by 50% for patients who experienced a mild infusion reaction.

2. In all studies, what are the adverse events that lead to Erbitux termination?

3. What is the incidence of renal failure in colorectal caner patients who received Ertibux? Did any cases of renal failure occur in head & neck cancer?

4. Under Adverse Reactions/Postmarketing Experience, please confirm that there are no postmarketing adverse reactions to be included here.

(b) (4)

Thank you

Sickafuse, Sharon

From: Shannon, Kevin
Sent: Tuesday, September 11, 2007 1:55 PM
To: 'Deborah.Lynch@imclone.com'
Cc: Sickafuse, Sharon; Cheryl.Anderson@imclone.com; Summers, Jeff
Subject: RE: STN125084/103 Creatinine Values

Hi Deb:
I have a follow-up question regarding this.
I had hoped that the oversight in listing all creatinine values in one column (but with two different sets of units) would have been corrected. I may have missed something, but I received only the explanation, but no corrected lab table.

To allow FDA to complete a timely review, please provide the following:
CREATININE VALUES (all with identical units) by patient, treatment arm, at BASELINE and during FOLLOW-UP.
If you have any questions, please don't hesitate to give me a call.
Thanks,
kevin
301-796-2007

From: Deborah.Lynch@imclone.com [mailto:Deborah.Lynch@imclone.com]
Sent: Friday, August 17, 2007 5:53 PM
To: Shannon, Kevin
Cc: Sickafuse, Sharon; Cheryl.Anderson@imclone.com
Subject: Re: STN125084/103

Kevin,

Attached please find the requested clarification regarding the serum creatinine values contained in the CO17 TOX dataset. The attached clarification, discussed during our August 14th teleconference was found to be acceptable to address your concerns.

In addition to this transmission, this response will be filed as an amendment to STN BL 125084/103.

Thanks,
Deb

Deborah Lynch
ImClone Systems Incorporated
33 ImClone Drive
Branchburg, NJ 08876
908) 541-8026
deborah.lynch@imclone.com

"Shannon, Kevin" <Kevin.Shannon@fda.hhs.gov>

08/08/2007 04:22 PM

To Deborah.Lynch@imclone.com

cc "Sickafuse, Sharon" <sharon.sickafuse@fda.hhs.gov>

Subject STN125084/103

Hi Deb:

Another question came up today. Regarding serum creatinines in the CO17 TOX dataset...

Values range from 0.03 to 96,000.

There must be some decimal point error.

've again attached by JMP table. Could your team please clarify this. As it is, I cannot analyze these values.
Thanks,
Kevin
<<Creatinine Analysis 8.8.07.JMP>>

Sickafuse, Sharon

'om: Sickafuse, Sharon
nt: Tuesday, September 04, 2007 6:27 PM
o: CDER-TB-EER
Subject: request for compliance check for STN 125084/103

Please perform a compliance check for the following sBLA:

Sponsor: ImClone Systems, Inc.

Product: Cetuximab (Erbitux)

License #: 1695

Purpose of sBLA: Submit data from confirmatory study of Cetuximab monotherapy for colorectal cancer to convert from accelerated approval to full approval for this indication.

Action due date: October 2, 2007

Cetuximab is manufactured at the following facilities:

Drug Substance Manufacture:

ImClone Systems, Incorporated
33 ImClone Drive
anchburg, NJ 08876
ontact: Cheryl Anderson, 908-541-8060
Establishment number: 3002889358

Lonza Biologics, Incorporated
101 International Drive
Pease International Tradeport
Portsmouth, NH 03801
Contact: Kim Keyser, 603-610-4613
Establishment number: 3001451441

(b) (4)

Sickafuse, Sharon

From: Shannon, Kevin
Sent: Sunday, August 12, 2007 10:56 AM
To: 'Deborah.Lynch@imclone.com'
Cc: Sickafuse, Sharon
Subject: STN125084/103

Hi Deb:

Hope you are enjoying a respite from the heat and humidity as we are this weekend.

I have another question, which may possibly be answered in the new dataset table which you will hopefully provide us early in the week.

Question: What are the % incidence and grades (via BMS analysis) of INFUSION REACTIONS? As we have learned, AEs may have been captured differently..."chills/rigors" under one category are not the same, presumably, as "rigors/chills" under another, assuming the busy clinician/investigator on-site discerned this difference and accurately recorded the events. As we know, infusion reactions for cetuximab commonly include events such as chills, rigors, fever, dyspnea, urticaria, flushing, hypotension, angioedema, HA, bronchospasm. Are your analysts equating hypersensitivity rxns (HSK) to infusion reactions - if so, that should be clearly stated. In my opinion HSR are not all immune-mediated and thus some infusion rxns will be missed if we consider infusion reactions to be ONLY those related to HSRs. I do not see a specific entry for Infusion-related AEs in Table 4, the AE Incidence table which we talked so much about last week. Before I spend a lot of time trying to piece these data together, could you please forward this question to your appropriate people so that we can include an appropriate line on incidence and grading of infusion reactions in the label? I would hope your reply would provide not only the "bottom line" answer with incidence rates (n/%) and grades(n/%), but would also include a clear method of analysis with rationale.

THANK YOU VERY MUCH,
kevin

Sickafuse, Sharon

From: Shannon, Kevin
Sent: Friday, August 10, 2007 1:38 PM
To: 'Deborah.Lynch@imclone.com'
Cc: Sickafuse, Sharon
Subject: STN125084/103

Attachments: Patient histories - Cause of death.doc

I'm sorry to bother you again, Deb, but I've encountered a couple patient deaths that were attributed to progressive disease or cancer death, which are possibly related to other causes. In the attached Word document, I've provided the patient ID#'s, brief pertinent clinical histories with my interpretation of the cause of death. Based on my review of the available CRFs, both patients did certainly have progressive neoplastic disease, but the proximal event leading to death did not appear to be directly related to colon cancer.

Would you please have the appropriate members of your Imclone/BMS team review these two patient histories and provide feedback regarding proximal cause of death?

Thanks very much.

Hope you have a quiet weekend.
Kevin

Patient histories - Cause of d...

PATIENT CAVA0021

50yoM with colon CA with extensive metastatic deposits in right abdomen, pelvis and liver was randomized on Apr 15, 2005. He received infusions of Erbitux on April 18, April 25, May 2, 2005, after which he left on a cruise on May 4, 2005. It appears that cultures obtained on May 2, 2005 (prior to his departure on cruise) subsequently became positive for Klebsiella. He received appropriate care onboard ship, was subsequently hospitalized, but had rapid decline with septic parameters. He expired on (b) (6). His extremely rapid decline just days after leaving on a cruise indicates the proximal cause of death to be more likely due to Gram negative sepsis rather than progressive colon carcinoma.

PATIENT AUXA0247

72yoF with mCRC was randomized on September 14, 2004, received Erbitux 9/16/04 – 10/7/04, developed abdominal pain and was admitted to the hospital on (b) (6) with bowel obstruction. Initial evaluation of abdominal CT (b) (6)) was interpreted as "bowel obstruction secondary to colorectal cancer. She was discharged to the palliative care unit for end of life care and died on (b) (6) " The formal CT reading clearly confirms SBO, however the cause is likely "due to the right Spigelian hernia." Dilated bowel lead into the hernia, with a compressed loop more distally. Neoplastic disease was noted to have been progressive; however the proximal cause of death may have been related to hi-grade SBO and strangulation of bowel loop, with subsequent intra-abdominal catastrophe. Spigelian hernias carry very high risk of bowel strangulation, necrosis, and perforation if not promptly corrected by surgical reduction.

Sickafuse, Sharon

From: Shannon, Kevin
Sent: Wednesday, August 08, 2007 4:23 PM
To: 'Deborah.Lynch@imclone.com'
Cc: Sickafuse, Sharon
Subject: STN125084/103

Attachments: Creatinine Analysis 8.8.07.JMP

Hi Deb:

Another question came up today. Regarding serum creatinines in the CO17 TOX dataset...

Values range from 0.03 to 96,000.

There must be some decimal point error.

I've again attached by JMP table. Could your team please clarify this. As it is, I cannot analyze these values.
Thanks,
Kevin

Creatinine Analysis 8.8.07.JMP...

Sickafuse, Sharon

From: Shannon, Kevin
Sent: Wednesday, August 08, 2007 11:30 AM
To: 'Deborah.Lynch@imclone.com'
Cc: Sickafuse, Sharon
Subject: STN BL 125084/103

Attachments: Tox by arm -10% 8.7.07.JMP

Hi Deb: As I mentioned today, I am working on the AE table, which is Table #4 in your red-lined label. I am having trouble confirming all of the incidence percentages. Most values are exactly the same as we obtain. A few a slightly more than 1% off. The items I'd like to ask your team to review are the following:

FIRST ISSUE:
Rash/Desquamation BSC arm, any grade...table states 6%. My calculations based on the raw data from CO17 TOX raw dataset indicate that there was a 3% incidence (8 patients/274):

CA225-025-CAVA-34
CA225-025-CASS-4
CA225-025-CAAJ-16
CA225-025-AUXA-69
CA225-025-AUXA-483
CA225-025-AUXA-424
CA225-025-AUXA-400
CA225-025-AUXA-389

dditional discrepancies:

Fatigue, BSC arm, Any grade: Imclone 76%, FDA calculations 82%
Fever, Erbitux arm, Any grade: 30 % v. 28%
Anorexia, BSC, Any grade, 65 v 68%
Other GI, Erbi, Any, 23 v 21%
Other GI Erbi, G3/4, 10 v 8%
Neuro-sensory BSC, Any, 36 v 39%
Dyspnea BSC, Any, 43 v 45%.

I am including my JMP dataset below which reflects my computations.

SECOND ISSUE:
My initial analysis used the exact preferred terms used by BMS, and we agreed on most of the incidicence figures with the above few exceptions. However, I note that other AE data was captured under slightly different preferred terms. For example:

"Chills, rigors" is a preferred term (Toxicity_) which exists under THREE different categories (FLU-LIKE SYMPTOMS, HYPERSENSITIVITY REACTIONS, and UU).

Another example is the preferred term," fever", which exists under four categories (FLU-LIKE SYMPTOMS nd UU, and "drug fever" under HYPERSENS. and UU).

Another example: "Rash/desquamation" should probably be consolidated with "Rash."

It appears that these data which are captured under slightly different terms should be consolidated. Do you agree? If so, please provide a corrected analysis. If not, please provide an explanation.

Please call me or email if my comments above are unclear.
Thanks.

Kevin

Tox by arm -10% 8.7.07.JMP (18...

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

Date: [redacted]

To: ImClone Systems, Inc. Erbitux sBLA STN [redacted] file

From: Karen D. Jones, Chief Project Management Staff
Division of Biologic Oncology Products
Office of Oncology Drug Products

Subject: Mid-Cycle Review Team Meeting

Attendees:
Kevin Shannon, Jeff Summers, Joseph Gootenberg, Patricia Keegan, Richard Pazdur, Kyung Y. Lee, Mark Rothmann, Karen Jones and J. Lloyd Johnson (by phone)

SUPPLEMENT:

- Sponsor: ImClone Systems, Incorporated
- Product: Erbitux
- Type: BLA Efficacy Supplement, STN 125084/103
- Intended Change : to revise the package insert to provide survival data on Cetuximab monotherapy in the treatment of patients with EGFR-expressing metastatic colorectal carcinoma (b) (4) or who are not suitable candidates to receive, irinotecan an oxaliplatin-based chemotherapy
- Action Goal Date: October 2, 2007

REVIEW TEAM:

- Kevin Shannon, M.D., Medical Officer, OODP, DBOP
- Kyung Y. Lee, Ph.D., Biostatistician, OB, DBV
- Carole Broadnax, M.S., OMP, DDMAC
- J. Lloyd Johnson, M.S., OMP, DSI
- Sharon Sickafuse, M.S., RPM, OODP, DBOP

DISCUSSION:

Supplement Overview/DDMAC and DSI Report: Karen Jones, on behalf of Sharon Sickafuse, provided packages to the meeting attendees that contained copies of the meeting agenda, the January 12, 2007 pre-sBLA meeting minutes, the clinical presentation, the statistical presentation and the supplement reviewer's guide and proposed labeling submitted by ImClone. STN 125084/103 has been designated as a priority review submission with an action goal date of October 2, 2007. This supplement is the first Erbitux supplement requiring labeling in PLR format.
Ms. Jones noted that the DDMAC reviewer on the review team, Carole Broadnax, was unable to attend this meeting but had sent a message that she had no information to present at this time. Ms. Jones also noted that the Division of Scientific Investigation reviewer, J. Lloyd Johnson, was unable to attend the meeting in person, but had provided the following information to be relayed to the team: DSI has no inspection results to report as of this meeting date. DSI has issued inspection assignments for two Canadian sites. The clinical site inspections are scheduled to be completed during the month of August. Results will be communicated following completion of the inspections.

Status of Clinical/Statistical Review: presented by Drs. Kevin Shannon and Kyung Lee. Dr. Shannon noted that ImClone is seeking regular approval for third line therapy of metastatic colorectal cancer. After providing background on the product, current labeled indications, a history of relevant clinical trials conducted, and the regulatory history of the BLA, Dr. Kevin Shannon discussed the clinical trials submitted in the supplement including the study design, study endpoints, inclusion and exclusion criteria, treatment plan, statistical plan and the efficacy and safety data reviewed to date. Dr. Kyung Lee discussed the efficacy results including analyses of overall survival (OS), progression-free survival, objective response rate, and sensitivity and subgroup analyses of OS.

Other Discussion Items:

- **Advisory Committee-** the review team and supervisory staff decided that an advisory committee meeting is not needed for this supplement.
- **Labeling-** time did not permit discussion of the proposed labeling.

Action Items:

- Dr. Pazdur asked that at the next joint FDA-EMEA teleconference EMEA be requested to review the approval of Erbitux in Europe.
- Dr. Keegan requested that Dr. Shannon review the EPIC study high-level flash report.
- Dr. Keegan requested that Dr. Lee conduct an analysis to see if EGFR staining and rash grade correlates with response rate.

Cetuximab sBLA, STN 125084/103

Communication Summary
Kevin Shannon, Medical Officer

June 13, 2007

In a teleconference with ImClone, FDA requested clarification of a discrepancy in the CA225025 CSR. Section 8.3 (p57) stated that "SAEs were only collected for the cetuximab + BSC group." The text then refers to Supplemental Table S6.4. However, among your datasets is Dataset CO17AER, with a description "serious adverse events - raw". Within this dataset are events that have occurred in both treatment arms. Please explain this apparent discrepancy. Are the events in the dataset for the BSC arm truly SAEs?

Cetuximab sBLA, STN 125084/103

Communication Summary
Kevin Shannon, Medical Officer

June 12, 2007

Email sent to ImClone requesting reconciliation of differences in datasets.

Hi Debbie: Dr. Lee (stats) and I are having difficulty with Major Protocol Violations assessment.

Specifically, from your dataset CO17 NCIC Derived, there are 37 patients in the BSC arm and 27 patients in the Erbitux arm who had major violations (total patients = 64). Please see the summary tables below, which are derived from your dataset.

Major Violations by Patients 6...

Major Protocol Violations by A...

Yet, on page 34 of the CSR, "a total of 58 subjects met the criteria of major protocol violation, 13 in the cetuximab group and 45 in the BSC group. Nine subjects continued treatment with cetuximab after an episode of G3/4 HSR and 48 subjects received concurrent anticancer therapy. The text refers to supplemental tables S2.4 andS2.5. These two tables summary data on 58 subjects.

How can we reconcile these differences between the CO17 Derived Dataset and the text/ tables, both with respect to total patients who had violations and with the correct distribution of patients between arms of the study?

If the question isn't clear, please let me know.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125084/103

JUN 12 2007

ImClone Systems, Incorporated
Attention: Cheryl Anderson
Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Anderson:

Please refer to the supplement to your biologics license application (BLA) for Cetuximab, submitted under section 351 of the Public Health Service Act, and to our filing letter dated June 1, 2007. While conducting our filing review we identified the following potential review issues:

1. Hyperlinks in the electronic submission have been identified that are not functional. For example, the co17.xpt link will not open the dataset in the "Dataset Description for Study CA225025." Please provide a plan for ensuring that all links in the submission are functional and a timeframe for correcting this deficiency.

2. A considerable number of errors/omissions have been identified in the CO17_TOX: Adverse Event dataset. For example:

   a. Patient CA225-025-AUXA-3, line 3 form date 2/13/04, initially indicates alopecia is a baseline condition. Confusingly, on line 5 dated 3/16/04, alopecia is again listed, but is NOT labeled as a baseline condition.

   b. Patient CA225-025-AUXA-4, headache onset DT 6/2/04, no resolution, but LR_DT is 2/15/06. This indicates that the headache lasted 1 and 1/2 years.

   c. Patient AUXA-54, headache not present at baseline and no onset date provided.

   d. Patient AUXA-121, headache not present at baseline and no onset date provided.

   e. Patient AUXA-287, headache not present at baseline and no onset date provided.

   f. Patient AUXA-54, vomiting not present at baseline and no onset date and no resolution date provided.

g. Patient AUXA-121, coded as having infection without neutropenia with no onset date and no resolution date recorded on case report form dated July 24, 2004. There is no antecedent form.

Because of the number of apparent inconsistencies in this dataset with respect to recording onset and resolution dates for adverse events, it appears that data were not captured in a systematic manner. Please provide a detailed explanation of the methods used to capture onset and resolution dates of adverse events and perform a review to identify and correct all in consistencies in the adverse event dataset.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 796-2320.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

BLA/NDA/PMA
Review Committee Assignment Memorandum

STN: [redacted]

☒ Initial Assignment
☐ Change

Applicant: ImClone Systems, Incorporated

Product: Cetuximab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
	Reg. Project Manager	Admin/Regulatory		
	Reviewer	Admin/Regulatory		
		Product*		
	Reviewer	Product*		
	Reviewer	Product		
	Reviewer	Clinical		
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
	Reviewer	Biostatistics		
Lloyd Johnson	Reviewer	BiMo	Leslie Ball	5-31-07
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
	Reviewer	Labeling		
		Other		

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Sharon Sickafuse — 5-31-07

Name Printed — Signature — Date

Memo entered in RMS by: _____ Date: _____ QC by: _____ Date: _____

6/4

Cetuximab sBLA, STN 125084/103

Communication Summary
Kevin Shannon, Medical Officer

May 27, 2007

In an email to ImClone (Deborah Lynch), FDA made the following request:

> Hi Deb:
> Could you please tell me what countries Erbitux is approved in, and for what indications?
> I've searched the ImClone website, but I could not find this information.
> THANK YOU.

Cetuximab sBLA, STN 125084/103

Communication Summary
Kevin Shannon, Medical Officer

May 25, 2007

In a teleconference, FDA requested a SAS dataset to include the individual patient number and individual site number for all patients in stud CA225025. Also requested were contact phone numbers for two sites from Study CA225025 (Site 013 and Site 029) to allow for the scheduling of FDA audits.

Applicant:	Imclone
Short Summary:	survival data on cetuximab monotherapy for colorectal cancer
RPM:	Sharon Sickafuse
Office/Division:	OODP/DBOP

Filing worksheet Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed	(Y) N	
❑ including list of all establishment sites and their registration numbers	Y N	
❑ If foreign applicant, US Agent signature.	Y N	
Comprehensive Table of Contents	(Y) N	
Debarment Certification with correct wording (see * below)	(Y) N	
User Fee Cover Sheet	(Y) N	
User Fee payment received	(Y) N	
Financial certification &/or disclosure information	(Y) N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	(Y) N	request submitted 4-12-07.
Pediatric rule: study, waiver, or deferral	(Y) N	
Labeling:	(Y) N	
❑ PI –non-annotated	(Y) N	
❑ PI –annotated	(Y) N	
❑ PI (electronic)	(Y) N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y N	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	
❑ proprietary name (for review)	Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ legible	(Y) N	
❑ English (or translated into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement:		
❑ description and results of studies performed to evaluate the change	Y N	
❑ relevant validation protocols	Y N	
❑ list of relevant SOPs	Y N	
if clinical supplement:		
❑ changes in labeling clearly highlighted	(Y) N	
❑ data to support all label changes	(Y) N	
❑ all required electronic components, including electronic datasets (e.g. SAS)	(Y) N	
if electronic submission:		
❑ required paper documents (e.g. forms and certifications) submitted	(Y) N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication? no
If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? yes PMC #1 under STN 125084/0

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: _____
- Dates: _____

Recommendation (circle one): (File) RTF

RPM Signature: Sharon Sickafuse

Chief, Project Management Staff concurrence: Karen Jones

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y)	N	
❑ Biopharmaceutics and associated analytical methods	(X)	N	NA
❑ Clinical pharmacology [includes immunogenicity]	Y	N	NA
❑ Clinical Efficacy [for each indication]	(Y)	N	
❑ Clinical Safety	(Y)	N	
❑ Synopses of individual studies	(Y)	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	
Study Reports and related information [5.3]	(Y)	N	
❑ Biopharmaceutic	Y	N	NA
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	NA
❑ Pharmacokinetics (PK)	Y	N	NA
❑ Pharmacodynamic (PD)	Y	N	NA
❑ Efficacy and Safety	(Y)	N	
❑ Postmarketing experience	(Y)	N	
❑ Case report forms	(Y)	N	
❑ Individual patient listings (indexed by study)	(Y)	N	
o electronic datasets (e.g. SAS)	(Y)	N	
Literature references and copies [5.4]	(Y)	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
❑ legible	(Y)	N	
❑ English (or certified translation into English)	(Y)	N	
❑ compatible file formats	(Y)	N	
❑ navigable hyper-links	(Y)	N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y)	N	

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records ❑ protocols for clinical trials present ❑ all electronic submission components usable	(Y) N (Y) N (Y) N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements ❑ conducted in compliance with requirements for informed consent	(Y) N (Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electronic datasets complete & usable?	BIMo sites identified?
CA225025	(Y) N	Y N NR	(Y) N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): (File) RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes (No)

Reviewer: Kyung Yul Lee Type (circle one): Clinical Clin/Pharm (Statistical)
(signature/ date)

Concurrence:

Branch Chief: _____ Division. Director: Alaka Chakravarty
(signature/ date) (signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
☐ Biopharmaceutics and associated analytical methods	Y (N)	N/A - Efficacy Supplement
☐ Clinical pharmacology [includes immunogenicity]	Y (N)	
☑ Clinical Efficacy [for each indication]	(Y) N	
☑ Clinical Safety	(Y) N	
☑ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y (N)	N/A - Efficacy supplement
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	Y N	
☐ Biopharmaceutic	Y (N)	
☐ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y (N)	
☐ Pharmacokinetics (PK)	Y (N)	
☐ Pharmacodynamic (PD)	Y (N)	
☐ Efficacy and Safety	(Y) N	
☐ Postmarketing experience	(Y) N	
☐ Case report forms	(Y) N	
☐ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y N	
☐ legible	(Y) N	
☐ English (or certified translation into English)	(Y) N	
☐ compatible file formats	(Y) N	
☐ navigable hyper-links	Y (N)	Has been reported to Sponsor
☐ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
▫ summary reports reference the location of individual data and records	(Y) N	
▫ protocols for clinical trials present	(Y) N	
▫ all electronic submission components usable	Y (N)	- all links not working
statement for each clinical investigation: ▫ conducted in compliance with IRB requirements	(Y) N	
▫ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	N/A - Cetuximab used as single agent
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y (N)	Onset & resolution dates not consistently recorded.
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	(Y)	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y)	N	
adequate characterization of product specificity or mode of action	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	N	N/A - efficacy supplement
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	N	N/A - efficacy supplement
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
CA 225-025	(Y)	N	Y	N	NR	Y	N	Y	N	NR
CA 225-041	(Y)	N	Y	N	NR	Y	N	Y	N	NR
CA 225-045	(Y)	N	Y	N	NR	Y	N	Y	N	NR
INCL CP02-0144	(Y)	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Yes. This is a confirmatory study to determine survival benefit. Another drug in this class has failed to demonstrate OS.

Is an Advisory Committee needed?

NO

Recommendation (circle one): (File) RTF

For BLA and Efficacy BLS: Were any potential review issues identified? (Yes) No

Reviewer: K Shannon 5/21/07 Type (circle one): (Clinical) Clin/Pharm Statistical
(signature/ date)

Concurrence:

~~Branch Chief~~: V Summer Division Director: P. Keegan 5-24-2007
Acting Team Leader (signature/ date) (signature/ date)

BLA/BLS Regulatory Filing Review

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy . An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD)..

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125084/1103 Product: Cetuximab Applicant: Imclone

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): (Traditional) CTD

Filing Meeting: Date 5-21-07 Committee Recommendation (circle one): (File) RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

RPM: Sharon Sickafuse 5-21-07
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - X Part A – RPM
  - ___ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - ___ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - X Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Kyung Lee Kevin Shannon
- ☐ Memorandum of filing recommendation:
  - ___ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
- ☐ Memo of Filing Meeting

Cetuximab sBLA, STN 125084/103

Communication Summary
Kevin Shannon, Medical Officer

May 22, 2007

In a brief teleconference, FDA requested clarification regarding the AUXA sites in Study CA225025. FDA noted that in appendix 1.9.D of the CSR (Enrollment by Center), that 252 patients were enrolled under a single AUXA code. FDA also noted that the AUXA code represents the patients enrolled by the Australasian Gastro-Intestinal Trials Group, but requested clarification if all 252 patients were at a single site or multiple sites.

Cetuximab sBLA, STN 125084/103

Communication Summary
Kevin Shannon, Medical Officer

May 11, 2007

Teleconference including numerous members from ImClone, BMS and Jeff Summers and Kevin Shannon. FDA requested additional clarification on the use of the variables used within the AE datasets for assessment of toxicities in Study CA225025.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drugs Evaluation & Research - Food & Drug Administration
Division of Monoclonal Antibodies
NIH Campus, Building 29B, Room 3NN18, HFD-123
5600 Fishers Lane, Rockville, MD 20857
Telephone (301) 827-0850
Facsimile (301) 827-0852

Date: [redacted]

From: Chana Fuchs, Ph.D.

To: BLA 125084/103 File

Sponsor: ImClone Systems Inc
License Number: 1695

Subject: BLA [redacted] Categorical Exclusion for Environmental Assessment

This efficacy supplement is for use of Erbitux as a single agent for overall su rvival when administered in addition to best supportive care in treatment of EGFR expressing mCRC to increase overall survival.

The sponsor has submitted a categorical exclusion under 21 CFR 25.31 (b). There is no information in this supplement indicating that any additional environmental information is warranted.

The claim of categorical exemption is accepted.

Cetuximab sBLA, STN 125084/103

Communication Summary
Kevin Shannon, Medical Officer

May 8, 2007

A brief teleconference included Deborah Lynch, Jeff Summers and Kevin Shannon. FDA requested information as to why six patients were removed from the BSC analysis set of trial CA225025.

BLA/NDA/PMA
Review Committee Assignment Memorandum

STN: [redacted]

☒ Initial Assignment
☐ Change

Applicant: ImClone Systems, Incorporated

Product: Cetuximab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Sharon Sickafuse	Reg. Project Manager	Admin/Regulatory	K. Jones	4-9-07
	Reviewer	Admin/Regulatory		
		Product*		
	Reviewer	Product*		
	Reviewer	Product		
Kevin Shannon	Reviewer	Clinical	P. Keegan	4-6-07
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
Kyung Y. Lee	Reviewer	Biostatistics	M. Rothmann	3-23-07
	Reviewer	BiMo		
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
Carole Broadnax	Reviewer	Labeling		4-23-07
		Other		

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Sharon Sickafuse
Name Printed Signature

5-7-07
Date

Memo entered in RMS by: _____ Date: _____ QC by: _____ Date: _____

S:\DARP\FORMS\BLA Committee Assignment.doc
Final: 4/16/02; 4/18/02;6/14/02;7/14/03

ENTERED 5/22

Cetuximab sBLA, STN 125084/103

Communication Summary
Kevin Shannon, Medical Officer

May 7, 2007

Email communication sent to Cheryl Anderson, ImClone:

Hi Cheryl,

Thanks in advance for your help.

There were just a few items that we are requesting your help on at this time...

(1) The Roadmap link does not function.

(2) What AE dictionary was used? Was it NCI CTCAE v.2 for all four studies?

(3) What does the column heading "week" in the dataset "CO17_TOX Adverse events - raw" pertain to? It does not seem to consistently correspond to the week# of Erbitux therapy at the time of onset of the AE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125084/103

APR 25 2007

ImClone Systems, Incorporated
Attention: Cheryl Anderson
Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Anderson:

We have received your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

STN	Name of Biological Product
BL 125084/103	Cetuximab / Erbitux

Reason for the submission: To revise the package insert to provide survival data on Cetuximab monotherapy in the treatment of patients with EGFR-expressing metastatic colorectal carcinoma (b) (4) following, or who are not suitable candidates to receive irinotecan- or oxaliplatin-based chemotherapy.

Date of Supplement: March 30, 2007

Date of Receipt: April 2, 2007

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on February 12, 2004, for the pediatric study requirement for this application until December 31, 2007.

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:
http://www.fda.gov/oc/datacouncil/spl.html

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Sharon Sickafuse, at (301) 796-2320.

Sincerely,

Karen D. Jones for

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Thursday, [redacted] 11:35 AM
To: 'anderson.cheryl@imclone.com'
Subject: information request for STN [redacted]

Hi Cheryl, I have the following information request which needs to be submitted as an amendment:

A table of information by investigative site, address, PI, # of patients accrued, and number of Grade 3 - 5 toxicities per site.

Thanks

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: [redacted]

From: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products PK

Subject: Designation of Priority for Supplemental BLA Review
Sponsor: ImClone Systems, Inc.
Product: Cetuximab
Indication: monotherapy for colorectal cancer

To: STN [redacted]

The review status of this file is designated to be:

☐ Standard (10 mon.) ☒ Priority (6 mon.)

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	December 13, 2006
APPLICATION:	IND 5804
SPONSOR:	ImClone Systems, Incorporated
DRUG NAME:	Cetuximab
INDICATION:	Treatment of colorectal cancer
TYPE OF MEETING:	Type B
MEETING RECORDER:	Sharon Sickafuse

FDA ATTENDEES:

Office of Oncology Drug Products
Division of Biologic Oncology Products
Lee Pai-Scherf, M.D.
Sharon Sickafuse, M.S.
Kaushik Shastri, M.D.

Office of Biostatistics
Division V
Mark Rothmann, Ph.D.
Yuan-Li Shen, Ph.D.

Office of Clinical Pharmacology
Division V
Hong Zhao, Ph.D.

SPONSOR ATTENDEES:

ImClone Systems, Inc.
Cheryl Anderson, Vice President, Regulatory Affairs
Margaret. Dalesandro, Vice President, Project Portfolio and Strategic Planning
Terry Katz, Senior Director, Biostatistics
Eric Rowinsky, M.D., Vice President and Chief Medical Officer
Hagop Youssoufian, M.D., Vice President, Clinical Research

Bristol-Myers Squibb, Inc.
Martin Birkhofer, M.D., Vice President, Medical Affairs
Renzo Canetta, M.D., Vice President, Oncology Global Clinical Research
Fred Frullo, Director, Oncology Global Regulatory Sciences
Nancy Gustafson, Director, Biostatistics
Christiane Langer, M.D, Director, Clinical Research

Merck KGaA
Otmar Pfaff, Regulatory Strategy

BACKGROUND: As part of the February 12, 2004, accelerated approval of Cetuximab for Cetuximab, used in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy and for Cetuximab, administered as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy, ImClone agreed to the following postmarketing commitment (PMC) to verify the clinical benefit of Cetuximab therapy:

> To complete Protocol CA225006, "A Phase III, Randomized, Open-Label, Multicenter Study of Irinotecan and Cetuximab versus Irinotecan as Second-Line Treatment in Patients with Metastatic, EGFR-Positive Colorectal Carcinoma" (EPIC study). This protocol was accepted for Special Protocol Assessment on April 25, 2003. Patient accrual will be completed by June 30, 2005, the study will be completed by December 31, 2006, and final study report submitted by June 30, 2007.

On November 7, 2006, ImClone submitted a meeting request to discuss data from study CA225006 as well as study CA225025, "A Phase 3 Randomized Study of Cetuximab and Best Supportive Care Versus Best Supportive Care in Patients with Pretreated Metastatic Epidermal Growth Factor Receptor (EGFR)-Positive Colorectal Carcinoma" (amendment 868). (Study CA225025 is being conducted by the National Cancer Institute of Canada Clinical Trials Groups). The meeting package was submitted on November 24, 2006, as amendment 874.

Draft FDA responses were communicated to ImClone on December 11, 2006.

MEETING OBJECTIVES: To discuss data from studies CA225025 (b) (4) and PMC #1.

SPONSOR QUESTIONS AND FDA RESPONSES:

1. *In light of the statistically significant effect on overall survival with Erbitux in the refractory metastatic colorectal cancer patient population enrolled into study CA225025, does FDA agree that the submission of a study report for this study could satisfy the requirement for a demonstration of clinical benefit with Erbitux treatment in the setting of metastatic colorectal cancer and that the study could therefore be considered to address the relevant post-marketing commitment leading to approval of Erbitux for colorectal cancer?*

   FDA Response:

   Results from the CA225025 study would support regular approval for the use of Erbitux monotherapy as third line therapy for metastatic colorectal cancer.

(b) (4)

Discussion: (b) (4)

Results from CA225025 would (b) (4) support conversion to regular approval of Erbitux administered as a single agent. (b) (4)

(b) (4)

FDA asked for an update on the status of the CRYSTAL study. The CRYSTAL study is a Phase 3 study of Erbitux plus FOLFIRI vs. FOLFIRI alone in patients with previously untreated colorectal cancer. The primary endpoint is progression-free survival (PFS) as determined by an independent review committee. The trial is powered to examine overall survival. ImClone stated that this trial is almost completed and asked if a positive PFS result from the CRYSTAL study would support conversion of Erbitux plus chemotherapy to regular approval. Dr. Pai-Scherf stated that this matter will be the subject of further internal discussion and the decision will be communicated to ImClone at a later time.

FDA recommended that ImClone submit a meeting request to discuss the results of the CRYSTAL study. (b) (4)

Follow-up: (b) (4)

2. *The CA225025 study provides important new information on the efficacy of Erbitux as monotherapy in patients whose disease had progressed after both oxaliplatin and irinotecan containing therapies. Does FDA agree that the data from this study could form the basis for an efficacy supplement?*

FDA Response:

We note that the CA225025 protocol was first submitted to the FDA on October 16, 2006, after results of the study had been analyzed. Assuming that the FDA determines that CA225025 is a well designed and well conducted study, yes.

Discussion: ImClone stated that the protocol and analysis plan for the CA225025 study were submitted prior to the data lock and data analysis. ImClone plans to submit a sBLA for this study by the end of March 2007. FDA asked that ImClone submit a proposed Table of Contents for the proposed sBLA as soon as possible.

In response to FDA questions, regarding the CA225005 study, ImClone stated that the study was conducted in New Zealand, Canada, and Australia. Both arms of the trial had equal data collection. They also collected data on duration of response, subsequent therapy after progression, and the number of cross-overs and will include this data in the sBLA. In addition to CA225005, the sBLA will contain supporting data from the following single arm, Phase 2 monotherapy studies:

Study 045 (n=110) safety and efficacy data will be submitted
Study 041 (n=742) limited safety data will be submitted
Study 0144 (n=346) safety and efficacy data will be submitted

3. *If the answer to question #2 is positive, would the FDA agree that the following claim could be supported by data from study CA225025:*

(b) (4)

FDA Response:

Data from study CA225025 could support the following claim:

(b) (4)

(b) (4)

ATTACHMENTS/HANDOUTS:
ImClone's Presentation