An Open-label, Randomized, Phase 3 Clinical Trial of ABX-EGF Plus Best Supportive Care Versus Best Supportive Care in Subjects with Metastatic Colorectal Cancer

Amgen Protocol Number (ABX-EGF) 20020408
BB-IND 8382

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Amendment 3:	1 February 2005
Amendment 4	**26 April 2005**

[a] Immunex Corporation is a Washington corporation and a wholly owned subsidiary of Amgen Inc. and its affiliates. Amgen Inc. is conducting this study on behalf of Immunex Corporation (Immunex).

Confidentiality Statement

Investigator's Agreement

I have read the attached protocol entitled "An Open-label, Randomized, Phase 3 Clinical Trial of ABX-EGF Plus Best Supportive Care Versus Best Supportive Care in Subjects with Metastatic Colorectal Cancer" dated 12 September 2003, amended 25 October 2003, 7 June 2004, 1st February 2005 **and 26 April 2005** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

I agree to ensure that Financial Disclosure Statements will be completed before study initiation, during the study if there are changes that affect financial disclosure status, and after the study is completed by:

- Myself (including, if applicable, my spouse [or legal partner] and dependent children)
- My subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Immunex.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

Protocol Synopsis

Title	An Open-label, Randomized, Phase 3 Clinical Trial of ABX-EGF plus Best Supportive Care Versus Best Supportive Care in Subjects with Metastatic Colorectal Cancer
Study Phase	3
Indication	Third-and fourth-line monotherapy in subjects with metastatic colorectal cancer
Primary Objective	To assess whether ABX-EGF plus best supportive care (BSC) improves progression-free survival time compared with BSC alone as third or fourth line therapy in subjects with metastatic colorectal cancer
Secondary Objectives	To evaluate survival time, objective response, duration of response, time to response, time to disease progression, time to treatment failure, duration of stable disease, patient-reported outcomes (PRO), and the safety profile of ABX-EGF plus BSC compared with BSC alone as third or fourth line therapy in subjects with metastatic colorectal cancer
Study Design	This is an open-label, randomized, multicenter study. Eligible subjects will be randomized in a 1:1 ratio to receive ABX-EGF plus BSC or BSC alone as third- or fourth-line treatment. Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2) and by region. Prior to study entry and in order to confirm eligibility, the investigator or designee will review relevant clinical documents to ensure the subject has developed progressive disease or relapsed while on or after prior chemotherapy (as defined in Section 3.1.1). In addition the investigator or designee will review existing radiological images to confirm disease progression following the most recent chemotherapy regimen. Radiographic documentation for disease progression is only required for the most recent chemotherapy regimen. Ultrasound and clinical evidence of disease progression, eg, rising CEA levels, are acceptable indicators of disease progression following earlier chemotherapy regimens. At regular time-points post-randomization, the prior chemotherapy case report form, the prior radiotherapy case report form and these radiological images will be sent to an Independent Eligibility Review Committee (IERC) who will conduct a second review to confirm the subject met this inclusion criterion. ABX-EGF will be administered by intravenous (IV) infusion at a dose of 6 mg/kg once every 2 weeks until subjects

	develop progressive disease or are unable to tolerate study drug. BSC will be defined in this study as the best palliative care available as judged appropriate by the investigator and will include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated. For the purpose of this study, BSC will not include anti-neoplastic chemotherapy. During the treatment phase subjects on both study arms will be evaluated for tumor response at weeks 8, 12, 16, 24, 32, 40, and 48, and every 3 months thereafter until disease progression (responding disease will be confirmed no less than 4 weeks after the criteria for response are first met). Subjects with symptoms suggestive of disease progression should be evaluated for tumor response at the time symptoms occur. Subjects in the BSC arm determined to have progressive disease will be discontinued from the treatment phase of this study, undergo a safety follow-up visit within 4 weeks of disease progression, and may, if informed consent obtained, be eligible to receive ABX-EGF on a separate protocol (protocol 20030194). Subjects in the ABX-EGF plus BSC arm determined to have progressive disease will be discontinued from the treatment phase of this study, and undergo a safety follow-up visit 4 weeks after the last assigned treatment. When any subject discontinues dosing for any reason, he or she will undergo a safety follow-up visit. Following their last assigned treatment, all subjects will be followed for survival approximately every 3 months through 2 years after their randomization in the study. Every effort should be made to follow tumor assessment until progression for subjects discontinuing the treatment phase for any reason other than progressive disease. An independent Data Monitoring Committee (DMC) will meet to conduct planned safety reviews after the first 150 ABX-EGF treated subjects have had the opportunity to complete 8 weeks of treatment. These reviews will include all data on incidence of human anti-human antibody (HAHA) formation, grade 3 and grade 4 toxicities, serious adverse events including deaths, and events leading to withdrawal. If concerns arise, the DMC may request additional reviews or recommend modifying or suspending randomization in the study.
Primary Endpoint and Secondary Endpoints	<u>Primary:</u> • progression-free survival

	Secondary: • survival time and best objective response over time (co-secondary) • duration of response • time to response • time to progression • time to treatment failure • duration of stable disease • patient-reported outcomes Safety: Incidence of adverse events (including all, serious, grade 3, grade 4, and treatment related events), changes in laboratory values and vital signs, incidence of HAHA formation, skin rash, dose adjustments, concomitant medications and changes in ECOG performance status.
Sample Size	The planned sample size is approximately 430 subjects randomized.
Summary of Subject Eligibility Criteria	Inclusion: • competent to comprehend, sign, and date an IEC/IRB-approved informed consent form • man or woman 18 years of age or older • pathologic diagnosis of colorectal adenocarcinoma (diagnostic tissue obtained by tissue biopsy) • metastatic colorectal carcinoma • ECOG performance status of 0, 1, or 2 • subject must have documented evidence of disease progression during or following treatment with fluoropyrimidine, irinotecan, and oxaliplatin for metastatic colorectal cancer (see Section 3.1.1). Radiographic documentation of disease progression during or within 6 months following the most recent chemotherapy regimen is required. The time interval between documented tumor progression and study entry must not exceed 6 months. Before randomization, the investigator or designee must review all documentation to ensure that the subject has developed progressive disease or relapsed while on or after prior chemotherapy. In addition, the investigator or designee will review existing radiological images to confirm disease progression following the most recent chemotherapy regimen. Radiographic documentation for disease progression is only

	required for the most recent chemotherapy regimen. Ultrasound and clinical evidence of disease progression, e.g. rising CEA levels, are acceptable indicators of disease progression following earlier chemotherapy regimens. The prior chemotherapy case report form, the prior radiotherapy case report form and these radiological images will be sent post-randomization to an IERC who will conduct a second review to confirm the subject met this inclusion criterion. • subject may have received prior radiotherapy (target lesions must not have been irradiated). • subject must have received at least 2 but no more than 3 prior chemotherapy regimens for metastatic colorectal cancer • if history of other primary cancer, subjects will be eligible only if he or she has: - Curatively resected non-melanomatous skin cancer - Curatively treated cervical carcinoma in situ - Other primary solid tumor curatively treated with no known active disease present and no treatment administered for the last 5 years • unidimensionally measurable disease: must be greater than or equal to 20 mm using conventional techniques (CT scan or MRI) or spiral CT scan • paraffin-embedded tumor tissue available for immunohistochemistry studies of epidermal growth factor receptor (EGFr) expression (archived tissue is acceptable) • tumor expressing EGFr by immunohistochemistry (membrane staining must be positive in $\geq$ 1% of evaluated tumor cells; eligibility will be based on staining and evaluation conducted at a central laboratory) • hematologic function, as follows: ANC $\geq 1.5 \times 10^9$ cells/L platelet count $\geq 100 \times 10^9$/L • renal function, as follows: Creatinine < 2.0 mg/dL • hepatic function, as follows: AST $\leq$ 3 x ULN (if liver metastases $\leq$ 5 x ULN) ALT $\leq$ 3 x ULN (if liver metastases $\leq$ 5 x ULN)

	Bilirubin ≤ 2 x ULN
	Exclusion: • any kind of disorder that compromises the ability of the subject to give written informed consent and/or comply with the study procedures • symptomatic brain metastases requiring treatment • use of systemic chemotherapy or radiotherapy within 30 days before randomization • subject who, in the absence of disease progression, discontinued therapy with fluoropyrimidine, irinotecan and/or oxaliplatin because of toxicity • prior EGFr targeting agents • prior anti-tumor therapies including prior experimental agents or approved anti-tumor small molecules and biologics with short serum half-life (less than 1 week) within 30 days before randomization, or prior experimental or approved proteins/antibodies with longer serum half-life (e.g. Avastin) within 3 months before randomization. • chemotherapy other than fluoropyrimidine (or raltitrexed), irinotecan, and oxaliplatin for colorectal carcinoma in accordance with specified regimens (leucovorin and levamisole are not considered as chemotherapy in this exclusion criterion) • unresolved complication that, in the opinion of the investigator, does not qualify the subject for randomization • myocardial infarction within 1 year before randomization • subject with a history of interstitial pneumonitis or pulmonary fibrosis or evidence of interstitial pneumonitis or pulmonary fibrosis on baseline chest CT-scan • female subject of childbearing potential not consenting to use adequate contraceptive precautions during the course of the study and for 6 months after the last ABX-EGF infusion • male subject of reproductive potential not consenting to use adequate contraceptive precautions during the course of the study and for 1 month after the last ABX-EGF infusion • subject who is pregnant or breast-feeding • subject unwilling or unable to comply with study

	requirements • subject known to be human immunodeficiency virus positive • history of any chronic medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risks associated with study participation or study drug administration or may interfere with the interpretation of study results • subject allergic to the ingredients of the study medication or to *Staphylococcus* protein A
Investigational Product (ABX-EGF) Dosage and Administration	ABX-EGF is a fully human monoclonal antibody directed against the EGFr. ABX-EGF will be supplied at a concentration of 20 mg/mL in 10-cc vials. ABX-EGF will be diluted in approximately 100 mL pyrogen-free 0.9% sodium chloride solution, USP/PhEur (saline solution) and infused by an infusion pump over approximately 1 hour (in the event a subject's actual body weight requires greater than a 150 mL volume infusion, ABX-EGF will be administered over approximately 90 minutes). ABX-EGF will be administered by IV infusion using an in-line filter (0.22 micron) set up at a dose of 6 mg/kg administered once every 2 weeks until subjects develop progressive disease or are unable to tolerate study drug.
Best Supportive Care Dosage and Administration	BSC will be defined in this study as the best palliative care available as judged appropriate by the investigator and according to institutional guidelines and will include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated. For the purpose of this study, BSC will not include anti-neoplastic chemotherapy.
Control Group	Best supportive care
Procedures	A signed and dated informed consent form must be obtained before any study-specific procedures are done. All clinical samples will be analyzed at a central laboratory, unless otherwise noted. Screening: All subjects will be screened for eligibility before randomization. Prior to study entry and in order to confirm eligibility, the investigator or designee will review relevant clinical documents to ensure the subject has developed progressive disease or relapsed while on or after prior

	chemotherapy (as defined in Section 3.1.1). In addition the investigator or designee will review existing radiological images to confirm disease progression following the most recent chemotherapy regimen. Radiographic documentation for disease progression is only required for the most recent chemotherapy regimen. Ultrasound and clinical evidence of disease progression, e.g. rising CEA levels, are acceptable indicators of disease progression following earlier chemotherapy regimens. Post-randomization, the prior chemotherapy case report form, the prior radiotherapy case report form and these radiological images will be sent to an IERC who will conduct a second review to confirm the subject met this inclusion criterion. The following will be assessed: • medical history, vital signs, weight, ECOG performance status, physical examination, electrocardiogram • recording of concomitant medications • CT scans of the abdomen and pelvis, chest and of all other sites of disease. Magnetic resonance imaging (MRI) is acceptable to assess extent of disease if used throughout the study. • hematology and serum chemistry panels • carcinoembryonic antigen (CEA) level • assessment of fresh or archived tumor tissue for determination of EGFr expression (may be completed at any time before randomization and can be assessed on primary or metastatic tissue) • urine or serum sample for pregnancy test (if applicable) The blood collections for CEA, hematology and serum chemistry panels will be performed within 7 days before randomization. If applicable, the pregnancy test will be performed within 72 hours before randomization and is the only test that may be conducted at a local laboratory in this study. All other screening procedures will be performed within 4 weeks (28 days) before randomization with the exception of the determination of EGFr expression, which may be completed at any time before randomization. Randomization: Randomization will be stratified by ECOG performance status (0 or 1 versus 2) and by region (Western Europe versus Central and Eastern Europe versus Rest of World). Study day 1 (week 1) is defined as the day of randomization. Baseline procedures (including the first

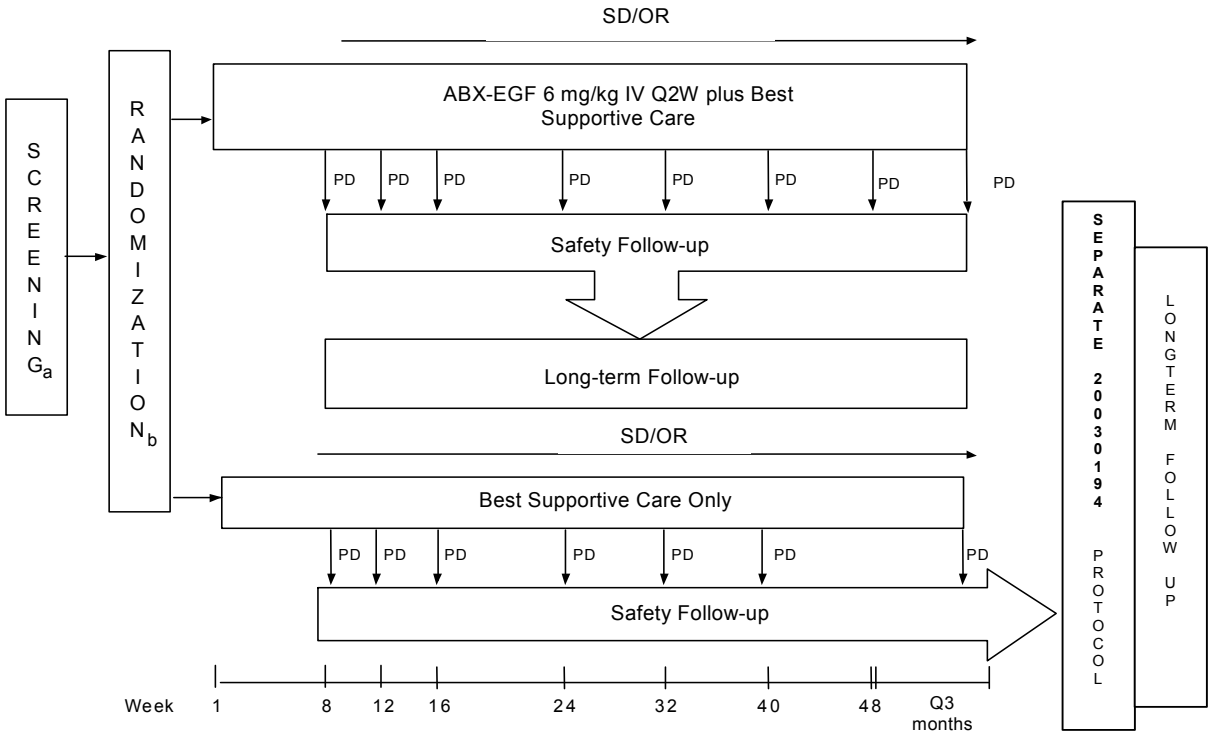
	dose for subjects randomized to ABX-EGF) may occur within the 3 days following randomization. Treatment Phase: During the treatment phase, subjects in both study arms will be evaluated for tumor response at weeks 8, 12, 16, 24, 32, 40 and 48 and every 3 months thereafter until disease progression (responding disease will be confirmed no less than 4 weeks after the criteria for response are first met). Subjects with symptoms suggestive of disease progression should be evaluated for tumor response at the time symptoms occur. The following will be assessed throughout the treatment phase: • vital signs (every 2 weeks; within 30 minutes before the ABX-EGF infusion, approximately 30 minutes after the start of the ABX-EGF infusion, upon completion of the ABX-EGF infusion, and approximately 30 minutes after completion of the ABX-EGF infusion; a ± 10 minutes time window is allowed for the vital signs readings during the treatment phase) • physical examination (every 4 weeks on both arms, and before the infusion on the ABX-EGF arm) • weight (every 2 weeks, before the ABX-EGF infusion on ABX-EGF arm; every 4 weeks on BSC arm) • ECOG performance status (every 4 weeks on both arms, and before the infusion on the ABX-EGF arm) • hematology and serum chemistry panels (every 4 weeks on both arms, and before the infusion on the ABX-EGF arm) • urine sample for magnesium and creatinine to calculate fractional excretion of magnesium (at week 1 on both arms and before the infusion on the ABX-EGF arm) • CEA level (within 7 days of the radiological tumor assessments, including confirmatory scans) • CT scans of the abdomen and pelvis, and chest X-ray (CXR) or chest CT scan (chest CT must be obtained if baseline chest CT was abnormal) will be performed to evaluate tumor response at weeks 8, 12, 16, 24, 32, 40, and 48, and every 3 months thereafter during the treatment phase until disease progression. If CXR is abnormal a chest CT will be

	performed. Tumor assessments must include all sites of disease. The tumor assessments must be conducted within 3 days of next scheduled ABX-EGF infusion (or clinic visit for subjects on the BSC arm). MRI will be acceptable if performed at screening. Responding disease will be confirmed no less than 4 weeks after the criteria for response are first met. Throughout the duration of the study, subjects should be followed using the same techniques and equipment as the baseline scans. In addition to the investigator's assessment, scans of all subjects evaluated for disease response will be read centrally by a panel of at least 2 blinded independent radiologists unaffiliated with the sponsor and the conduct of the study. • serum sample for immunogenicity testing (including HAHA analysis) at weeks 1, 7, and 23; both arms (before the ABX-EGF infusion in the ABX-EGF arm) • serum sample for pharmacokinetic (PK) analysis ; ABX-EGF arm only (within 30 minutes before the ABX-EGF infusion and within 15 minutes after the ABX-EGF infusion at weeks 7 and 23) • serum sample (at weeks 1, 5, 9, 13, 17, 25, 33 and 41 before the ABX-EGF infusion) for analysis of the level and expression of proteins involved in EGFr signaling; all time points in ABX-EGF arm only, at week 1 only in BSC arm • patient reported outcomes (PRO) assessments (before any other study procedure): – validated NCCN/FACT colorectal symptom index, symptom and feelings scale of the Dermatology Life Quality Index 92 (DLQI92) and 1 bother question (once every 2 weeks for the first 8 weeks, and monthly thereafter during the treatment phase) – validated EORTC-QLQ-C30, question 29 and 30 and validated EUROQOL EQ-5D (monthly during the treatment phase) • resource utilization assessment: hospitalization and outpatient usage (monthly during the treatment phase) • recording of transfusions, procedures and concomitant medications (at every visit) • recording of adverse events, including assessment of skin-related toxicities (the skin-related toxicities will be assessed every 2 weeks before the ABX-EGF infusion until resolution and upon increase in

	grade of the skin-related toxicity requiring the subject to come back to the clinic for treatment or observation) Safety Follow-Up Visit: When any subject discontinues dosing for any reason, she or he will undergo a safety follow-up visit. Subjects in the ABX-EGF arm will have a safety follow-up visit conducted 4 weeks after the last assigned treatment. Subjects on the BSC arm will have a safety follow-up visit conducted within 4 weeks after disease progression is observed. Unless otherwise indicated, the following will be collected: • ECOG performance status • physical examination • hematology and serum chemistry panels • CEA level (within 7 days of tumor assessment) • CT scans of the abdomen and pelvis and CXR or chest CT scan (chest CT must be obtained if baseline chest CT was abnormal). If CXR is abnormal a chest CT will be performed. Tumor assessments must include all other sites of disease. MRI will be acceptable if performed at screening. This assessment will not be performed if the subject has discontinued the study because of progressive disease • serum sample for analysis of the level and expression of proteins involved in EGFr signaling; both arms • serum sample for immunogenicity testing (including HAHA analysis); both arms. If positive HAHA are detected by the time of the safety follow-up visit, serum samples will continue to be collected for HAHA analysis every 3 months until they return to a negative or baseline value • patient reported outcomes assessment: validated NCCN/FACT colorectal symptom index, symptom and feelings scale of the Dermatology Life Quality Index 92 (DLQI92), 1 bother question, validated EORTC-QLQ-C30, question 29 and question 30 and validated EUROQOL EQ-5D • resource utilization assessment: hospitalization and outpatient usage • recording of transfusions, procedures and concomitant medications • recording of adverse events, including assessment of skin-related toxicities if these toxicities have not resolved by this visit

	• all subjects with a serious adverse event (SAE) ongoing at the time of the safety follow-up visit will continue to be followed up until resolution of the SAE Long-Term Follow-Up: Following their last assigned treatment, all subjects will be followed for survival approximately every 3 months through 2 years after their randomization in the study. Follow up will consist of telephone contact reports or clinic visits.
Statistical Considerations	<u>Efficacy:</u> To adjust for stratification by baseline ECOG performance status and region a stratified log-rank test will be used to compare the 2 study arms for progression-free survival time. The analysis will be performed at the 5% significance level. If the log-rank test for progression-free survival time is significant, the co-secondary endpoints of survival time and best objective response rate over time will be analyzed simultaneously. To control for multiple testing, survival time will be analyzed controlling at the 4% significance level while response rate will be analyzed at 1% significance level. The primary analyses for progression-free survival and best objective response rate over time will coincide, however survival time will be analyzed sequentially with the primary analysis being performed after the last subject has had the opportunity to be followed for 1-year following randomization. A 1% significance test of survival time will be performed at the interim analysis that coincides with the primary analysis of progression-free survival time and objective response rate. The nominal significance level for the primary analysis on survival time will be calculated to preserve an overall 4% significance level based on the proportion of events shared between the interim and primary analyses. All other efficacy endpoints will be analyzed descriptively including point estimates and 95% confidence intervals. <u>Safety:</u> The incidence of adverse event endpoints and the incidence of HAHA formation will be summarized with frequency counts and percentages for each study arm. Changes in laboratory values and vital signs will be summarized with descriptive statistics for each study arm. Concomitant medications, skin rash, dose adjustments and changes in ECOG performance status will be explored descriptively.
Sponsor/Licensee	Immunex Corporation

Study Design and Treatment Schema



[a] Informed consent is to be obtained before any study specific procedures occur. Blood collections for CEA, hematology and chemistry panels must be performed within 7 days of randomization. If applicable, pregnancy testing must be performed within 72 hours prior to randomization and may be conducted at a local laboratory. All other screening procedures must be completed within 28 days before randomization, with the exception of the determination of EGFr expression, which may be completed at any time prior to randomization.

[b] Randomization of subjects into this study will be completed through an IVR system on study day 1 (week 1) of the treatment phase.

Note: OR (objective response) = complete response or partial response
SD = stable disease
PD = progressive disease

ABX-EGF will be administered by intravenous (IV) infusion at a dose of 6-mg/kg once every 2 weeks until subjects develop progressive disease or are unable to tolerate study drug. Subjects will be evaluated for tumor response at weeks 8, 12, 16, 24, 32, 40 and 48 and every 3 months thereafter during the treatment phase until disease progression (responding disease will be confirmed no less than 4 weeks after the criteria for response are first met). Subjects determined to have progressive disease will be discontinued from the treatment phase of the study. Subjects on the BSC arm will be eligible to receive ABX-EGF on a separate protocol 20030194.

When any subject discontinues for any reason, she or he will undergo a safety follow-up visit within 4 weeks from disease progression on the BSC arm, and 4 weeks after the last assigned treatment on the ABX-EGF arm.

Following their last assigned treatment, all subjects will be followed for survival approximately every 3 months through 2 years after their randomization in the study.

Study Glossary

Abbreviation/Acronym	Definition
ALT	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CR	Complete response
CRF	Case report form
CT	Computed Tomography
CXR	Chest X-ray
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFr	Epidermal growth factor receptor
HAHA	Human Anti-human Antibodies
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
MAHA	Monkey Anti-human Antibodies
MUGA	Multiple gated acquisition
OR	Objective response
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported outcome
RECIST	Response evaluation criteria in solid tumors
RBC	Red blood cell
SC	Subcutaneous
SD	Stable disease
TGFα	Transforming growth factor alpha
WBC	White blood cell

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1. OBJECTIVES

1.1 Primary

To assess whether ABX-EGF plus best supportive care (BSC) improves progression-free survival time compared with BSC alone as third or fourth line therapy in subjects with metastatic colorectal cancer.

1.2 Secondary

To evaluate survival time, objective response, duration of response, time to response, time to disease progression, time to treatment failure, duration of stable disease, patient reported outcomes, and the safety profile of ABX-EGF plus BSC compared with BSC alone as third or fourth line therapy in subjects with metastatic colorectal cancer.

2. BACKGROUND AND RATIONALE

2.1 Disease

Colorectal cancer accounts for a substantial portion of the cancer burden and constitutes a major health problem. The most recent EUCAN database reports that in 1998, 217,500 new cases of cancer of the colon and rectum and 111,800 deaths associated with these cancers were recorded in the European Union (EUCAN database**,** 2003). In 2003, it is estimated that more than 147,500 new cases of the colon and rectum (105,500 for colon and 42,000 for rectum) will be diagnosed and over 57,100 deaths associated with these cancers will occur in the United States (Jemal et al, 2003). Treatment of stage IV disease is palliative, with response rates of approximately 40%, median survival of 14 to 17 months, and no cure except in subjects with isolated, resectable liver or lung metastases (Skibber et al, 2001).

Chemotherapy with fluorouracil (FU) and leucovorin (LV) had been the standard first-line treatment for metastatic colorectal carcinoma for more than 10 years (Poon et al, 1989; Buroker et al, 1995). Irinotecan, or CPT-11, has been shown to have both second-line and first-line activity in this disease (Conti et al, 1996; Pitot et al, 1997; Cunningham et al, 1998; Rothenberg et al, 1999). Regimens containing irinotecan plus FU and LV (IFL) were reported to result in significantly longer progression-free and overall survival compared with FU and LV alone as first-line therapy for metastatic disease (Saltz et al, 2000; Douillard et al, 2000).

In 2002, Eloxatin™ **(**oxaliplatin**)** was approved in the USA for use in combination with infusional 5**-**FU and LV for the second-line treatment of subjects with metastatic colorectal cancer. This approval was based on the response rate and improved time-to-tumor progression seen in a 3-arm study. Thirteen of 152 subjects (9%) in the combination oxaliplatin and FU/LV arm experienced partial tumor responses, compared with 2 of 156 subjects (1.2%) in the single-agent oxaliplatin arm and none of 151 subjects in the infusional FU/LV arm. The median time to tumor progression was improved by approximately 2 months in the oxaliplatin plus infusional FU/LV combination arm. However, even with the combination of FU/LV and oxaliplatin, the median progression-free survival is only 9.0 months (de Gramont et al, 2000).

In 2003, oxaliplatin used in combination with infusional 5-FU and LV was approved in the USA for use in first-line treatment of advanced carcinoma of the colon and rectum. This approval was based on significantly longer time-to-tumor progression, longer overall survival, and significantly higher confirmed response rate seen in a 3-arm study of oxaliplatin + 5-FU/LV (arm A) versus oxaliplatin + irinotecan (arm B) versus irinotecan + 5-FU/LV (arm C). Ninety-five (45.2%) of the 210 subjects in arm A experienced complete or partial responses, compared with 74 (34.4%) of 215 subjects in arm B, and 69 (32.5%) of 212 subjects in arm C. The median time-to-tumor progression was 8.7 months in arm A, 6.5 months in arm B, and 6.9 months in arm C, with median survival times of 19.4, 17.6, and 16.6 months, respectively (Eloxatin™ package insert, 2003).

Despite these advances, metastatic colorectal carcinoma cannot be cured with currently available chemotherapy regimens, and there is a need for more effective therapies.

2.2 EGF Receptor

The epidermal growth factor receptor (EGFr) is a 170,000-dalton transmembrane glycoprotein that functions to promote cell growth in a variety of normal and transformed tissues. Expression of EGFr is frequently associated with malignant transformation in carcinomas of the prostate, breast, ovary, lung, kidney, and colon, among others (Gullick, 1991). Concomitant with EGFr expression, one of the receptor ligands, usually transforming growth factor-alpha (TGFα), is also typically upregulated. Autocrine stimulation via the EGFr is thought to play a critical role in tumor progression in many different tumors. Thus, antibodies that bind to the receptor and block ligand binding may inhibit tumor growth. In mouse xenograft models with human tumors, anti-EGFr

antibodies have been shown to both inhibit tumor growth and eradicate established tumors (Baselga and Mendelsohn, 1994; Yang et al, 1999).

2.3 EGF Receptor in Colorectal Cancer

Colorectal cancer cells have been shown to express EGF and EGFr mRNA (Shirai et al, 1995; Porebska et al, 2000). In an autocrine fashion, colorectal cancer cells secrete EGF and respond to it through the cell-surface receptor thus sustaining their malignant phenotype (Qu et al, 1994; Saeki et al, 1995; Wang et al, 1998). Furthermore, studies show that EGF expression is strongly increased during tumor progression (Tong et al, 1998). Differential expression of these factors correlates with the presence of colorectal cancer. Specifically, between 51% and 70% of colorectal cancer cells stain positively for EGFr compared with 44% of noninvolved mucosal cells (Saeki et al, 1995; Porebska et al, 2000).

Among colorectal cancer cases with lymph node involvement, 62% stained positively for EGFr (Rajagopal et al, 1995). Antisense EGFr RNA was found to be an antiproliferative agent in colorectal cancer cells (Rajagopal et al, 1995). In vitro studies demonstrated that disruption of EGFr expression by expressing antisense EGFr mRNA down-regulated the malignant behavior of colorectal cancer cells and blocked the ability of exogenous EGF to stimulate malignant cell behavior (Wang et al, 1998). One study showed that an EGFr inhibitor induced cytostasis and apoptosis in EGFr ligand-dependent colorectal cancer cells (Karnes et al, 1998).

Blocking the EGFr by using an anti-EGFr monoclonal antibody may provide a therapeutic strategy in colorectal cancer. Cetuximab (IMC-C225), a chimeric monoclonal antibody directed against the EGFr, has been reported to have both single-agent activity and activity in combination with chemotherapy in subjects with colorectal carcinoma (Rubin et al, 2000; Saltz et al, 2001). However, approximately 3% of subjects have been reported to experience a serious allergic event within minutes of the initial infusion of this molecule (Cohen et al, 2000). EMD 72000, a humanized monoclonal antibody that binds EGFr, has also been reported to have single-agent activity in this cancer (Schleucher et al, 2002). Oral tyrosine kinase inhibitors that block EGFr signal transduction (ie, ZD1839, OSI-774) are also being evaluated in subjects with colorectal cancer.

2.4 ABX-EGF Background

ABX-EGF is a high affinity ($K_d = 5 \times 10^{-11}$ M) fully human IgG_2 monoclonal antibody generated using XenoMouse® technology developed by Abgenix Inc. directed against human EGFr. This monoclonal antibody blocks the ligands EGF and TGF-α from binding to EGFr, inhibits tumor growth, and elicits both tumor regression and eradication of established tumors in murine xenograft tumor models (Yang et al, 1999). Nearly all clinical studies conducted to date, have used ABX-EGF derived from a hybridoma cell line. In order to optimize the manufacturing process to meet the demands of increased clinical and potential commercial supply, the manufacturing process has undergone a number of modifications and the cell line from which ABX-EGF is derived has changed to Chinese Hamster Ovary (CHO) cells. A comparability assessment of ABX-EGF derived from the original manufacturing process and hybridoma cell line with that derived from the optimized process and CHO cell line has been undertaken. This assessment included biophysical testing, pharmacology and pharmacokinetic assessment and a one-month toxicology study. ABX-EGF derived from the optimized process and CHO cell line is currently being tested in an ongoing phase 1 study.

2.5 Preclinical Pharmacology

The antineoplastic effects of ABX-EGF in vivo have been demonstrated using human xenograft mouse models. ABX-EGF was shown to inhibit the growth of human epidermoid carcinoma A431 xenografts in athymic mice versus the control study arm resulting in the complete regression of large (up to 1.2 cm^3) established A431 tumors, regardless of initial tumor size. Lower doses of ABX-EGF administered twice weekly for 3 weeks inhibited growth of preexisting solid tumors more effectively than suboptimal doses of m225 antibody (a murine version of IMC-C225). Furthermore, a single injection of 1 mg ABX-EGF resulted in significant and prolonged tumor inhibition.

The antitumor activity of ABX-EGF appears to be correlated with the number of EGFr molecules on the cell surface and the activity of this signaling pathway in different tumor cell types. Tumors expressing 17,000 or more EGFr molecules per cell showed significant growth inhibition when treated with ABX-EGF. ABX-EGF had no effect on tumors with $<$ 11,000 EGFr molecules per cell. These data suggest that expression of EGFr on tumors is accompanied by tumor growth dependency on the EGFr pathway (Yang et al, 2001). Blocking the pathway with neutralizing anti-EGFr antibodies such as

ABX-EGF can lead to growth arrest and regression. Please refer to the ABX-EGF Investigator's Brochure for further detail on in vivo studies.

2.6 Preclinical Toxicology and Pharmacokinetics

The results of the ABX-EGF toxicology studies (1-month and 3-month duration) have identified diarrhea and skin rash as the principal toxicities (see Investigator's Brochure for details). Cardiotoxicity was observed in the first toxicity study (the only toxicology study in which fluid support was not provided) and is considered to be secondary to dehydration, which can be aggravated by diarrhea; indeed, in subsequent studies where animals were provided with fluid support, cardiotoxicity was not observed. Pharmacokinetics data were nonlinear, and the production of monkey anti-human antibodies (MAHA) against ABX-EGF in the low-dose animals caused a significant decrease in exposure over the course of the 3-month study. A single dose pharmacokinetic study in cynomolgus monkeys, a 1-month toxicity study in cynomolgus monkeys and a tissue binding study in both human and cynomolgus monkey tissue indicated that ABX-EGF manufactured by the original process is comparable to ABX-EGF manufactured with an optimized process.

2.7 Dose Selection

To date, the dose that has been most extensively evaluated in clinical studies is 2.5 mg/kg administered once weekly. This dose was chosen to provide optimal receptor blockade, as evidenced by a 100% incidence of skin rash, a pharmacodynamic effect of EGFr blockade. However, a less-frequent dosing schedule for ABX-EGF will provide significant advantages to both the patient and healthcare provider. To this effect, the pharmacokinetic (PK) data available from ongoing studies have been modeled to estimate the ABX-EGF dose that would be required when given once every 2 weeks to achieve the ABX-EGF trough concentration that is achieved with 2.5 mg/kg given on a weekly basis.

Modeling predictions indicated that a dose of 6 mg/kg given once every 2 weeks should maintain a trough concentration at or above the EGFr sink saturation level (IC_{90}) and be comparable to that achieved with weekly dosing at 2.5 mg/kg (40 to 50 μg/mL). Furthermore, the change to 6 mg/kg given once every 2 weeks is not expected to affect the safety profile, as EGFr blockade appears to be maximal at the 2.5-mg/kg once weekly dose. No dose-dependent trends in adverse events other than the incidence of skin toxicity, which reached a plateau at 2.5 mg/kg/week, were observed. While the skin

rash severity did not appear to be dose-dependent, additional dose-related adverse events are not anticipated.

2.8 Clinical Experience

To date, more than 500 subjects with cancer have been enrolled in ABX-EGF phase 1 and 2 clinical studies and have received hybridoma-derived ABX-EGF doses ranging from 0.01 mg/kg to 5 mg/kg given once weekly, 6 mg/kg given once every 2 weeks, to 9.0 mg/kg given once every 3 weeks. ABX-EGF has been generally well tolerated when administered as monotherapy in the phase 1 and 2 studies conducted. Phase 2 studies in renal cell cancer (RCC), colorectal carcinoma, and non-small cell lung cancer (NSCLC) are currently in progress. ABX-EGF derived from the optimized manufacturing process and CHO cell line is currently being evaluated in the ongoing phase 1 clinical study (ABX-9901) described below.

The following referenced studies reflect the reported SAEs at the time of the last ABX-EGF Investigator's Brochure update (ABX-EGF Investigator's Brochure, 2003). Please refer to the safety information included in the IND safety letters for further updates.

2.8.1 Phase 1 Clinical Trial

A phase 1 clinical trial is being conducted with ABX-EGF in subjects with advanced carcinoma at doses ranging from 0.01 mg/kg to 5.0 mg/kg given once weekly, 6.0 mg/kg given once every two weeks, to 9.0 mg/kg given once every 3 weeks. Subjects who have stable or responding disease are eligible for treatment in a phase 1 maintenance therapy trial in which they can receive ABX-EGF at the same dose level and dosing schedule for up to 6 months.

Fifty-two subjects, including subjects with colorectal, renal, prostate, pancreatic, non-small cell lung, and esophageal carcinoma, have received ABX-EGF by IV infusion weekly for 4 weeks in the initial study. Subjects treated at doses up to 1.0 mg/kg also received a loading dose of twice their weekly dose. Subsequent subjects received once weekly doses ranging from 0.75 mg/kg to 5.0 mg/kg without a loading dose. An acneiform skin rash was observed in a dose-related fashion but has not been dose limiting. At doses of 2.0 mg/kg once weekly or greater, all but 1 subject has experienced skin rash. ABX-EGF was well tolerated with no dose limiting toxicities (DLT) observed up to 5.0 mg/kg/week (n = 3 at 5.0 mg/kg).

As of 14 January 2004, 7 subjects have received 4 doses of hybridoma-derived ABX-EGF at a dose of 6 mg/kg administered every 2 weeks and have been followed for 12 weeks. Ten subjects have received 4 doses of CHO-derived ABX-EGF at the same dose and schedule in an ongoing cohort of this study. In the subjects receiving CHO-derived ABX-EGF, 4 subjects have been followed for 12 weeks, 6 subjects for 10 weeks, and 5 subjects for 8 weeks. In those subjects, most adverse events reported were mild-to-moderate in severity. All subjects reported skin rash, which was grade 1 or 2 except in one subject in whom it was grade 3. One subject was treated with oral prednisone for grade 2 skin rash and a dose was held per protocol; the 3rd and 4th doses were subsequently reduced. Three subjects were tested for HAHA at week 10 and all HAHA results were found to be negative. Serious adverse events were reported in 3 subjects and felt not to be related to ABX-EGF. Chronic Myelogenous Leukemia (CML) was reported in 1 subject after a single dose of ABX-EGF; upon review of screening labs it appeared that this condition was present but undiagnosed before administration of ABX-EGF. This event of CML was determined to be not related to ABX-EGF. Acute renal failure was reported in 1 subject; this event was determined to be due to complications associated with an elective radio-ablation procedure and not due to ABX-EGF. A third subject experienced 2 serious adverse events of opioid toxicity (lethargy, myoclonic jerks) due to an increase in the prescribed narcotic dose and urinary retention/obstruction due to tumor progression; these events occurred greater than 30 days following the last dose of study drug, but within the 49-day follow up period. In addition, this subject was enrolled on another experimental protocol and had been treated with another therapy prior to the serious adverse events. Both events were determined by the investigator to be not related to ABX-EGF. No other serious adverse events were reported. In subjects receiving CHO-derived ABX-EGF at a dose of 6 mg/kg every 2 weeks, most adverse events reported were mild-to-moderate in severity. All subjects reported mild to moderate skin rash (grade 1 or 2). None of the subjects had dose held or reduced because of skin toxicity. Seven subjects were tested for HAHA at week 10 and all HAHA results were found to be negative. One subject reported 2 serious adverse events, 1 episode of chest pain related to a pre-existing pleural effusion and 1 episode of abdominal pain resulting from underlying tumor progression; both events were determined by the investigator to be not related to ABX-EGF.

As of 25 March 2004, 17 subjects received CHO-derived ABX-EGF at a dose of 9 mg/kg administered every 3 weeks. One subject discontinued the study after the 3rd dose of

ABX-EGF due to disease progression. Two subjects reported serious adverse events after the 2nd dose of ABX-EGF. The first subject was hospitalized for nausea and vomiting; the event was determined by the investigator to be not related to ABX-EGF. The second subject developed hypomagnesemia (Mg^{2+}=0.9 mg/dL) requiring intravenous magnesium; the event was determined by the investigator to be probably related to ABX-EGF.

A partial response with regression of liver metastases has been observed in 1 subject with colorectal carcinoma who received ABX-EGF 2.5 mg/kg. This subject received 10 months of therapy before progressing. A second subject with colorectal cancer treated at the 1.5-mg/kg dose had stable disease and received 4 months of therapy before progressing. In addition, stable disease has been observed in 4 other subjects: 1 subject with esophageal carcinoma who received ABX-EGF 0.1 mg/kg after a loading dose of 0.2 mg/kg, 1 subject with prostate cancer who received 0.75 mg/kg after a loading dose of 1.5 mg/kg, and 2 subjects with NSCLC who received 3.5 mg/kg. All 4 subjects went on to receive further drug in the phase 1 maintenance therapy trial; the subject with esophageal cancer progressed after 7 months of ABX-EGF therapy, while the subject with prostate cancer achieved a minor response but progressed after a total of 8 months of therapy. One subject with NSCLC progressed after 4 months, whereas the other subject with NSCLC progressed after 7 months of therapy.

2.8.2 Phase 2 and Phase 3 Clinical Trials

ABX-EGF is being studied as a monotherapy and in combination with chemotherapy in several phase 2 and phase 3 clinical studies.

A multicenter, open label, 2-part, phase 2 clinical trial evaluating the safety and efficacy of ABX-EGF in subjects with renal cell carcinoma is ongoing. The first part of the study involved open-label, sequential enrollment of approximately 20 subjects to 1 of 4 escalating dose levels of ABX-EGF (1.0, 1.5, 2.0, and 2.5 mg/kg). The second part of the study included weekly administration of ABX-EGF at a dose of 2.5 mg/kg. The most frequently reported adverse event was acneiform or maculopapular skin rash (90%). Other adverse events reported in $\geq$ 15% of subjects included fatigue, nausea, diarrhea, cough, dyspnea, and fatigue. Thirty-six serious adverse events were related to complications of progressive disease. Tumor regression was seen in 5 subjects (5.6%) and consisted of 3 partial responses and 2 minor responses (1.0, 1.5, and 2.5 mg/kg doses); 44 subjects (50%) had stable disease (Schwartz et al, 2002).

A multicenter, open-label, single arm, phase 2 clinical trial evaluating ABX-EGF 2.5 mg/kg IV weekly as second- or third-line treatment in subjects with metastatic colorectal cancer is ongoing. Subjects with stable or responding disease at the end of each 8-week cycle are eligible for additional cycles until disease progression or intolerability to study drug. A planned futility analysis evaluating the response rate at week 8 of cycle 1 showed that approximately 10% of subjects (4/44) who had previously failed treatment that included a fluoropyrimidine (with or without leucovorin) and either irinotecan or oxaliplatin, or a fluoropyrimidine (with or without leucovorin) and irinotecan and oxaliplatin exhibited a partial response (PR) to ABX-EGF treatment. Stable disease was also observed in approximately 52% of subjects (22/44) at week 8 of cycle 1 (Meropol et al, 2003).

The most frequently reported adverse events in the first 45 subjects were rash (100%), nausea (42%), asthenia (38%), abdominal pain (29%), and diarrhea (27%). The most frequently reported related (per the investigator) adverse events were rash (96%), asthenia (33%), dry skin (18%), stomatitis (18%), and nausea (16%). Skin-related toxicities were reported as grades 1 and 2, with 3 (7%) reported as grade 3; none were grade 4, required hospitalization, or resulted in discontinuation. Serious adverse events were reported in 7 subjects (16%), with 1 event, hematemesis, reported as related to ABX-EGF. No deaths within 30 days of study drug have been reported. The 6 deaths reported in this study occurred more than 30 days after ABX-EGF administration, with all reported to be associated with disease progression.

Additional phase 2 and phase 3 monotherapy studies are being conducted in subjects with CRC and subjects with prostate cancer who have failed prior therapy. After 8 weeks of treatment in the RCC study, 3 PRs were observed (3%), including 1 subject with a stable primary and partial response in metastatic disease and 2 subjects achieved a minor response or stable disease. In addition, disease stabilization was seen in 50% of subjects after 8 weeks of ABX-EGF treatment. All responses were observed at the weekly doses of 1.0 mg/kg (n = 22), 1.5 mg/kg (n = 22), and 2.5 mg/kg (n = 21). Phase 2 studies are also ongoing in first-line colorectal cancer and stage IIIB/IV NSCLC to evaluate the safety and efficacy of ABX-EGF in combination with chemotherapy.

2.8.3 Clinical Safety Experience

The below referenced studies reflect the reported SAE at the time of the last ABX-EGF Investigator's Brochure update (ABX-EGF Investigator's Brochure, 2003). Please review the updated safety information contained in the IND safety letters for further updates.

2.8.3.1 ABX-EGF Monotherapy Studies in Subjects with Cancer

ABX-EGF appears to be generally well tolerated when administered as monotherapy in the phase 1 and phase 2 studies conducted to date. The most common adverse event attributed to ABX-EGF is a dose-related, reversible, acneiform or maculopapular skin rash, which has been reported in approximately 90% of subjects. Less commonly reported skin effects are vesicular or exfoliative rash, skin erythema, and dry skin. Some skin-related toxicities have been associated with pain or pruritus. Other skin effects that have been infrequently reported include fissures of the fingers or toes, fingertip infection or inflammation. At the 2.5-mg/kg dose, as noted in Section 2.8.2, rash was observed in 100% of subjects.

Beyond skin manifestations, the most frequently reported adverse events in the monotherapy studies include asthenia, pain, constipation, nausea, fever, back pain, abdominal pain, anorexia, diarrhea, arthralgia, dizziness, increase cough, dyspnea, vomiting, and upper respiratory infection.

From these monotherapy studies, 15 subjects experienced serious adverse events reported by the investigators as possibly related to ABX-EGF. These include diarrhea (2), dyspnea (1), deep vein thrombosis (1), hematemesis (1), prothrombin level increased (1), vomiting (1), nerve compression (1), pulmonary embolism (1), hypomagnesaemia (1), dehydration (1), and cellulitis (1). In addition, two infusion associated SAEs were reported. The first subject experienced symptoms of dyspnea, rigors and wheezing , and the second experienced rigors and tachycardia. With the addition of pre-medication one subject went on to receive additional doses of ABX-EGF without difficulties. In the second case, the subject was discontinued from the study at the discretion of the investigator.

2.8.3.2 Studies of ABX-EGF in Combination with Chemotherapy

Phase 2 studies in combination with chemotherapy are currently ongoing in subjects with colorectal cancer and NSCLC.

When compared with the monotherapy studies, in the colorectal cancer study in which ABX-EGF was administered in combination with bolus 5-fluorouracil, leucovorin and irinotecan (n = 19), diarrhea was more frequently reported. The chemotherapy regimen (Saltz) is also closely associated with diarrhea (this study was amended to switch the chemotherapy to an infusional 5-FU based regimen [FOLFIRI]). In this study, the most frequent adverse events were diarrhea (83%), asthenia (72%), rash (72%), and nausea (72%). Serious, related diarrhea has been reported in 6 subjects (33%).

In the phase 2 NSCLC study where ABX-EGF is administered in combination with paclitaxel and carboplatin, approximately 80% of subjects have been reported to have a dose-related, reversible, acneiform or maculopapular skin rash similar to that seen in the phase 1 and 2 monotherapy studies. Reported less frequently are fingertip or nail bed infection and inflammation. Beyond these skin effects, the most frequent adverse events, other than skin rash, reported as related to ABX-EGF are asthenia, diarrhea, nausea, and throat irritation. Examining adverse events overall, regardless of relationship, the most frequently reported adverse events are nausea, asthenia, alopecia, myalgia, arthralgia, constipation, diarrhea, vomiting, and throat irritation.

Overall, twenty-four serious adverse events have been reported by the investigators to be possibly related to ABX-EGF during concomitant chemotherapy usage. Events reported in these subjects include: diarrhea (11), febrile neutropenia (2), pulmonary fibrosis (1), skin toxicity (1), stomatitis (1), mucosal inflammation (1), deep vein thrombosis (1), dehydration (3), hypovolemia (1), abdominal pain (3), rash (1), hypomagnesaemia (1), pyrexia (1), electrolyte imbalance (1), pulmonary embolism (1), vomiting (1), gastrointestinal hemorrhage, and cellulitis (1). The 1 death, reported as related to ABX-EGF, occurred 11 weeks after the last dose of ABX-EGF in a subject who had multiple predisposing factors for pulmonary embolism and cardiac arrest. Two deaths (hematemesis, ileus) occurred within 30 days of study drug administration, these deaths were not reported as related to ABX-EGF.

2.8.3.3 ABX-EGF in All Studies

A potential risk of administering ABX-EGF is the development of human anti-human antibodies (HAHA). HAHA formation due to ABX-EGF has not been detected in any subject tested to date with either the hybridoma-derived or CHO-derived ABX-EGF. Based upon early findings in toxicology studies, cardiac monitoring was included in clinical studies. After review of interim data on more than 300 subjects, there are no

indications of cardiac toxicity resulting from ABX-EGF treatment. As a result, cardiac monitoring is no longer part of the routine safety monitoring of subjects on ABX-EGF studies.

No trend of clinically significant increases or decreases in laboratory values has been detected with increasing doses of ABX-EGF.

2.9 Rationale

Phase 2 studies have shown that inhibition of the EGFr pathway can result in objective tumor responses in subjects with colorectal cancer; approximately 10% of subjects with late stage colorectal cancer showed an objective response to ABX-EGF in an ongoing phase 2 study, and stable disease was seen in an additional 52% (Meropol et al 2003). To date, no treatment options are available to subjects with colorectal cancer who have relapsed or failed prior second-line treatment. For these subjects, treatment options focus on ameliorating other aspects of their disease, as with supportive care therapy. ABX-EGF may provide an effective treatment option in this subject population. This phase 3 study is designed to test the efficacy and safety of ABX-EGF (at a dose of 6 mg/kg administered once every 2 weeks) plus BSC, as compared to BSC alone, as third- or fourth-line treatment in subjects with metastatic colorectal carcinoma. This clinical benefit may also result in improvement in subjects' self reported Global QOL scale.

2.10 Clinical Hypothesis

The clinical hypothesis is that ABX-EGF, using the proposed regimen, will safely increase progression-free survival in subjects with metastatic colorectal cancer who have failed available treatment options (ie, subjects who developed progressive disease or relapsed while on or after prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label, randomized, multicenter, phase 3 clinical study. Eligible subjects will be randomized in a 1:1 ratio to receive ABX-EGF plus BSC or BSC alone as third- or fourth- line treatment for metastatic colorectal cancer. Randomization will be stratified

by ECOG performance status (0 or 1 versus 2) and by region (Western Europe versus Central and Eastern Europe versus rest of World).

Prior to study entry and in order to confirm eligibility, the investigator or designee will review relevant clinical documents to ensure the subject has developed progressive disease or relapsed while on or after prior chemotherapy (as defined in Section 3.1.1**)**. In addition the investigator or designee will review existing radiological images to confirm disease progression following the most recent chemotherapy regimen. Radiographic documentation for disease progression is only required for the most recent chemotherapy regimen. Ultrasound and clinical evidence of disease progression, eg,rising CEA levels, are acceptable indicators of disease progression following earlier chemotherapy regimens. Post-randomization, the prior chemotherapy case report form, the prior radiotherapy case report form and these radiological images will be sent to an Independent Eligibility Review Committee (IERC) who will conduct a second review to confirm the subject met the inclusion criterion.

ABX-EGF will be administered by IV infusion at a dose of 6 mg/kg once every 2 weeks until subjects develop progressive disease or are unable to tolerate study drug.

BSC will be defined in this study as the best care available as judged appropriate by the investigator and according to institutional guidelines and will include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any symptomatic therapy as clinically indicated. For the purpose of this study, BSC will not include anti-neoplastic chemotherapy.

During the treatment phase subjects on both study arms will be evaluated for tumor response at weeks 8, 12, 16, 24, 32, 40 and 48, and every 3 months thereafter, until disease progression (responding disease will be confirmed no less than 4 weeks after the criteria for response are first met).

Subjects with symptoms suggestive of disease progression should be evaluated for tumor response at the time symptoms occur.

Subjects in the BSC arm determined to have progressive disease will be discontinued from the treatment phase of this study, undergo a safety follow-up visit within 4 weeks of disease progression, and, if informed consent obtained, may be eligible to receive ABX-EGF on a separate protocol (protocol 20030194).

Subjects in the ABX-EGF arm determined to have progressive disease will be discontinued from the treatment phase of this study and undergo a safety follow-up visit 4 weeks after the last assigned treatment.

When any subject discontinues dosing for any reason, she or he will undergo a safety follow-up visit. Following their last assigned treatment, all subjects will be followed for survival approximately every 3 months through 2 years after their randomization in the study. Every effort should be made to follow tumor assessment until progression for subjects discontinuing the treatment phase for any reason other than progressive disease.

In addition to the investigator's assessment, scans of all subjects evaluated for disease response will be reviewed centrally by a panel of at least 2 blinded, independent radiologists, unaffiliated with the sponsor and the conduct of the study who will perform a blinded read of scans to assess disease status. Throughout the duration of the study, the subjects should be followed using the same scanning techniques and equipment as in the baseline scans and all measurable lesions and non-measurable lesions identified at baseline will be followed per modified RECIST criteria.

3.1.1 Confirmation of Prior Disease Progression

Prior to study entry and in order to confirm eligibility, the investigator or designee will review relevant clinical documents to ensure the subject has developed progressive disease or relapsed while on or after prior fluoropyrimidine, irinotecan and oxaliplatin chemotherapy for metastatic colorectal cancer. Documentation specifying prior chemotherapy regimens, doses used, dates of treatment, best response to therapy and hospital where treatment was delivered will be reviewed. The time interval between documented tumor progression and study entry must not exceed 6 months. Radiographic documentation for disease progression is only required for the most recent chemotherapy regimen. Ultrasound and clinical evidence of disease progression, eg, rising CEA levels, are acceptable indicators of disease progression following earlier chemotherapy regimens. Post-randomization, the prior chemotherapy case report form, the prior radiotherapy case report form and these radiological images will be sent to an Independent Eligibility Review Committee (IERC) who will conduct a second review to confirm the subject met this inclusion criterion.

The criteria listed below will be used for confirmation of disease progression on prior chemotherapy:

- Subjects must have received a fluoropyrimidine.

- Subject must have received oxaliplatin for treatment of metastatic colorectal cancer at a dose intensity of greater than or equal to 30 mg/m^2/week over any period of 6 or more consecutive weeks; this will be calculated by taking the total dose administered in mg/m^2 during any period of 6 or more consecutive weeks and dividing by the number of weeks in that period of time. For subjects who discontinue treatment before 6 consecutive weeks, exposure will be considered adequate if the total dose received (mg/m^2) in that time frame divided by 6 is at least 30 mg/m^2 /week. Oxaliplatin must have been administered using a 5-fluorouracil or a capecitabine-containing regimen. This average dose reflects variations in clinical practice and allows for dose adjustments due to toxicity.

- Subject must have received irinotecan for the treatment of metastatic colorectal cancer at a dose intensity of greater than or equal to 65 mg/m^2/week over any period of 8 or more consecutive weeks; this will be calculated by taking the total dose administered in mg/m^2 during any period of 8 or more consecutive weeks and dividing by the number of weeks in that period of time. For subjects who discontinue treatment before 8 consecutive weeks, exposure will be considered adequate if the total dose received (mg/m^2) in that time frame divided by 8 is at least 65 mg/m^2 /week. This average dose reflects variations in clinical practice and allows for dose adjustments due to toxicity.

- Radiographic evidence of tumor progression following the most recent chemotherapy regimen, as defined by the WHO response criteria methods, must be provided. These criteria are: an increase of at least 25% in tumor surface area (longest diameter x greatest perpendicular diameter) in one or more measurable lesions, or the appearance of a new lesion. Subjects with infiltrative liver metastasis will be considered to have progressive disease if their tumor burden is estimated radiographically to have increased by at least 25%, or if new lesions develop. For the purpose of documenting disease progression, radiographic comparisons will be made to studies performed at the time of best response (responders) or to baseline studies (non-responders). For subjects with stable disease, radiographic comparisons will

be made to studies performed at the nadir of the tumor size (smallest sum observed).

- Ultrasound and clinical evidence of disease progression (eg, rising CEA levels) are acceptable indicators of disease progression following earlier chemotherapy regimens, but not the most recent chemotherapy regimen.

The IERC members will include at least one board-certified oncologist and one board-certified radiologist; all members will be external to the sponsor and unassociated with the conduct of the study. Records of all review assessments, radiological images and other relevant clinical documents will be archived. The review assessment will not be accessible to the study site, nor to the subject.

3.1.2 Safety Review

An independent Data Monitoring Committee (DMC) will review all SAE information on a monthly basis throughout the entire treatment phase of the study. In addition, the DMC will meet to conduct planned safety reviews after the first 150 ABX-EGF treated subjects have had the opportunity to complete 8 weeks of treatment. Enrollment may continue on study during this assessment. These reviews will include all data available on the incidence of HAHA formation, grade 3 and 4 toxicities, serious adverse events including deaths, and events leading to withdrawal. Unaudited data may be provided to the DMC. Barring extenuating data to the contrary, the DMC is expected to recommend suspending randomization on the study if the following is observed:

- 25 of the first 150 ABX-EGF treated subjects require permanent discontinuation of ABX-EGF for skin toxicities (see Section 6.2.2.2)

- 25 of the first 150 ABX-EGF treated subjects experience grade 4 diarrhea definitely related to ABX-EGF

In addition, the sponsor may request that the DMC conduct additional reviews on the basis of concerns stemming from safety reports that the sponsor receives (see Section 9 for a description of these reports). If concerns arise from either planned or unanticipated safety reviews, the DMC may request additional safety reviews or recommend modifying or stopping treatment on the study. The DMC members will include 2 board-certified oncologists with experience in the treatment of subjects with colorectal malignancies,

conduct and monitoring of clinical trials, and 1 biostatistician, all of whom will be external to the sponsor. Records of all meetings (including meeting minutes and recommendations) will be archived.

3.1.3 Tumor and Serum Samples

Tumor tissue will be submitted for all subjects; demonstration of EGFr expression is required for randomization in the study and will be conducted at a central laboratory. Tumor specimens will also be evaluated for analysis of the level and expression of proteins involved in EGFr signaling. In subjects on the ABX-EGF arm, before the ABX-EGF infusion begins, serum samples will be collected at weeks 1, 5, 9, 13, 17, 25, 33, 41 and at the safety follow-up, for analysis of the level and expression of proteins involved in EGFr signaling. Subjects on the BSC arm will have serum samples collected at week 1 and at the safety follow-up, for the same analyses.

3.2 Number of Centers

Approximately 110 centers will participate in this study in Western, Central and Eastern Europe, Canada and Australasia. Sites that do not randomize at least 1 subject within 3 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. The planned sample size is approximately 430 subjects randomized in a 1:1 ratio to receive ABX-EGF plus BSC or BSC alone.

3.4 Estimated Study Duration

The subject accrual period is planned for approximately 12 months. Subjects will remain on treatment until they develop disease progression or are unable to tolerate the study drug. The primary analysis of the efficacy endpoints (except survival time) in this study will be performed when 362 subjects have progressive disease documented by the IRC according to modified-RECIST or have died. It is expected that the desired number of events will have occurred when the 430th subject reaches approximately week 8, however the follow-up period will be extended if necessary to obtain the desired number of events. As such the estimated study duration is approximately 14 months.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (initials, age, sex, and race), date, and outcome of the screening process (i.e. enrolled into study, reason for ineligibility [if available], or refused to participate). All subjects screened for participation will need to sign an IEC/IRB approved informed consent before any study specific procedures are performed.

4.1 Inclusion Criteria

4.1.1 Disease related

- pathologic diagnosis of colorectal adenocarcinoma (diagnostic tissue obtained by tissue biopsy)
- metastatic colorectal carcinoma
- ECOG performance status of 0, 1, or 2
- subject must have documented evidence of disease progression during, or following treatment with a fluoropyrimidine, irinotecan, and oxaliplatin for metastatic colorectal cancer (see Section 3.1.1). Radiographic documentation of disease progression during or within 6 months following the most recent regimen is required. The time interval between documented tumor progression and study entry must not exceed 6 months. Before randomization, the investigator or designee must review all relevant clinical documents to ensure the subject has developed progressive disease or relapsed while on or after prior chemotherapy (as defined in Section 3.1.1). In addition, the investigator or designee will review existing radiological images to confirm disease progression on the most recent chemotherapy regimen. Radiographic documentation for disease progression is only required for the most recent chemotherapy regimen. Ultrasound and clinical evidence of disease progression, e.g. rising CEA levels, are acceptable indicators of disease progression following earlier chemotherapy regimens. The prior chemotherapy case report form, the prior radiotherapy case report form and these radiological images will be sent post-randomization to an IERC who will conduct a second review to confirm the subject met this inclusion criterion.

- unidimensionally measurable disease: must be greater than or equal to 20mm using conventional techniques (CT scan or MRI) or spiral CT scan
- if history of other primary cancer, subject will be eligible only if she or he has:
  - Curatively resected non-melanomatous skin cancer
  - Curatively treated cervical carcinoma in situ
  - Other primary solid tumor curatively treated with no known active disease present and no treatment administered for the last 5 years

4.1.2 Demographic

- man or woman 18 years of age or older

4.1.3 Laboratory

- paraffin-embedded tumor tissue (primary or metastasis) available for immunohistochemistry studies of EGFr expression (archived tissue is acceptable)
- tumor expressing EGFr by immunohistochemistry (membrane staining must be positive in $\geq$ 1% of evaluated tumor cells; eligibility will be based on staining and evaluation conducted at a central laboratory)
- hematologic function, as follows:
  - ANC $\geq$ 1.5 x 10^9 cells/L
  - platelet count $\geq$ 100 x 10^9/L
- renal function, as follows:
  - creatinine < 2.0 mg/dL
- hepatic function, as follows:
  - AST $\leq$ 3 x ULN (≤ 5 x ULN if liver metastases)
  - ALT $\leq$ 3 x ULN (≤ 5 x ULN if liver metastases)
  - bilirubin $\leq$ 2 x ULN

4.1.4 Medications

- subject may have received prior radiotherapy (target lesions must not have been irradiated).
- subject must have received at least 2 but no more than 3 prior chemotherapy regimens for metastatic colorectal cancer

4.1.5 Ethical

- subject must be competent to comprehend, sign and date a written IEC/IRB approved informed consent form (see Section 12.1).

4.2 Exclusion Criteria

4.2.1 Disease related

- symptomatic brain metastases requiring treatment
- myocardial infarction within 1 year before randomization
- subject with a history of interstitial pneumonitis or pulmonary fibrosis or evidence of interstitial pneumonitis or pulmonary fibrosis on baseline chest CT-scan
- unresolved complication that in the opinion of the investigator does not qualify the subject for randomization in the study
- history of any chronic medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risks associated with study participation or study drug administration or may interfere with the interpretation of study results

4.2.2 Medications

- use of systemic chemotherapy or radiotherapy within 30 days before randomization
- prior EGFr targeting agents
- prior anti-tumor therapies including prior experimental agents or approved anti-tumor small molecules and biologics with short serum half-life (less than 1 week) serum and tissue half-life within 30 days before randomization, or prior experimental or approved proteins/antibodies with longer serum half-life (e.g. Avastin) within 3 months before randomization.
- chemotherapy other than fluoropyrimidines (or raltitrexed), irinotecan, or oxaliplatin for colorectal carcinoma in accordance with the regimens specified (leucovorin and levamisole are not considered as chemotherapy in this exclusion criterion)
- subject who, in the absence of disease progression, discontinued therapy with fluoropyrimidine, irinotecan and/or oxaliplatin because of toxicity
- subject allergic to the ingredients of the study medication or to S*taphylococcus* protein A

4.2.3 General

- any kind of disorder that compromises the ability of the subject to give written informed consent and/or comply with study procedures
- female subject of childbearing potential not consenting to use adequate contraceptive precautions during the course of the study and for 6 months after the last ABX-EGF infusion
- male subject of reproductive potential not consenting to use adequate contraceptive precautions during the course of the study and for 1 month after the last ABX-EGF infusion
- subject who is pregnant or breast feeding
- subject known to be human immunodeficiency virus positive
- subject unwilling or unable to comply with study requirements

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, requires a copy of the site's written IEC/IRB approval of the protocol, informed consent form, and all other subject information and/or recruitment material (see Section 12.3). All subjects or legally acceptable representatives must personally sign and date the consent form before the study specific eligibility criteria screening procedures. A subject is considered enrolled when she or he is randomized in the study.

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the informed consent) will receive a subject identification number. This number will be used to identify the subject throughout the trial and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire trial; it must not be changed at the time of re-screening or randomization. This number will not necessarily be the same as the randomization number assigned for the study.

Subjects who do not meet eligibility may be re-screened at the discretion of the Investigator. Subjects that will not be re-screened or are determined not eligible after re-screen must be screen failed through the IVRS.

5.1 Treatment Assignment

An Interactive Voice Response System (IVRS) will be used for assigning each subject a four-digit PIN and randomization. Upon confirmation of eligibility, the site personnel will

telephone the IVRS to obtain a PIN. Instructions for using the IVRS will be provided to each site. After subject randomization through the IVRS, the pharmacist will receive a copy of the fax with the treatment assignment and he or she will be responsible for preparing the study drug for each subject assigned to the ABX-EGF arm.

5.2 Randomization

Subjects will be randomized through the IVRS. The randomization will be stratified by ECOG performance status (0 or 1 versus 2) and by region (Western Europe versus Central and Eastern Europe versus Rest of World). Subjects will be randomized in a 1:1 ratio to receive ABX-EGF plus BSC or BSC alone.

6. TREATMENT PROCEDURES

ABX-EGF will be the only investigational agent administered in this study.

6.1 Investigational Product Dosage, Administration, and Schedule

ABX-EGF will be administered by IV infusion at a dose of 6 mg/kg once every 2 weeks along with the BSC judged appropriate by the investigator until the subject develops progressive disease or is unable to tolerate study drug. The dose will be calculated based on the subject's baseline weight and will not be recalculated unless the weight changes at least $\pm$ 10%. The ABX-EGF dose will be diluted in approximately 100 mL of pyrogen-free 0.9% sodium chloride solution USP/PhEur (normal saline solution, supplied by the site). ABX-EGF concentration will not exceed 10 mg/mL. ABX-EGF should be infused within 19 hours of dilution in normal saline. ABX-EGF will be administered IV by an infusion pump through a peripheral line or indwelling catheter using a 0.22 micron in-line filter infusion set-up over approximately 1 hour by a trained healthcare professional (in the event a subject's actual body weight requires greater than 150 mL volume infusion, ABX-EGF must be administered over approximately 90 minutes). The volume of saline should be increased as needed to ensure the maximum concentration of the diluted solution does not exceed 10 mg/mL. The sponsor will provide the 0.22-micron in-line filter. The IV line should not be used for post infusion PK blood draws. Strict adherence to aseptic technique must be used during ABX-EGF preparation and administration. The bag should be labeled per site pharmacy SOPs and promptly forwarded to the clinical research center for infusion. Compliance will be assessed by regularly reviewing the ABX-EGF administration data recorded on the CRF with the subject's medical records.

The effects of overdose of ABX-EGF are not known.

Subjects on both study arms will receive BSC as deemed appropriate by the investigator throughout the duration of the study. BSC will be defined in this study as the best palliative care available as judged appropriate by the investigator and according to institutional guidelines and will include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated. For the purpose of this study, BSC will not include anti-neoplastic chemotherapy.

6.1.1 No Pre-medication for Routine ABX-EGF Infusions

ABX-EGF infusions should be administered without pre-medication. Infusion reactions WITHOUT pre-medication are expected to be uncommon. If during or after any infusion, a reaction occurs, pre-medication may be used for subsequent ABX-EGF infusions ONLY after discussion and approval from Amgen's Clinical Manager (see Section 9.2.3).

6.2 Dosage Adjustments

6.2.1 BSC Dosage Adjustments

When a subject experiences adverse events or serious adverse events that may require dosage adjustment or interruption these changes will be recorded in the concomitant medication CRF.

6.2.2 ABX-EGF Dosage Adjustment

6.2.2.1 Withholding ABX-EGF During Infusion

Subjects who experience any serious infusion reaction during ABX-EGF infusion will have the infusion stopped. Continuation of dosing will be based on the severity and resolution of the event, and will be at the joint discretion of the investigator and the sponsor. All subjects who have such events will be followed for safety.

In addition, the Amgen Global Safety representative should be notified immediately of any adverse events that are suspected to be infusion-related (even if they are not considered serious), such as:

- cytokine release syndrome: fever, chills, rigors/shakes, hypotension OR

- hypersensitivity reaction: fever, chills, bradycardia/cardiac arrest, generalized urticaria, wheezing, bronchospasm, respiratory arrest, acute respiratory distress syndrome, and/or arthralgia/myalgia

6.2.2.2 Skin-Related Toxicity Assessment and ABX-EGF Dose Modifications

All skin-related toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 with modifications (see Table 6-1).

Subjects who develop mild to moderate skin toxicity may be treated with concomitant medications for their symptoms at the discretion of the investigator (e.g. topical agents, oral antibiotics, etc).

Subjects who develop severe skin toxicity will have their next ABX-EGF dose held. Reasons for holding 1 dose of ABX-EGF include the following:

1) Symptomatic skin-related toxicity requiring narcotics, systemic steroids, or felt to be intolerable by subject
2) Skin infection requiring systemic IV antibiotic or IV antifungal treatment
3) Need for surgical debridement
4) Any skin-related serious adverse event

Table 6-1:

DERMATOLOGY/SKIN (from CTCAE version 3.0 with modification)

Adverse Event (Short Name)	Grade 1	Grade 2	Grade 3	Grade 4
Nail changes (Nail changes)	Discoloration; ridging (koilonychias; pitting), paronychia: intervention not indicated	Partial or complete loss of nail(s); pain in nailbed(s), paronychia: intervention indicated	Interfering with activities of daily living (ADL)	___
Erythema (Erythema)	Painless erythema	Painful erythema	Erythema with desquamation*	Life-threatening; disabling
Pruritus/itching (Pruritus)	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	___
Rash:acne/acneiform (Acne)	Intervention not indicated	Intervention indicated	Associated with pain requiring narcotic analgesics, ulceration, or desquamation*	___
Rash/desquamation* (Rash) ***[use for non-acneiform rash or non-folliculitis rash]***	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation* or other lesions covering < 50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation* covering ≥ 50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis
Ulceration (Ulceration)	___	Superficial ulceration < 2 cm size; local wound care; medical intervention indicated	Ulceration ≥ 2 cm size; operative debridement, primary closure or other invasive intervention indicated (eg,hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (eg,complete resection, tissue reconstruction, flap, or grafting)

*Desquamation is defined as sloughing of skin and does not apply to dry flaking skin.

- If after 2 weeks from withholding dose, the adverse event has improved to ≤ Grade 2, (using the Dermatology/Skin table from CTCAE version 3.0 with modifications, Table 6-1) the subject has recovered to the point where symptomatic skin-related toxicity is no longer felt to be intolerable, systemic steroids are no longer required or, in the case of skin infection, systemic IV antibiotic or IV antifungal treatment is no longer required, ABX-EGF will be restarted at 50% of the original dose (3 mg/kg).

  - If, after reinstating the dose of ABX-EGF at 50% of the original dose, the subject experiences skin toxicity requiring further need to withhold the dose of ABX-EGF (see reasons 1, 2, 3, and 4 above), ABX-EGF will be permanently discontinued and the subject will be followed for safety and survival.

  - If the 50% (3 mg/kg) dose reduction is tolerated for 2 doses, the ABX-EGF dose will be escalated to 75% (4.5 mg/kg) of the original dose. If the 75% dose reduction is tolerated for 2 additional doses, the ABX-EGF dose will be further escalated to the original dose (6 mg/kg). If after restarting the dose of ABX-EGF and escalating to 75% of the original dose or to the original dose, the subject experiences skin toxicity requiring further need to withhold the dose of ABX-EGF (see reasons 1, 2, 3, and 4 above), the next dose of ABX-EGF will be held.

  - If after 2 weeks from withholding dose for the second time, the adverse event has improved to ≤ Grade 2, the subject has recovered to the point where symptomatic skin-related toxicity is no longer felt to be intolerable, systemic steroids are no longer required or, in the case of skin infection, systemic IV antibiotic or IV antifungal treatment is no longer required, ABX-EGF will be restarted at 50% of the original dose (3 mg/kg). If the 50% dose reduction is tolerated for 2 doses, the ABX-EGF will be escalated to 75% of the original dose (4.5 mg/kg). If the 75% dose reduction is tolerated for 2 additional doses, the ABX-EGF dose will be further escalated to the original dose (6 mg/kg). If after reinstating the dose of ABX-EGF at 50% of the original dose and escalating to 75% or 100% of the original dose, the subject experiences a skin toxicity requiring the dose of ABX-EGF to be held (see reasons 1, 2, 3, and 4), the subject will be permanently discontinued and followed for safety and survival.

- If after 2 weeks of withholding dose, the adverse event has NOT improved to Grade 2 (using the Dermatology/Skin table from CTCAE version 3.0 with modifications, Table 6-1), the subject has NOT recovered to the point where symptomatic skin-related toxicity is no longer felt to be intolerable, systemic steroids are no longer required or in the case of skin infection, systemic IV antibiotic or IV antifungal treatment is no longer required, ABX-EGF will be permanently discontinued and the subject will be followed for safety and survival.

6.2.2.3 Photo-based Coding Scale

To characterize the appearance of all skin-related toxicities, including nail changes, a photo-based coding scale will be used to score the appearance of the physical exam findings; scoring for the photo-based coding scale will be recorded on the designated case report form; it should NOT be recorded on the adverse event case report form.

6.2.3 ABX-EGF Missed Doses or Delayed Doses

ABX-EGF administration should ideally occur on the same day of the week throughout the study. However, if ABX-EGF dose cannot be administered as scheduled, every attempt should be made to administer the drug within 3 days of the scheduled dose (up to 3 days before the schedule dose or up to 3 days after the scheduled dose). If it is necessary to change a subject's visit from the originally scheduled date, the subsequent visits should still continue at the previously scheduled days/dates. If the dose is not administered within the 3-day window, the dose will be considered a missed dose and the next scheduled dose should be given at the time of the regularly scheduled dose (eg,if a subject misses the week 5 dose, the next dose should be given at week 7 even if the subject is available at week 6). Missed doses will not be made up. BSC administration should occur according to the investigator's assessment.

6.2.4 Discontinuation of ABX-EGF

Any grade 3 or grade 4 major organ toxicity (using the NCI common toxicity criteria version 2.0), with the exception of ABX-EGF-related skin toxicity as per Section 6.2.2.2, considered related to ABX-EGF may require discontinuation of study drug and should be discussed with the sponsor. A subject who experiences any toxicity that requires permanent discontinuation of ABX-EGF will be withdrawn from treatment and will be followed for safety and survival.

6.3 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide the best supportive care except other investigational agents. Best supportive care will include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusion, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated, and will be administered as judged appropriate by the investigator (for the purpose of this study, best supportive care will not include anti-neoplastic chemotherapy, see Section 6.4).

All previous medications and therapies for cancer prior to randomization in the study will be recorded on the appropriate CRF. All prescription and non-prescription concomitant medications that are ingested, applied or injected on an ongoing basis at randomization, as well as changes in such concomitant medication and any newly prescribed or over the counter concomitant medications taken during the study (i.e. until safety follow up) should be recorded on the appropriate CRF.

The use of topical or oral antibiotics to treat skin-related toxicities is at the investigator's discretion; such use should be recorded on the concomitant medication CRF.

Hypomagnesemia is seen more frequently in subjects with cancer when compared to the general population. If observed in this study, hypomagnesemia should be treated as clinically appropriate according to local medical practice, and a serum chemistry panel and urine sample for fractional excretion of magnesium should be collected.

Elective surgical procedures must be discussed with Amgen prior to the surgery.

6.4 Proscribed Therapy During Treatment Phase

Antineoplastic chemotherapy is proscribed during the treatment phase. Subjects must be withdrawn from study if they receive any of the following during the treatment phase of the study:

- investigational agents,
- anti-EGFr targeting agents other than ABX-EGF,
- experimental or approved anti-tumor therapies (e.g. Avastin), chemotherapy,

- radiotherapy (with the exception of radiotherapy for pain control limited to bone metastases)

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (Appendix A) for an outline of procedures required at each visit.

7.1 Screening

A signed and dated IEC/IRB approved informed consent form (see Appendix K) must be obtained before any study specific procedures are performed. All clinical samples will be analyzed at a central laboratory, unless otherwise noted. Procedures that are part of routine care are not considered study specific procedures. All subjects will be screened for eligibility before randomization. The screening process begins on the date the subject signs the IEC/IRB approved informed consent form and continues until randomization. Only eligible subjects will be enrolled into the study.

Prior to study entry and in order to confirm eligibility, the investigator or designee will review relevant clinical documentation, to ensure the subject has developed progressive disease or relapsed while on or after prior chemotherapy (as defined in Section 3.1.1). Documentation specifying prior chemotherapy regimens, doses used, dates of treatment, best response to therapy and hospital where treatment was delivered will be reviewed. The time interval between documented tumor progression and entry must not exceed 6 months. In addition, the investigator or designee will review existing radiological images to confirm disease progression following the most recent chemotherapy regimen. Radiographic documentation for disease progression is only required for the most recent chemotherapy regimen. Ultrasound and clinical evidence of disease progression, eg, rising CEA levels, are acceptable indicators of disease progression following earlier chemotherapy regimens. Post-randomization, the prior chemotherapy case report form, the prior radiotherapy case report form and these radiological images will be sent to an Independent Eligibility Review Committee (IERC) who will conduct a second review to confirm the subject met this inclusion criterion.

All subjects must have the following procedures completed within 28 days (unless otherwise noted) before randomization:

- review of the inclusion and exclusion criteria

- medical history and review of prior colorectal cancer therapies
- recording of concomitant medications
- central laboratory assessment of fresh or archival tumor tissue (primary or metastasis) for determination of EGFr expression may be done any time before randomization.
- physical examination, including weight
- vital signs readings: blood pressure, resting pulse, respiration rate and temperature
- ECOG performance status assessment
- laboratory tests (within 7 days before randomization):
  - hematology panel: CBC with differential, WBC count, absolute neutrophil count (ANC), WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), RBC count, hemoglobin, hematocrit, and platelet count
  - serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid
  - carcinoembryonic antigen (CEA) level
  - urine or serum pregnancy test for women of childbearing potential (within 72 hours before randomization, may be performed at a local laboratory)
- ECG
- CT scans of the abdomen, pelvis and chest for tumor assessment. Tumor assessments must also include all other sites of disease. MRI is acceptable to assess disease extent if it is used throughout the study.

7.2 Randomization

Randomization will be stratified by ECOG performance status (0 or 1 versus 2) and by region (Western Europe versus Central and Eastern Europe versus Rest of World).

Study day 1 (week 1) is defined as the day of randomization. Baseline procedures (including the first dose for subjects randomized to ABX-EGF) may occur within the 3 days following randomization (see Section 5).

7.3 Treatment Phase

During the treatment phase, study personnel will see subjects on both arms in the clinic every 2 weeks. Refer to the Schedule of Assessments (Appendix A) for an outline of the procedures required at each visit.

ABX-EGF will be administered by IV infusion at a dose of 6 mg/kg given once every 2 weeks commencing at week 1 (e.g. dosing will occur at week 1,3,5,7,etc.) until subjects develop progressive disease or are unable to tolerate study drug. BSC will be defined in this study as the best care available as judged appropriate by the investigator and according to institutional guidelines and will include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any symptomatic therapy as clinically indicated. For the purpose of this study, BSC will not include anti-neoplastic chemotherapy.

The following procedures must be completed before study drug administration, unless otherwise indicated:

- patient reported outcomes assessment (before any other study procedure) for a total of 19 questions and 1 scale. All subjects will complete the PRO questionnaires at the investigational site. The study coordinator should review all questionnaires for completeness (the reason must be recorded if the subjects do not complete the questionnaires):
    - validated NCCN/FACT colorectal symptom index (9 questions), symptom and feelings scale from the DLQI92 (2 questions and 1 scale), the bother question (1 question) every other week for the first 8 weeks and monthly thereafter during the treatment phase
    - validated EORTC-QLQ-C30 question 29 and question 30 (2 questions) and validated EUROQOL EQ-5D (5 questions) monthly during the treatment phase

Note: Subjects who are blind or illiterate may have the patient-reported outcomes questionnaires read to them by the study staff. The study staff doing the reading cannot however interpret any of the questions for the subject. A subject may be exempted from completing the questionnaires if he or she is unable to read the questionnaires in one of the available languages.

- resource utilization assessment: hospitalization and outpatient usage every 4 weeks.
- recording of transfusions, procedures and concomitant medications (at every visit)
- vital signs readings (every 2 weeks; within 30 minutes before the ABX-EGF infusion, approximately 30 minutes after the start of the ABX-EGF infusion, upon completion of the ABX-EGF infusion, and approximately 30 minutes after completion of the ABX-EGF infusion, allowing a $\pm$ 10-minute time window): blood pressure, resting pulse, respiration rate, and temperature.
- physical examination (every 4 weeks on both study arms, and before the infusion on the ABX-EGF arm)
- weight (every 2 weeks, before the ABX-EGF infusion on ABX-EGF arm; every 4 weeks on BSC arm)
- ECOG performance status (every 4 weeks on both study arms, and before the infusion on the ABX-EGF arm)
- laboratory tests:
    - hematology panel: CBC with differential, WBC count, absolute neutrophil count (ANC), WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), RBC count, hemoglobin, hematocrit, and platelet count (every 4 weeks on both study arms, and before the infusion on the ABX-EGF arm)
    - serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid (every 4 weeks on both study arms, and before the infusion on the ABX-EGF arm)

- urine sample for magnesium and creatinine to calculate fractional excretion of magnesium (at week 1 on both study arms and before the infusion on the ABX-EGF arm)

- CEA level (within 7 days of radiologic tumor assessments, including confirmatory scans)

- subjects in the ABX-EGF arm will have ABX-EGF PK serum samples drawn within 30 minutes before the ABX-EGF infusion and within 15 minutes after the ABX-EGF infusion at weeks 7 and 23.

- subjects in the ABX-EGF arm will have serum samples collected at weeks 1, 5, 9,13, 17, 25, 33 and 41 before the ABX-EGF infusion, for analysis of the level and expression of proteins involved in EGFr signaling. Subjects in the BSC arm will have serum samples collected at week 1 only.

- subjects in both arms will have serum samples collected for immunogenicity testing (including HAHA analysis [within 30 minutes before the ABX-EGF infusion in the ABX-EGF arm]) at weeks 1, 7 and 23.

- CT scans of the abdomen and pelvis, and CXR or chest CT scan (a chest CT must be obtained if baseline chest CT was abnormal) will be performed to evaluate tumor response (at weeks 8, 12, 16, 24, 32, 40 and 48, and every 3 months thereafter during the treatment phase until disease progression). If CXR is abnormal a chest CT will be performed. The tumor assessments must also include all other sites of disease. The tumor assessment must be conducted within 3 days of the next scheduled ABX-EGF infusion (or clinic visit for subjects on the BSC arm), responding disease will be confirmed no less than 4 weeks after the criteria for response are first met. Every effort should be made to complete scans until disease progression for subjects discontinuing treatment for any reason other than progressive disease. MRI will be acceptable if performed at screening. Throughout the duration of the study, subjects should be followed using the same technique and equipment as in the baseline scans.

7.4 Safety Follow-up Visit

When any subject discontinues dosing for any reason, he or she will undergo a safety follow-up visit. Subjects in the ABX-EGF arm will have a safety follow-up visit conducted 4 weeks after their last assigned treatment. Subjects in the BSC arm will have a safety follow-up visit conducted within 4 weeks after disease progression is observed (ie, if a subject on the BSC arm has the safety follow up assessments on the day of terminating the treatment phase, the subject will be considered as having completed the safety follow up visit). Unless otherwise indicated, the following assessments will be obtained:

- physical examination including vital signs
- ECOG performance status
- laboratory tests:
  - hematology panel: CBC with differential, WBC count, absolute neutrophil count (ANC), WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), RBC count, hemoglobin, hematocrit, and platelet count
  - serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorous, and uric acid
  - CEA level (within 7 days of the radiologic tumor assessment)
  - serum sample for immunogenicity testing (including HAHA analysis); both arms. If positive HAHA are detected by the time of the safety follow-up visit, serum samples will continue to be collected for HAHA analysis every 3 months until they return to a negative or baseline value.
- serum sample for analysis of the level and expression of proteins involved in EGFr signaling; both arms
- patient reported outcomes assessment: NCCN/FACT colorectal symptom index, EORTC-QLQ-C30 question 29 and question 30, EUROQOL EQ-5D, symptom and feelings scale of the DLQI92, and 1 bother question
- resource utilization assessment: hospitalization and outpatient usage

- CT scans of the abdomen and pelvis, and CXR or chest CT scan (a chest CT must be obtained if baseline chest CT was abnormal) will be performed to evaluate tumor response. If CXR is abnormal a chest CT will be performed. The tumor assessments must also include all other sites of disease. Every effort should be made to complete CT scans through progression for subjects discontinuing the treatment phase for any reason other than progressive disease. MRI will be acceptable if performed at screening. Throughout the duration of the study, subjects should be followed using the same technique and equipment as in the baseline scans. This assessment will not be performed if the subject has discontinued due to progressive disease.

- recording of transfusions, procedures and concomitant medications

- recording of adverse events, including skin-related toxicities if the toxicities have not resolved by this visit

- all subjects with a serious adverse event (SAE) ongoing at the time of the safety follow-up visit will continue to be followed up until resolution of the SAE

7.5 Long-Term Follow-Up Clinic Visit or Telephone Contact

Following their last assigned treatment, all subjects will be followed for survival approximately every 3 months through 2 years after their randomization in the study.

7.6 Tumor Response Assessment

Baseline tumor measurement will be determined during screening. Tumor response will be monitored throughout the study beginning at week 8. Unidimensionally measurable disease is an eligibility requirement in order to allow for tumor response measurement using a modified version of RECIST (see Appendix D).

Baseline tumor measurement will be determined during screening and will be used to prospectively identify all sites of disease present at the start of treatment.

At baseline, CT scans of the chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease is required. Magnetic resonance imaging (MRI) is acceptable to assess disease extent if used throughout the study. A chest x-ray will be performed during the treatment phase of the study if the baseline chest CT scan is found to be normal. In the event the chest-x-ray is found to be abnormal during the treatment

phase, a chest CT scan will be obtained. If the baseline chest CT scan is found to be abnormal, a chest CT scan will be performed throughout the treatment phase. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up.

A switch from CT to MRI (or visa versa) of the liver is considered the only acceptable change in modality and should not preclude response assessment if, in the judgment of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to IV contrast for CT scan while on trial. This change would require the pre-approval of the Medical Monitor. CT and MRI are the best currently available and most reproducible methods of measuring index lesions selected for response assessment.

Ultrasound should not be used for assessment of visceral index lesions for the pre-study documentation of progression following the most recent chemotherapy regimen or the on study efficacy evaluation but can be used to assess superficial lesions such as skin lesions or lymph nodes or masses during on study efficacy evaluation. Lesions identified on CXR are not acceptable as measurable lesions, since CT scan of the chest is required if the CXR is positive.

During the treatment phase subjects on both arms will be evaluated for tumor response at weeks 8, 12, 16, 24, 32, 40 and 48 and every 3 months thereafter until disease progression (responding disease will be confirmed no less than 4 weeks after the criteria for response are first met).

Subjects with symptoms suggestive of disease progression should be evaluated for tumor response at the time symptoms occur.

Subjects in the BSC arm determined to have progressive disease will be discontinued from the treatment phase of this study, undergo a safety follow-up visit within 4 weeks of disease progression, and may, if informed consent is obtained, be eligible to receive ABX-EGF on a separate protocol 20030194. Subjects in the ABX-EGF arm determined to have progressive disease will be discontinued from the treatment phase of this study and undergo a safety follow-up visit conducted 4 weeks after the last assigned treatment. Every effort should be made to follow tumor assessment until progression for subjects discontinuing the treatment phase for any reason other than progressive disease.

In addition to the investigator's assessment, scans of all subjects evaluated for disease response will be reviewed centrally by a panel of at least 2 blinded independent radiologists unaffiliated with the sponsor and the conduct of the study. Blinded reviews will not be accessible to the study site nor to the subject.

7.7 Disease Progression

Disease progression will be defined per the modified RECIST criteria (see Appendix D). If a new therapy (i.e. radiation, small molecule, immunotherapy, or chemotherapy) is administered after documented disease progression, the subject will continue to be followed for safety and survival.

If disease progression is documented by the modified RECIST criteria, subjects on the BSC arm may be enrolled on a separate protocol (protocol 20030194) and receive ABX-EGF. If disease progression is documented by the modified RECIST criteria, subjects randomized to the ABX-EGF arm will be discontinued from the treatment phase of the study and followed for safety and survival only.

Disease progression is not considered an adverse event. Signs and symptoms of disease progression should be recorded as adverse events or serious adverse events.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

A subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. Any subject who withdraws consent to participate in the study will be removed from further treatment and/or study observation immediately upon the date of request. The subject may need to undergo additional tests or tapering of the medication to withdraw safely, but the data generated should not be included in the subject's study data.

Subjects who request to stop study treatment or withdraw from study treatment because of the investigator's or sponsor's concern, before completion of the protocol-specified study duration, will be strongly encouraged to continue the schedule of study observations, provided the subject has not withdrawn full consent.

If the subject is withdrawn because of an adverse event or disease progression, the investigator must arrange for the subject to have follow-up visits until the adverse event

has resolved or stabilized. The procedures that will be required at the end of the study are listed in Section 7.4.

Reasons for removal from ABX-EGF or BSC might include:

- withdrawal of consent
- administrative decision by the investigator or sponsor
- pregnancy (report on Pregnancy Notification Worksheet, see Appendix I)
- ineligibility (with the exception of those subjects who are not confirmed by the IERC to have developed progressive disease or relapsed while on or after prior chemotherapy post-investigator assessment)
- significant protocol deviation
- subject noncompliance
- adverse event (report on adverse event CRF)
- disease progression

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable CRFs.

8.2 Replacement of Subjects

Subjects who are randomized into the study will not be replaced. This study will enroll approximately 430 subjects.

9. ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

9.1 Definitions

9.1.1 Adverse Events

An adverse event is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a preexisting medical condition (diabetes, congestive heart failure, rheumatoid arthritis) that occurs after randomization whether or not considered to be investigational product-related. The NCI common toxicity version 2.0 will be used to

grade all adverse events, except for ABX-EGF related skin toxicity, which will be graded as per protocol Section 6.2.2.2.

A worsening of an existing medical condition is one that was present at baseline (e.g. cancer, diabetes, migraine headaches, gout) and became more severe, more frequent, or increased in duration during investigational product treatment.

Abnormal laboratory values should not be reported as adverse events; however, any clinical consequences of the abnormality should be reported as adverse events.

Hospitalization for elective surgery or routine clinical procedures that is not the result of an adverse event (i.e. elective surgery for a pre-existing condition or surgical insertion of central line) need not be considered adverse events and should not be recorded on the adverse event CRF.

Disease progression is not considered an adverse event. Signs and symptoms of disease progression should be recorded as adverse events.

9.1.2 Serious Adverse Events

A serious adverse event is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator's or sponsor's opinion on the relationship to investigational product. This includes, but may not be limited to, any event that (at any dose):

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- is a persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

A hospitalization that meets the regulatory requirement for the "serious" criteria is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility.

Any event that does not exactly meet this definition yet in the investigator's opinion represents a significant hazard, can be assigned the "other significant hazard" regulatory reporting serious criteria.

Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasia.

9.2 Reporting Procedures for All Adverse Events

9.2.1 All Adverse Events

All adverse events occurring after randomization observed by the investigator or reported by the subject (whether or not attributed to investigational product) and for up to 28 days after last dose of study drug, will be reported on the case report form.

Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable. The following need to be documented by the investigator: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, and action taken. The investigator may be asked to provide follow-up information.

All deaths occurring on study must be reported to the sponsor including deaths 30 days after the last investigational product dose and deaths occurring anytime up to the last formal follow-up observational period, whichever is longer. All medically confirmed deaths should be reported to Amgen Global Safety on a SAE form, and the autopsy reports should be provided when available.

The investigator should notify the ethics committees of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms

cease or the condition becomes stable. If the subject was permanently withdrawn from the study or investigational product as a result of a serious adverse event, this information must be included in either the initial or follow-up Serious Adverse Event Report form and the End of Study CRF.

As mentioned in Section 9.1, all laboratory data will be separately analyzed for toxicity and should not be recorded as adverse events on the CRF unless a clinical adverse event is associated, or unless it fits the definition for a serious adverse event.

This study will use the NCI common toxicity criteria version 2.0 for grading adverse events except for ABX-EGF related skin toxicity that will be graded as per protocol Section 6.2.2.2. The relationship of adverse events to the investigational product will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the investigational product?' Answer Yes or No. These grading scales are further described in Appendix F.

9.2.2 Urgent Communication of Suspected Infusion-related Events

The Amgen Clinical Manager should be notified immediately of any adverse events that are suspected to be infusion related (even if they are not considered serious), such as:

- cytokine release syndrome: fever, chills, rigors/shakes, hypotension, OR
- hypersensitivity reaction: fever, chills, bradycardia/cardiac arrest, wheezing, bronchospasm, generalized urticaria, respiratory arrest, acute respiratory distress syndrome, and/or arthralgia/myalgia.

9.2.3 Serious Adverse Event Reporting Procedures

All serious adverse events must be reported to the sponsor within 1 working day of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report form (see Appendix G) and faxed to << insert local office details >>. Investigators should not wait to receive additional information to fully document the event before notifying the sponsor of the serious adverse event.

Any serious adverse event, if brought to the attention of the investigator at any time after cessation of study drug, and considered by the investigator to be possibly related to study drug, should be reported. For safety information, please contact:

ABX-EGF Protocol 20020408
Clinical Manager
Amgen Ltd. (Cambridge)
+ 44 (0) 1223 436237
+ 44 (0) 1223 228125 (Fax)

10. STATISTICAL CONSIDERATIONS

10.1 Study Design

This is an open label, randomized, multicenter study designed to test the clinical hypothesis that ABX-EGF, using the proposed regimen, will safely increase progression-free survival in metastatic colorectal cancer subjects who have failed available treatment options (i.e., subjects who have developed progressive disease or relapsed while on or after prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy). Subjects will be randomized based on a local assessment of prior treatment failure.

Subjects will be randomized to ABX-EGF plus BSC or BSC alone in a 1:1 ratio. The randomization will be stratified by ECOG performance status (0 or 1 versus 2) and by region (Western Europe versus Central and Eastern Europe versus Rest of World).

The primary analysis of efficacy data will utilize on-study radiographic data assessed centrally according to modified-RECIST criteria. A sensitivity analysis for the progression-free survival and objective response rate will be performed using the locally read scan data. The primary analysis of all efficacy endpoints will be performed on the All Enrolled Analysis (ITT) set. As a secondary analysis the efficacy endpoints will be analyzed on the Adjudicated Prior Failures analysis set.

Following their last assigned treatment, all subjects will be followed for survival approximately every 3 months through 2 years after their randomization in the study. During this time attempts will be made to follow tumor progression for subjects withdrawing for reasons other than progression or where progression was not confirmed centrally: any such scans will be reviewed when subjects die, progress or have been followed for 2-years. Furthermore, subjects determined to have progressed whilst receiving BSC alone, and who provide informed consent, may enroll in a separate study (20030194). Subjects will be followed for tumor response in protocol 20030194, as in this study. Scans may be reviewed centrally when each subject completes protocol 20030194.

In study 20030194 radiographic data will be read centrally if the following criteria are met:

- a subject is withdrawn from this study (protocol 20020408) due to disease progression (as determined by the investigator) and
- the subject's disease progression is not corroborated by the independent review committee.

In this situation, the IRC data derived from the radiographs taken in protocol 20030194 will be used in the primary efficacy analysis in this study (protocol 20020408).

The primary analysis of the efficacy endpoints (with the exception of survival time for which an interim analysis will be performed) in this study will be performed when 362 subjects have progression documented by the IRC according to modified-RECIST or have died. The primary analysis of the trial is expected to occur after the 430th randomized subject has been followed for approximately 8-weeks. However the follow-up period may be extended to achieve the desired number of events. The primary analysis on survival time will be performed after the last subject has had the opportunity to complete 1 year follow up following randomization into the trial. Following completion of the 2-year long-term follow-up descriptive statistics will be provided for all data collected.

To adjust for stratification by baseline ECOG performance status and region a stratified log-rank test will be used to compare the 2 study arms for progression-free survival time. The analysis will be performed at the 5% significance level.

If the log-rank test for progression-free survival time is significant, the co-secondary endpoints of survival time and best objective response rate over time will be analyzed simultaneously. To control for multiple testing, survival time will be analyzed controlling at the 4% significance level while response rate will be analyzed at 1% significance level. The primary analyses for progression-free survival and best objective response rate over time will coincide, however survival time will be analyzed sequentially with the primary analysis being performed after the last subject has had the opportunity to complete 1 year following randomization. A 1% significance test of survival time will be performed at the interim analysis that coincides with the primary analysis of progression-free survival time and objective response rate. The nominal significance level for the

primary analysis on survival time will be calculated to preserve an overall 4% significance level based on the proportion of events shared between the interim and primary analyses. Descriptive summaries alone will be provided at the end of the 2-year long-term follow up.

Safety will be assessed by summarizing the incidence of adverse events (including all, serious, grade 3, grade 4, and treatment related), changes in laboratory values, and incidence of HAHA formation, with descriptive statistics. A DMC will meet to conduct planned safety reviews after the first 150 ABX-EGF treated subjects have had the opportunity to complete 8 weeks of treatment. This review will include available data on the incidence of HAHA formation, grade 3 and grade 4 toxicities, serious adverse events including deaths, and events leading to withdrawal. If concerns arise, the DMC may request additional safety reviews or recommend modifying or stopping the study.

10.2 Study Endpoints, Subsets, and Covariates

10.2.1 Study Endpoints

All endpoints relating to tumor response and/or progression will be based on the blinded retrospective read performed by the central imaging laboratory and the modified RECIST criteria.

10.2.1.1 Primary Efficacy

Progression-free survival time: time from randomization date to date of the first observed disease progression or death (whichever comes first) [Subjects who have not progressed while on study and have not died while on study will be censored at the last evaluable disease assessment date.]

10.2.1.2 Secondary Efficacy

Survival time: time from randomization date to death date [Subjects who have not died while on study or are lost to follow-up will be censored at their last contact date.]

Best objective response over time: incidence of either a complete response (CR) or partial response (PR) (CRs and PRs will be confirmed no less than 4 weeks after the criteria for response are first met) [Subjects prematurely discontinuing without a post-baseline tumor assessment or subjects with an observed CR or PR that is not confirmed will be considered non-responders.] The best response observed per subject over the course of the study at the point of the analysis will be used in the analysis.

Duration of response: calculated for only those subjects who respond, time from first objective response to first observed progression of disease or death if the death was due to disease progression (whichever comes first) [Subjects who have not progressed while on study or died for reasons other than disease progression while on study will be censored at their last evaluable assessment date.]

Time to response: time from randomization date to first objective response [Subjects with SD at their last evaluable assessment date will be censored at this date and subjects with progressive disease while on study will be censored after the last response is observed for all subjects.]

Time to disease progression: time from randomization date to date of first observed progression or date of death if the death was due to disease progression (whichever comes first) [Subjects who have not progressed while on study or died for reasons other than disease progression while on study will be censored at their last evaluable assessment date.]

Time to treatment failure: time from randomization date to date the decision was made to end the treatment phase for any reason. [Subjects who complete the treatment phase (48 weeks) or who remain in the treatment phase 8 weeks after the last subject is randomized will be censored at this time.]

Duration of stable disease: calculated for only those subjects with a best response of SD, time from date of enrollment to date of first observed progression or death date, if the death was due to disease progression (whichever comes first); subjects who have not progressed while on study or died for reasons other than disease progression while on study will be censored at their last evaluable assessment date.

10.2.1.3 Safety

Safety endpoints will include the incidence of adverse events (including all, serious, grade 3, grade 4, and treatment related events), changes in laboratory values and vital signs, incidence of HAHA formation, skin rash, dose adjustments, concomitant medications and changes in ECOG performance status.

10.2.1.4 Patient Reported Outcomes

The co-primary PRO endpoints are the time adjusted AUC for EUROQOL EQ-5D index and the time adjusted AUC for NCCN/FACT CRC subscale. The time adjusted AUC's for

each of NCCN/FACT Physical Well-Being subscale, NCCN/FACT functional Well-Being subscale, EORTC-QLQ-C30 Global Quality of Life subscale, Dermatology and De Novo "Bother" Life Quality Index 92 (DLQI92) and the EUROQOL EQ-5D VAS are secondary endpoints.

The NCCN/FACT colorectal index and the EUROQOL EQ-5D are validated scales that have been used extensively with cancer patients. The DLQI92 symptoms and feelings scale is a validated and independent domain of the DLQI92. The bother question is a new unvalidated question. The EORTC-QLQ-C30 global quality of life subscale is the average of 2 questions (overall quality of life and overall health). These questions constitute a validated independent domain within the EORTC and provide an overall judgment of health status and quality of life (McDowell and Newell, 1996).

10.2.2 Analysis Subsets

The primary efficacy analysis of all efficacy endpoints will be conducted on the All Enrolled (ITT) analysis set defined as all consented and randomized subjects.

As a secondary analysis of all efficacy endpoints the Adjudicated Prior Failures analysis set, defined as all consented and randomized subjects who are determined by the independent eligibility review committee to have developed progressive disease or relapsed while on or after prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy will be used.

A sensitivity analysis may be performed on the efficacy endpoints progression-free survival and survival time for the impact of protocol deviations using the Per Protocol (PP) analysis set, defined as the subjects in the Adjudicated Prior Failures analysis set without important protocol deviations thought to impact on these efficacy analyses.

The primary PRO will be conducted on the subset of subjects in the All Enrolled (ITT) analysis set who have at least 1 post-baseline PRO assessment (PRO All Enrolled analysis set). Secondary analyses for the PRO endpoints will be performed for subjects in the Adjudicated Prior Failures analysis set (PRO Adjudicated Prior Failures analysis set) who have at least 1 post-baseline PRO assessment.

The safety analysis will be conducted on all consented, randomized subjects in the BSC arm and all consented subjects who received at least 1 dose of ABX-EGF in the ABX-EGF arm. This subset will be referred to as the safety analysis set.

The analyses of long-term data will be performed on the efficacy and safety analysis sets.

10.2.3 Covariates

The primary analyses for efficacy endpoints will be adjusted for the stratification of ECOG performance status (0 or 1 versus 2) and by region (Western Europe versus Central and Eastern Europe versus Rest of World) at randomization.

In addition, a covariate analysis of the primary analysis will be performed and subgroup analyses on endpoints may be performed for each of the following subsets:

- age: < 65, ≥ 65, and ≥ 75 years
- sex: male and female
- race: white and other categories depending on frequency observed
- ECOG performance status: 0/1 and 2
- region: Western Europe, Central and Eastern Europe versus rest of World
- primary diagnosis: colon versus rectum
- EGFr immunohistochemistry membrane staining in 1-9% of evaluated tumor cells versus membrane staining in ≥ 10% of evaluated tumor cells
- EGFr immunohistochemistry staining intensity; subjects with > 0% 3+ intensity membrane staining at baseline versus subjects with 0% 3+ membrane staining intensity at baseline
- Prior chemotherapy regimen: subjects who progressed while on prior chemotherapy versus subjects progressed after discontinuation of prior chemotherapy

- Maximum skin rash grade (0, 1, 2, 3 and 4) using CTCAE version 3 with modifications (Table 6-1)

Tumor tissue samples obtained may be analyzed to evaluate the level and expression of proteins involved in EGFR signaling. This exploratory work may investigate the potential role of tumor biomarkers such as:

- Tumor tissue expression of HER 1 (EGFr), HER 2, and HER 3 homo- and heterodimer protein assessment
- Tumor tissue RNA signaling pathway analysis to determine tumor gene profile
- Tumor tissue total HER 2 protein
- **Tumor tissue EGFr gene amplification (FISH)**

Additional tumor biomarkers may also be explored, as well as additional analysis incorporating efficacy information on subject outcome. The analyses of these data may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints. **FISH (fluorescence in-situ hybridization) analysis will be conducted on existing tumor samples within the remit of current informed consent, where local regulations permit.**

10.3 Sample Size Considerations

Progression-Free Survival Time

The primary objective of this study is to demonstrate a statistically significant reduction in the overall disease progression rate for ABX-EGF plus BSC versus BSC alone. The median progression-free survival for BSC alone is assumed to be 2.5 months. The sample size goal is to achieve at least 90% power for a 2-sided 1% significance level test given a hazard ratio (ABX-EGF plus BSC : BSC) of 0.67. Assuming exponential progression-free survival, the hypothesized treatment effect translates into a 50% relative median increase, 2.5 vs 3.75 months, or a 14% absolute increase in the 6-month progression-free rate, 19% vs 33%.

No published data exist on median time-to-progression or median progression-free survival time in subjects receiving BSC who have previously developed progressive disease or relapsed while on or after prior fluoropyrimidine and irinotecan and oxaliplatin chemotherapy. However, results have been published from a phase 3 trial (Rothenberg et al, 2003) in subjects who have previously failed fluoropyrimidine and subsequently

given treatment considered to have low activity (oxaliplatin as monotherapy). In this trial, the median time-to-progression was 1.6 months (95% CI, 1.4, 2.7) in the oxaliplatin arm. Because the BSC arm in the current study will have failed more treatments than the oxaliplatin arm in the study cited above, it is anticipated that the BSC arm will have a shorter median progression-free survival time. A time of 2.5 months was chosen as a conservative estimate yet still lower than 2.7 months, the upper bound of the 95% CI for the median time-to progression in the oxaliplatin arm. A 50% increase (1.3 months) in median progression-free survival time is thought to be clinically meaningful.

The primary analysis will be performed on the All Enrolled (ITT) analysis set. To achieve the sample size goal, at least 362 subjects in total must have either documented evidence of objective progression by the modified-RECIST criteria or have died.

All subjects will be followed for at least 8-weeks from randomization. The number of subjects required to achieve the progression event target has been estimated based on the sample size assumptions and the observed and projected accrual. A total of 430 subjects need to be randomized. If necessary, the minimum follow-up will be extended for the 430 subjects in order to achieve the event target.

10.4 Access to Individual Subject Treatment Assignments

Treatment assignments will not be masked in this open-label study.

10.5 Interim Analysis and Early Stopping Guidelines

An independent DMC will assess safety during the course of the trial. The DMC members will include 2 board-certified oncologists with experience in the treatment of subjects with colorectal malignancies, conduct and monitoring of clinical trials, and 1 biostatistician, all of whom will be external to the sponsor. The DMC will have written operating procedures agreed upon by all members before monitoring begins. Records of all meetings (including meeting minutes and recommendations) will be archived.

The DMC will review all SAE information on a monthly basis throughout the entire treatment phase of the study. In addition, the DMC will meet to conduct planned safety reviews after the first 150 ABX-EGF treated subjects have had the opportunity to complete 8 weeks of treatment. These reviews will include all available data on incidence of HAHA formation, grade 3 and grade 4 toxicities, serious adverse events including deaths, and events leading to withdrawal. Unaudited data may be provided to

the DMC. Barring extenuating data to the contrary, the DMC is expected to recommend suspending randomization on the study is the following is observed:

- 25 of the first 150 ABX-EGF treated subjects require permanent discontinuation of ABX-EGF for skin toxicities (see Section 6.2.2.2)

- 25 of the first 150 ABX-EGF treated subjects experience grade 4 diarrhea definitely related to ABX-EGF

The sponsor may request that the DMC conduct additional reviews on the basis of concerns stemming from safety reports that the sponsor receives (see Section 9 for a description of these reports). If concerns arise from either planned or unplanned safety reviews, the DMC may request additional reviews or recommend modifying or suspending randomization on the study.

The primary analyses for progression-free survival and best objective response rate over time will coincide, however survival time will be analyzed sequentially with an interim analysis performed at the time of the primary analysis on progression-free survival and best objective response rate. The primary analysis for survival time will be performed after the last subject has had the opportunity to complete 1 year follow up from the date of randomization. To control for multiple testing, survival time will be analyzed controlling at the 4% significance level while response rate will be analyzed at 1% significance level. Furthermore, a 1% significance test of survival time will be performed at the interim analysis that coincides with the primary analysis of progression-free survival time and objective response rate. The nominal significance level for the primary analysis on survival time (after 1-year follow up) will be calculated to preserve an overall 4% significance level based on the proportion of events shared between the interim and primary analyses.

10.6 Planned Methods of Analysis

10.6.1 General Approach/Considerations

For continuous endpoints, the mean, either the standard error (for efficacy endpoints) or standard deviation (for other measures), median, 25th percentile, 75th percentile, minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided.

The primary analyses will be based on the All Enrolled (ITT) analysis set and will be stratified for baseline ECOG performance status (0 or 1 versus 2) and by region (Western Europe versus Central and Eastern Europe versus Rest of World). The data from the IRC will be used in the primary analysis of all endpoints. Estimates of treatment differences will be calculated with 2-sided 95% confidence intervals and inferential hypothesis testing will be performed at the 5% significance level using a 2-sided alternative hypothesis. If superiority of ABX-EGF plus BSC over BSC for progression free survival is established the co-secondary endpoints of survival time and best objective response rate over time will be analyzed simultaneously. To control for multiple testing, survival time will be analyzed controlling at the 4% significance level while response rate will be analyzed at 1% significance level. The primary analyses for progression-free survival and best objective response rate over time will coincide however survival time will be analyzed sequentially with the primary analysis being performed after the last subject has had the opportunity to complete 1-year long-term follow-up. A 1% significance test of survival time will be performed at the interim analysis that coincides with the primary analysis of progression-free survival time and best objective response rate. The nominal significance level for the primary analysis on survival time will be calculated to preserve an overall 4% significance level based on the proportion of events shared between the interim and primary analyses. Descriptive statistics will be provided after completion of the 2-year long term follow up.

Sensitivity analyses on the efficacy endpoints may be performed using the Adjudicated Prior Failure and the Per Protocol analysis sets and the investigators assessment of images.

For analyses involving the stratified log-rank test, the proportional hazards assumption will be checked graphically in each stratum. If there are obvious deviations from proportional hazards, alternate methods will be used to assess the robustness of the stratified log-rank statistic.

For the primary analysis, any scan that is rated UE (unevaluable) by the central review will be omitted from the analysis (considered as if there was no scan).

10.6.2 Analyses of Key Study Endpoints

10.6.2.1 Progression-Free Survival Time

A stratified version of the log-rank test will be used to compare the 2 arms for progression-free survival time. This analysis will be performed at a 2-sided significance level of 0.05. In addition, Kaplan-Meier curves will be presented for each arm. Kaplan-Meier quartiles with 2-sided 95% confidence intervals will be calculated and Kaplan-Meier progression-free survival rates with 2-sided 95% confidence intervals will be calculated at weeks 8, 12 and 16 for each study arm. For these analyses, subjects who have no disease progression while on study and have not died while on study will be censored at the last evaluable disease assessment date.

A secondary analysis of progression-free survival will be undertaken using the methods described for the primary analysis however the log-rank test will adjust for baseline ECOG performance status (0 or 1 versus 2), region (Western Europe versus Central and Eastern Europe versus Rest of World) and the covariate EGFr baseline expression (1-9%, $\geq$10%).

10.6.2.2 Survival Time

If superiority of ABX-EGF plus BSC over BSC for progression free survival is established the co-secondary endpoints of survival time and best objective response rate over time will be analyzed simultaneously. To control for multiple testing survival time will be analyzed controlling at the overall 4% significance level. Furthermore survival time will be analyzed sequentially with the primary analysis being performed after the last subject has had the opportunity to complete 1-year long term follow up. A 1% significance test of survival time will be performed at the interim analysis that coincides with the primary analysis of progression-free survival time. The nominal significance level for the primary analysis on survival time will be calculated to preserve the an overall 4% significance level based on the proportion of events shared between the interim and primary analyses.

A stratified version of the log-rank test will be used to compare both arms for survival time at each of the interim and primary analyses. In addition, Kaplan-Meier curves will be presented for each arm. Kaplan-Meier quartiles with 2-sided 95% confidence intervals will be calculated and Kaplan-Meier survival rates with 2-sided 95% confidence intervals will be calculated at weeks 8, 12 and 16 for each arm. For these analyses, subjects who

have not died while on study or are lost to follow-up will be censored at their last contact date.

10.6.2.3 Best Objective Response

If superiority of ABX-EGF plus BSC over BSC for progression free survival is established the co-secondary endpoints of survival time and best objective response rate over time will be analyzed simultaneously. To control the significance level for simultaneous testing of these secondary endpoints at the 5% level, response rate will be analyzed at 1% significance level. The primary analyses for best objective response rate over time will be performed at the time of the primary analysis of progression-free survival. The response rate will be compared with a Fisher's Exact test. Wilson's score method with continuity correction will be used to assess the difference in rates as described by Newcombe, Stats in Med, 1998.

10.6.2.4 Duration of Response

For subjects with an objective response, the duration of response will be summarized with a Kaplan-Meier curve for each arm. In addition, Kaplan-Meier quartiles with 2-sided 95% confidence intervals will be calculated for each arm. Subjects who responded and have not progressed while on study or died for reasons other than disease progression while on study will be censored at their last evaluable assessment date. Subjects without an objective response will not be included in this analysis.

10.6.2.5 Time to Response

Time to response will be summarized with a Kaplan-Meier curve for each arm. In addition, Kaplan-Meier quartiles with 2-sided 95% confidence intervals will be calculated for each arm. Subjects with SD at their last evaluable assessment date will be censored at this date and subjects with progressive disease while on study will be censored after the last response is observed for all subjects.

10.6.2.6 Time to Progression

A Kaplan-Meier curve will be presented for time to progression for each arm. In addition, Kaplan-Meier quartiles with 2-sided 95% confidence intervals will be calculated and Kaplan-Meier rates of subjects yet to progress with 2-sided 95% confidence intervals will be calculated at weeks 8, 12 and 16 for each arm. For these analyses, subjects who

have not progressed while on study or died for reasons other than disease progression while on study will be censored at their last evaluable assessment date.

10.6.2.7 Time to Treatment Failure

A Kaplan-Meier curve will be presented for time to treatment failure for each arm. In addition, Kaplan-Meier quartiles with 2-sided 95% confidence intervals will be calculated and Kaplan-Meier rates of subjects yet to fail with 2-sided 95% confidence intervals will be calculated at weeks 8, 12 and 16 for each arm. For these analyses, subjects still receiving study treatment at the completion of the treatment phase will be censored at the date of their last dose date on study.

10.6.2.8 Duration of Stable Disease

For subjects without a CR or PR, the duration of response will be summarized with a Kaplan-Meier curve for each arm. In addition, Kaplan-Meier quartiles with 2-sided 95% confidence intervals will be calculated for each arm. Subjects without SD while on study will be given a duration of 0 and subjects with SD at their last evaluable assessment date will be censored at this date.

10.6.2.9 Patient-Reported Outcomes

To explore for differences in patient-reported outcomes (PRO) between the 2 arms, analysis of covariance will be used to account for baseline values and for stratification. The primary analysis of all PRO endpoints will be the time-adjusted area under the curve (AUC) from week 8 through to week 16. The AUC will be divided by the number of study days between the subject's visits. The primary PRO analyses of all endpoints will be performed on the subset of subjects in the All Enrolled (ITT) analysis set who have at least 1 post-baseline PRO assessment (PRO All Enrolled analysis set).

The PRO data will be summarized 2 ways: primarily as imputed and secondly as observed. The as observed method will calculate the AUC using only the available data available over the period of analysis. The imputed method will impute values for subjects with missing data at a given week: -

- Subjects who die will have the worst score possible imputed for values after death except for the EUROQOL EQ-5D endpoints, which will be assigned a value of 0.

- Subjects missing all data beyond a certain point for reasons other than death will have the value of their last observation carried forward to subsequent time points.

- Subjects missing values in between 2 non-missing values will have their last observation carried forward unless the subsequent value occurred after disease progression. If the latter is the case, the subsequent non-missing value will be carried backward to the point of progression.

- If the baseline data is missing then the missing data will be imputed using first observation carried backwards.

To explore the sensitivity of the primary analysis of the PRO endpoints the analysis of covariance methods described for the primary analysis will be repeated for: -

- Sensitivity for analysis set: The primary endpoints will be re-analyzed using the PRO Adjudicated Prior Failures analysis set with imputation for missing data, over the period weeks 8 through to 16.

- Sensitivity for imputation method: The primary endpoints will be re-analyzed using the PRO All Enrolled (ITT) analysis set without imputation for missing data, over the period weeks 8 through to 16.

- Sensitivity for time period: The primary endpoints will be re-analyzed using the PRO All Enrolled (ITT) analysis set with imputation for missing data, over the period baseline through week 48.

Change in PRO endpoints derived from the questionnaires used in this study will be summarized with descriptive statistics for each study arm at the weeks at which they are assessed.

10.6.2.10 Safety

Subject incidence rates of adverse events (including all, serious, grade 3, grade 4, and treatment related) will be tabulated for weeks 1-8 by arm using the NCI common toxicity criteria version 2.0 with the exception of ABX-EGF related skin toxicity per Section 6.2.2.2. Exposure adjusted incidence of adverse events will be computed by study arm for the entire treatment phase. Tables and/or narratives of “on-study” deaths, serious

adverse events will also be provided. Any skin rash occurring on the study will be characterized.

Changes in laboratory values and vital signs will be summarized by arm with descriptive statistics. The incidence of HAHA formation will be tabulated by arm. Concomitant medications, dose adjustments and changes in ECOG performance status will be evaluated.

10.6.2.11 Long-term Data Analyses

No hypothesis testing will be performed at the end of the 2-year long-term follow-up. Instead, Kaplan-Meier curves along with point estimates and 95% confidence intervals for the quartiles will illustrate the efficacy endpoints using all data collected in this study.

Long-term safety data will be reported descriptively.

11. INVESTIGATIONAL PRODUCT

ABX-EGF is a fully human monoclonal antibody directed against the EGFr and will be administered intravenously.

11.1 ABX-EGF

ABX-EGF will be packaged by Amgen and distributed using Amgen's clinical trial drug distribution procedures. Each vial of ABX-EGF will contain 10 mL of a sterile protein solution containing a 20-mg/mL solution of ABX-EGF. The vials will contain approximately 200 mg of study drug and are for single dose use only. Boxes of ABX-EGF will contain 12 or 25 vials of study drug. Amgen International Clinical Logistics will conduct initial shipments of drug and 0.22 micron in-line filters and ongoing re-supply. ABX-EGF must be diluted in approximately 100 mL pyrogen-free 0.9% sodium chloride solution, USP/PhEur (saline solution) and administered IV by an infusion pump through a peripheral line or indwelling catheter using a 0.22 micron in-line filter infusion set-up over approximately 1 hour by a trained healthcare professional. The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL (in the event a subject's actual body weight requires greater than a 150 mL volume infusion, ABX-EGF must be administered over approximately 90 minutes). The volume of saline should be increased as needed to ensure the maximum concentration of the diluted solution does not exceed 10 mg/mL. The manufacturing batch (or lot

number) of ABX-EGF (investigational product) is to be recorded on each subject's Drug Administration case report form.

11.2 Other Drugs

All other commercially available drugs (including BSC drugs) will not be provided by the sponsor. These drugs will be formulated, packaged, labeled, and stored according to local manufacturer, supplier, and institutional procedures. The investigator will be responsible for obtaining supplies of these drugs.

11.3 Compliance in Investigational Product Administration

When investigational product is dispensed for administration to the subject during a study, the investigator or responsible person will determine the level of compliance with the administration of the investigational product. The subject's investigational product compliance (eg, amount used/amount expected to be used in interval between visits) will be recorded on the Drug Administration case report forms.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

An informed consent form template is provided in Appendix K for use by the investigator to prepare the informed consent document to be used at his or her site. A letter from the clinical study manager will communicate updates to the template. The written informed consent document should be prepared in the language(s) of the potential subject population.

Before a subject's participation in the trial, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

The informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the

signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject or legally acceptable representative is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject or legally acceptable representative and allow for questions. Thereafter, both the subject or legally acceptable representative and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

12.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the sponsor, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB's continuance of approval must be sent to the sponsor.

12.3 Pre-study Documentation Requirements

The investigator is responsible for forwarding the following documents to the sponsor for review before study initiation by the sponsor can occur:

- signed and dated protocol signature page (Investigator's Agreement)
- copy of approved informed consent form
- copy of the IEC/IRB approval of the protocol, consent form and subject information sheet
- up-to-date curricula vitae of principal investigator and all co/sub-investigators
- the IEC/IRB composition and/or written statement that the IEC/IRB is in compliance with regulations
- laboratory normal ranges and documentation of laboratory certification (or equivalent)
- signed study contract
- completed FDA form 1572
- Financial Disclosure, completed Financial Disclosure statements for the principal investigator, all sub-investigators, and their spouses (legal partners) and dependent children

12.4 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the sponsor, subjects should be identified by their initials and a subject study number only. Documents that are not for submission to the sponsor (e.g. signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(ies), and the IEC/IRB direct access to review the subject's original

medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12.5 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

Protocol amendments must be made only with prior sponsor approval. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The investigator must send a copy of the approval letter from the IEC/IRB to the sponsor.

Both the sponsor and the investigator reserve the right to terminate the study, according to the study contract. The investigator should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the sponsor.

13.2 Study Documentation and Storage

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on case report forms will be included on the sponsor's Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the sponsor and/or applicable regulatory authorities. Elements should include:

- subject files containing completed case report forms, informed consents, and supporting copies of source documentation
- study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation (see Section 12.3), and all correspondence to and from the IEC/IRB and the sponsor
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the sponsor and the investigator. If the investigator wishes to assign the study records to another party or move them to another location, he or she must notify the sponsor in writing of either the new responsible person or the new location or both.

13.3 Study Monitoring and Data Collection

The sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (eg, case report forms and other pertinent data) provided that subject confidentiality is respected.

The sponsor or its designee monitor is responsible for inspecting the case report forms at regular intervals periodically throughout the study to verify adherence to the protocol; completeness, accuracy and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical

records and other study-related records needed to verify the entries on the case report forms.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from the sponsor's clinical quality assurance department (or designees). Inspection of site facilities (ie, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP and applicable regulatory requirements.

All paper case report forms should be typed or filled out with a black or blue ballpoint pen and must be legible.

- Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator on the sponsor Delegation of Authority Form. No erasures, correction fluid, or tape may be used. Corrections to electronic forms will be automatically documented via the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at the sponsor. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and return to the sponsor.
- The principal investigator will sign and date the indicated places on the case report form. These signatures will indicate that the principal investigator inspected or reviewed the data on the case report form, the data queries, and the site notifications, and agrees with the content.
- Sponsor's clinical data management department will correct the following CRF issues without notification to site personnel:

- misspellings that do not change the meaning of the word (excluding adverse events and medications)
- location of data recorded on an incorrect CRF (eg,moving lab data from general comments to the appropriate lab table)
- date errors that occur into the new year
- standard time to 24-hour clock
- 2 digit months entered as a three letter month (ie,11 as NOV)
- if 1 of the 3 header identifiers (ie, site number subject number or initials is missing or incorrect, a correction will be made based on cross-referencing
- temperature unit errors (Fahrenheit vs. Centigrade)
- weight unit errors (pounds vs. kilograms) if a baseline weight has been established
- administrative data (e.g. event names for unscheduled visits or retests)
- clarifying “other, specify” if data are provided (e.g. race, physical exam)
- fraction will be converted into decimals
- if both the end date and a status of continuing is indicated (eg,for adverse event, concomitant medications, hospitalization), the end date will supersede
- if a death on-study is recorded, the date of death will be entered as a stop date for all continuing events, procedures, concomitant medication, etc.
- deletion of obvious duplicate data (e.g. same results sent twice with the same date but different clinical planned events – week 4 and early termination)
- if an indication for concomitant medications indicates prophylactic use (and prophylaxis is not checked), prophylaxis will be checked
- for adverse events that record action taken code = 01 (none) and any other action code, 01 (none) may be deleted as it is superseded by other existing data
- body system codes left blank on medical history and physical examination will be added appropriately

- if equivalent units or terms are recorded instead of the acceptable sponsor's standard (e.g. cc for mL, SQ for SC route, Not Examined for Not Done), the sponsor's units or terms will be used. If unit for topical medications is left blank, OT (other) will be entered
- if the answer to a YES or NO question is blank or obviously incorrect (e.g. Answers to the following questions do not reflect the data that are recorded or missing: Were there any adverse events? Concomitant medications? Hospitalizations?)
- correct CRF page numbers

13.4 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

13.5 Publication Policy

To coordinate dissemination of data from this study, the sponsor encourages the formation of a publication committee consisting of several principal investigators and appropriate sponsor staff. The committee is expected to solicit input and assistance from other investigators and sponsor staff as appropriate. Membership on the committee (both for investigators and sponsor staff) does not guarantee authorship—the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 1997), which states:

> Each author should have participated sufficiently in the work to take public responsibility for the content. Authorship credit should be based on only substantial contributions to (a) conception and design, or analysis and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met.

All publications (e.g. manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to the sponsor for corporate review. The Clinical Trial Agreement among the institution, principal investigator, and the sponsor will detail the procedures for, and timing of, the sponsor's review of publications.

13.6 Compensation

Subjects will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent (Appendix K); which describes any compensation that will be provided during the study. Depending on the type of study, subjects may be compensated for other inconveniences not associated with study-related injuries (e.g. child care costs).

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15. APPENDICES

Appendix A. Schedule of Procedures (Screening through Week 16)

	Screening		Week															
Study Procedures	- 28 Days	-7 Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Informed Consent	X																	
Eligibility Criteria	X																	
Radiological image/report review	X																	
Medical History	X																	
Physical Examination	X		X				X				X				X			
Tumor Tissue Expressing EGFr[a]	X																	
Vital Signs[b,d]and weight[d]	X		X		X		X		X		X		X		X		X	
ECG	X																	
ECOG performance status	X		X				X				X				X			
Laboratory																		
Hematology[d]		X	X				X				X				X			
Chemistry[d]		X	X				X				X				X			
Urine / serum Pregnancy Test[c]		X																
urine sample for magnesium and creatinine to calculate fractional excretion of magnesium			**X**															
Serum for immunogenicity testing[e]			X						X									
CEA		X								X				X				X
Serum for EGFr signaling analysis[d] [all: ABX-EGF arm , wk1 only: BSC arm]			X				X				X				X			
PK[e,f]									X									
Procedures																		
CT Scans / Chest X-ray / Tumor Response[g]	X									X				X				X
General/Others																		
NCCN/FACT and DLQI92			X		X		X		X		X				X			
EORTC-QLQ-C30 and EUROQOL EQ-5D			X				X				X				X			
ABX-EGF Infusion [ABX-EGF arm only]			X		X		X		X		X		X		X		X	
Adverse Event/ Skin Toxicity Assessments[d]			X		X		X		X		X		X		X		X	
Concomitant Medications,Transfusions Procedures	X		X		X		X		X		X		X		X		X	
Resource Utilization			X				X				X				X			

[a] may be done anytime before **randomization**

[b] blood pressure, resting pulse, respiration rate, and temperature within 30 minutes before, **approximately 30 minutes after the start of,** upon completion of, **and approximately 30 minutes after,** the ABX-EGF infusion

[c] within 72 hours of **randomization,** when applicable and may be performed at a local laboratory

[d] must be completed/recorded before ABX-EGF infusion

[e] serum sample drawn within 30 minutes before ABX-EGF infusion

[f] serum sample drawn 15 minutes post ABX-EGF infusion

[g] CT scans of abdomen and pelvis and CXR or chest CT (chest CT must be obtained at baseline: chest CT must be obtained if CXR is abnormal), and all other sites of disease

Appendix A. Schedule of Procedures

(Week 17 Through Week 48)

Study Procedures	Week																															
	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Vital Signs[a,b] and Weight[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
ECOG Performance Status	X				X				X				X				X				X				X				X			
Physical Examination	X				X				X				X				X				X				X				X			
Laboratory																																
Hematology[b]	X				X				X				X				X				X				X				X			
Chemistry[b]	X				X				X				X				X				X				X				X			
Serum for Immunogenicity Testing[c]							X																									
CEA								X[f]								X[f]								X[f]								X
Serum for EGFr **signaling** analysis[b][all ABX-EGF arm]	X								X								X								X							
PK[c,]							X																									
Procedures																																
CT Scans/Chest X-ray/Tumor Response[e]								X[f]								X[f]								X[f]								X
General/Others																																
NCCN/FACT and DLQI92	X				X				X				X				X				X				X				X			
EORTCQLQC30 and EUROQOL EQ5D	X				X				X				X				X				X				X				X			
ABX-EGF Infusion	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Adverse Event/Skin Toxicity Assessments[b]	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Concomitant medications, transfusions, procedures	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Resource Utilization	X				X				X				X				X				X				X				X			

[a] blood pressure, resting pulse, respiration rate, and temperature within 30 minutes before, **approximately 30 minutes after the start of,** upon completion of**, and approximately 30 minutes after** the ABX- EGF infusion;
[b] must be completed/recorded before ABX-EGF infusion
[c] serum sample drawn within 30 minutes before ABX-EGF infusion
[d] serum sample drawn 15 minutes post ABX-EGF infusion
[e] CT scans of abdomen, pelvis and chest X-ray or chest CT (chest CT will be obtained if chest X-ray is abnormal)
[f] complete or partial response must be confirmed **no less than** 4 weeks after the criteria for response are first met, CEA at the time of turmor assessment

Appendix A. Schedule of Procedures (Week 49 Through Disease Progression, Safety Follow-Up)

Study Procedures	Week 49 Until Disease Progression; 12 Week Repeated Treatment Periods												Safety Follow-up Visit[f]
	1	2	3	4	5	6	7	8	9	10	11	12	
Vital signs [a,b] and Weight	X		X		X		X		X		X		X
ECOG Performance Status	X				X				X				X
Physical Examination	X				X				X				X
Laboratory													
Hematology[b]	X				X				X				X
Chemistry[b]	X				X				X				X
Serum for Immunogenicity Testing[c]													X[g]
CEA												X[e]	X
Serum-EGFr signaling analysis (all: ABX-EGF arm; follow-up: BSC arm)[b]													X
PK													X
Procedures													
CT Scans/Chest X-ray/Tumour Response[d]												X[e]	X
General/Others													
NCCN/FACT and DLQI92	X				X				X				X
EORTCQLQC30 and EUROQOL EQ5D	X				X				X				X
ABX-EGF Infusion	X		X		X		X		X		X		
Adverse Events/Skin Toxicity Assessments[b]	X		X		X		X		X		X		X
Concomitant Medications, Transfusions, and Procedures	X		X		X		X		X		X		X
Resource Utilization	X				X				X				X

[a] blood pressure, resting pulse, respiration rate, and temperature within 30 minutes before, approximately 30 minutes after the start of, upon completion of, and approximately 30 minutes after completion of ABX-EGF infusion; weigh at safety follow-up visit
[b] must be completed/recorded before ABX-EGF infusion
[c] serum sample drawn within 30 minutes before ABX-EGF infusion
[d] CT scans of abdomen, pelvis and chest X-ray or chest CT (chest CT will be obtained if chest X-ray is abnormal)
[e] complete or partial response must be confirmed no less than 4 weeks after the criteria for response are first met, CEA at time of tumor assessment
[f] must occur 4 weeks after last treatment in ABX-EGF plus BSC arm and within 4 weeks after disease progression in BSC arm
[g] if positive HAHA at Safety Follow-up, must be followed every 3 months until value becomes negative or baseline

Appendix B. Tumor Sample Collection for Measurement of EGFr Expression

EGFr expression on the subject tumor samples will be determined at a central laboratory using an EGFr immunohistochemistry kit (DakoCytomation EGFR PharmDx™ kit).

Tissue blocks are requested for immunohistochemistry studies for epidermal growth factor receptor (EGFr) expression. Remaining tissue block will be returned to the investigational site.

If tissue blocks are not available, up to sixteen (minimum of ten) slides containing 1 unstained tissue section per slide taken from a paraffin block should be sent to the central laboratory for staining before subjects are enrolled into the study (tissue should be either current biopsy tissue or most recent archival tumor tissue).

Sections should be 5 microns thick and placed one section to a slide.

“Positively charged” or “plus” slides (coated with a polysilane component that helps the sections stick) will be supplied by the central laboratory.

Fresh biopsies (if/when available) are to be bisected at the investigational site.

One half of each fresh biopsy is to be flash-frozen and stored at the investigational site until a shipment is requested from the sponsor; one half of each fresh biopsy is to be fixed and embedded in paraffin (slides should be taken from a fresh biopsy whenever available at Screening).

The Specimen Report Form provided by the central laboratory should accompany tumor sample shipments.

Note: Slides that are collected and not needed for the purpose of evaluating EGFr expression for this study will be stored refrigerated (2-8^{o}C) at the central laboratory for additional analysis of the expression and level of proteins involved in EGFr signaling.

Appendix C. ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e. light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix D. Guide to Using Modified RECIST Criteria for Review of Disease Response

The RECIST Criteria were developed and published by Therasse et al (2000) and will be employed in the independent review of this study with modifications based on current practices of the medical community.

Eligibility

To be eligible, subjects must have at least one unidimensionally measurable lesion greater than or equal to 20 mm using conventional techniques (CT scan or MRI) or spiral CT scan.

Measurable Lesions

Measurable target lesions are defined at baseline as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) greater than or equal to 20 mm using conventional techniques (CT or MRI) or spiral CT scan.
Target lesions must not be chosen from a previously irradiated field.
The distribution of the target lesions should be representative of the subject's overall disease.

Non-Measurable Lesions

All other lesions (longest diameter less than 20 mm), including small lesions and other truly non-measurable lesions are considered non-measurable and characterized as non-target lesions.

This will include any measurable lesions beyond the maximum number of 10 that were not chosen as target lesions

Other examples of non-measurable lesions include bone lesions, peptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions and also abdominal masses that are not confirmed and followed by imaging techniques**,** and groups of lesions that are small and numerous.

Lesions clinically measured by the investigator, and not imaged by radiographic methods (ie,skin nodules and palpable lymph nodes) will automatically be considered non-target lesions.

Method

All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks (28 days) before randomization in the study.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up evaluations.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguous reconstruction algorithm. Spiral CT should be performed by use of a 5-8 mm contiguous reconstruction algorithm.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, in this protocol, a baseline chest CT will be performed. A chest X-ray or a chest CT scan will be performed to evaluate tumor response during the treatment phase. A chest X-ray will be performed if the baseline chest CT scan was found to be normal. In the event the chest X-ray is found to be abnormal during the treatment phase, a chest CT will be obtained. If the baseline chest CT scan was shown to be abnormal, a chest CT scan will be performed throughout the treatment phase.

Use of ultrasound (US) should not be used to measure tumor lesions for eligibility or on study determination. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules or to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.

Baseline Documentation of "Target" and "Non-Target" Lesions

Baseline images will be used to prospectively identify all sites of disease present at the start of treatment. Sites of disease will be characterized as either target or non-target lesions

Up to 10 target lesions (a maximum of 5 per organ) will be chosen to measure over the course of therapy. The distribution of these target lesions should be representative of the subject's overall disease status.

Target lesions should be selected on the basis of their size ($\geq$ 20 mm) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

All other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded and measured over the course of therapy. This includes any measurable lesions that were not chosen as target lesions.

Evaluation of Overall Response:

The subject response will be assessed based on the response of the target lesions, the response of the non-target lesions and the presence or absence of new lesions.

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of the longest diameters (SLD)

Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the nadir SLD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the nadir LD since the treatment started
Unable to Evaluate (UE):	A target lesion(s) was not measured or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.
Not Applicable (NA)	No target lesions were identified at baseline
Not Done (ND)	Scans were not performed at this time point to evaluate the target lesions
Too Small To Measure (TSTM)	Target lesions decrease in size to less than 5 mm in any dimension
Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions
Incomplete Response/ Decreased Non Target Lesions/ Stable Disease (IR/SD):	Persistence of one or more non-target lesion(s) not qualifying for either CR or PD
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. Progressive disease of non-target lesions will be assessed when the SLD of the lesion(s) has increased by 25% or greater and the lesion(s) measure $\geq$ 10 mm in one dimension at the time of progression
Unable to Evaluate (UE)	Any non-target lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
Not Applicable (NA)	No non-target lesions identified at baseline

Not Done (ND) Scans were not performed at this time point to evaluate non-target lesions

Target Lesions	Non-Target Lesions	New Lesions	Response
CR	CR	No	CR
CR	IR/SD	No	PR
CR	UE/ND	No	PR
PR	Non-PD	No	PR
PR	UE/ND	No	UE
SD	Non-PD	No	SD
SD	UE/ND	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
UE	Non-PD	No	UE
ND	Non-PD	No	UE
NA*	IR/SD	No	SD
NA*	CR	No	CR
NA*	NA**	No	UE

NA* = No target lesions identified at baseline
NA** = No non-target lesions identified at baseline

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at the time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

Response Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence, or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

Blinded Central Review

In addition to the investigator's assessment, all scans will be maintained for a blinded central review by a panel of at least 2 radiologists unaffiliated with the sponsor and the conduct of the study. A third blinded radiologist (adjudicating radiologist) will review any readings that are inconsistent between the 2 radiologists.

Appendix E. Laboratory Sample Collection and Shipping Instructions

A CENTRAL LABORATORY WILL MEASURE THE FOLLOWING LABORATORY TESTS, UNLESS OTHERWISE NOTED:

Hematology:

CBC w/ differential
White blood cells count (WBC)
Absolute Neutrophil Count (ANC)
WBC differential (diff)
-Neutrophils
-Eosinophils
-Basophils
-Lymphocytes
-Monocytes
Red blood cell count (RBC)
Hemoglobin (Hgb)
Hematocrit (Hct)
Platelet count (Plt)

Urine:
Magnesium
Creatinine

Serum Chemistry:

Sodium (Na)
Potassium (K)
Chloride (Cl)
Bicarbonate (HCO3)
Blood Urea Nitrogen (BUN)
Creatinine (Cr)
Albumin
Total protein
Total bilirubin (Bili)
Alkaline phosphatase (alk Phos)
Alanine aminotransferase (ALT, SGPT)
Aspartate aminotransferase (AST, SGOT)
Calcium (Ca)
Phosphorous (PO4)
Uric Acid
Magnesium
LDH

Tumor marker:

Carcinoembryonic Antigen (CEA)

Females Only: Urine or serum pregnancy test (if applicable), may be performed at a local laboratory

Serum samples for immunogenicity testing, PK, and analysis of the level and expression of proteins involved in EGFr signaling:

- The central laboratory will supply containers for sample collection and packaging materials.
- Serum samples for immunogenicity testing (including HAHA analysis), PK, and analysis of the level and expression of proteins involved in EGFr signaling, will be shipped from the site to the central laboratory, according to the instructions provided to each site in the prepared investigator's manual.

Appendix F. Adverse Event Assessments

Is there a reasonable possibility that the event may have been caused by investigational product? No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by investigational product. The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when investigational product is readministered
- does not follow a temporal sequence from administration of investigational product

Yes = There is a reasonable possibility that the event may have been caused by investigational product. The adverse event:

- follows a temporal sequence from administration of investigational product
- is a known response to the investigational product based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of investigational product
- reappears or worsens when investigational product is readministered

Adverse Events Standard Grading Score

Please refer to the NCI common toxicity criteria version 2.0, for adverse event grading information (see study manual provided separately), with the exception of ABX-EGF related skin toxicity which will be graded as per protocol Section 6.2.2.2.

Appendix G. Serious Adverse Event Form

AMGEN *(indicate protocol no.)* **20020408**

❑ **New** SAE Report *or* ❑ **Follow-up** SAE Report

Clinical Trial Serious Adverse Event Report

NOTIFY AMGEN WITHIN ONE WORKING DAY • FAX TO:

Site No. | Subject ID No. | Subject Initials

1. STUDY INFORMATION

Investigator: | Phone No.: ( ) | Reporter: | Phone No.: ( )

Institution: | Fax No. ( )

2. SUBJECT INFORMATION

Sex: ❑ F ❑ M | Race: | Date of Birth: Day Month Year

3. RELEVANT MEDICAL HISTORY INCLUDING ALLERGIES: _____

4. *Information in this section must be entered on the Adverse Event Summary CRF.*

Adverse Event Diagnosis or Syndrome (if known) OR Sign(s) / Symptom(s) *List one event per line, list MAIN event first.*	Date Started Day Month Year	Date Ended, Changed in Severity or Resulted in Death Day Month Year	Severity 01 Mild 02 Moderate 03 Severe 04* Life threatening 05* Fatal	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by investigational product? No ✓ Yes ✓	Action Taken with Investigational Product 01 Still being administered 02 Permanently discontinued 03 Withheld	If hospitalization required, indicate Date Admitted and Date Discharged, if appropriate. Date Admitted *(if appropriate)* Day Month Year	Date Discharged *(if appropriate)* Day Month Year	Outcome of Event 01 Resolved 02 Resolved with sequelae 03 Resolving 04 Not resolved

SERIOUS CRITERIA CODES: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability / capacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard

5. PRODUCT NAME *(enter name)*

Abx-EGF or BSC

❑ Blinded ❑ Open Label

	INITIAL							CURRENT						
	Start Date Day Month Year	Stop Date Day Month Year	Dose	Route	Freq.	Start Date Day Month Year	Stop Date Day Month Year	Dose	Route	Freq.

6. DESCRIBE EVENT: Summary of event to include treatments, appropriate labs, relevant concomitant medications: _____

Probable etiology: _____

Final diagnosis: ❑ None ❑ Yes - indicate: _____

Co-suspect drugs: ❑ None ❑ Yes - indicate: _____

Signature: _____ ***Title***: _____ ***Date***: _____

FOR INTERNAL USE ONLY:

AER # : _____ Date Received: _____ CTS: _____ DRC Date: _____

v 4.02 15Apr03sb

Appendix H. Pharmacy Guide

ABX-EGF Packaging and Formulation

ABX-EGF will be packaged by Amgen and distributed using Amgen's clinical trial drug distribution procedures. Each vial of ABX-EGF will contain 10 mL of a sterile protein solution containing a 20-mg/mL solution of ABX-EGF. The vials will contain approximately 200 mg of study drug and are for single dose use only. Boxes of ABX-EGF will contain 12 or 25 vials of study drug. The sponsor or its designee will conduct initial shipments of drug and 0.22-micron in-line filters and on-going re-supply.

ABX-EGF Labeling

Each vial of study drug will be labeled with the following: ABX-EGF 20 mg/mL, 10.0 mL I.V., Immunex, 2°C - 8°C. The Caution statement will differ depending on the country where the study drug will be administered.

ABX-EGF Storage

The supplied investigational drug must be stored at 2-8°C in a secured area upon receipt. As study drug contains no preservatives, vials are designed for single use only. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow study drug to freeze and do not use if contents freeze in transit or in storage. If vials fall out of specified temperature requirement please contact the sponsor or its designee for instructions.

Records of the actual storage conditions during the period of the study must be maintained (ie, records of the date and time and initials of person checking, and the "working day" temperatures of the refrigerator used for storage of trial supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording.

ABX-EGF Preparation

NOTE: ABX-EGF is a protein and should be handled gently to avoid foaming, which may lead to denaturation of the protein product.

The pharmacist using aseptic techniques will prepare ABX-EGF for infusion. The dose of ABX-EGF will be based upon the subject's baseline weight. The dose will not be recalculated unless the weight changes at least ±10% from the baseline weight. The calculated amount of ABX-EGF will be removed from the vials and added to

approximately 100 mL of pyrogen-free 0.9% sodium chloride solution, USP/PhEur. The total concentration infused should not exceed 10 mg/mL of ABX-EGF (in the event a subject's actual body weight requires greater than a 150 mL volume infusion, ABX-EGF must be administered over approximately 90 minutes). The volume of saline should be increased as needed to ensure the maximum concentration of the diluted solution does not exceed 10 mg/mL. The study drug will be infused within 19 hours of dilution and will be labeled per site pharmacy SOPs. The bag should be labeled per site pharmacy SOPs and promptly forwarded to the clinic center for infusion. The sponsor will provide 0.22-micron in-line filters to the sites for study drug infusion.

Supply and Return of ABX-EGF

At study initiation and as needed thereafter, study drug will be shipped to a responsible person (ie, a pharmacist) at the Investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form and Investigational Product Accountability record. The Proof of Receipt Form should then be faxed to the sponsor and the original retained at the site. At the end of the study, or as directed, all study drug supplies, including unused, partially used, or empty containers, will be retained at the site until a representative of the sponsor or its designee can audit drug accountability records and arrange for the destruction or return of used and unused study medication to the sponsor or its designee (or alternative disposition if authorized by the sponsor and in compliance with applicable regulatory requirements).

ABX-EGF and 0.22 Micron Filter Accountability

An Investigational Product Accountability Record for the investigational product ABX-EGF mandated by the protocol must be kept current and should contain:

- dates and quantities of investigational product received from the sponsor
- manufacturing batch or lot numbers for product received
- subject's identification (subject number and initials)
- date and quantity of investigational product dispensed (and remaining, if from individual subject drug units)
- initials of the dispenser
- dose preparation records
- date and quantity of drug returned to the Investigator/pharmacy, if appropriate

Any discrepancies must be documented and subsequently reported to the sponsor immediately. Where applicable, describe whether the returned investigational product will need to be counted.

The Return of Investigational Product for Destruction Form must be completed and included in the shipment of used and unused investigational product to the sponsor or its designee. At the end of the study, the Final Investigational Product Reconciliation Statement must be completed and provided to the sponsor or its designee.

Documentation of the filter lot numbers will be recorded on the 0.22 micron filter accountability record located in the Pharmacy Guide.

All inventories of study drug and supplies must be made available for inspection by an authorized sponsor representative(s) and regulatory agency inspector(s). The Investigator is responsible for the accountability of all used and unused trial supplies.

Best Supportive Care

Best supportive care treatment will be prepared and stored according to the investigator's assessment.

Appendix I. Pregnancy Notification Form

AMGEN Project No.	Site No.	Subject ID No.	Subject Initials

PREGNANCY NOTIFICATION WORKSHEET

Did subject withdraw from the study? 0 ☐ No 1 ☐ Yes

Sex ①	① SEX CODES:
	1 Female subject **0** Male subject partner

Estimated Date of Conception		
Day	Month	Year

Test Article Administration Start Date			Test Article Administration Stop Date		
Day	Month	Year	Day	Month	Year

Fax to Amgen International Clinical Safety 1-888-814-8653

Date Faxed to Amgen ICSD		
Day	Month	Year

Form Completed By: _____ Date: _____

v1.02 03 Sep02 sb

DISTRIBUTION: *White* - Amgen; *Pink* - Investigator

Appendix J. Administrative Matters

I Responsibilities of the Investigator

The responsibilities of the investigator are:

To ensure that he/she has sufficient time to conduct and complete the study and adequate staff and appropriate facilities that are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand;

To submit an up-to-date curriculum vitae and other credentials (ie, medical license number in the United States) to the sponsor and – where required – to relevant authorities;

To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study;

As indicated on FDA form 1572, the Principal Investigator is responsible for assuring that all study site personnel, including sub-investigators and other study staff members, adhere to all FDA regulations and GCP guidelines regarding clinical trials both during and after study completion;

Any advertisements used to help recruit subjects must be submitted to the appropriate IEC/IRB for review and approval before using the ad for subject recruitment;
The Principal Investigator must notify their IEC/IRB *in writing* of any serious and/or unexpected AEs;

The Principal Investigator is also responsible for informing their IEC/IRB of the progress of the study and for obtaining annual IEC/IRB renewal (if appropriate). The IEC/IRB must be informed at the time of completion of the study. The Principal Investigator should provide their IEC/IRB with a summary of the results of the study.
Pre-study documentation:
The sponsor must receive the following documentation before initiation of the trial:

- Signed FDA form 1572
- Curricula vitae of the Principal Investigator and all sub-investigators

- Signed cover page of this protocol
- Copy of the correspondence(s) from the ERC/IRB indicating approval of the protocol and consent form
- Copy of the names and occupations of ERC/IRB members
- Copy of the IEC/IRB approved informed consent form
- Clinical laboratory reference ranges for all tests required in the protocol that will be performed at the site's local laboratory and a copy of the laboratory license(s) or accreditation(s)
- Study signature log
- Financial Disclosure

II Protocol Amendments

The Investigator should not implement any deviation from, or changes to, the protocol without written agreement by the sponsor and prior review and documented approval from the IEC/IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to subjects, or when the change(s) involves only logistical or administrative aspects of the trial (ie, change of Monitor(s), change of telephone number(s)).

III Subject Privacy

Immunex Corp., as the sponsor of the study, is concerned for the individual subject's privacy. Therefore, all subject data collected will be treated confidentially, identified only by a subject identification code and initials.

In compliance with Federal guidelines regarding the monitoring of clinical studies, Immunex Corp. and/or FDA representatives may review that portion of the subject's medical record that is directly related to the study. This shall include all study-relevant documentation (including medical histories to verify eligibility, laboratory test results to verify transcription accuracy, treatment and diagnostic reports, admission/discharge summaries for hospital admissions occurring while the subject is on study, and autopsy reports for deaths occurring during or in temporal proximity to the study).

As part of the required content of informed consent, subjects must be informed that Immunex Corp., its designee, and/or a representative of the FDA may review their records. Should access to the medical record require a separate waiver or

authorization, the Investigator is responsible for obtaining such permission from the subject in writing before the subject is entered into this study.

IV Sponsor's Termination of Study

The sponsor reserves the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be tendered.

V Case Report Form Instructions

Before screening the first potential subject, the Investigator will provide a list showing the signature and handwritten initials of all individuals authorized to make or change entries on case report forms (CRFs). If the authorized individuals should change during the study, the Investigator is to inform the sponsor.

CRFs (and subject diary cards, if applicable) will be supplied by the sponsor for recording all data. It is the responsibility of the investigator or sub-investigator to ensure that CRFs (and subject diary cards) are legible and completely filled in with a black ink ballpoint pen. Each CRF or other document collected for data entry will have the subject identification number entered as required. The PIN is a numeric code assigned to each subject as a unique identifier that also maintains subject confidentiality.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialed, dated and justified by the authorized individual making the change. Do not obliterate, write over, use correction fluid, or erase the original entry when making a correction.

When a subject completes a visit, the Investigator or designated staff will make every attempt to complete relevant CRFs within a timely manner of the last data becoming available. Similarly, when a subject completes a study, the Investigator or designated staff will make every attempt to complete relevant CRFs within a timely manner of the subject's last visit. This also applies to forms for potential study participants who were not randomized to a study arm.

An original (top copy) CRF must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While a sponsor professional Monitor or sponsor's Designee (ie, CRO) at the site will review completed CRFs, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors and documentation and approval by the Investigator.

Any questions or comments related to the CRF should be directed to the assigned Clinical Monitor. The sponsor will provide CRF guidelines that will provide detailed instructions as to how each CRF should be completed to minimize errors.

VI Monitoring by the Sponsor

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject is completed. After the last subject visit, the sponsor's professional Monitor or Designee (ie, CRO) will complete the closeout visit and collect all new and outstanding CRFs.

The purpose of these visits is to ensure Immunex sponsored studies are being conducted in compliance with the relevant Good Clinical Practice regulations/guidelines, to verify adherence to the protocol and to ensure the completeness and accuracy of data entered on the CRF and Drug Accountability Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records that will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. The Investigator must make adequate time and space for these visits available.

The investigator must ensure access to reasonable space and adequate qualified personnel for monitoring visits.

VII Archiving Data

The investigator must retain a copy of the protocol, approvals, and other study related documents for 2 years after study medication approval or at least 2 years after the formal discontinuation of clinical development of the study medication. Subject records and CRFs as well as drug disposition records must be kept in an easily retrievable form for 15 years from study completion or until disposal has been agreed in writing with The sponsor.

The investigator must have a 'key' linking the subject's study identification number (ie, treatment number) to the subject's clinical file (the sponsor can provide a confidentiality form to maintain this key). If the investigator relocates or retires, he/she must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a backup exists and a hard copy can be obtained from it if required.

The sponsor agrees to retain its copy of the protocol, approvals, and all other documents related to the study, including certificates relating to any audit or inspection procedures carried out by the sponsor.

VIII Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for Immunex Corp. or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from study start to beyond the conclusion of the study.

When an Investigator signs the protocol, he/she agrees to allow the Drug Regulatory Agency and Immunex auditors to inspect his/her study records. Furthermore, if an Investigator refuses an inspection, his/her data will not be accepted in support of a New Drug Registration and/or Application.

The sponsor has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of drug development. The sponsor may use Regulatory Compliance staff that audits sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that Immunex sponsored studies are in accordance with the relevant Good Clinical Practices regulations/guidelines and that these are being followed.

To accomplish these functions, Regulatory Compliance selects sites to audit. These audits usually take 1 to 2 days. The sponsor audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on drug accountability. The sponsor audit therefore helps

prepare an Investigator for a possible regulatory agency inspection as well as assuring The sponsor of the validity of the database across sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- ERC/IRB approval
- Medication accountability
- Approved study protocol and amendments
- Informed consent of the subjects
- Medical records supportive of CRF data
- Reports to the ERC/IRB and the sponsor
- Record retention

The sponsor will gladly help investigators prepare for an inspection.

IX Confidentiality and Publication

You agree that all information communicated to you by the sponsor is the exclusive property of the sponsor and you will ensure that the same shall be kept strictly confidential by you or any other person connected with the work and shall not be disclosed by you or such person to any third party without the prior written consent of the sponsor. You shall communicate the results of the work promptly to the sponsor.

All rights and interests worldwide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of the Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of the sponsor.

Appendix K. Informed Consent Form

Informed Consent Template

Amendment 2 Version

Subject Informed Consent

20020408

AN OPEN-LABEL, RANDOMIZED, PHASE 3 CLINICAL TRIAL OF ABX-EGF PLUS BEST SUPPORTIVE CARE VERSUS BEST SUPPORTIVE CARE IN SUBJECTS WITH METASTATIC COLORECTAL CANCER

1. BACKGROUND INFORMATION

a. What is this document?

This document is an invitation to participate in an investigational research study named above, and it provides information that will assist you in making an informed decision about whether or not you wish to participate. If you do decide to take part you will be given a copy of this information sheet to keep.

b. What is a research study?

A research study tests promising new treatments (study drugs) or new combinations of treatments in subjects to find out whether the treatments are safe and effective for a particular disease.

c. What is the purpose of this research study?

The purpose of the study is to determine whether the study drug ABX-EGF when administered with best supportive care is an effective and safe treatment for metastatic colorectal cancer compared to best supportive care administered alone. This study is being conducted at approximately 110 centers in Europe, Australia and Canada and is being conducted under the direction of Dr. _____ at_____ (location).

d. Who is funding this clinical study?

Immunex Corporation, a Washington Corporation and a wholly owned subsidiary of Amgen and its affiliates, a for-profit Pharmaceutical/Biotechnology company, is funding this clinical study. Immunex Corporation is the "sponsor" of the study, and Amgen is conducting the study on behalf of Immunex Corporation.

e. Why have I been asked to participate in this study?

Despite recent advances, colorectal cancer that has spread to other parts of the body (metastatic colorectal cancer) cannot be cured with currently available treatment. You are being asked to take part in this research study because your body is not responding

or has not responded to chemotherapies previously administered to you and your cancer may be relapsing.

Your participation in this study is voluntary. If you decide not to participate or you withdraw from the study, there will be no loss of medical care and other treatments will be available for your illness or condition. Your participation in other clinical studies will not be affected if you do not participate or you withdraw.

f. How many other people like me (subjects) will be participating in this study?

Approximately four hundred and thirty subjects will be entered into this trial.

g. What kind of study drug(s) will be tested in this study?

The study drug tested is a monoclonal antibody called ABX-EGF and the information provided below explains what it is and how it works.

The growth of colorectal cancer may be affected by the interactions of the growth factor known as "epidermal growth factor" (EGF) with its receptor. Therapy that is aimed at blocking this growth factor interaction may prove to be an effective treatment for colorectal cancer.

Antibodies are proteins that can be found circulating in your blood stream. The study drug, ABX-EGF, is a manufactured antibody that is being developed by Immunex Corp. in partnership with Abgenix, Inc. This antibody is directed against the receptor for EGF. ABX-EGF has been shown to turn off the activity of EGF receptor and to stop the growth of cancer cells in several laboratory tests. If the same is observed in subjects that receive ABX-EGF as a treatment, it is possible that their cancer will improve or resolve.

ABX-EGF is considered experimental, and regulatory agencies have not approved it as a treatment for colorectal cancer. The study drug ABX-EGF will be administered in this study along with best supportive care.

h. What is best supportive care?

Best supportive care is the best care available for your cancer as judged appropriate by Dr. _____, and according to the hospital guidelines. The best care available may include antibiotics, analgesics (pain medicine), radiation therapy to control pain related to your bone metastases, corticosteroids, transfusions, psychotherapy, growth factors or any other therapy as indicated by Dr. _____. In this research study, best supportive care does not include chemotherapy.

i. What are my chances that I will get the test drug?

Your chance of receiving the study drug ABX-EGF along with best supportive care, and your chance of receiving best supportive care alone is the same at the time of study entry (like tossing a coin). However, if after receiving best supportive care treatment alone, your cancer is progressing, you may be eligible to receive the study drug ABX-EGF on a new study (Protocol 20030194).

j. Will I know which treatment product I am receiving?

This study is not blinded which means that both you and your doctor will know whether you are receiving the study drug ABX-EGF along with best supportive care or best supportive care only.

k. Who decides if I get the study drug or best supportive care?

You will be randomly selected to receive either ABX-EGF along with best supportive care or best supportive care only. However, if your cancer is progressing while you are receiving best supportive care alone, you may be eligible to receive the study drug ABX-EGF on a new study (Protocol 20030194).

l. How long is the study?

Your participation in this study will last until your disease progresses or you are unable to tolerate the treatment with this study drug.

The study includes a screening visit approximately 4 weeks before the start of your treatment, your treatment (until your disease progresses or you are unable to tolerate the study drug), and a follow-up visit 4 weeks after your last treatment, or within 4 weeks from when your cancer has progressed. Following your last visit you will also be contacted by telephone or clinic visit approximately every 3 months for up to 2 years (24 months) after the date of your randomization in the study to ask about your health status.

m. How often will I need to visit the hospital, clinic, or doctor's office?

If you decide to participate in this study, you will need to come to the doctor's office every 2 weeks or more frequently as determined by your doctor. Additional visits to the hospital or local Radiology Department will be required at week 8, 12, 16 and then every 2 or 3 months. If your cancer is improving an additional visit to the Radiology Department one month later will be required. You may be asked to return for one additional visit 4 weeks after your last study treatment, or within 4 weeks from when your cancer has progressed. Following your last visit, you will then be contacted by clinic visit or telephone approximately every 3 months for 2 years (24 months) after the date of your randomization in the study.

n. What will I be responsible for if I participate in this study?

You will be asked not to participate in any other clinical trials taking another investigational product (study drug). You will also be asked not to receive any of the following during the course of the study and for 1 month after the last dose of your treatment:

- experimental or approved anti-tumor therapy
- any agent targeting the EGF receptor other than the ABX-EGF study drug
- chemotherapy for your cancer
- any radiotherapy other than for pain related to your bone metastases

If you are a woman of childbearing potential or if you have been post-menopausal for less than 6 months, you will be asked to be abstinent or to use a form of contraception during the course of the study and for 6 months after your last treatment.

If you are a woman who is breastfeeding, you will be asked to discontinue breastfeeding during the course of the study and for 1 month after the last treatment.

Male subjects will be asked to use adequate contraception upon entry into this study and for 1 month after their last treatment.

o. What happens when the research study ends?

This study will end when you decide you no longer want to participate; when your doctor decides it is in your best interest not to continue receiving the study treatment; or if your doctor has determined that your cancer has got worse, or if the sponsor decides to terminate the study. If this happens, you may be asked to undergo certain tests and procedures 4 weeks after your last study treatment, or within 4 weeks from when your cancer has progressed. If there are any abnormal blood test results from the last visit or if your doctor wants to make sure that you have not experienced any unusual effect from the drug, you may be asked to return to the clinic for additional visits.

p. Who has reviewed the study?

The study has been reviewed and approved by [insert IRB/ERC], an independent panel, which includes doctors, nurses and non- medical people.

2. WHAT PROCEDURES WILL BE DONE IN THIS RESEARCH STUDY?

You will be asked at each study visit about side effects. Laboratory work may be done before and periodically during the study to monitor any changes in your blood. Heart function will be monitored with blood tests.

You will be evaluated by your doctor to determine if you are a candidate for this study during a screening visit in which various tests and procedures will be performed. Once you are determined to be eligible for the study, you will enter the treatment phase (which lasts until your disease progresses or you are unable to tolerate the study drug). After your last study treatment, you will be asked to return for a safety follow-up visit. You will then be contacted by clinic visit or telephone approximately every 3 months for 2 years after the date of your randomization in the study (long-term follow-up). The procedures conducted during these different study phases are described below:

<u>Screening visit:</u>

Documentation related to your previous cancer treatments and some of the CT scans or MRI images from your previous cancer treatments will need to be reviewed by your doctor for the purpose of reviewing your eligibility to enroll in this study.

Tumor tissue will be required during your Screening. Tissue from a previous biopsy may be used if available, otherwise a fresh biopsy will be needed. Tests will be performed on the tumor tissue to determine the level of EGF receptor in your tumor cells. A certain level of EGF receptor is required for eligibility in the study. Additional tests may be conducted on the tumor tissue to evaluate the level and expression of proteins involved

in EGF signaling. Your medical history and weight will be taken, and you will undergo a physical examination. You will also undergo an electrocardiogram, a CT or MRI scan of your abdomen, pelvis, and other sites of disease, and a chest CT scan to assess the extent of your disease.

Approximately 3 tablespoons of blood will be taken for blood analysis. The blood will be used for complete blood count, CEA level (a marker for your cancer) and chemistry profile.

If you are a woman who could be pregnant, a urine or serum pregnancy test will be performed to ensure you are not pregnant before you can receive the study treatment as it may carry unknown or possible risk to a fetus.

If all the initial screening requirements are met, you may be allowed to receive study treatment, and you will be randomly assigned to one of the 2 study arms.

Treatment phase:

During the treatment phase of the study, you will visit the clinic every 2 weeks at which time your study treatment (study drug ABX-EGF along with best supportive care or best supportive care alone) will be administered. The study drug ABX-EGF is administered at a dose of 6 mg/kg administered once every 2 weeks through a small needle that will be inserted into your vein (intravenous). The best supportive care treatment will be administered according to your doctor's assessment. It will take about an hour for the study drug ABX-EGF to be administered. Prior to this infusion, approximately 30 minutes after the start of the infusion, upon completion of the infusion, and approximately 30 minutes after the infusion, you will be observed closely and your vital signs (blood pressure, temperature, respiration rate and pulse) will be taken. In the event you experience a side effect related to the infusion of your study drug treatment, your doctor will consult with the sponsor and may decide to temporarily interrupt your dosing schedule, reduce the dose, or discontinue your treatment.

Approximately 3 tablespoons of blood will be taken during the study, and approximately 1 tablespoon of urine will be collected once on the day when you receive your first study drug administration for routine laboratory tests. The routine laboratory tests include complete blood count and chemistry profile. Approximately 1 tablespoon of blood will also be collected three times during the study to test for antibodies against the study drug ABX-EGF.

Serum samples will be taken on up to 8 occasions (prior to the administration of the study drug) throughout the study. These samples will be maintained for analysis of the level and expression of proteins involved in EGF signaling. Approximately 1 tablespoon of blood will be collected for this test.

Approximately 1 tablespoon of blood will be taken for pharmacokinetic testing during the study (up to two times during your ABX-EGF treatment) if you are assigned to receive ABX-EGF plus best supportive care treatment. This test will determine the levels of study drug ABX-EGF in your blood in order to learn how it is absorbed, distributed and excreted by your body.

You will undergo a physical examination every 4 weeks during your treatment. You will also undergo a CT or MRI scan of your abdomen, pelvis, and all other sites of disease, and a chest X-ray or chest CT scan (depending on the results of your previous chest CT

scan) to assess the extent of your disease at week 8, week 12, week 16 and then every 2 or 3 months. A blood sample for the determination of CEA level will be taken at this time.

You will be asked to complete a questionnaire that asks about your colorectal cancer and any effects the treatment may have on your skin every other week for the first 8 weeks and monthly thereafter during your study drug treatment. You will also be asked to complete a questionnaire asking about your general health status once a month during your study treatment.

If you experience skin-related toxicities (a very common side-effect of the study drug as described later in this document), it is possible that your doctor will take photographs of these toxicities. Your identity will not be disclosed in these photographs.

I read this section, and I decided that I will have photographs taken: _____ (Initials)

I read this section, and I decided that I would rather NOT have photographs taken: _____ (Initials)

Safety follow-up visit:

Four weeks after your last study treatment or within 4 weeks from when your cancer has progressed, a safety follow-up visit will need to be performed. At this time, approximately 3 tablespoons of blood will be taken for blood work, CEA level, and chemistry profile. Approximately 1 tablespoon of blood will also be collected to test for antibodies against the study drug ABX-EGF. (If antibodies are detected, a blood sample will be collected every 3 months to repeat the test for antibodies. Samples will be taken until antibodies are no longer detected). Also, a serum sample (approximately 1 tablespoon of blood) will be taken and maintained for analysis of the level and expression of proteins involved in EGFr signaling. You also will undergo a physical exam and will be asked to complete a questionnaire that asks about your colorectal cancer and any effects the treatment may have on your skin, as well as your general health status. A CT scan or MRI scan of your abdomen, pelvis, and other sites of disease, and a chest X-ray or chest CT scan will also be performed to assess the extent of your disease. No scan will be performed if you discontinue the study due to progression of your cancer. If you experience skin-related toxicities, it is possible that your doctor will take photographs of these toxicities.

Long-term follow-up:

Following your last treatment, you will be followed approximately every 3 months for 2 years after the date of your randomization in the study by either returning to the clinic for a visit or by telephone contact to inquire about your health status.

3. POTENTIAL RISKS AND DISCOMFORTS

a. What are the general risks of participating in this research study?

More than 500 patients have been treated with ABX-EGF, either alone or combined with other cancer treatments. Since this is an investigational product, not all of the potential side effects in humans are known. In addition to the possible side effects listed below, there is always the risk of uncommon or unexpected side effects that you may experience when ABX-EGF is given alone or when combined with other therapies.

You will be closely monitored throughout this study by your doctor. Your doctor will discuss with you any questions regarding risks, discomforts, and side effects.

If significant new findings develop during the course of the study that might affect your willingness to participate, information will be reported to you as soon as possible. If you have any concerns about this study at any time you should contact Dr. _____(Principal Investigator) at (___) _____ (24 hour phone number).

b. What are the known side effects of this study drug?

Very Common (may occur in 10 or more patients in 100)

Mild to moderate acne-like skin rash has been reported in 80 to 90% of patients treated with ABX-EGF and has also been observed with other drugs known to block the epidermal growth factor receptor. This rash commonly resembles acne. The rash often involves the face and upper chest but can affect any area of the skin. Some rashes have been associated with itching or pain. If you develop a rash your physician may decide to treat the rash, however it generally resolves once the ABX-EGF is withheld, or discontinued. Other reported skin effects are fissures (skin breakdown or splitting) on the fingers or toes, fingertip/nail bed infection or inflammation.

Other common side effects that you might also experience include one or more of the following: nausea, loss of appetite, abdominal pain, fatigue, diarrhea and vomiting, dizziness, muscle aching, joint pain, anxiety and fever.

Common (may occur between 1 and 9 patients in 100)

Common side effects that have been observed include slight swelling in your hands and feet, blood clots in the legs and less commonly in the lungs, cough and shortness of breath.

Another side effect reported has been a decrease in the serum magnesium level.

Uncommon (may occur between 1 and 9 patients in 1000)

One of the uncommon side effects that you may experience is a moderate- to-severe facial swelling.

In another drug similar to ABX-EGF, lung complications known as pneumonitis or fibrosis have been commonly observed. To date, subjects receiving ABX-EGF have experienced similar events but less commonly. These complications are generally treatable, but in some cases may result in permanent lung damage.

Because ABX-EGF is administered intravenously, you could experience infusion reactions or an allergic response such as fever, chills, shaking, decrease in blood pressure, wheezing, itching, nausea and rash. These reactions have occurred and have been recorded as mild to moderate in nature.

c. What are the potential side effects of this drug ?

Many investigational drugs have potential side effects and the same is true of ABX-EGF. Often these potential effects are identified because of the action of similar drugs or the normal response of your body to medication. There is a possibility of developing a severe allergic reaction to ABX-EGF. If you develop a severe allergic reaction, you may experience one or more of these symptoms: itching, hives, shortness of breath, wheezing, sudden drop in blood pressure, swelling around the mouth or eyes, fast pulse sweating, or even loss of life.

ABX-EGF has been made from specially designed mice; these mice make fully human antibodies that do not have a mouse protein thereby decreasing the likelihood of an allergic reaction when given to people. There is a possibility that your body's immune system may develop antibodies against ABX-EGF. These antibodies are known as human anti-human antibodies (HAHA). If you develop a HAHA response, you may not be able to receive further treatment with ABX-EGF.

d. Other Information

Some animals treated with ABX-EGF experienced diarrhea and weight loss. If the diarrhea was not treated, some of these animals developed degeneration of the myocardium (heart muscle), likely due to dehydration. Heart damage has also been observed in some patients treated with an antibody that is directed to a receptor closely related to the EGF receptor. In over 300 patients treated with ABX-EGF, all of whom have had their heart function closely monitored, no heart damage has been detected. However, if you experience any symptoms that you believe may be heart related immediately contact your local emergency number and your investigator.

e. What are the risks associated with procedures done in this research study?

<u>Blood Collection</u>

The risks associated with blood collection commonly include discomfort, pain, redness and swelling and/or bruising where the blood is taken from your arm. Sometimes bleeding can occur at the place where blood is drawn. Fainting and infection are rare occurrences associated with blood collection.

<u>Risks of Skin Biopsy</u>

(a sample of your skin)

You may experience temporary pain and bruising. Infection is rare. Your doctor may sew up the area where the biopsy is taken.

<u>Risks of a Bone Scan</u>

(an imaging test to detect the extent of your cancer)

There is a slight risk of damage to cells or tissue from the low amount of radiation released by the radioactive tracer used for this test. Most of the tracer will be eliminated from your body within a day. Allergic reactions to the tracer are very rare, but you may experience some swelling and discomfort at the injection site, that can be relieved by a warm compress on your arm.

Risks of a MRI Scan

(an imaging test to measure the size of your tumor)

You may feel claustrophobic or anxious. You may experience some discomfort and fatigue from lying in a confined space. There are no known effects from exposure to the magnetic fields. The contrast agent will be injected into the vein and may cause a few people to experience nausea, headache, hot flushes, dizziness and irregular heartbeat as well as discomfort from the injection needle. Please tell your doctor if you have any metal plates or clips in your body.

Risks of a CT Scan

(a computerized picture to locate and measure your tumor)

You may feel some discomfort or anxiety when lying inside the CT scanner. The contrast material (dye) is injected and may cause you to get a metallic taste in your mouth, to feel warm and rarely cause nausea or vomiting. You will be exposed to some radiation through this procedure. There is always a slight risk of damage from being exposed to any radiation, including the low amount of x-rays used for the CT scan. If you are especially concerned with radiation exposure, please discuss this with your doctor.

f. Can the side effects of this study drug or study specific procedures be harmful to my family, my offspring, or me?

Some research medications or procedures may cause severe birth defects, and / or mental retardation to a fetus (unborn baby). It is not yet known if ABX-EGF causes any side effects in pregnant or nursing women, the unborn baby, or in the sperm from the male. Preliminary results in animal studies show that administration of ABX-EGF during pregnancy may result in loss of pregnancy.

Women of Childbearing Potential

If you are pregnant, or think you are pregnant, it is important for you to notify the investigator immediately before you receive any ABX-EGF. Immunex will request from the Investigator information regarding your pregnancy if you become pregnant while on study.

If you participate in this study, you must be willing to agree to the following: have a pregnancy test done before beginning your participation, ensure that there is no possibility that you become pregnant during your study participation, and agree to use an approved method of birth control during the study period and for at least 6 months after your last dose of ABX-EGF.

If you are a woman who is breastfeeding, you will be asked to discontinue breastfeeding during the course of the study and for 6 months after the last dose of ABX-EGF.

Sexually Active Male

If your partner is pregnant, or may be pregnant, it is important that you tell your doctor immediately. Immunex will request information on this pregnancy if your partner becomes pregnant while on study.

If you participate in this study, you and your partner must be both willing to use an approved method of birth control (double barrier preferred) during the study period and for at least 1 month after your last dose of ABX-EGF.

4. POTENTIAL BENEFITS

a. What are the expected therapeutic benefits of this study drug?

Participation in this study may allow your cancer to improve. This however may not occur, nor may it be permanent if it does. It is expected that this study will produce information that may lead to a more effective treatment of your disease.

Receiving best supportive care may assist in relieving the symptoms associated to your disease. If your cancer grows after you have received best supportive care alone, you may become eligible to receive ABX-EGF treatment under a separate study to which you will need to consent (Protocol 20030194).

If you were receiving ABX-EGF plus BSC during the study and your disease is either stable or responding you may continue to receive ABX-EGF treatment until you develop progressive disease or are unable to tolerate study treatment.

b. Will I benefit from participating in this research study? Will others?

You may receive no direct benefits from participating in this study. However, it is expected that this study will produce information that may lead to more effective treatment of other colorectal cancer subjects.

5. ALTERNATIVE THERAPY

a. If I choose not to participate in this study, are there other treatments or medications available to me, instead of this research drug?

Other types of therapies may be available for your cancer, which your doctor can offer to you if you choose not to participate in this study.

b. Are there benefits with these other treatments? Are there risks?

Your doctor will discuss the benefits and risks of these other treatments.

6. POTENTIAL COSTS/REIMBURSEMENTS

a. What will this study cost me?

Your participation in this study should not result in any additional costs other than those associated with the treatment of your cancer. All costs related to routine medical treatment of your cancer will be billed to your insurance company or other government health care programs. However, due to the investigational nature of this research study, some insurance companies or government health care programs may limit their obligation to pay for experimental treatments and their consequences. In those cases, you may be responsible for payment of all charges related to the medical care you receive for treatment of your cancer.

b. Will I be reimbursed for any normal expenses that I incur as a result of participating in the study?

The sponsor of the study will cover the costs associated with study specific procedures in this research study, which are not part of your routine care.

You will not be paid any money for participating in this study.

7. CONFIDENTIALITY

a. How will the confidentiality of my records be maintained?

The confidentiality of your medical records will be maintained to the extent permitted by the applicable laws. Clinical data derived from your medical records may also be sent by Immunex to its parent company, Amgen, which is based in the USA where data protection laws are not as comprehensive as in the European Union. This information will be treated in the strictest confidence and your name will not be shown on any forms sent to Amgen. If results of the trial are published, your identity will remain confidential.

b. Who will have access to my medical information if I sign this informed consent form?

It is a requirement that your involvement in this study be noted in your medical records. Direct access to your records will be required by authorized representatives of the sponsor or its designee to check the information collected for the study.

Your medical records, CT scans, MRI images and chest X-rays will be reviewed and members of either the institutional review board/independent ethics committee responsible for this site or a regulatory agency may make copies of them. In addition, copies of your medical records, your CT scans or MRI images and chest x-rays will be sent to and reviewed by an independent company for the purposes of reviewing your eligibility for randomization in this research study and assessing your response to the study treatment. Your medical records, CT scans, MRI images and chest X-rays may also be sent to regulatory agencies (including the FDA).

The sponsor would like your permission to use, reproduce and/or distribute the CT scans, MRI images, chest X-rays and/or photographs taken of you during the study for education purposes, in scientific lectures, journal articles and textbooks. The sponsor would also like your permission to have the above published, circulated or presented in

any way either alone or with other written, printed, graphic or audio matter to members of the medical, nursing, pharmaceutical and related professions, as well as to the public at large. The sponsor may edit, reduce, enlarge or otherwise change the CT scans, MRI images, chest X-rays and photographs. Your identity will not be disclosed. Any photographs taken of you during this study for possible use in future Immunex research studies, publications, scientific seminars, and educational materials will be blocked to assure your anonymity. Your decision to allow the sponsor to use the above for educational and scientific purposes is voluntary.

I read this section, and I decided that I will allow the sponsor to use my CT scans, MRI images, chest X-rays and/or photographs for educational and scientific purposes: _____ (Initials)

I read this section, and I decided that I would rather NOT allow the sponsor to use my CT scans, MRI images, chest X-rays and /or photographs for educational and scientific purposes: _____ (Initials)

By signing this consent form, you (or your legally acceptable representative), authorize access to this confidential information.

The confidentiality of your medical records will be maintained to the extent permitted by the applicable laws. If results of the trial are published, your identity will remain confidential.

8. COMPENSATION FOR INJURY

a. What do I do if I think I have an injury/illness related to my participation in this study?

If you think you have an injury/illness that is related to the study, you should immediately notify <<*insert name*>>, the investigator, or one of the staff members working on the study. The investigator and the study staff may be reached at <<*insert address and telephone number*>>.

If you have a study-related injury/illness, the investigator and the study staff will make sure that you receive necessary treatment.

b. If I have an injury/illness related to my participation in the study, will I be compensated in any way?

The sponsor or its designee will compensate you for reasonable medical expenses for the treatment of any injury/illness that is directly related to the properly administered study drug. This compensation follows the guidelines produced by the [insert country relevant board]. A copy of these guidelines is available on request. The sponsor will not compensate you for treatment that is paid for by a third party.

The sponsor will also not compensate you for other injury- or illness-related costs, such as lost wages. You are not waiving any legal rights by participating in this study.

The investigator and/or study staff will provide you with additional information about any financial compensation that may be available.

9. BIOLOGICAL SAMPLES

Will I be compensated for the use of any of my biological samples?

You should know it is possible that through the use of your sample in research, a commercial pharmaceutical product may be developed. If you decide to sign this consent form you are releasing (giving) to Amgen Inc., your blood sample, the by-products of your sample, and any products developed from the sample or use of the sample. Amgen, other researchers, or research companies may patent or sell discoveries that result from this research. Neither Amgen nor the principal investigator will compensate you if this happens.

10. DATA PROTECTION

<<Please insert country-relevant information>>

11. ASSURANCES

If I agree to participate in this study, what can I be assured of?

- Your participation is voluntary and you are free to withdraw from the research study at anytime without prejudice to your future care. If you decide to withdraw, you should notify your doctor so that your part in the study may be stopped in an orderly manner and your future care can be discussed.
- <<*Investigator's name*>>or the sponsor may choose to withdraw you from this research study at any time.
- You or your legally acceptable representative will be kept informed, in a timely manner, of any information that may relate to your willingness to continue participation in the study. At the discretion of your doctor(s) and the sponsor, you or your legally acceptable representative may be asked to sign a revised informed consent or consent addendum that provides this information.
- You may ask questions at any time about this study. If you feel that you have experienced an adverse reaction to the research drug(s) or procedures, or if you feel unusually unwell during the study, you should contact <<*contact name, home and business telephone numbers*>>.

If you have any questions about the informed consent process or your rights as a research subject then you should contact <<*contact name, telephone, and address*>>.

12. SIGNATURES

You have had all alternative treatments discussed with you.

You have been informed and agree that Amgen's research using biological materials (blood, tissue, etc) collected from you in this study, or materials derived from your biological materials, may lead to the development of commercial pharmaceutical products. Amgen and other researchers may use these materials and may patent or

commercialize discoveries or inventions that result from this research. Neither Amgen nor other participants in this research will compensate you if this happens.

All of your concerns and questions about this research study have been answered to your satisfaction.

In signing this document you confirm that you agree to be part of this study and you have received your own copy of this document.

Subject's Signature	Date[1]	PRINT Subject's Name
Person who conducted the informed consent discussion	Date[1]	PRINT Name of the person who conducted the informed consent discussion

Each person who signs the consent must personally enter the date for his/her signature.

[Additional signature and date lines may be added, as required by different institutions, local practices, or as consent situations require]

Thank you for considering taking part in this study.

Appendix K. Addendum TUMOR TISSUE SAMPLE TESTING

Subject Informed Consent Addendum – Amendment 2

Protocol Number: 20020408

Protocol Title: An Open-label, Randomized, Phase 3 Clinical Trial of ABX-EGF Plus Best Supportive Care Versus Best Supportive Care in Subjects with Metastatic Colorectal Cancer

RE: Initial Screening of Tumor Biopsy Samples for EGFr Expression, to Determine Eligibility for the Above Trial

This Addendum to the Informed Consent is in addition to the main informed consent for this study. Please read this form and make sure that you receive satisfactory answers to any questions that you might have before you decide to sign it.

Purpose and Background

What is this document?
This document forms part of an invitation to possibly take part in an investigational research study, named above, and to provide some information that will help you decide whether to provide a tumor tissue sample for testing, for eligibility.

What is eligibility?
In order for you to be eligible to enter the above study, certain conditions have to be met. One of these conditions is that a sample of your tumor must be tested for the level of a certain protein that it contains. If your tumor tissue sample has the correct amount of this protein in it, then you may be eligible to enter the research study.

What is being tested for?
The protein being tested for is called the Epidermal Growth Factor Receptor. The growth of colorectal cancer may be affected by the interactions of a growth factor known as Epidermal Growth Factor (EGF) with its receptor. A sample of your tumor tissue will be tested to find out the number of EGF receptors it contains.

Who is funding this study?
Immunex Corporation, a Washington Corporation and a wholly owned subsidiary of Amgen and its affiliates, a for-profit Pharmaceutical/ Biotechnology company, is funding this clinical study. Immunex Corporation is the 'sponsor' of the study, and Amgen is conducting the study on behalf of Immunex Corporation.

Subject Requirements: What you will have to do

By signing this consent form, you agree to have a sample of your tumor tissue tested for EGF receptor expression. Tissue from surgery or a previous biopsy may be used if available, otherwise a fresh biopsy will be needed.

Benefits

At this time, there is no direct benefit to you; however if your tumor tissue sample has enough of the EGF receptors present then you may be eligible to enter the research study. This will also be dependent on meeting other conditions that also affect your eligibility to take part. These will be described to you in another informed consent document like this one, which can be provided to you by your doctor if you want to read it now.

Physical Risks and Discomfort

If you have not had previous surgery for your colorectal cancer then a biopsy will be taken. The possible side effects associated with a biopsy are pain, bowel perforation and/or bleeding. If you have already had surgery for your colorectal cancer then a biopsy may be taken from your liver, or less likely, from your lung. The possible side effects associated with a liver and lung biopsy are pain, infection and/or bleeding. Additional side effects for lung biopsy include a pneumothorax (free air in the chest outside the lung) and/or respiratory failure.

What will happen to your tissue sample?

If you are eligible to take part in this research study:

If you have enough of the EGF receptors in your tumor tissue sample, the Sponsor company (Immunex Corporation) will keep some of the remaining tissue sample for 2 years after commercialisation of the research study drug. This may be used for further testing of the level and expression of proteins involved in EGFr signalling.

If you are not eligible to take part in this research study:

If you do not have enough of the EGF receptors in your tumor tissue sample, then the Sponsor company will keep none of the remaining sample. The pathology department of the hospital may, however, keep the sample, according to local hospital procedures.

Will I be compensated for the use of any of my biological samples?

You should know it is possible that through the use of your sample in research, a commercial pharmaceutical product may be developed. If you decide to sign this consent form you are releasing (giving) to Amgen Inc., your blood sample, the by-products of your sample, and any products developed from the sample or use of the sample. Amgen, other researchers, or research companies may patent or sell discoveries that result from this research. Neither Amgen nor the principal investigator will compensate you if this happens.

Participation

Taking part in this tumor tissue sample testing procedure is completely voluntary; however, you will not be eligible to enter to the main part of the study if you decline to have your tissue sample tested.

Potential Costs/Reimbursement

There will be no costs to you for providing a tumor tissue sample for testing. In addition, you will receive no monetary compensation for providing the sample.

Compensation for Injury

If you are physically injured by the properly performed tumor tissue biopsy and you have followed the instructions given to you by the study personnel, the Sponsor of this study, Immunex Corporation, will cover the reasonable medical expenses necessary to treat the injury.

Confidentiality: Personal Information and Results

Your participation in this tumor tissue sample testing procedure is confidential. The testing on your sample will be performed by a third party (a company that Immunex Corporation will contract this testing to) with your characteristic information (for example, male or female, date of birth and initials attached to a sample screening number). The Sponsor has been careful to implement procedures to protect your identity and privacy. The doctor in charge of this study will keep your original signed informed consent form for the tumor tissue sample testing in a secure location. Your name will not be in any publications or reports about this tissue testing.

Direct access to your medical records may be required by authorized representatives of Immunex Corporation to check the information collected for the study. Members of the Institutional Review Board and/or a regulatory agency may also review your medical records. By signing this consent form, you authorize access to this confidential information.

Whom to Contact for Answers to Questions about Research and Contact in the Event of an Injury

If you have questions about this research, in general or want to know your rights, or you believe you have suffered an injury related to this <u>additional</u> tissue biopsy, you should call:

Principal Investigator at telephone number (XXX) XXX-XXXX.
If you have questions concerning your rights as a research subject, you may contact: [Independent person such as IRB Chairperson] at telephone number (XXX) XXX-XXXX.

Assurance

My signature below indicates that:
1. I agree to have a biopsy of my colorectal cancer tissue (unless a biopsy sample already exists).

2. I agree to allow the tumor tissue sample to be used for testing the amount of EGF receptors it contains.

3. I agree to allow the use of my tumor tissue sample for future research involved with the main study if I am eligible to continue into the main study.

4. I understand that the Principal Investigator and Immunex Corporation, the Sponsor of this study, *will not compensate me* in the event that a commercial product is developed by this research.

CONSENT FOR TUMOR TISSUE SAMPLE TESTING

Subject's name _____ (please print)

You have read this consent form and have been given a copy of it. You have also been given the opportunity to ask any and all questions about the tumor tissue sample testing and all the questions asked were answered to your satisfaction. You understand the risks and benefits of the biopsy and tumor tissue sample testing as described in this document. By signing this consent form, you agree to allow your tumor tissue sample to be tested for EGF receptor expression.

SUBJECT
SIGNATURE:_____DATE[1]_____

SIGNATURE: _____ DATE[1] _____
(Signature of the Person Administering the Informed Consent)

_____
(Printed Name and Title of Person Administering the Informed Consent)

[1]Each person who signs the consent document must personally enter the date of their signature. Additional signature and date lines may be added, as required by different institutions, local practices or as consent situations require.