

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)

injection, for intravenous infusion

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 with squamous cell carcinoma of the head and neck treated with Erbitux and radiation therapy and in 3% of patients with squamous cell carcinoma of the head and neck treated with cetuximab in combination with platinum-based therapy with 5-fluorouracil (5-FU). Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux administration. (5.2, 5.6)

RECENT MAJOR CHANGES

Boxed Warning	11/2011
Indications and Usage	
Squamous Cell Carcinoma of the Head and Neck (1.1)	11/2011
Dosage and Administration	
Squamous Cell Carcinoma of the Head and Neck (2.1)	11/2011
Warnings and Precautions	
Cardiopulmonary Arrest (5.2)	11/2011
Dermatologic Toxicity (5.4)	01/2012
Hypomagnesemia and Electrolyte Abnormalities (5.6)	11/2011

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 locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU. (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)

- Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations. (1.2, 12.1, 14.2)

DOSAGE AND ADMINISTRATION

- Premedicate with an H₁ antagonist. (2.3)
- Administer 400 mg/m² initial dose as a 120-minute intravenous infusion followed by 250 mg/m² weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux one week prior to initiation of radiation therapy. Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grade 3 infusion reaction. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneiform 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)
- **Hypomagnesemia:** Periodically monitor during and for at least 8 weeks following the completion of Erbitux. Replete electrolytes as necessary. (5.6)

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: 01/2012

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: SERIOUS INFUSION REACTIONS and** 3 **CARDIOPULMONARY ARREST**

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

9 **Cardiopulmonary Arrest:** Cardiopulmonary arrest and/or sudden death occurred in
10 2% of patients with squamous cell carcinoma of the head and neck treated with Erbitux
11 and radiation therapy in Study 1 and in 3% of patients with squamous cell carcinoma of
12 the head and neck treated with European Union (EU)-approved cetuximab in
13 combination with platinum-based therapy with 5-fluorouracil (5-FU) in Study 2. Closely
14 monitor serum electrolytes, including serum magnesium, potassium, and calcium, during
15 and after Erbitux administration. [See *Warnings and Precautions (5.2, 5.6)*, *Clinical*
16 *Studies (14.1)*.]

17 **1 INDICATIONS AND USAGE**

18 **1.1 Squamous Cell Carcinoma of the Head and Neck** 19 **(SCCHN)**

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

23 Erbitux is indicated in combination with platinum-based therapy with 5-FU for the first-
24 line treatment of patients with recurrent locoregional disease or metastatic squamous cell
25 carcinoma of the head and neck. [See *Clinical Studies (14.1)*.]

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

29 **1.2 Colorectal Cancer**

30 Erbitux, as a single agent, is indicated for the treatment of epidermal growth factor
31 receptor (EGFR)-expressing metastatic colorectal cancer after failure of both irinotecan-
32 and oxaliplatin-based regimens. Erbitux, as a single agent, is also indicated for the
33 treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant
34 to irinotecan-based regimens. [See *Warnings and Precautions* (5.7), *Clinical Studies*
35 (14.2).]

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

43 Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not
44 shown a treatment benefit for Erbitux in patients whose tumors had *KRAS* mutations in
45 codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer
46 with these mutations [see *Clinical Pharmacology* (12.1), *Clinical Studies* (14.2)].

47 **2 DOSAGE AND ADMINISTRATION**

48 **2.1 Squamous Cell Carcinoma of the Head and Neck**

49 Erbitux in combination with radiation therapy or in combination with platinum-based
50 therapy with 5-FU:

- 51 • The recommended initial dose is 400 mg/m² administered one week prior to
52 initiation of a course of radiation therapy or on the day of initiation of platinum-
53 based therapy with 5-FU as a 120-minute intravenous infusion (maximum
54 infusion rate 10 mg/min). Complete Erbitux administration 1 hour prior to
55 platinum-based therapy with 5-FU.
- 56 • The recommended subsequent weekly dose (all other infusions) is 250 mg/m²
57 infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of
58 radiation therapy (6–7 weeks) or until disease progression or unacceptable
59 toxicity when administered in combination with platinum-based therapy with

60 5-FU. Complete Erbitux administration 1 hour prior to radiation therapy or
61 platinum-based therapy with 5-FU.

62 Erbitux monotherapy:

- 63 • The recommended initial dose is 400 mg/m² administered as a 120-minute
64 intravenous infusion (maximum infusion rate 10 mg/min).
- 65 • The recommended subsequent weekly dose (all other infusions) is 250 mg/m²
66 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease
67 progression or unacceptable toxicity.

68 **2.2 Colorectal Cancer**

- 69 • The recommended initial dose, either as monotherapy or in combination with
70 irinotecan, is 400 mg/m² administered as a 120-minute intravenous infusion
71 (maximum infusion rate 10 mg/min).
- 72 • The recommended subsequent weekly dose, either as monotherapy or in
73 combination with irinotecan, is 250 mg/m² infused over 60 minutes (maximum
74 infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

75 **2.3 Recommended Premedication**

76 Premedicate with an H₁ antagonist (eg, 50 mg of diphenhydramine) intravenously
77 30–60 minutes prior to the first dose; premedication should be administered for
78 subsequent Erbitux doses based upon clinical judgment and presence/severity of prior
79 infusion reactions.

80 **2.4 Dose Modifications**

81 **Infusion Reactions**

82 Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC
83 Grade 3 infusion reaction.

84 Immediately and permanently discontinue Erbitux for serious infusion reactions,
85 requiring medical intervention and/or hospitalization. [See *Warnings and Precautions*
86 (5.1).]

87 **Dermatologic Toxicity**

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

Table 1: Erbitux Dose Modification Guidelines for Rash

Severe Acneiform 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		

90 **2.5 Preparation for Administration**

91 **Do not administer Erbitux as an intravenous push or bolus.**

92 Administer via infusion pump or syringe pump. Do not exceed an infusion rate of
 93 10 mg/min.

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

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

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

99 **3 DOSAGE FORMS AND STRENGTHS**

100 100 mg/50 mL, single-use vial

101 200 mg/100 mL, single-use vial

102 **4 CONTRAINDICATIONS**

103 None

104 **5 WARNINGS AND PRECAUTIONS**

105 **5.1 Infusion Reactions**

106 Serious infusion reactions, requiring medical intervention and immediate, permanent
107 discontinuation of Erbitux included rapid onset of airway obstruction (bronchospasm,
108 stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction,
109 and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in
110 2–5% of 1373 patients in Studies 1, 3, 4, and 5 receiving Erbitux, with fatal outcome in
111 1 patient. [See *Clinical Studies (14.1, 14.2).*]

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

114 Monitor patients for 1 hour following Erbitux infusions in a setting with resuscitation
115 equipment and other agents necessary to treat anaphylaxis (eg, epinephrine,
116 corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer
117 to confirm resolution of the event in patients requiring treatment for infusion reactions.

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

120 **5.2 Cardiopulmonary Arrest**

121 Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated
122 with radiation therapy and Erbitux as compared to none of 212 patients treated with
123 radiation therapy alone in Study 1. Three patients with prior history of coronary artery
124 disease died at home, with myocardial infarction as the presumed cause of death. One of
125 these patients had arrhythmia and one had congestive heart failure. Death occurred 27,
126 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. In Study 2, fatal cardiac disorders and/or sudden death occurred in 7 (3%) of 219 patients treated with EU-approved cetuximab and platinum-based therapy with 5-FU as compared to 4 (2%) of 215 patients treated with chemotherapy alone. Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin. Carefully consider use of Erbitux in combination with radiation therapy or platinum-based therapy with 5-FU 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, 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 Studies 1, 3, and 5, as well as other studies, in colorectal cancer and head and neck cancer. Interrupt Erbitux for acute onset or worsening of pulmonary symptoms. Permanently discontinue Erbitux for confirmed ILD.

5.4 Dermatologic Toxicity

Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia inflammation, infectious sequelae (for example *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis occurred in patients receiving Erbitux therapy. Acneiform rash occurred in 76–88% of 1373 patients receiving Erbitux in Studies 1, 3, 4, and 5. Severe acneiform rash occurred in 1–17% of patients.

Acneiform 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 therapy. [See *Dosage and Administration* (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

159 Erbitux, radiation therapy, and cisplatin (100 mg/m²) in patients with locally advanced
160 SCCHN. Two of 21 patients died, one as a result of pneumonia and one of an unknown
161 cause. Four patients discontinued treatment due to adverse events. Two of these
162 discontinuations were due to cardiac events.

163 **5.6 Hypomagnesemia and Electrolyte Abnormalities**

164 In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of
165 365 patients receiving Erbitux in Study 4 and two other clinical trials in colorectal
166 cancer and head and neck cancer, respectively, and was severe (NCI CTC Grades 3 and
167 4) in 6–17%.

168 In Study 2, where EU-approved cetuximab was administered in combination with
169 platinum-based therapy, the addition of cetuximab to cisplatin and 5-FU resulted in an
170 increased incidence of hypomagnesemia (14% vs. 6%) and of Grade 3–4
171 hypomagnesemia (7% vs. 2%) compared to cisplatin and 5-FU alone. In contrast, the
172 incidences of hypomagnesemia were similar for those who received cetuximab,
173 carboplatin, and 5-FU compared to carboplatin and 5-FU (4% vs. 4%). No patient
174 experienced Grade 3–4 hypomagnesemia in either arm in the carboplatin subgroup.

175 The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred
176 days to months after initiation of Erbitux. Periodically monitor patients for
177 hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks
178 following the completion of Erbitux. Replete electrolytes as necessary.

179 **5.7 Epidermal Growth Factor Receptor (EGFR) Expression** 180 **and Response**

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

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

190 **6 ADVERSE REACTIONS**

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

- 193 • Infusion reactions [See *Boxed Warning, Warnings and Precautions (5.1).*]
- 194 • Cardiopulmonary arrest [See *Boxed Warning, Warnings and Precautions (5.2).*]
- 195 • Pulmonary toxicity [See *Warnings and Precautions (5.3).*]
- 196 • Dermatologic toxicity [See *Warnings and Precautions (5.4).*]
- 197 • Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions*
198 *(5.6).*]

199 The most common adverse reactions with Erbitux (incidence $\geq 25\%$) are cutaneous
200 adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and
201 infection.

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

205 Across Studies 1, 3, 4, and 5, Erbitux was discontinued in 3–10% of patients because of
206 adverse reactions.

207 **6.1 Clinical Trials Experience**

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

211 The data below reflect exposure to Erbitux in 1373 patients with colorectal cancer or
212 SCCHN in randomized Phase 3 (Studies 1 and 4) or Phase 2 (Studies 3 and 5) trials
213 treated at the recommended dose and schedule for medians of 7 to 14 weeks. [See
214 *Clinical Studies (14).*]

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

219 **Infections:** The incidence of infection was variable across studies, ranging from
220 13–35%. Sepsis occurred in 1–4% of patients.

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

222 **Squamous Cell Carcinoma of the Head and Neck**

223 ***Erbix in Combination with Radiation Therapy***

224 Table 2 contains selected adverse events in 420 patients receiving radiation therapy either
225 alone or with Erbitux for locally or regionally advanced SCCHN in Study 1. Erbitux was
226 administered at the recommended dose and schedule (400 mg/m² initial dose, followed
227 by 250 mg/m² 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 ^a	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction ^b	15	3	2	0
Infection	13	1	9	1
Chills ^a	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
Alanine Transaminase, high ^c	43	2	21	1
Aspartate Transaminase, high ^c	38	1	24	1
Alkaline Phosphatase, high ^c	33	<1	24	0

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

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				
Acneiform Rash ^d	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

^a Includes cases also reported as infusion reaction.

^b 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”.

^c Based on laboratory measurements, not on reported adverse events, the number of subjects with tested samples varied from 205–206 for Erbitux plus Radiation arm; 209–210 for Radiation alone.

^d Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

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

230 ***Late Radiation Toxicity***

231 The overall incidence of late radiation toxicities (any grade) was higher in Erbitux in
232 combination with radiation therapy compared with radiation therapy alone. The following
233 sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%),
234 subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus
235 (44% versus 35%), skin (42% versus 33%). The incidence of Grade 3 or 4 late radiation
236 toxicities was similar between the radiation therapy alone and the Erbitux plus radiation
237 treatment groups.

238 ***Study 2: EU-Approved Cetuximab in Combination with Platinum-based*** 239 ***Therapy with 5-Fluorouracil***

240 Study 2 used EU-approved cetuximab. Since U.S.-licensed Erbitux provides
241 approximately 22% higher exposure relative to the EU-approved cetuximab, the data

provided below may underestimate the incidence and severity of adverse reactions anticipated with Erbitux for this indication. However, the tolerability of the recommended dose is supported by safety data from additional studies of Erbitux [see *Clinical Pharmacology* (12.3)].

Table 3 contains selected adverse events in 434 patients with recurrent locoregional disease or metastatic SCCHN receiving EU-approved cetuximab in combination with platinum-based therapy with 5-FU or platinum-based therapy with 5-FU alone in Study 2. Cetuximab was administered at 400 mg/m² for the initial dose, followed by 250 mg/m² weekly. Patients received a median of 17 infusions (range 1–89).

Table 3: Incidence of Selected Adverse Events (≥10%) in Patients with Recurrent Locoregional Disease or Metastatic SCCHN

System Organ Class Preferred Term	EU-Approved Cetuximab plus Platinum-based Therapy with 5-FU (n=219)		Platinum-based Therapy with 5-FU Alone (n=215)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Eye Disorders				
Conjunctivitis	10	0	0	0
Gastrointestinal Disorders				
Nausea	54	4	47	4
Diarrhea	26	5	16	1
General Disorders and Administration Site Conditions				
Pyrexia	22	0	13	1
Infusion Reaction ^a	10	2	<1	0
Infections and Infestations				
Infection ^b	44	11	27	8
Metabolism and Nutrition Disorders				
Anorexia	25	5	14	1
Hypocalcemia	12	4	5	1
Hypokalemia	12	7	7	5
Hypomagnesemia	11	5	5	1

Table 3: Incidence of Selected Adverse Events (≥10%) in Patients with Recurrent Locoregional Disease or Metastatic SCCN

System Organ Class Preferred Term	EU-Approved Cetuximab plus Platinum-based Therapy with 5-FU (n=219)		Platinum-based Therapy with 5-FU Alone (n=215)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Skin and Subcutaneous Tissue Disorders				
Acneiform Rash ^c	70	9	2	0
Rash	28	5	2	0
Acne	22	2	0	0
Dermatitis Acneiform	15	2	0	0
Dry Skin	14	0	<1	0
Alopecia	12	0	7	0

^a Infusion reaction defined as any event of “anaphylactic reaction”, “hypersensitivity”, “fever and/or chills”, “dyspnea”, or “pyrexia” on the first day of dosing.

^b Infection – this term excludes sepsis-related events which are presented separately.

^c Acneiform rash defined as any event described as “acne”, “dermatitis acneiform”, “dry skin”, “exfoliative rash”, “rash”, “rash erythematous”, “rash macular”, “rash papular”, or “rash pustular”.

Chemotherapy = cisplatin + 5-fluorouracil or carboplatin + 5-fluorouracil

251 For cardiac disorders, approximately 9% of subjects in both the EU-approved cetuximab
252 plus chemotherapy and chemotherapy-only treatment arms in Study 2 experienced a
253 cardiac event. The majority of these events occurred in patients who received
254 cisplatin/5-FU, with or without cetuximab as follows: 11% and 12% in patients who
255 received cisplatin/5-FU with or without cetuximab, respectively, and 6% or 4% in
256 patients who received carboplatin/5-FU with or without cetuximab, respectively. In both
257 arms, the incidence of cardiovascular events was higher in the cisplatin with 5-FU
258 containing subgroup. Death attributed to cardiovascular event or sudden death was
259 reported in 3% of the patients in the cetuximab plus platinum-based therapy with 5-FU
260 arm and 2% in the platinum-based chemotherapy with 5-FU alone arm.

261 **Colorectal Cancer**

262 ***Erbixux Monotherapy***

263 Table 4 contains selected adverse events in 562 patients receiving best supportive care
 264 (BSC) alone or with Erbixux monotherapy for metastatic colorectal cancer in Study 4.
 265 Erbixux was administered at the recommended dose and schedule (400 mg/m² initial
 266 dose, followed by 250 mg/m² weekly).

Table 4: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma^a Treated with Erbixux Monotherapy

Body System Preferred Term	Erbixux plus BSC (n=288)		BSC alone (n=274)	
	Any Grades ^b	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 ^c	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

Table 4: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma^a Treated with Erbitux Monotherapy

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

^a Adverse reactions occurring more frequently in Erbitux-treated patients compared with controls.

^b Adverse events were graded using the NCI CTC, V 2.0.

^c 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

267 **Erbitux in Combination with Irinotecan**

268 The most frequently reported adverse events in 354 patients treated with Erbitux plus
 269 irinotecan in clinical trials were acneiform rash (88%), asthenia/malaise (73%), diarrhea
 270 (72%), and nausea (55%). The most common Grades 3–4 adverse events included
 271 diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%).

272 **6.2 Immunogenicity**

273 As with all therapeutic proteins, there is potential for immunogenicity. Immunogenic
 274 responses to cetuximab were assessed using either a double antigen radiometric assay or

275 an ELISA assay. Due to limitations in assay performance and sampling timing, the
276 incidence of antibody development in patients receiving Erbitux has not been adequately
277 determined. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of
278 1001) of evaluable patients without apparent effect on the safety or antitumor activity of
279 Erbitux.

280 The incidence of antibody formation is highly dependent on the sensitivity and specificity
281 of the assay. Additionally, the observed incidence of antibody (including neutralizing
282 antibody) positivity in an assay may be influenced by several factors including assay
283 methodology, sample handling, timing of sample collection, concomitant medications,
284 and underlying disease. For these reasons, comparison of the incidence of antibodies to
285 Erbitux with the incidence of antibodies to other products may be misleading.

286 **6.3 Postmarketing Experience**

287 The following adverse reaction has been identified during post-approval use of Erbitux.
288 Because this reaction was reported from a population of uncertain size, it was not always
289 possible to reliably estimate its frequency or establish a causal relationship to drug
290 exposure.

- 291 • Aseptic meningitis

292 **7 DRUG INTERACTIONS**

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

296 **8 USE IN SPECIFIC POPULATIONS**

297 **8.1 Pregnancy**

298 **Pregnancy Category C**

299 There are no adequate and well-controlled studies of Erbitux in pregnant women. Based
300 on animal models, EGFR has been implicated in the control of prenatal development and
301 may be essential for normal organogenesis, proliferation, and differentiation in the
302 developing embryo. Human IgG is known to cross the placental barrier; therefore,
303 Erbitux may be transmitted from the mother to the developing fetus, and has the potential

304 to cause fetal harm when administered to pregnant women. Erbitux should be used during
305 pregnancy only if the potential benefit justifies the potential risk to the fetus.

306 Pregnant cynomolgus monkeys were treated weekly with 0.4 to 4 times the recommended
307 human dose of cetuximab (based on body surface area) during the period of
308 organogenesis (gestation day [GD] 20–48). Cetuximab was detected in the amniotic fluid
309 and in the serum of embryos from treated dams at GD 49. No fetal malformations or
310 other teratogenic effects occurred in offspring. However, significant increases in
311 embryoletality and abortions occurred at doses of approximately 1.6 to 4 times the
312 recommended human dose of cetuximab (based on total body surface area).

313 **8.3 Nursing Mothers**

314 It is not known whether Erbitux is secreted in human milk. IgG antibodies, such as
315 Erbitux, can be excreted in human milk. Because many drugs are excreted in human milk
316 and because of the potential for serious adverse reactions in nursing infants from Erbitux,
317 a decision should be made whether to discontinue nursing or to discontinue the drug,
318 taking into account the importance of the drug to the mother. If nursing is interrupted,
319 based on the mean half-life of cetuximab [see *Clinical Pharmacology* (12.3)], nursing
320 should not be resumed earlier than 60 days following the last dose of Erbitux.

321 **8.4 Pediatric Use**

322 The safety and effectiveness of Erbitux in pediatric patients have not been established.
323 The pharmacokinetics of cetuximab, in combination with irinotecan, were evaluated in
324 pediatric patients with refractory solid tumors in an open-label, single-arm, dose-finding
325 study. Erbitux was administered once weekly, at doses up to 250 mg/m^2 , to 27 patients
326 ranging from 1 to 12 years old; and in 19 patients ranging from 13 to 18 years old. No
327 new safety signals were identified in pediatric patients. The pharmacokinetic profiles of
328 cetuximab between the two age groups were similar at the 75 and 150 mg/m^2 single dose
329 levels. The volume of the distribution appeared to be independent of dose and
330 approximated the vascular space of $2\text{--}3 \text{ L/m}^2$. Following a single dose of 250 mg/m^2 , the
331 geometric mean $\text{AUC}_{0\text{--}\infty}$ (CV%) value was $17.7 \text{ mg}\cdot\text{h/mL}$ (34%) in the younger age
332 group (1–12 years, $n=9$) and $13.4 \text{ mg}\cdot\text{h/mL}$ (38%) in the adolescent group (13–18 years,
333 $n=6$). The mean half-life of cetuximab was 110 hours (range 69 to 188 hours) for the
334 younger age group, and 82 hours (range 55 to 117 hours) for the adolescent age group.

335 **8.5 Geriatric Use**

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

340 Clinical studies of Erbitux conducted in patients with head and neck cancer did not
341 include sufficient number of subjects aged 65 and over to determine whether they
342 respond differently from younger subjects.

343 **10 OVERDOSAGE**

344 The maximum single dose of Erbitux administered is 1000 mg/m² in one patient. No
345 adverse events were reported for this patient.

346 **11 DESCRIPTION**

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

353 Erbitux is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small
354 amount of easily visible, white, amorphous cetuximab particulates. Erbitux is supplied at
355 a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use
356 vials. Cetuximab is formulated in a solution with no preservatives, which contains
357 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate,
358 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

359 **12 CLINICAL PHARMACOLOGY**

360 **12.1 Mechanism of Action**

361 The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane
362 glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including
363 EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal

364 epithelial tissues, including the skin and hair follicle. Expression of EGFR is also
365 detected in many human cancers including those of the head and neck, colon, and rectum.

366 Cetuximab binds specifically to the EGFR on both normal and tumor cells, and
367 competitively inhibits the binding of epidermal growth factor (EGF) and other ligands,
368 such as transforming growth factor- α . *In vitro* assays and *in vivo* animal studies have
369 shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of
370 receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis,
371 and decreased matrix metalloproteinase and vascular endothelial growth factor
372 production. Signal transduction through the EGFR results in activation of wild-type
373 KRAS protein. However, in cells with activating *KRAS* somatic mutations, the mutant
374 KRAS protein is continuously active and appears independent of EGFR regulation.

375 *In vitro*, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against
376 certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that
377 cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No
378 anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR
379 expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor
380 xenograft models in mice resulted in an increase in anti-tumor effects compared to
381 radiation therapy or chemotherapy alone.

382 **12.3 Pharmacokinetics**

383 Erbitux administered as monotherapy or in combination with concomitant chemotherapy
384 or radiation therapy exhibits nonlinear pharmacokinetics. The area under the
385 concentration time curve (AUC) increased in a greater than dose proportional manner
386 while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m² as the dose increased
387 from 20 to 200 mg/m², and at doses >200 mg/m², it appeared to plateau. The volume of
388 the distribution for cetuximab appeared to be independent of dose and approximated the
389 vascular space of 2–3 L/m².

390 Following the recommended dose regimen (400 mg/m² initial dose; 250 mg/m² weekly
391 dose), concentrations of cetuximab reached steady-state levels by the third weekly
392 infusion with mean peak and trough concentrations across studies ranging from 168 to
393 235 and 41 to 85 μ g/mL, respectively. The mean half-life of cetuximab was
394 approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were
395 similar in patients with SCCHN and those with colorectal cancer.

396 Erbitux had an approximately 22% (90% confidence interval; 6%, 38%) higher systemic
397 exposure relative to the EU-approved cetuximab used in Study 2 based on a population
398 pharmacokinetic analysis. [See *Clinical Studies (14.1)*.]

399 **13 NONCLINICAL TOXICOLOGY**

400 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

413 **13.2 Animal Pharmacology and/or Toxicology**

414 In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to
415 4 times the weekly human exposure (based on total body surface area), resulted in
416 dermatologic findings, including inflammation at the injection site and desquamation of
417 the external integument. At the highest dose level, the epithelial mucosa of the nasal
418 passage, esophagus, and tongue were similarly affected, and degenerative changes in the
419 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of
420 the animals at the highest dose level beginning after approximately 13 weeks of
421 treatment.

422 **14 CLINICAL STUDIES**

423 **14.1 Squamous Cell Carcinoma of the Head and Neck**
 424 **(SCCHN)**

425 Study 1 was a randomized, multicenter, controlled trial of 424 patients with locally or
 426 regionally advanced SCCHN. Patients with Stage III/IV SCCHN of the oropharynx,
 427 hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either
 428 Erbitux plus radiation therapy or radiation therapy alone. Stratification factors were
 429 Karnofsky Performance Status (60–80 versus 90–100), nodal stage (N0 versus N+),
 430 tumor stage (T1–3 versus T4 using American Joint Committee on Cancer 1998 staging
 431 criteria), and radiation therapy fractionation (concomitant boost versus once-daily versus
 432 twice-daily). Radiation therapy was administered for 6–7 weeks as once daily, twice
 433 daily, or concomitant boost. Erbitux was administered as a 400 mg/m² initial dose
 434 beginning one week prior to initiation of radiation therapy, followed by 250 mg/m²
 435 weekly administered 1 hour prior to radiation therapy for the duration of radiation
 436 therapy (6–7 weeks).

437 Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were
 438 Caucasian, and 90% had baseline Karnofsky Performance Status ≥80. There were
 439 258 patients enrolled in U.S. sites (61%). Sixty percent of patients had oropharyngeal,
 440 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor
 441 stage. Fifty-six percent of the patients received radiation therapy with concomitant boost,
 442 26% received once-daily regimen, and 18% twice-daily regimen.

443 The main outcome measure of this trial was duration of locoregional control. Overall
 444 survival was also assessed. Results are presented in Table 5.

Table 5: 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

445 Study 2 was an open-label, randomized, multicenter, controlled trial of 442 patients with
446 recurrent locoregional disease or metastatic SCCHN conducted outside the U.S. using an
447 EU-approved cetuximab as the clinical trial material. Erbitux provides approximately
448 22% higher exposure relative to the EU-approved cetuximab used in Study 2; these
449 pharmacokinetic data, together with the results of Study 2 and other clinical trial data
450 establish the efficacy of Erbitux at the recommended dose [see *Clinical Pharmacology*
451 (12.3)].

452 Patients with no prior therapy for recurrent locoregional disease or metastatic SCCHN
453 were randomized (1:1) to receive EU-approved cetuximab plus cisplatin or carboplatin
454 and 5-FU, or cisplatin or carboplatin and 5-FU alone. Choice of cisplatin or carboplatin
455 was at the discretion of the treating physician. Stratification factors were
456 Karnofsky Performance Status (<80 versus ≥ 80) and previous chemotherapy. Cisplatin
457 (100 mg/m^2 , Day 1) or carboplatin (AUC 5, Day 1) plus intravenous 5-FU
458 ($1000 \text{ mg/m}^2/\text{day}$, Days 1–4) were administered every 3 weeks (1 cycle) for a maximum
459 of 6 cycles in the absence of disease progression or unacceptable toxicity. Cetuximab was
460 administered at a 400 mg/m^2 initial dose, followed by a 250 mg/m^2 weekly dose in
461 combination with chemotherapy. Patients demonstrating at least stable disease on
462 cetuximab in combination with chemotherapy were to continue cetuximab monotherapy
463 at 250 mg/m^2 weekly, in the absence of disease progression or unacceptable toxicity after
464 completion of 6 planned courses of platinum-based therapy. For patients where treatment
465 was delayed because of the toxic effects of chemotherapy, weekly cetuximab was
466 continued. If chemotherapy was discontinued for toxicity, cetuximab could be continued
467 as monotherapy until disease progression or unacceptable toxicity.

468 Of the 442 randomized patients, the median age was 57 years, 90% were male, 98% were
469 Caucasian, and 88% had baseline Karnofsky Performance Status ≥ 80 . Thirty-four percent
470 of patients had oropharyngeal, 25% laryngeal, 20% oral cavity, and 14% hypopharyngeal
471 primary tumors. Fifty-three percent of patients had recurrent locoregional disease only
472 and 47% had metastatic disease. Fifty-eight percent had AJCC Stage IV disease and
473 21% had Stage III disease. Sixty-four percent of patients received cisplatin therapy and
474 34% received carboplatin as initial therapy. Approximately fifteen percent of the patients
475 in the cisplatin alone arm switched to carboplatin during the treatment period.

476 The main outcome measure of this trial was overall survival. Results are presented in
477 Table 6 and Figure 1.

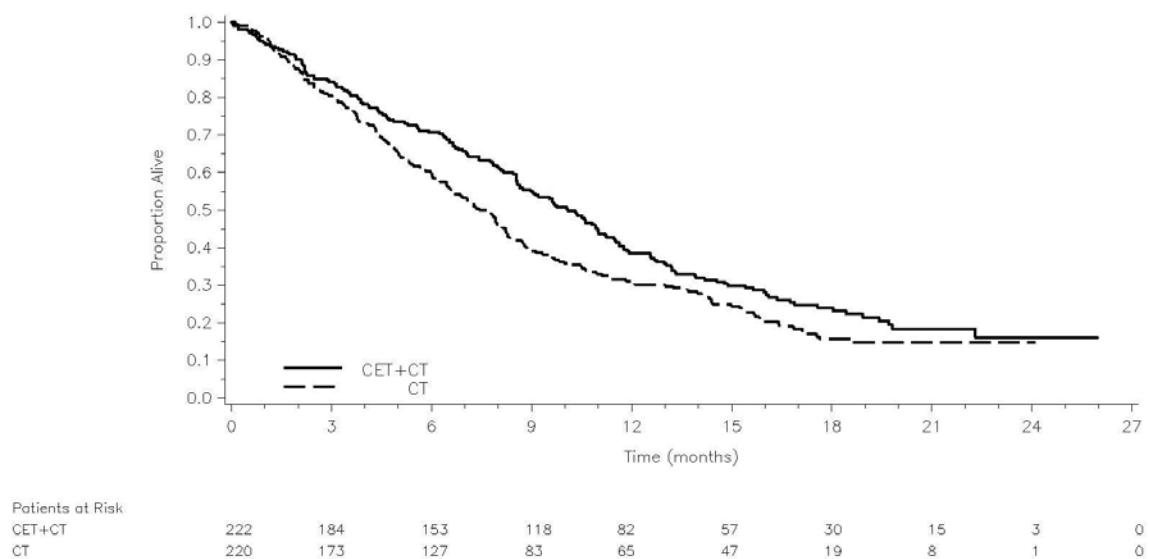
Table 6: Study 2: Clinical Efficacy in Recurrent Locoregional Disease or Metastatic SCCHN

	EU-Approved Cetuximab + Platinum-based Therapy + 5-FU (n=222)	Platinum-based Therapy + 5-FU (n=220)	Hazard Ratio (95% CI ^a)	Stratified Log-rank p-value
Overall Survival				
Median duration (months)	10.1	7.4	0.80 (0.64, 0.98)	0.034
Progression-free Survival				
Median duration (months)	5.5	3.3	0.57 (0.46, 0.72)	<0.0001
	EU-Approved Cetuximab + Platinum-based Therapy + 5-FU	Platinum-based Therapy + 5-FU	Odds Ratio (95% CI ^a)	CMH ^b test p-value
Objective Response Rate	35.6%	19.5%	2.33 (1.50, 3.60)	0.0001

^a CI = confidence interval

^b CMH = Cochran-Mantel-Haenszel

Figure 1: Kaplan-Meier Curve for Overall Survival in Patients with Recurrent Locoregional Disease or Metastatic Squamous Cell Carcinoma of the Head and Neck



CT = Platinum-based therapy with 5-FU
CET = EU-approved cetuximab

484 In exploratory subgroup analyses of Study 2 by initial platinum therapy (cisplatin or
485 carboplatin), for patients (N=284) receiving the EU-approved cetuximab plus cisplatin
486 with 5-FU compared to cisplatin with 5-FU alone, the difference in median overall
487 survival was 3.3 months (10.6 versus 7.3 months respectively; HR 0.71; 95% CI 0.54,
488 0.93). The difference in median progression-free survival was 2.1 months (5.6 versus
489 3.5 months respectively; HR 0.55; 95% CI 0.41, 0.73). The objective response rate was
490 39% and 23% respectively (OR 2.18; 95% CI 1.29, 3.69). For patients (N=149) receiving
491 cetuximab plus carboplatin with 5-FU compared to carboplatin with 5-FU alone, the
492 difference in median overall survival was 1.4 months (9.7 versus 8.3 months; HR 0.99;
493 95% CI 0.69, 1.43). The difference in median progression-free survival was 1.7 months
494 (4.8 versus 3.1 months respectively; HR 0.61; 95% CI 0.42, 0.89). The objective response
495 rate was 30% and 15% respectively (OR 2.45; 95% CI 1.10, 5.46).

496 Study 3 was a single-arm, multicenter clinical trial in 103 patients with recurrent or
497 metastatic SCCHN. All patients had documented disease progression within 30 days of a
498 platinum-based chemotherapy regimen. Patients received a 20-mg test dose of Erbitux on
499 Day 1, followed by a 400 mg/m² initial dose, and 250 mg/m² weekly until disease
500 progression or unacceptable toxicity.

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

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

505 **14.2 Colorectal Cancer**

506 **Erbitux Clinical Trials in EGFR-Expressing, Recurrent, Metastatic** 507 **Colorectal Cancer**

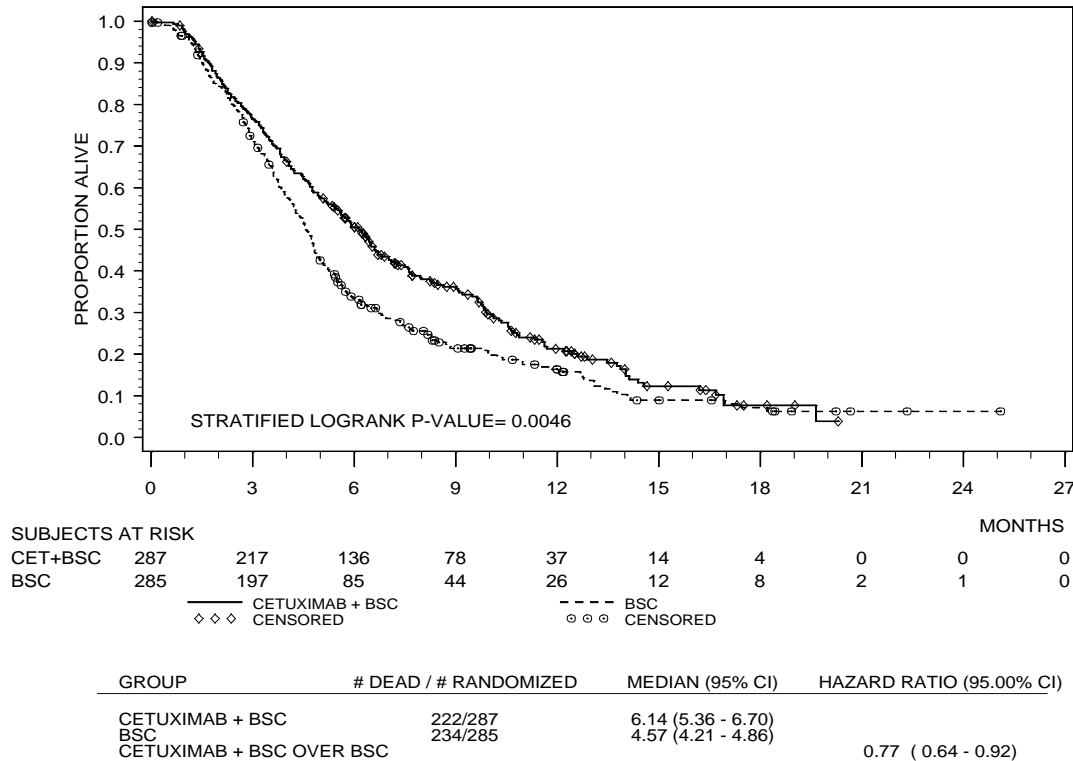
508 Study 4 was a multicenter, open-label, randomized, clinical trial conducted in
509 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal
510 cancer (mCRC). Patients were randomized (1:1) to receive either Erbitux plus best
511 supportive care (BSC) or BSC alone. Erbitux was administered as a 400 mg/m² initial
512 dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity.

513 Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were
514 Caucasian, and 77% had baseline ECOG Performance Status of 0–1. All patients were to

515 have received and progressed on prior therapy including an irinotecan-containing
516 regimen and an oxaliplatin-containing regimen.

517 The main outcome measure of the study was overall survival. The results are presented in
518 Figure 2.

519 **Figure 2:** **Kaplan-Meier Curve for Overall Survival in Patients with**
520 **Metastatic Colorectal Cancer**



521

522 Study 5 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing
523 recurrent mCRC. Patients were randomized (2:1) to receive either Erbitux plus irinotecan
524 (218 patients) or Erbitux monotherapy (111 patients). Erbitux was administered as a
525 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or
526 unacceptable toxicity. In the Erbitux plus irinotecan arm, irinotecan was added to Erbitux
527 using the same dose and schedule for irinotecan as the patient had previously failed.
528 Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every
529 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. Of the 329 patients, the
530 median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline
531 Karnofsky Performance Status ≥80. Approximately two-thirds had previously failed
532 oxaliplatin treatment.

533 The efficacy of Erbitux plus irinotecan or Erbitux monotherapy, based on durable
534 objective responses, was evaluated in all randomized patients and in two pre-specified
535 subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In
536 patients receiving Erbitux plus irinotecan, the objective response rate was
537 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months,
538 and median time to progression was 4.1 months. In patients receiving Erbitux
539 monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%),
540 median duration of response was 4.2 months, and median time to progression was
541 1.5 months. Similar response rates were observed in the pre-defined subsets in both the
542 combination arm and monotherapy arm of the study.

543 **Lack of Efficacy of Anti-EGFR Monoclonal Antibodies in Patients With**
544 **mCRC Containing *KRAS* Mutations**

545 Retrospective analyses as presented in Table 7 across seven randomized clinical trials
546 suggest that anti-EGFR monoclonal antibodies are not effective for the treatment of
547 patients with mCRC containing *KRAS* mutations. In these trials, patients received
548 standard of care (ie, BSC or chemotherapy) and were randomized to receive either an
549 anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy. In all studies,
550 investigational tests were used to detect *KRAS* mutations in codon 12 or 13. The
551 percentage of study populations for which *KRAS* status was assessed ranged from 23% to
552 92%. [See *Clinical Pharmacology* (12.1).]

Table 7: Retrospective Analyses of Treatment Effect in the Subset of Patients with mCRC Containing *KRAS* Mutations Enrolled in Randomized Clinical Trials

Population (n: ITT ^a)	Treatment	Number of Patients with <i>KRAS</i> Results (% ITT)	Number of Patients with <i>KRAS</i> mutant (mAb ^b /control)	Effect of mAb on Endpoints: <i>KRAS</i> Mutant ^c
1 st line treatment mCRC (1198)	FOLFIRI ± Erbitux	540 (45%)	105/87	PFS^b: no difference OS ^b : no difference ORR ^b : decreased
1 st line treatment mCRC (337)	FOLFOX-4 ± Erbitux	233 (69%)	52/47	ORR: decreased PFS: decreased OS: no difference
1 st line treatment mCRC (1053)	oxaliplatin or irinotecan-based chemotherapy, bevacizumab ± panitumumab	oxaliplatin 664 (81%)	135/125	PFS: decreased OS: no difference ORR: increased
		irinotecan 201 (87%)	47/39	ORR: decreased PFS: decreased OS: decreased
1 st line treatment mCRC (736)	bevacizumab, capecitabine, oxaliplatin ± Erbitux	528 (72%)	98/108	PFS: decreased OS: decreased ORR: decreased
2 nd line treatment mCRC (1298)	irinotecan ± Erbitux	300 (23%)	49/59	OS: decreased PFS: no difference ORR: increased
Study 4 3 rd line treatment mCRC (572)	BSC ± Erbitux	394 (69%)	81/83	OS: no difference PFS: no difference ORR: increased
3 rd line treatment mCRC (463)	BSC ± panitumumab	427 (92%)	84/100	PFS: no difference OS: no difference ORR: no difference

^a ITT: intent-to-treat.

^b mAb: EGFR monoclonal antibody; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

^c Results from the primary efficacy endpoint are in bold. A given endpoint is designated as “decreased” if there was a numerically smaller result and as “increased” if there was a numerically higher result in the mAb group than in the control group.

553 **16 HOW SUPPLIED/STORAGE AND HANDLING**

554 Erbitux[®] (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL,
555 single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid
556 containing no preservatives.

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

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

559 Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased
560 particulate formation may occur at temperatures at or below 0° C. This product contains
561 no preservatives. Preparations of Erbitux in infusion containers are chemically and
562 physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at
563 controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining
564 solution in the infusion container after 8 hours at controlled room temperature or after
565 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

566 **17 PATIENT COUNSELING INFORMATION**

567 Advise patients:

- 568 • To report signs and symptoms of infusion reactions such as fever, chills, or breathing
569 problems.
- 570 • Of the potential risks of using Erbitux during pregnancy or nursing and of the need
571 to use adequate contraception in both males and females during and for 6 months
572 following the last dose of Erbitux therapy.
- 573 • That nursing is not recommended during, and for 2 months following the last dose of
574 Erbitux therapy.
- 575 • To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months
576 following the last dose of Erbitux.

577 Erbitux[®] is a registered trademark of ImClone LLC a wholly-owned subsidiary of
578 Eli Lilly and Company.

579 Manufactured by ImClone LLC a wholly-owned subsidiary of Eli Lilly and Company,
580 Branchburg, NJ 08876 USA
581 Distributed and marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
582 Co-marketed by Eli Lilly and Company, Indianapolis, IN 46285 USA



Bristol-Myers Squibb

Lilly

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