CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

125147/0

MEDICAL REVIEW(S)

TERTIARY REVIEW
BL STN 125147/0

DATE: Sept 26, 2006

FROM: Patricia Keegan, M.D., Director
Division of Biologic Oncology Products/OODP/CDER/OND

SUBJECT: Recommendation for Approval Action on BL STN 125147/0

TO: BL STN 125147/0

Introduction:

Amgen, Inc. has requested accelerated approval for Vectibix™, a human monoclonal antibody, for the third-line treatment of metastatic colorectal cancer. The request for accelerated approval is based on the results of a single, multi-national, open-label, randomized (1:1), controlled trial in 463 patients, in which a clinical modest but highly significant prolongation in time to progression or death was confirmed by an independent committee of radiologists and oncologists who were masked to treatment assignment. Although the median progression-free survival times in both the Vectibix and treatment arms were similar (approximately 8 weeks), the mean PFS was longer [96 days among patients randomized to Vectibix™ and 60 days among patients receiving best supportive care (BSC)]. In addition, the objective response rate among patients randomized to Vectibix™ as confirmed by the independent assessment committee was 8%, which is similar to the response rates observed with other active agents at this advanced stage of disease.

The trial failed to show evidence of an impact on overall survival. Based on data with 5-FU based chemotherapy, improvements in PFS are generally accompanied by improvements in overall survival. This is the basis for the recommendation by the ODAC committee that PFS is reasonably likely to predict an effect on overall survival and is an acceptable endpoint in support of accelerated approval. The reason for the failure to demonstrate that an effect on PFS resulted in an effect on OS in this study remains unclear. Among the considerations are 1) that Vectibix™ has no effect on survival impact, 2) that longer follow-up in the BSC arm as compared to the panitumumab arm obscured an impact on survival, as discussed by Dr. Rothmann in his review, 3) that the study is underpowered to detect a very marginal effect predicted by a modest improvement in PFS (average of 36 days), or 4) that the large proportion of patients in the control arm, half of whom initiated panitumumab therapy 8 weeks after study randomization, obscured detection of an impact on survival. Amgen Inc. has committed to conduct a randomized trial of chemotherapy alone vs. chemotherapy and Vectibix™ in second-line treatment of metastatic colorectal cancer. The primary endpoint of this trial is overall survival and the trial is intended to verify the clinical benefit of Vectibix™ and more definitively determine effects, if any, on overall survival.

The toxicities observed in the clinical trial appear to be, primarily, a result of pharmacologic effects on normal tissues. These toxicities include dermatologic toxicities (from erythema to desquamation), nail changes (predominantly paronychia), oral and GI mucosal toxicity (mucositis, diarrhea), and ocular toxicities in EGFR expressing normal tissues. In addition, toxicities included those observed in among products that affect the EGFR signaling pathway (pulmonary fibrosis), toxicities observed with antibodies which competitively inhibit EGF binding (hypomagnesemia, hypocalcemia, and hypokalemia), and toxicities observed with infusions of large doses of proteins (infusion reactions) were also observed. The majority of these toxicities responded to medical management without requiring termination of Vectibix; serious adverse events resulting in hospitalization or death were uncommon.

Product information:

Vectibix™ (panitumumab) is a recombinant, human IgG2 kappa monoclonal antibody with an approximate molecular weight of 147 kDa that binds specifically to the human Epidermal Growth Factor Receptor (EGFR). Panitumumab is produced in genetically engineered mammalian (Chinese Hamster Ovary) cells.

The ligand to which Vectibix™ binds, the EGFR, is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1, c-ErbB-1), HER2/*neu*, HER3, and HER4. EGFR is a transmembrane glycoprotein that is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum. Interaction of EGFR with its normal ligands (*e.g.*, EGF, transforming growth factor-alpha) leads to phosphorylation and activation of a series of intracellular tyrosine kinases, which in turn regulate transcription of molecules involved with cellular growth and survival, motility, proliferation, and transformation.

Panitumumab binds specifically to EGFR on both normal and tumor cells, and competitively inhibits the binding of ligands for EGFR. Non-clinical studies show that binding of panitumumab to the EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased pro-inflammatory cytokine and vascular growth factor production, and internalization of the EGFR. *In vitro* assays and *in vivo* animal studies demonstrate that panitumumab inhibits the growth and survival of selected human tumor cell lines expressing EGFR.

Given the specific nature of the binding of panitumumab to the EGFR, the presence of EGFR on malignant cells is considered to be required in order for panitumumab to exert its effect. The detection of EGFR on malignant cells in clinical studies was established by the use of immunohistochemical assessment of EGFR on tumor specimens using the DAKO PharmDx assay kit. Unlike other monoclonal antibodies (e.g., Herceptin), in which efficacy was increased as a function of the number of receptor molecules on the

tumor cell, no correlation was identified between the number of receptor molecules and drug activity. Nonetheless, the target of panitumumab is well established and the presence of EGFR at a level which is presently unknown is likely to be critical to result in clinical anti-tumor activity and thus selection of patients who may benefit from panitumumab treatment. Approximately 30% of the patients screened for study entry were not enrolled due lack of expression of EGFR in >1% of the tumor cells. There are no efficacy data in this population (EGFR "negative") and extension of the study results to this population is not valid.

Regulatory History

This is the initial approval for Vectibix™, which will be granted as an accelerated approval for the treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Another monoclonal antibody (Erbitux, Imclone Systems), that also binds specifically to EGFR and competitively inhibits binding of EGF ligand to the receptor, received accelerated approval from the U.S. Food and Drug Administration (FDA) on February 12, 2004 for use in combination with irinotecan for treatment of patients with EGFr-expressing, metastatic colorectal carcinoma who are refractory to irinotecan-based chemotherapy. Accelerated approval was also granted for use as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

On June 10, 2003, a teleconference was held between representatives of Amgen Inc., and FDA to discuss the acceptability of the trial design of an ongoing European trial (Study 20020408) to serve as the sole and primary study in support of a license application as well as to discuss a proposal to request fast track designation, and the clinical development program intended to support a license application for Vectibix™. A synopsis of the protocol for study 20020408 was submitted to the US IND (IND 8382) on May 9, 2003. During the June 10, 2003 teleconference call, FDA stated that modifications of the trial would be needed, that progression-free survival was preferable to overall response rate as the primary objective of the study, and that FDA would need to evaluate studies intended to verify clinical benefit (thus supporting conversion to full approval). FDA requested that the clinical protocol and all protocol-related documents be submitted to the US IND in order to provide a better assessment of the adequacy of the trial.

On June 19, 2003, a meeting was held between Amgen, Inc., and FDA to discuss the status of the product characterization of panitumumab and proposals for establishing comparability between murine hybridoma-derived material, Chinese Hamster Ovary (CHO)-cell derived material manufactured in —, and a scaled-up version of CHO-cell derived material manufactured in — In addition to physico-chemical characterization, Amgen Inc. was asked to provide data on comparability of the pharmacokinetic and immunogenicity profile of panitumumab from

the three manufacturing procedures as a means of assessing comparability. In discussions regarding data required to support alternate dosing regimens in product labeling, FDA stated that pharmacokinetic data would not suffice and safety and efficacy data were needed.

On July 16, 2003, Amgen submitted to protocols 20030167 and 20020408 to BB-IND 8283 for review under a Request for Special Protocol Assessment. Study 20030167 was a single-arm study of Vectibix™ in third-line or fourth-line treatment of EGFR-expressing metastatic colorectal cancer in Study 20030167. The primary objective of the trial was demonstration a durable overall response rate of $\geq$ 10% in support of an initial, accelerated approval. The trial was accepted under a Request for Special Protocol Assessment in January 9, 2004. As noted below, during the Dec. 6, 2004 meeting with Amgen, Inc., FDA was informed that the trial was terminated prematurely due to slow accrual following the approval of Erbitux in February 2004. Study 20020408 was a randomized trial of panitumumab versus best supportive care in the treatment of third-line or fourth-line treatment of EGFR-expressing metastatic colorectal cancer. FDA did not accept the trial under an SPA agreement during the initial review and Amgen, Inc. informed the FDA that the protocol would be initiated in Europe, thus effectively withdrawing the request for SPA.

On Dec. 6, 2004, after submission of additional information requested by FDA during the June 10, 2003 teleconference, representatives of Amgen met with FDA to revisit the early question of the use of study 20020408 as the primary study to support a license application, in lieu of study 20030167, which was no longer meeting accrual goals. While FDA found the design of 20020408 acceptable in support of accelerated approval, FDA also stated that the ability of the study to support full approval was contingent on the magnitude of the effects on progression-free survival. FDA also re-affirmed that the primary analysis of tumor-related endpoints (PFS and ORR) be based on the results of a central review committee that was masked to treatment assignment.

On May 24, 2005, a meeting was held to discuss modifications to the statistical analysis plan for study 20020408 and the content/format of clinical data, clinical pharmacology and pharmacokinetic data, and toxicology data needed to support a proposed license application. FDA provided comments regarding the indication statement, the lack of efficacy data to support — timing of submission of data (i.e., submission of a survival analysis subsequent to submission of the clinical review unit would be considered a major amendment), and the need for a supplement to the PMA for the DAKO EGFR PharmDx kit regarding use for selection of patients for entry into the pivotal study of Vectibix.

On May 26, 2005, a meeting was held to discuss the CMC data to be submitted in a future license application. Many of the questions could not be addressed without review

of data and Amgen, Inc. was informed that a decision regarding acceptability of certain CMC information would be made during the review of the application.

October 5, 2005 meeting to discuss the timing and content of a supplemental PMA for the DAKO EGFR PharmDx kit. Both CDER and CDRH confirmed that such a supplement was necessary and review should be conducted on both applications simultaneously.

October 12, 2005 teleconference to discuss the proposal for submission and archiving of radiological images used as the basis for determination of tumor response and progression status by the independent review committee.

On Nov. 22, 2005, the FDA met with Amgen to reach agreement on the submission of the BLA under the CMA Pilot 1 program. Agreements were reached regarding the schedule of submission of the reviewable units and further discussion of the content and format of the reviewable units and expectations regarding post-marketing commitments for a confirmatory study, studies in pediatric patients, and studies to further elucidate the utility of EGFR detection in the selection of patients for treatment with Vectibix.

Accepted into the Continuous Marketing Application (CMA) Pilot 1

- First unit (non-clinical studies) submitted Dec. 15, 2005
- Second unit (CMC) submitted February 24, 2006
- Third unit (Clinical) submitted March 28, 2006
- 74-day deficiencies letter issued June 9, 2006
- Discipline review letter for Pharmacology/toxicology issued Jun 15, 2006
- Discipline review letter for Chemistry, Manufacturing, and Controls (CMC) unit issued Aug. 29, 2006

Efficacy Review (See primary reviews by Ruthann Giusti M.D., Kallappa Koti, Ph.D, and Mark Rothmann, Ph.D.)

The effectiveness of Vectibix was established in a single, randomized, open-label trial in which evaluated in an open-label, multi-center, randomized (1:1), active-controlled study conducted in Europe, which enrolled a total of 463 patients. Patients were required to have progressed on or following treatment with a regimen(s) containing a fluoropyrimidine, oxaliplatin, and irinotecan; this was confirmed by an independent review committee (IRC) for 75% of the patients. In addition, all patients were required to have EGFR expression defined as at least 1+ membrane staining in tumor cells by the DakoCytomation EGFR pharmDx® test kit. The initial protocol required at least 1+ staining in ≥ 10% of tumor cells; this was amended after enrollment of 99 patients (21% of the study population) to permit enrollment of patients with at least 1+ staining in ≥ 1%

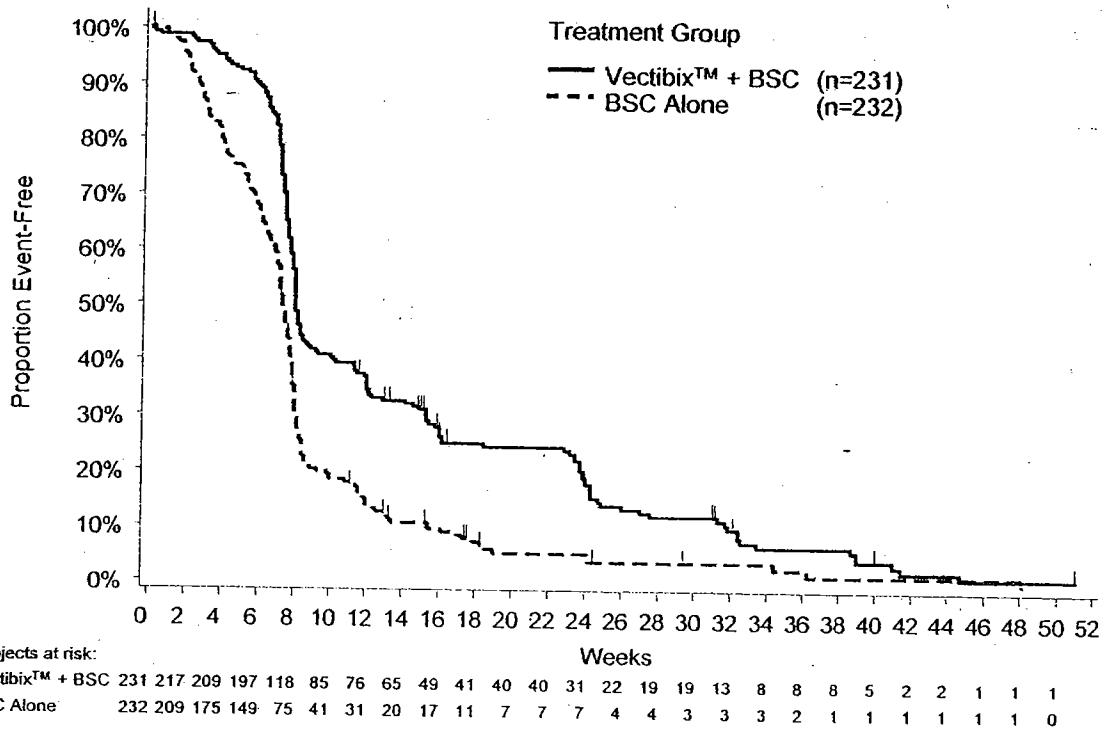
of tumor cells. Despite this change, approximately 30% of the patients evaluated for study entry were deemed ineligible due to failure to meet criteria for EGFR expression. Because this represents a substantial proportion of the general population of patients with metastatic colorectal cancer in whom the safety and effectiveness has not been studied, the Indications and Usage and other relevant aspects of the labeling clearly state that Vectibix therapy is intended for use only in patients whose tumors express EGFR.

Patients were randomized 1:1 to receive panitumumab at a dose of 6 mg/kg given once every 2 weeks plus best supportive care (BSC) (n = 231) or BSC alone (n = 232) until investigator-determined disease progression. Randomization was stratified based on ECOG performance status (0–1 vs. 2) and geographic region (Western Europe, eastern/central Europe, or other). The primary objective of the trial was progression-free survival, with secondary endpoints of estimation of objective response rate, response duration, overall survival and toxicity profile. The primary analyses of progression-free survival (PFS), objective response, and response duration were based on events confirmed by the independent review committee (IRC) composed of a panel of radiologists and a medical oncologist who were masked to treatment assignment. Upon investigator-determined disease progression, patients in the BSC-alone arm were eligible to receive panitumumab; radiologic imaging and clinical information were collected until disease progression was confirmed by the IRC. In the primary analysis of PFS, the IRC-determined time to progression event was used for patients in the BSC arm even if that event occurred while the patient was receiving panitumumab following an unconfirmed investigator-determined progression event.

Among the 463 patients, 63% were male, the median age was 62 years, 40% were 65 years or older, 99% were Caucasian, 86% had a baseline ECOG performance status of 0 or 1, and 67% had colon cancer. The median number of prior therapies for metastatic disease was 2.4. The membrane-staining intensity for EGFR was 3+ in 19%, 2+ in 51%, and 1+ in 30% of patients' tumors. The percentage of tumor cells with EGFR membrane staining in the following categories: ≥ 35%, > 20%–35%, 10%–20%, 1%–< 10% was 38%, 8%, 31%, and 22%, respectively

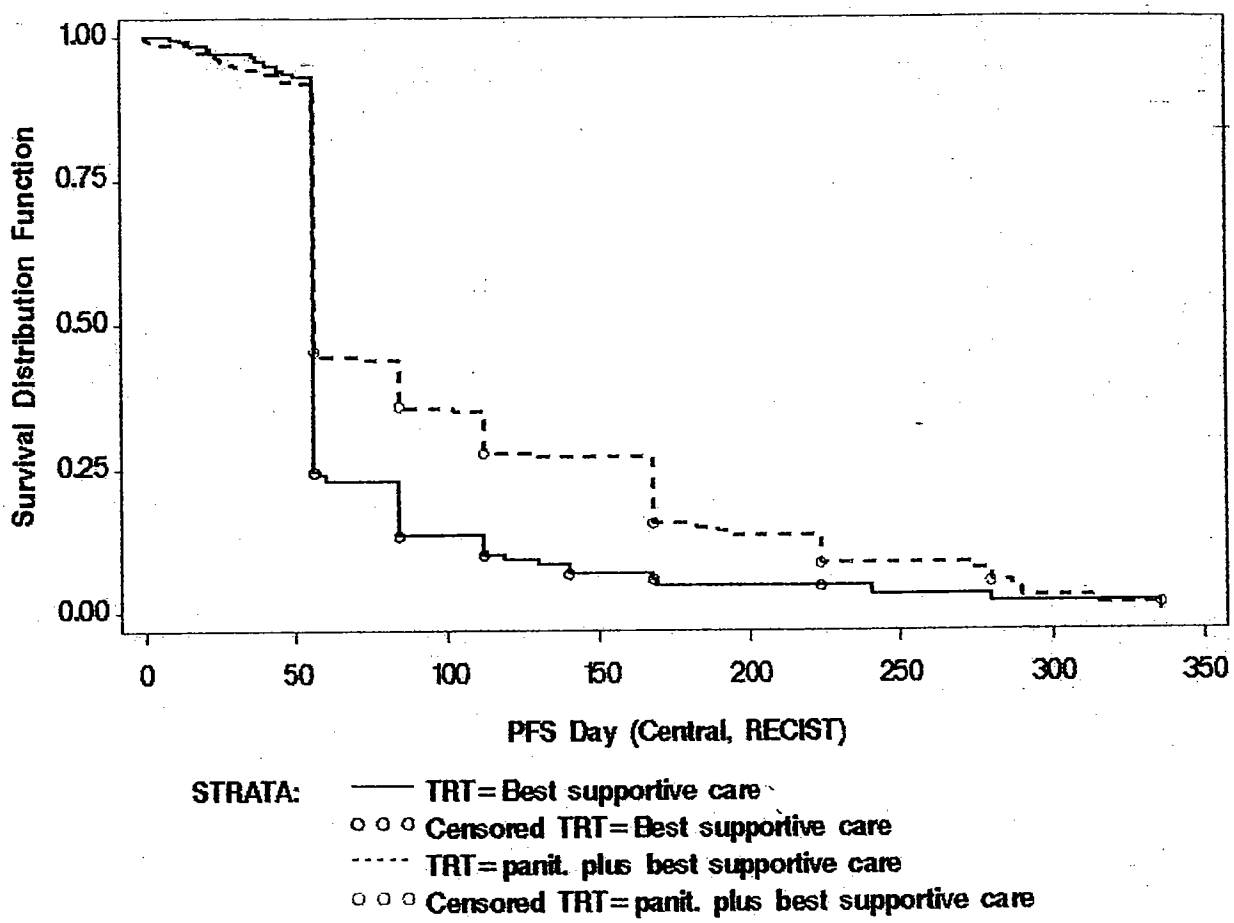
Based upon IRC determination of disease progression, a statistically significant prolongation in PFS was observed in patients receiving Vectibix™ compared to those receiving BSC alone ($p<0.001$, stratified log-rank test) . The mean PFS was 96 days (13.8 weeks) in the Vectibix™ arm and 60 days (8.5 weeks) in the BSC arm. Hazard ratios are not provided in product labeling because the underlying assumptions of the Cox Proportional Hazards model used to generate the hazard ratio are not met. Specifically, the hazards are not proportional over time and this analysis is not valid. Kaplan Meier curves for progression-free survival, based on IRC documented events, are presented in the figure immediately below.

Kaplan-Meier Plot of Progression-Free Survival as Determined by the IRC



In a series of sensitivity analyses, including one adjusting for potential ascertainment bias, i.e., more frequent assessment for progressive disease prior to a study specified time point, PFS was still significantly prolonged among patients receiving panitumumab as compared to controls.

Sensitivity Analysis for PFS
In Which Outcomes in Non-specified Visits Imputed to Occur on Nearest Protocol-specified Time for Assessment

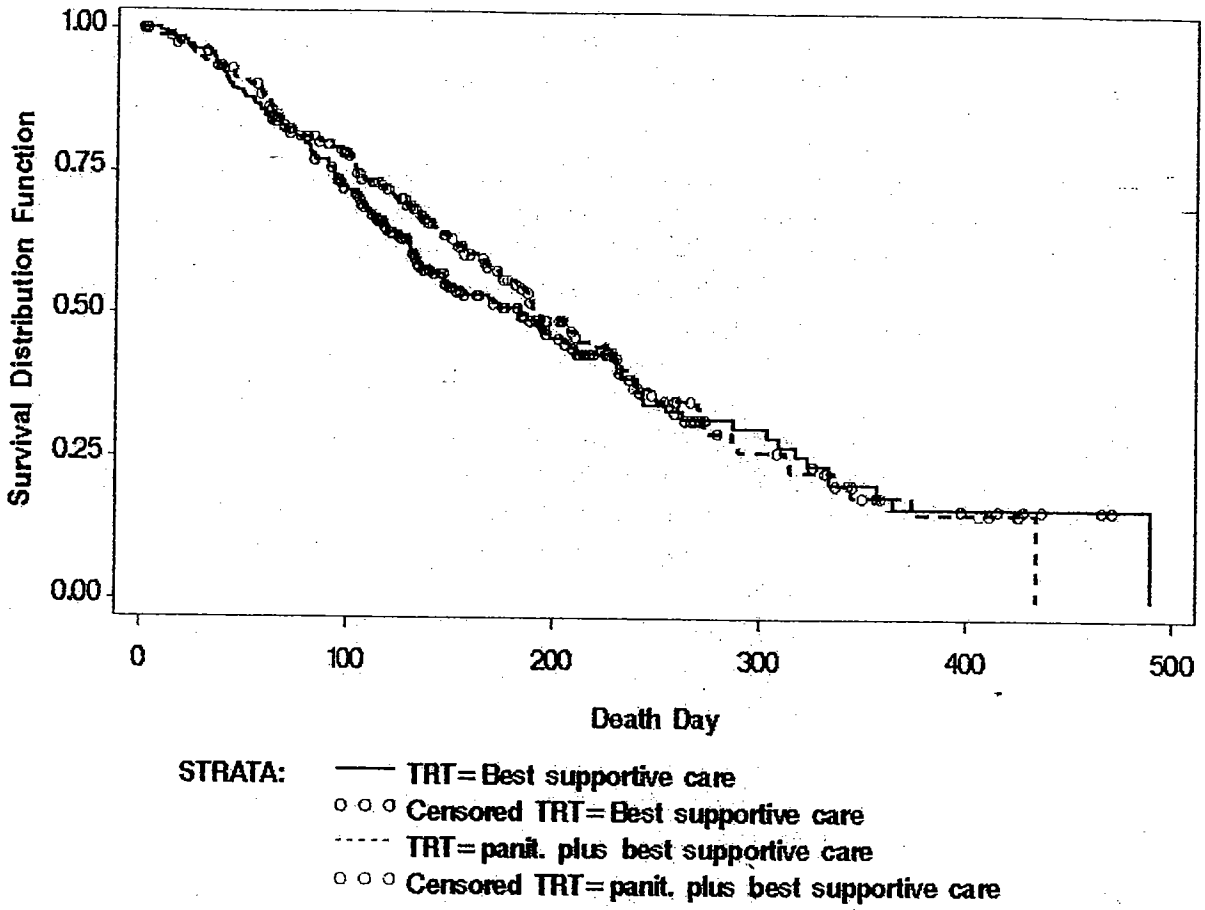


Of the 232 patients randomized to BSC, 75% of patients crossed over to receive Vectibix™ following investigator determination of disease progression; the median time to cross over was 8.4 weeks (0.3–26.4 weeks).

There were 19 partial responses identified by the IRC in patients randomized to Vectibix™ for an overall response of 8% (95% CI: 5.0%, 12.6%). No patient in the control arm had an objective response identified by the IRC. The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks).

There was no difference in overall survival observed between the study arms. Kaplan-Meier curves for overall survival, by study arm, are presented in the figure below.

Analysis of Overall Survival by Treatment Arm



BioResearch Monitoring

BioResearch monitoring audits were conducted at the four clinical sites with the highest accrual. Inspectional findings confirmed that the study conduct was acceptable and confirmed data integrity against primary source documents. No 483s were issued at any of the sites.

Safety Review (See primary review by Ruthann Giusti, M.D.)

Safety data are available from 15 clinical trials in which 1467 patients received Vectibix™; of these 1293 received Vectibix™ monotherapy and 174 received Vectibix™ in combination with chemotherapy. The following additional subgroups were evaluated for assessment of the toxicity profile of panitumumab:

- Patients with mCRC receiving panitumumab monotherapy (n=789).
- Patients. with any cancer diagnosis, receiving panitumumab in combination with other chemotherapy regimens (n=174)

- Patients enrolled in studies with defined interval assessments of serum magnesium levels (n = 812.)
- Patients enrolled in the randomized, controlled, pivotal trial who received at least one dose of panitumumab (n=229) or best supportive care only (n=234)

In general, data from the controlled clinical trial was evaluated most closely to assess for drug related toxicities, although the entire database and other specified subsets were also evaluated to further assess signals identified in the randomized controlled studies or to investigate for toxicities anticipated from the pharmacologic activity of panitumumab (i.e., in normal tissues expressing EGFR) or observed in related products affecting the EGFR signaling pathway (antibody-mediated inhibition and intracellular tyrosine-kinase inhibitors). In the clinical studies and in most clinical trials, exposure to panitumumab based on short-term (less than 6 months) intermittent dosing schedules (e.g., every other week dosing). In the randomized, controlled trial, the median number of doses was 5 (range 1 to 26 doses) and 71% of patients received 8 or fewer doses. The population had a median age of 62 years (range: 27 to 82 years); 63% were male; and 99% were white with < 1% black, < 1% Hispanic and 0% other.

The most common adverse events observed in clinical studies of Vectibix™ (n=1467) were skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea.

The most serious adverse events observed were pulmonary fibrosis, severe dermatologic toxicity complicated by infections sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.

Treatment-related adverse events requiring discontinuation of Vectibix™ were infusion reactions, severe skin toxicity, paronychia, and pulmonary fibrosis.

One adverse event that has not been previously identified in trials of EGFR-inhibitors (small or large molecules) or with protein products in general, is deafness. This finding was reported in 6 of the 174 patients who receive panitumumab in combination with other chemotherapeutic agents. Because ototoxocity/neurotoxiticy is a well-described adverse reaction occurring with several chemotherapeutic agents, attribution to panitumumab is uncertain. The Office of Surveillance and Epidemiology has been asked to specifically monitor this toxicity during post-marketing reporting.

The product used in the pivotal study differs from the product to be marketed, primarily in terms of manufacturing scale — vs. —. In order to assess for differences in toxicity profile, information was provided in the 120-day safety update regarding all clinical safety experience with ongoing trials of the — CHO-sourced product. The medical officer's review did not identify quantitative or qualitative differences in the toxicity profiles between the products from the two manufacturing processes.

OSE reviews

(See primary reviews by Carole Broadnax and Jinhee L. Jahng, Pharm.D., Safety Evaluator)

The Division of Drug Marketing, Advertising and Communications (DDMAC) deemed the trade name, Vectibix, acceptable. DDMAC made a number of suggestions for revision of the physician package insert which were sent to and accepted by Amgen in final labeling. The review division identified suggested revisions that were not medically or scientifically justified with DDMAC, resulting in withdrawal of a limited number of proposed changes by the DDMAC reviewer.

The Division of Medication Errors and Technical Support found the trade name, Vectibix, to be acceptable. DMETS made a number of suggestions for revision of carton container and vial labeling which were sent to and accepted by Amgen in final carton/vial/container labeling.

The Safety conference held Sept 12, 2006, between the review team and members of the Office of Surveillance and Epidemiology was held to discuss adverse events of concern to be monitored closely in the post-marketing setting. The review team requested targeted surveillance of pulmonary toxicity, infectious events in the setting of severe cutaneous toxicity, ocular toxicity, and infusion reactions requiring hospitalization or death, and electrolyte abnormalities resulting in hospitalization or death. A review of post-marketing adverse event reports approximately one year after approval is planned.

Clinical Pharmacology (See primary review by Angela Men)

The clinical pharmacology data in this submission was reviewed at an OCP Briefing was held on August 9, 2006. The reviewer and discipline concurrence state that the clinical pharmacology data support approval of this application.

Single dose and multiple dose pharmacokinetic characterization were derived primarily from a population pharmacokinetic (PK) analysis. The analysis explored the potential effects of selected covariates on panitumumab PK. Results suggest that age (26-85 years), gender, race (15% non-White), tumor type (mCRC, lung cancer or renal cancer), mild to moderate renal dysfunction, mild to moderate hepatic dysfunction and EGFR membrane staining intensity (1+, 2+, or 3+) in tumor cells have no apparent impact on the pharmacokinetics of panitumumab. Serum panitumumab concentrations appeared to be lower in Japanese subjects than those observed in non-Japanese subjects. Additional evaluation of the effects on race (Japanese) and age (<21 years) on panitumumab pharmacokinetics will be explored in two agreed-upon post-marketing commitments.

The manufacturing process for panitumumab evolved significantly throughout the clinical development program; major changes included a shift from a murine hybridoma expression system to a Chinese Hamster Ovary (CHO)-cell expression system, and scale up of the CHO-cell derived material from — used in the pivotal trial to a — used in a limited number of clinical studies and intended to supply the commercial market. The PK profiles of panitumumab administered at dose and schedule of 6 mg/kg every 2 weeks in patients with cancer showed were comparable between the murine hybridoma and — CHO-derived products. The PK profiles of panitumumab administered at dose and schedule of 6 mg/kg every 2 weeks in patients with cancer showed were comparable between the — and — CHO-derived products were also considered comparable despite a finding that the 90% confidence intervals of the parameter ratios were slightly outside the 80 to 125%

range; these differences were attributed to the cross-study nature of the comparison involving a limited number of patients.

An assessment of the correlation between panitumumab exposure and efficacy endpoints could not be determined due to the lack of sufficient PK data and low overall response rate (8%) in the pivotal study. A logistic regression analysis assessing the relationship between panitumumab doses and the incidence of dermatologic toxicity suggested that the incidence of toxicity increased until dose/schedules achieving complete blockade of the EGFR occurred (2.5 mg/kg every week). The incidence and duration of dermatologic toxicity were correlated with the duration of Panitumumab exposure, but not with trough levels.

No studies on the metabolism of Panitumumab have been performed in humans or in animals, for reasons discussed in ICH S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), regarding the expected consequences of metabolism of biotechnology-derived pharmaceuticals. Similarly P_{450} enzyme system is not expected to play any role in panitumumab biotransformation.

Although no formal drug-drug interaction studies were conducted, potential effects of PK drug-drug interactions between panitumumab and irinotecan were evaluated through a cross-study comparison. While irinotecan did not have an effect on the PK of Panitumumab, a decrease of approximately 30% on C_{max} and AUC of irinotecan, and its active metabolite, SN-38, was observed when Irinotecan-containing chemotherapy was administered concurrently with panitumumab. The clinical relevance of this finding is unknown and refers to an unlabeled use of panitumumab (combination with chemotherapy rather than as monotherapy. Therefore the information has not been included in product labeling. However the application will further investigate the clinical relevance of any interactions in a required Phase 4 commitment for this BLA, specifically, the randomized, controlled study of an irinotecan-containing regimen (FOLFIRI) with or without panitumumab that is intended to confirm clinical benefit of panitumumab through an effect on overall survival. In addition, the applicant will conduct a formal phase 1 drug interaction study between panitumumab and irinotecan as an agreed upon post-marketing commitment (PMC).

Pharmacology/Toxicology (See primary review by Anne Pilaro, Ph.D.)

The pharmacology and toxicology reviewer identified no deficiencies that would preclude approval. In general, the reviewer stated that observed panitumumab toxicities were extensions of its pharmacologic activity, reflected in the clinical studies, and may be monitored and treated appropriately in the clinical setting. Non-clinical data submitted in support of the application included tissue binding studies in human and cynomolgus monkey tissue panels, pharmacologic activity studies, acute and chronic (26-week) toxicology studies in cynomolgus monkeys, pharmacokinetic studies in nude mice and in cynomolgus monkeys. Tissue binding studies demonstrated that Vectibix bound with moderate to strong intensity to surface epidermal growth factor receptor (EGFr) in samples of both human and cynomolgus monkey skin, tonsil, breast, and prostate, and in urothelium of the ureter and urinary bladder, and uterine endometrium and cervical squamous epithelium in monkeys.

Pharmacologic activity studies conducted in human tumor cell lines *in vitro* and in human tumor xenografts in nude mice. Tumor xenograft studies provided evidence that administration of Vectibix, alone or in combination chemotherapeutic agents, resulted in delayed tumor growth in human colon, epidermoid, breast, or pancreatic cancers. When used in combination, Vectibix resulted in additive, but not synergistic, anti-tumor activity.

Toxicology and assessment of the pharmacokinetic profile was evaluated in nude mice and cynomolgus monkeys. The relevance of the cynomolgus monkeys was established by tissue cross-reactivity studies in human and cynomolgus tissue panels. However, toxicology studies in cynomolgus monkeys were limited in some animals by the development of an anti-panitumumab antibody response, which altered both the pharmacokinetic profile and coincided with resolution of toxic effects. Severe dermatologic and gastrointestinal toxicities were noted at all dose levels in cynomolgus monkeys treated weekly with 7.5, 15, 30, or 60 mg/kg panitumumab for 4, 13, or 26 weeks. These doses correspond to approximately 1.25 to 10-fold greater than the proposed human dose of 6 mg/kg panitumumab administered every two weeks, and approximately 3 to 24-fold higher than the proposed 2.5 mg/kg/week panitumumab dose, when adjusted for body weight. Observed toxicities included decreases in body weight and food consumption, decreases in serum calcium, phosphate, and magnesium, and dose-dependent clinical signs consisting of soft or watery stool, alopecia, skin rash, erythema, flaking and/or dryness, suppurative dermatitis, erosions, sloughing, and ulcerations, and in several studies, early mortalities secondary to the severity of the skin lesions. These changes occurred with increased frequency and severity as both the dose and duration of panitumumab increased, and only partially reversible following discontinuation of panitumumab treatment.

Hypomagnesemia, hypocalcemia, and hypophosphatemia were also observed in several of the nonclinical, repeat-dose toxicity studies of ABX-EGF in cynomolgus monkeys, and have also been reported in clinical trials of panitumumab. Clinical toxicities not predicted by the animal studies included infusion reactions in < 2% of panitumumab treated, colorectal cancer patients, occurring within 24 hours of the first dose.

Reproductive toxicology studies were conducted in cynomolgus monkeys. Panitumumab treatment inhibited ovarian function in non-pregnant female monkeys, and was abortifacient, although not teratogenic when administered to pregnant animals from GD20 through GD48, throughout organogenesis. These findings were reflected in the relevant PRECAUTIONS subsections of product labeling.

CMC (See primary reviews by Chana Fuchs, Ph.D. and Brenda Uratani)

Pantimumab is a human IgG2-kappa monoclonal antibody that competitively inhibits binding of EGF and other ligands to the EGF receptor. The retention of critical pharmacologic activity is determined in lot release through potency assays. Potency assessments of panitumumab

The panitumumab drug substance manufacturing process has been modified a number of times during clinical development. Biochemical comparability study results between successive processes were submitted and reviewed under IND for appropriateness.

Significant changes in the manufacturing process were introduced during clinical development program and prior to the initiation of the pivotal trial; these changes included a change from a murine hybridoma cell line to a CHO cell line expression system, a change in manufacturing facility and in the manufacturing processes. Biochemical and biophysical analysis showed that although there were some biochemical and biophysical differenees between panitumumab produced by the 2 processes, there was sufficient supporting data to say that product from the clinical CHO process was, by *in vitro* data, functionally equivalent to product from the hybridoma.

The pivotal trial used panitumumab produced at Amgen Washington from CHO cells at the — scale. The commercial product is produced at Amgen Fremont from CHO cells at the — scale. Based on biochemical and biophysical data from a formal comparability study, the clinical — and commercial — products appear comparable.

The facilities inspectional staff identified significant deficiencies at a contract facility — during facilities inspections. Deficiencies in the physical structure, specifically with regard to — required corrective actions. Corrective actions in the form of changes in structural components and implementation of additional controls were provided in the response by Amgen to the 483 items in a series of communications to FDA. The final response was received on Sept. 6, 2006. Based on that final response, the TFRB staff determined that the outstanding issues had been addressed. It is the intent of TFRB to conduct an expedited surveillance inspection post-approval and to confirm implementation of all corrective actions at that post-approval inspection.

Labeling Review:

FDA recommended the following major changes in content and format of the proposed physician package insert

1. Boxed Warnings:

    - Addition of a Boxed Warnings section for infusion reactions. Dermatologic toxicity. Severe infusion reactions were observed with Vectibix and, based on experience with other monoclonal antibodies; severe reactions may result in death. The recommended management of severe infusion reactions is interruption of dosing.
    - Addition of a Boxed Warnings section for dermatologic toxicity. Dermatologic toxicities were included because of the risks of sepsis. The recommended management of severe dermatologic toxicities is interruption of dosing.

    Inclusion of a Boxed Warnings was felt appropriate because of the serious nature of the toxicities and because appropriate physician intervention is necessary to manage and prevent more serious sequelae, which can be best highlighted in Boxed Warnings.

2. Description

   - Characterization of formulation changed from [redacted] to mass (mg) units

3. Clinical Pharmacology:

   - Section re-organized for consistency with ordering of information in other product labels for monoclonal antibodies
   - Removed statements regarding [redacted] because data supporting these statements deemed not reliable.

4. Human Pharmacokinetics

   - Information regarding [redacted] replaced with statement that pharmacokinetics are greater than dose proportional at lower doses and become dose-proportional at doses above 2 mg/kg.
   - Summary statistics for PK properties modified based on the analysis and conclusions by Dr. Men, OCP reviewer.

5. Clinical Studies

   - Removed table providing [redacted] and replaced with a figure of the K-M curve for PFS based on IRC-determined events.
   - Removed references to [redacted]
   - Removed statements regarding [redacted]
   - Removed [redacted] to not provide substantial evidence of effectiveness in support of labeling claims.

6. Indications:

   - Revised to [redacted]
   - Addition of "EGFR-expressing" qualifier to indication statement, because only patients with evidence of EGFR-expression in tumor were enrolled in the pivotal study. This subgroup represents only 70% of patients with metastatic colorectal cancer.

7. Warnings/Precautions:

- Addition of non-clinical data in the WARNINGS: Dermatologic toxicities subsection to include information on the severe dermatologic toxicities and deaths in monkeys treated with panitumumab.
- Added WARNINGS subsection on Infusion Reactions because of the severe nature of a limited number of events which suggest the potential for fatal events and because risks of serious events can be minimized by appropriate management.
- Title of WARNINGS subsection on — changed to Pulmonary Fibrosis, to provide greater clarity on description of events
- Added WARNINGS subsection on Electrolyte — because risks of serious events can be minimized by appropriate management.
- Title of WARNINGS subsection on — changed to Diarrhea to provide greater clarity on description of events and to provide clarification of the scope of the events (also occurs at increased incidence in patients receiving panitumumab monotherapy)
- Title of PRECAUTIONS subsection — changed to Photosensitivity to provide greater clarity on description of events
- Added PRECAUTIONS subsection on EGF Receptor Testing for consistency with and to include important information on text kit qualification when such a kit is necessary for selection of patients for whom the product is indicated.
- PRECAUTIONS: Information for Patients subsection strengthened to include instruct physicians to counsel patients regarding risks of pulmonary fibrosis and embryofetal lethality and to counsel patients regarding risks of, and need to adhere to laboratory monitoring for, electrolyte depletion.
- Modification of PRECAUTIONS: Drug Interactions subsection for accuracy regarding lack of formal testing and to remove misleading statements regarding —
- Modification to PRECAUTIONS: Carcinogenesis subsection for accuracy and to remove potentially misleading statements regarding —
- Modifications to the PRECAUTIONS section of the label, including revision of the language regarding potential impairment of fertility by panitumumab, and to the Pregnancy subsections based on non-clinical studies.

8. Adverse Reactions:
   - Modified Table in ADVERSE REACTIONS section to limit data to the randomized trial, so that data on comparator arm can be included.
   - Deleted — and placed the information for each category of adverse reactions in discrete subsections under WARNINGS or PRECAUTIONS.
9. Dosage and Administration:

- Removed references to —

- Streamlined Dose Modifications subsection for clarity and include separate subsection of directions for dose modification in the event of infusion reactions.

Post-marketing commitments:

The following required post-marketing commitments will be performed by Amgen

Study to verify clinical benefit:

1. To submit a final study report for study 20050181, entitled, "A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer" which is intended to verify the clinical benefit of Panitumumab through demonstration of an effect on overall survival.

Studies required under the Pediatric Research Equity Act (PREA)

2. To conduct a Phase 1 study, Protocol 20050252 entitled, "A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of Panitumumab in Children with Refractory EGFR-expressing Solid Tumors" in children and adolescents (1-18 years of age) to provide the initial safety assessment and establish the pharmacokinetics in pediatric patients.

3. Based on the results of the Phase 1 study described above (i.e., provided that a safe and tolerable dose of Vectibix™ can be determined for children), Amgen will conduct a Phase 2 study to further assess the safety and to estimate the anti-tumor activity of Vectibix™ in a pediatric population with EGFR-expressing tumors.

Agreed-upon post-marketing commitments include the following:

- To provide mature survival data from the pivotal study (20020408)
- To further assess the relationship between EGFR-expression in tumors and clinical outcomes from the confirmatory trial
- To submit data further characterizing the toxicity profile of the — CHO-sourced product from the confirmatory trial
- To provide data characterizing the immunogenicity profile of the the — CHO-sourced product from the confirmatory trial
- To provide the results of a clinical study (20050184) assessing the impact of clinical management of dermatologic toxicities due to Vectibix™

- To conduct and provide the results of a formal drug-drug interaction study for Vectibix™ and irinotecan
- To provide the data characterizing the pharmacokinetic profile of Vectibix™ in the Japanese population
- To provide information regarding the role of EGFR in post-natal development.

Recommendation:

I concur with the recommendations of the review team that the supplement should be approved with the agreed-upon labeling. I also concur with the required and agreed upon post-marketing commitments.

MEDICAL TEAM LEADER REVIEW
BL STN 125147/0

DATE: Sept 26, 2006

FROM: Kaushik Shastri, M.D. Team Leader
Division of Biologic Oncology Products/OODP/CDER/OND

SUBJECT: Recommendation for Approval Action on BL STN 125147/0
Product: Panitumumab (Vectibex ™)

TO: BL STN 125147/0

This reviewer recommends accelerated approval of panitumumab (Vectibix™), a new molecular entity, for the treatment of EGFR-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens (third line therapy). The applicant has not provided sufficient data to evaluate the efficacy of panitumumab therapy

The recommendation for accelerated approval is based on demonstration of an effect on progression-free survival (PFS) which is a surrogate endpoint reasonably likely to predict an effect on the clinical benefit endpoint of survival. The applicant has demonstrated an improvement in PFS ($p< 0.0001$) among subjects with EGFR-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens who were randomized to receive panitumumab in addition to Best Supportive Care (BSC) (n=231) or BSC alone (n=232). The median and mean PFS were 56 and 96.4 days, respectively for subjects receiving panitumumab and 51 and 59.7 days, respectively for subjects receiving BSC alone. Nineteen partial responses, as determined by central review, and no complete responses were observed among the 231 subjects randomized receive panitumumab for an overall response rate of 8% (95% CI: 5.3, 12.5%). The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks). The response rate is similar to the that observed with other active agents at this advanced stage of disease. The trial failed to show evidence of an impact on overall survival. This may be a result of a large number of patients from the best supportive care crossing over to the active treatment arm within a short period of time on study (about 50% crossed over within 8 weeks). Amgen Inc., has committed to conduct a randomized trial of chemotherapy alone vs. chemotherapy and Vectibix™ in second-line treatment of metastatic colorectal cancer. The primary endpoint of this trial is overall survival and the trial is intended to verify the clinical benefit of Vectibix™ and more definitively determine effects, if any, on overall survival.

The safety profile of Panitumumab was acceptable for the indicated population. Evaluation of clinical safety is based on comparison of Panitumumab experience with the best supportive care arm in the pivotal study (n=231 and BSC alone n= 232) supplemented by other single arm and earlier phase studies in subjects with mCRC treated with Panitumumab providing a safety database of over 900 patients. The most common adverse events were skin rash, hypomagnesemia, paronychia, fatigue abdominal pain and diarrhea. The most serious adverse events were pulmonary fibrosis, dermatologic toxicity complicated by infection and death, infusion reactions, abdominal pain, nausea and diarrhea.

Patients with mCRC eligible to third line treatment having failed at least two prior therapies have a uniformly poor prognosis. Despite the modest effect size, the benefit-to-risk assessment is favorable for the approval recommendation for Panitumumab under accelerated approval guidelines. The sponsor has committed to confirming clinical benefit of survival advantage as a post-marketing commitment.

CLINICAL REVIEW

Application Type: BLA
Submission Number: 125147
Submission Code: Original

Letter Date: 2006-03-28
Stamp Date: 2006-03-28
PDUFA Goal Date: 2006-09-28

Reviewer Name: Ruthann Marie Giusti 9/26/2006
Review Completion Date: 2006-09-25

Team Leader: Kaushikumar Shastri 9/26/06

Division Director: Patricia Keegan

Established Name: Panitumumab
(Proposed) Trade Name: Vectibix™
Therapeutic Class: Anti-Epidermal Growth Factor Receptor Monoclonal Antibody, Humanized
Applicant: Amgen, Inc.

Priority Designation: P

Formulation: Single use vials containing 100, 200, or 400 mg panitumumab in a 5, 10, and — mL nominal fill volume, respectively
Dosing Regimen: 6mg/kg IV every other week until disease progression
Indication: Treatment of metastatic EGFr-expressing carcinoma of the colon or rectum
Intended Population: Patients with EGFr-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan containing chemotherapy regimens.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The United States Food and Drug Administration (FDA) Office of Oncology Drug Products (OOP) Division of Biologic Oncology Drug Products (DBOP) Clinical review team recommends accelerated approval of panitumumab (Vectibix™), a new molecular entity, for the treatment of EGFR-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. The recommendation for accelerated approval is based on demonstration of an effect on progression-free survival (PFS) which is a surrogate endpoint reasonably likely to predict an effect on the clinical benefit endpoint of survival.

The applicant has demonstrated an improvement in PFS ($p< 0.0001$) among subjects with EGFR-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens who were randomized to receive panitumumab in addition to Best Supportive Care (BSC) (n=231) or BSC alone (n=232). The median and mean PFS were 56 and 96.4 days, respectively for subjects receiving panitumumab and 51 and 59.7 days, respectively for subjects receiving BSC alone.

Nineteen partial responses, as determined by central review, were observed among the 231 subjects randomized receive panitumumab for an overall response rate of 8% (95% CI: 5.3, 12.5%). No complete responses were observed. The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks). Currently no data are available that demonstrate an improvement in disease-related symptoms or increased survival associated with panitumumab treatment in the target population.

The safety profile of Panitumumab was acceptable for the indicated population. Evaluation of clinical safety is based primarily on the experience of 920 subjects with mCRC treated with panitumumab monotherapy. The most common adverse events were skin rash, hypomagnesemia, paronychia, fatigue abdominal pain and diarrhea. The most serious adverse events were pulmonary fibrosis, dermatologic toxicity complicated by infection and death, infusion reactions, abdominal pain, nausea and diarrhea.

It should be noted that patients with mCRC who have progressed following irinotecan- and oxaliplatin- based chemotherapy have very limited treatment options and a uniformly poor prognosis. Therefore, despite the modest effect size, the benefit-to-risk assessment is compelling for the approval recommendation under accelerated approval guidelines.. The

sponsor is committed to confirming clinical benefit of survival advantage as a post-marketing commitment.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

- Pharmacovigilance / Safety Reporting: The Sponsor will provide annual progress reports as required under 21CFR§ 601.70
- The Sponsor will submit the following to the FDA:
  - Additional safety and efficacy data with the — scale-up product
  - Drug-drug interaction studies to assess the potential pharmacologic impact of the combination Vectibix™ with irinotecan
  - Data to assess the clinical management of dermatologic toxicity
  - /

1.2.2 Required Phase 4 Commitments

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To submit a final study report for study 20050181, entitled, "A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer" which is intended to verify the clinical benefit of Panitumumab through demonstration of an effect on overall survival. This protocol was accepted for Special Protocol Assessment on May 3, 2006. Patient accrual began on June 30, 2006, and will be completed by September 30, 2009. The final study report will be submitted by March 30, 2010.

2. To conduct a Phase 1 study, Protocol 20050252 entitled, "A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of Panitumumab in Children with Refractory EGFR-expressing Solid Tumors" in children and adolescents (1-18 years of age) to provide the initial safety assessment and establish the pharmacokinetics in pediatric patients.

   a. Based on the data submitted in response to 11a and 11b, either submit a

request for waiver from the commitment to conduct studies in children between the ages of 12 and 24 months, or a confirmation that no amendment of the current waiver for subjects below the ages of 12 months will be requested.

b. To conduct a Phase 1 study, Protocol 20050252 entitled, "A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of Panitumumab in Children with Refractory Solid Tumors" in children and adolescents (up to 18 yr of age) to provide the initial safety assessment and establish the pharmacokinetics in pediatric patients with solid tumors in which, based on clinical study and published literature information, an EGFr inhibitor drug has been shown to have clinical activity.

3. Based on the results of the Phase 1 study described above (i.e., provided that a safe and tolerable dose of Vectibix™ can be determined for children), Amgen will conduct a Phase 2 study to further assess the safety and to estimate the anti-tumor activity of Vectibix™ in a pediatric population with EGFR-expressing tumors.

1.2.3 Other Phase 4 Requests

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70:

4. To submit a summary of the final results of overall survival (OS), with 12-month minimal follow up from Study 20020408, 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." This will include only the survival data. It will be followed by submission of the final clinical study report, including 24-month follow up of overall survival. The final protocol was submitted on July 16, — patient accrual began January 16, 2004. The study will be completed by March 15, 2007, an interim study report including 12 month OS data will be submitted by October 30, 2006, and the final study report will be submitted by September 30, 2007.

5. To submit interim and final study reports based on data obtained in study 20050181, entitled, "A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer", that addresses clinical utility of EGFr testing with the Dako PharmDx EGFR kit as a means for selecting patients who will benefit when Vectibix™. The report will include both summary analyses of safety and efficacy as a function of EGFr test results and primary datasets. This protocol was accepted for Special Protocol Assessment on May 3, 2006. Patient accrual began on June 30, 2006, the study completed (PFS data cut off) by February 28, 2008. An interim study report will be provided by August 30, 2008, and a final study report will be submitted by March 30, 2010.

6. To submit interim and final study reports based on data obtained in study 20050181, entitled, "A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer", characterizing the toxicity profile of the commercially marketed product. The report will include comparative analyses of safety between study arms, case report forms for all patients with deaths during treatment or who discontinued treatment or underwent dose modification of Panitumumab for adverse events, narrative summaries for all serious adverse events, and summary data characterizing Panitumumab and chemotherapy drug exposure (e.g., dose intensity over fixed time periods). In addition, primary data will be provided in SAS-compatible electronic datasets. This protocol was accepted for Special Protocol Assessment on May 3,

2006. Patient accrual began on June 30, 2006, the study will be completed (PFS data cut off) by February 28, 2008. An interim study report will be provided by August 30, 2008, and a final study report will be submitted by March 30, 2010.

7. To submit interim and final study report based on data obtained in study 20050181, entitled, "A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer" characterizing the immunogenicity profile of the commercial product, and impact of an anti-Vectibix™ binding and neutralizing antibodies on the pharmacokinetic, safety and efficacy profile of Vectibix™. The report will include both summary analyses and the primary datasets used to generate the summary analyses, in electronic, SAS-compatible format. This protocol was accepted for Special Protocol Assessment on May 3, 2006. Patient accrual began on June 30, 2006, the study will be completed (PFS data cut off) by February 28, 2008. An interim study report will be provided by August 30, 2008, and a final study report will be submitted by March 30, 2010.

8. To submit a final study report for study 20050184, entitled "A Phase 2, Open-label, Randomized Clinical Trial of Skin Toxicity Treatment of Subjects Receiving Second-line FOLFIRI or Irinotecan Only Chemotherapy Concomitantly with Panitumumab" containing an evaluation of the clinical management of Vectibix™-induced skin toxicities. The report will include both summary analyses of safety as a function of medical management and primary datasets from this study and from any reference studies used for comparative safety analyses, which will include information on medical interventions and toxicity onset, severity and clinical course. The final protocol was submitted on March 28, 2006. Patient accrual began on April 19, 2006, and the study will be completed by May 15, 2008. A final study report will be submitted by
November 30, 2008.

9. To conduct a Phase 1 drug interaction study (number not assigned), entitled "Open Label, 2-Cohort, Randomized Study to Assess the Potential Pharmacokinetic Drug-Drug Interaction between Irinotecan and Panitumumab in Subjects with Colorectal Cancer" which will provide a formal assessment of pharmacokinetic drug-drug interactions. The final study report will provide summary analyses of pharmacokinetic and safety information and primary data used to generate the analyses in an electronic, SAS-compatible dataset. The final protocol will be submitted by August 31, 2007. Patient accrual will begin by December 31, 2007, and the study will be completed (Last PK sample for last enrolled patient) by April 1, 2009. The final study report will be submitted by August 30, 2009.

10. To submit a final study report for study 20040192 entitled, "A Phase 1 Clinical Study of ABX-EGF (Panitumumab) Evaluation of the Safety and PK of ABX-EGF in Japanese Subjects with Advanced Solid Tumors" that characterizes the pharmacokinetic profile of Vectibix™ in the Japanese population. The final study

report should provide summary analyses and primary data, including pharmacokinetic data, in both the Japanese and non-Asian population that will permit an assessment of differences in pharmacokinetics, if any, based on race/ethnicity. The study will be completed (database lock) by June 30, 2006, and the final study report will be submitted by April 1, 2007.

11. To submit the following information regarding the role of EGFr in post-natal lung, gastrointestinal, neurologic, bone, or pancreatic development in humans.

    a. Copies of all published literature reports of nonclinical or clinical data addressing the role of EGFr in post-natal human respiratory and gastrointestinal tract, neurologic, skeletal, and endocrine development.

    b. Identification (by Study Number) of any previously submitted final study reports, and submission of any additional data (including primary data) from non-clinical studies of panitumumab conducted by, or under a contractual arrangement for, Amgen in young (pre-pubertal) non-human primates. These data, including all findings in respiratory and gastrointestinal tract, and neurologic, bone, and endocrine organs from any panitumumab–treated juvenile animals from the aforementioned studies, will be summarized and discussed in context of toxicities observed in adult human respiratory and gastrointestinal tract, neurologic, skeletal, and endocrine organ systems.

12. To oversee the implementation of design and facility controls at the — as stated in the response to the quality discipline review letter dated September 6, 2006. This is to begin prior to the manufacturing of the next panitumumab fill —

13.

14. To submit proposed revisions to release specifications and shelf-life specifications for panitumumab drug substance after — commercial manufacturing runs which reflect increased manufacturing experience. The proposed revisions to the quality control system, data from the — ommercial manufacturing runs, and the analysis plan used to support the proposed specifications will be submitted as a supplement to the BLA no later than June 2008.

15.

16. To submit proposed revisions to release specifications and shelf-life specifications

for panitumumab drug product after — commercial manufacturing runs to reflect increased manufacturing experience. These revisions to the quality control system, data from the — commercial manufacturing runs, and the analysis plan used to create the proposed specifications will be submitted as a supplement to the BLA no later than December 2007.

17.

18. To perform stability testing of one drug substance lot annually for each year in which panitumumab drug substance is manufactured, As part of the post approval commitment, the ongoing stability program will continue until testing of all remaining timepoints from the lots used to support the approved shelf life have been reached. These stability data will be submitted in the annual reports. The first update on stability will be included in the annual report submitted by April 2007. Additionally, lots that are manufactured following significant changes to the approved manufacturing process or facility, the first lot — — step and lots that are reprocessed outside of the approved manufacturing process will be placed on stability.

19. To perform stability testing on at least one marketed drug product lot; annually. Lots will be randomly selected and placed on stability. Vial presentations selected will vary from year to year to ensure a balanced program. The first update will be included in an annual report to be submitted by April 2007. In the event that no drug product from a particular vial presentation was manufactured during a given year, a stability study is not required. Additionally, Lots that are manufacture following any significant changes to the approved manufacturing process or facility, and lots that have been reprocessed outside of the approved manufacturing process will be placed on stability.

20. To include CCI testing as a component of the post approval drug product stability program using each vial configuration (5 mL, 10 mL, 20 mL) as they are added to the stability program, with testing at the — month time-points to demonstrate container closure integrity throughout shelf life. A supplemental stability protocol to include CCI testing will be submitted by September 2007.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Panitumumab is a human IgG2 monoclonal antibody which binds to the Epidermal Growth Factor receptor (EGFr), a transmembrane receptor tyrosine kinase (RTK) of the ERbB (HER) family that is abnormally activated in many epithelial tumors including mCRC. Binding of panitumumab to the EGFr competitively inhibits the binding of its normal ligands including EGF and transforming growth factor-alpha, which are implicated in tumor growth, and stimulates receptor internalization, leading to a reduction of EGFr expression on the cell surface. Binding of panitumumab to the EGFr inhibits phosphorylation and activation of EGFr-associated kinases, resulting in inhibition of cell growth, and decreased vascular endothelial growth factor, interleukin-8, and other growth factor production. The epidermal growth factor receptor (EGFr) is constitutively expressed in many normal epithelial tissues, including the skin follicle, placenta, and mammary gland. Over-expression of EGFr is also detected in many human cancers including those of the colon and rectum. *In vitro* assays and *in vivo* animal studies have shown that panitumumab inhibits the growth and survival of several human tumor cells that over-express the EGFr.

The clinical development program has followed a traditional development approach with phase 1 studies to evaluate the safety and pharmacokinetics of escalating doses and different dosing schedules of panitumumab monotherapy in subjects with advanced solid tumors shown to express EGFr (mCRC, prostate, renal and non-small cell lung cancer). Based on the phase 1 and 2 experience, the focus of the clinical development program for panitumumab has been to evaluate its safety and efficacy in the treatment of subjects with mCRC, both in monotherapy and in combination therapy

The indication being sought in this application for the use of panitumumab for the treatment of patients with mCRC after failure of prior fluoropyrimidine- irinotecan- and oxaliplatin-containing chemotherapy regimens. Fast track designation was granted for this indication on May 12, 2005.

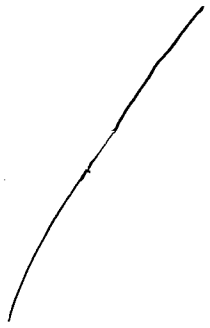
Amgen has submitted 15 clinical studies conducted in patients with a variety of solid tumors in the US, Europe, Canada, Australia, New Zealand, and Japan to support this license application, including 10 traditional phase 1 and 2 monotherapy trials enrolling subjects with mCRC and two combination therapy trials in mCRC and advanced lung cancer(20025409 and 20025404)(Appendix 10.1). Many of these trials are ongoing.

The pivotal study (20020408), a phase 3 randomized, controlled, open-label study evaluating the efficacy and safety of panitumumab plus BSC versus BSC alone, enrolled 463 subjects at 81 non-US sites. The primary endpoint for the pivotal study was PFS. Confirmation of clinical benefit will be assessed in a randomized, multi-center, phase 3 study of the safety and efficacy of standard second-line chemotherapy (FOLFIRI) plus Panitumumab compared to FOLFIRI alone (20050181). This study was approved under a Special Protocol Assessment on May 15, 2006.

1.3.2 Efficacy

Study 20020408 is a randomized phase 3 clinical study conducted in patients with refractory, metastatic colorectal cancer who had failed fluropyrimidine- irinotecan- and oxaliplatin-containing regimen(s). There is no effective therapy for this patient population.

This study was well-conducted. Stringent criteria were employed to validate prior therapy and prior treatment failure which was confirmed for 75% of the ITT population. Based upon Independent Radiology Review Committee (IRC) determination of disease progression, a statistically significant prolongation in PFS was observed in patients receiving panitumumab compared to those receiving BSC alone. There were 19 partial responses observed in patients randomized to panitumumab, for an overall response rate of 8% (95% CI: 5.3%, 12.5%). The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks). The objective response rate and duration of response in the panitumumab treated arm in this heavily pre-treated patient population is of note.



The additional single arm trials submitted to support the efficacy claim (20030167 and 20030250), while acceptable in design, contained insufficient numbers of subjects with adjudicated prior treatment failure (39 and 23 subjects respectively) on which to base an efficacy assessment. Centrally confirmed response rates appeared to be consistent with that reported for the pivotal trial.

1.3.3 Safety

Data in support of the safety of panitumumab monotherapy includes data from 13 trials enrolling subjects with mCRC and other solid tumors. Safety data has been analyzed for the following subsets:

- Study 20020408: with the safety experience of subjects randomized to receive panitumumab assessed relative to the safety experience of subjects randomized to receive BSC alone and followed up until the time of cross-over onto study

20030194)

- All mCRC Safety Set: all subjects with mCRC who received panitumumab monotherapy (either hybridoma- or CHO-derived) at any dose/schedule (n=920)
- Monotherapy-CHO Safety Set: all subjects treated with the — and — CHO-derived products at 6.0 mg/kg every other week (n=789).
- Combination Safety Set: Data from 174 subjects treated on two additional studies of panitumumab in combination with chemotherapy was also submitted for review.
- Hypomagnesemia Analysis Set: Laboratory data from subjects in all studies in which routine monitoring for hypomagnesemia was done.

Key safety findings concerning panitumumab therapy include:

- All subjects experienced adverse events, grade 3 or 4 adverse events occurred in approximately 60% of subjects, and serious adverse events occurred in approximately 40% of subjects treated with panitumumab monotherapy. Of these, approximately 10% of subjects withdrew as a result of an adverse event. Most adverse events experienced on study 20020408 were determined by the FDA Clinical Reviewer to be disease-related.
- Consistent with an anti-EGFr class effect cutaneous, mucosal and ocular toxicities occurred in 92% of panitumumab-treated subjects on study 20020408. In 18% of these subjects, the toxicity was grade 3-4 and dose interruption or delay occurred in 11% of panitumumab-treated patients. Cutaneous toxicity consisted of acneiform dermatitis, pruritis, and erythema. Eye-related toxicities occurred in 15% and included: conjunctivitis, ocular hyperemia, increased lacrimation and eye/eyelid rritation. Stomatitis and oral mucositis were reported in 6% each and one subject experienced grade 3 mucosal inflammation. Paronychia occurred in 24% and other nail disorders occurred in 9%.
- Infusion reactions occurred in 10/229(4%) of panitumumab-treated subjects on study 20020408; 2(1%) were grade 3. In one patient, panitumumab was discontinued due to a severe infusion reaction.
- Panitumumab administration was associated with a decrease in serum magnesium in 38% of subjects and was grade 3 or 4 in 8(4%) of subjects. Fatigue, muscle spasms, neuropathy were all reported in higher frequency among subjects in whom an adverse event of hypomagnesemia was also reported. However, hypomagnesemia did not appear to be associated with an increased risk of cardiac events. In a small number of subjects, hypomagnesemia was also associated with hypocalcemia.
- Cough was the only pulmonary toxicity noted to be in excess among subjects on the panitumumab arm of study 20020408. However, pulmonary fibrosis (fatal in one case) occurred in 2/1467 (1%) of patients enrolled in clinical trials of panitumumab.
- Extensive cardiac monitoring in early clinical development (MUGA scans and assessments of cardiac enzymes) and assessment of cardiac events doe not suggest that panitumumab monotherapy is associated with an increased risk of cardiotoxicity.
- No apparent difference in safety profile by sex, age, race (assessable only in mCRC/Monotherapy-CHO dataset), and primary tumor type (colon/rectum). No

clear differences by panitumumab cell-line (hybridoma vs. CHO). An in sufficient number of subjects have been treated to assess differences in the safety profile by product scale(

- Administration of panitumumab as part of an irinotecan- or paclitaxel/carboplatin-based combination regimen appeared to be associated with increased rate of toxicity (diarrhea, stomatitis/mucositis, hypomagnesemia and pulmonary toxicity)
- The incidence of binding antibodies to panitumumab as detected by acid dissociation ELISA was <1% (2/612) and as detected by the Biacore assay was 4.1% (25/610).

1.3.4 Dosing Regimen and Administration

The recommended dose of Vectibix™ is 6 mg/kg administered over 60 minutes as an intravenous infusion every 14 days. Doses higher than 1000 mg should be administered over 90 minutes.

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with Vectibix™

1.3.6 Special Populations

1.3.6.1 Effects of Age

In study 20020408, there were 276 subjects < 65 years (panit. = 135; BSC = 141) and 187 subjects ≥ 65 years (panit. = 96; BSC 91). Improvement in PFS was seen both among the subjects < 65 years (median PFS 56 and 49 days respectively; p<0.0001) and subjects ≥ 65 years (median 57 and 55 days, respectively; p=0.0016).

The safety data base from study 20020408 did not contain sufficient number of older subjects to determine whether the use of panitumumab was associated with age-related differences in safety. Exploration of the safety dataset of all subjects with mCRC treated with panitumumab monotherapy did not suggest an increased relative risk of toxicity among older subjects (<65 n=578; ≥ 65 n=342).

1.3.6.2 Effects of gender

In study 20020408, there were 294 male subjects (panit. = 146; BSC = 148) and 169

female subjects (panit. = 85; BSC 84). Improvement in PFS was seen among both males and females (median PFS 56 and 50 days respectively; p<0.0001) and among the 294 male (median 57 and 51 days, respectively; p<0.0001).

The safety data base from study 20020408 did not contain sufficient number of female subjects to determine whether the use of panitumumab was associated with gender-related differences in safety. Exploration of the safety dataset of all subjects with mCRC treated with panitumumab monotherapy suggested an excess of grade 3 or 4 integument/eye toxicity among males (M=81/552(15%) vs. F=36/336(10%)/χ^2 = 4.6; p=0.03). However, this analysis was not adjusted for multiple comparisons.

1.3.6.3 Effects of Race

In the pivotal efficacy study, 20020408, 99% (457/463subjects) were white. The small number of non-White subjects did not permit an assessment of safety or efficacy in this subpopulation. Exploration of the safety dataset of all subjects with mCRC did not suggest an increased toxicity as related to race/ethnicity (white n=805; non-white n=115).

1.3.6.4 Effects of Renal Impairment

No studies in patients with renal impairment were undertaken. No studies in patients with renal impairment were undertaken. Based on the excretion of proteins (including monoclonal antibodies), renal impairment is expected to have no impact on PK. These studies were not required pre-marketing or as post-marketing commitments

1.3.6.5 Effects of Hepatic Impairment

No studies in patients with hepatic impairment were undertaken. Based on the metabolic pathways for proteins (including monoclonal antibodies), hepatic impairment is expected to have no impact on PK. These studies were not required pre-marketing or as post-marketing commitments.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

GENERIC NAME:	PANITUMUMAB, RHUEGFR
Proposed Trade Names:	Vectibix™
Pharmacological Category:	Antineoplastic agent
New Molecular Entity:	Yes
Drug Class:	Recombinant human monoclonal antibody
Route of Administration:	Intravenous
Dose and regimen:	6 mg/kg every two weeks until disease progression
Population studied:	Adult Patients with EGFr-expressing metastatic colorectal cancer with disease progression following prior irinotecan- and oxaliplatin- containing therapy; Adult patients with other solid tumors

2.2 Currently Available Treatment for Indications

CRC is the third most common type of cancer in both men and women and the second most frequent cause of cancer-related deaths. CRC resulted in approximately 56,000 deaths in the US in 2005 [1]. Approximately 30% of all patients with CRC have metastatic disease at diagnosis, and 50% of early-stage patients will eventually develop metastatic or advanced disease[2]. The prognosis for patients with metastatic disease is poor with the 5-year survival rate < 10% [3].

Treatment of newly diagnosed metastatic colorectal cancer has evolved rapidly in the last 15 years accompanied with a doubling in OS. Prospective studies have demonstrated that the use of 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic disease prolongs survival and enhances quality of life in comparison to palliative care alone. The addition of irinotecan, a DNA topoisomerase 1 inhibitor, to either bolus 5-FU/LV (IFL) or infused 5-FU/LV (FOLFIRI), has resulted in improved outcomes compared with 5-FU/LV alone (Camposar Prescribing Information, 2005). Survival for patients with metastatic CRC has further improved following the introduction of 5-FU based chemotherapy combination regimens using oxaliplatin (Eloxatin Prescribing Information, 2005). Comparison of irinotecan, fluorouracil and leucovorin regimens with oxaliplatin, fluorouracil and leucovorin combination for the initial treatment of metastatic CRC have been conducted; results consistently show similar outcomes between irinotecan-based regimens and oxaliplatin-based regimens when combined with comparable fluorouracil therapies. Despite the choice of initial therapy, exposure to each of these cytotoxic agents at some time over the course of treatment has been associated with prolonged survival.

Two classes of biologics have recently been approved which expand the options for the treatment of mCRC: angiogenesis inhibitors and epidermal growth factor receptor inhibitors. Bevacizumab is a recombinant; humanized monoclonal IgG1 antibody directed against the vascular endothelial growth factor (VEGF) designed to block tumor

angiogenesis, which received full approval in the US in February 2004 in combination with irinotecan based chemotherapy for the first line treatment of metastatic CRC based on demonstration of improved OS, PFS and ORR. Cetuximab, a chimeric anti-EGFr monoclonal antibody directed against the extracellular binding domain of the epidermal growth factor receptor (EGFr) received accelerated approval in the US in February 2004 for use in combination with irinotecan for the treatment of a subgroup of patients with metastatic CRC (EGFr-expressing) who are refractory to irinotecan-based chemotherapy and as a single agent in patients who are intolerant of irinotecan-based chemotherapy. The accelerated approval was based on the surrogate endpoint of tumor response. The clinical benefit (ie, improved progression-free survival or overall survival) of cetuximab in this patient population has not yet been established.

Despite recent advances there are no FDA-approved drugs with full approval for patients with metastatic CRC who have failed prior (standard) chemotherapy treatments (eg fluorouracil, irinotecan, and oxaliplatin). These patients have only palliative or experimental treatment options available to them.

2.2.1 FDA's Rationale for Accelerated Approval

Drug approval in the United States requires adequate and well-controlled studies demonstrating that a drug is both safe and effective for the indication for which approval is sought (Federal Food, Drug, and Cosmetic Act, amend 1962). Approval requires the demonstration of either clinical benefit (e.g. prolongation of survival, relief of pain) or an effect on an established surrogate for clinical benefit.

The recommendation for accelerated approval for panitumumab as a single agent for patients with mCRC who have progressed following fluoropyrimidine-, irinotecan- , and oxaliplatin-containing chemotherapy regimens is based on PFS. From a regulatory perspective, progression-free survival is not an established surrogate but is considered a surrogate endpoint that is likely to predict effects on overall survival. As such, PFS can be used to support the accelerated approval of panitumumab compared to BSC in this disease setting. A significant benefit in progression-free survival was demonstrated among subjects in study 20020408 treated with panitumumab compared to those treated with best supportive care alone.

2.3 Availability of Proposed Active Ingredient in the United States

Panitumumab is a new molecular entity and currently is not marketed in this country.

2.4 Important Issues With Pharmacologically Related Products

Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that binds to the extracellular domain of the human EGFr and is produced in mammalian (murine myeloma) cell culture. Cetuximab (ERBITUX™) is indicated for use in combination with irinotecan for the treatment of EGFr-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Cetuximab is also indicated as a single agent for the treatment of EGFr-expressing mCRC patients who are intolerant to irinotecan-based chemotherapy. Cetuximab is also indicated for treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

Cetuximab has been associated with the following toxicities:

- Infusion Reactions: Severe infusions reactions, rarely fatal, have occurred with cetuximab infusion, including some with fatal outcomes. Approximately 90% of severe infusions were associated with the first infusion. Severe infusion reactions were characterized by airway obstruction (bronchospasm, strider, hoarseness), urticaria and hypotension. Monitoring for infusion reaction with immediate interruption of the cetuximab infusion and permanent discontinuation from further cetuximab treatment is recommend for those experiencing a severe infusion reaction.
- Pulmonary toxicity: Interstitial lung disease (ILD) was reported in 3/of 774 (<0.5%) of patients with advanced mCRC, including one patient with fatal non-cardiogenic pulmonary edema and two patients with pre-existing fibrotic lung disease who experienced acute exacerbation while receiving cetuximab in combination with irinotecan. The current cetuximab label includes the warning that cetuximab should be discontinued and the patient treated appropriately if ILD is confirmed.
- Dermatologic toxicity: Cetuximab monotherapy has been associated with a 90% incidence of dermatologic toxicities including acneiform rash, skin drying and fissuring, and inflammatory and infectious sequelae (blepharitis, chelitis, cellulitis, and cyst). Complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported. Monitoring for inflammatory and infectious sequelae following cetuximab therapy is recommended.
- Diarrhea and dehydration: Serious adverse events of diarrhea (6%) and dehydration (5%) were also seen with cetuximab administration
- Electrolyte disorders: Hypomagnesemia was identified as a cetuximab-related adverse reaction in the post marketing setting in subjects with SCCHN. The incidence of grade 3 or 4 hypomagnesemia was 13% among subjects treated with cisplatin plus cetuximab compared to 0% among subjects receiving cisplatin plus placebo. Hypokalemia and hypocalcemia were also increased among SCCHN subjects receiving cetuximab plus cisplatin compared to SCCHN subjects treated with cisplatin plus placebo.

COMMENT: The toxicity spectrum seen with panitumumab was similar to that seen with Cetuximab. The apparent lower incidence of infusion-related reactions may relate to how data were collected in the two applications. Because severe infusion reactions are

considered to carry a risk of fatal reactions, based on experience with monoclonal antibodies as a class, infusion-related events are noted in the boxed warning section of the panitumumab label.

2.5 Presubmission Regulatory Activity

2.5.1 Chronology of BLA 125147

Table 1. Chronology of BLA Milestones

02FEB01	IND 8382 SUBMITTED
10JUN03	EOP2 meeting (Clinical)
19JUN03	EOP2 meeting (CMC)
16JUL03	SPA submitted for protocol 20030167 and 20020408; 20030167 accepted with revisions 09JAN04; 20020408 launched in Europe prior to acceptance under SPA
06DEC04	Type C Meeting – Discuss status of ongoing trials
12MAY05	Fast Track designation granted
	Pre-BLA Discussions
24MAY05	Provide overview of clinical data; Discuss proposed presentation of clinical and preclinical information in the BLA
15SEP05	Discuss
22NOV05	Type B Meeting – Discuss the submission of the panitumumab BLA
22DEC05	BL 125147-0 Safety Reviewable unit received
23-FEB-06	BL 125147-0 Quality Reviewable unit received
27-MAR-06	BL 125147-0 Efficacy Reviewable unit received
15MAY06	SPA approved - Confirmatory study(20050181) - 2nd line mCRC
29AUG06	Type C Meeting - to discuss the pediatric drug development plan

2.5.2 Major Clinical Regulatory Agreements Panitumumab Development

The following major clinical regulatory agreements were made during the development of panitumumab:

10JUN03- End-of-Phase 2:

FDA agreed that:

- Colorectal cancer subjects who have failed 5-FU, leucovorin, irinotecan and oxaliplatin are an appropriate population to study for Accelerated Approval
- The design of study 20020408, with modifications, would be adequate in design to support Accelerated Approval
- Accelerated Approval may be granted based on demonstration of a medically important and durable objective response rate or improved time to progression

06DEC04- Type C Teleconference

- The proposed pivotal trial (20020408) and supporting studies for mCRC (20025405 and 20030167), and other supporting safety studies would be acceptable in design to support filing
- A significantly robust and durable improvement in PFS found in the pivotal study could support approval of panitumumab for the treatment of mCRC after failure of standard therapy. A robust and durable improvement in PFS at filing could lead to Accelerated Approval.
- A significant advantage in overall survival (OS) would be required for regular approval.
- Results should be based on central radiographic review
- Characterization of the study population based on EGFr detection assay kit would need to be included in the label.
- The proposed extrapolation of equivalent efficacy based on comparable minimum (trough) concentrations from 2.5 mg/kg weekly and 6.0 mg/kg once every two weeks to 9 mg/kg once every 3 weeks was not acceptable.
- The plan for establishing the PK comparability between — CHO and — CHO materials was acceptable

Pre-BLA meeting:

24MAY05 (type C)

- Amgen stated their intent to file for accelerated approval and to submit a supplement based on survival data
- FDA accepted the proposal to provide an integrated safety data base to support the target indication in the license application
- FDA agreed with the content and analysis for the 120-day safety report
- FDA requested a 9 month toxicology study for all products of this class

15 September 2005

- FDA agreed to coordinate the review of the data for the diagnostic kit and the clinical safety and efficacy data from the BLA concurrently so that approval for each constituent part of a combination product will be made simultaneously.

17 November 2005

- Agreement was reached on the content and format of — submission

22November 2005

- Amgen acknowledged that results from study 20020408 would not show an effect on overall survival and agreed to submit a confirmatory trial (20050181) under a Request for Special Protocol Assessment
- FDA stated that the efficacy data from study 20020408 should not be pooled with results from other single arm studies
- FDA agreed to accept the panitumumab application under the Pilot 1 Continuous Marketing Application

29August 2006

- FDA provided guidance concerning development of a study of panitumumab in pediatric subjects with solid tumors
- Amgen will submit a waiver for pediatric patients 0-12 months and a request for deferral for pediatric patients from 12-24 months based on the potential toxicity of panitumumab on the developing pulmonary and CNS development of children in this age group.

2.6 Other Relevant Background Information

There is no other information relevant to consideration of this submission.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

For a complete review and evaluation of the CMC data submitted in support of this application, please see the review by Drs. Chana Fuchs and Ruth Cordoba.

The assessment of the CMC review team was that the data submitted in the application support the conclusions that the manufacture of panitumumab is well controlled resulting in a pure and potent product. The product is free from endogenous or adventitious infectious

agents. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. Approval for human use was recommended. However, the CMC review team noted that:

"The panitumumab drug substance manufacturing process has been modified a number of times during clinical development. Biochemical comparability study results between successive processes were submitted and reviewed under IND for appropriateness. A significant change in manufacturing was implemented prior to initiation of pivotal trials with a switch from murine hybridoma to CHO cell substrate, change in manufacturing facility and in the manufacturing process. Biochemical and biophysical analysis, non-clinical and a small clinical pharmacokinetic (PK) comparability studies showed that although there were some biochemical and biophysical differences between panitumumab produced by the 2 processes, there was sufficient supporting data to say that product from the clinical CHO process was, by *in vitro* data, functionally equivalent to product from the hybridoma, The preclinical and clinical data found them sufficiently similar for use in the pivotal clinical study and ongoing clinical trials. The pivotal trials used panitumumab produced at Amgen Washington from CHO cells at the — scale. The commercial product is produced at Amgen Fremont from CHO cells at the — scale. A comparability study was submitted to the BLA. Based on biochemical and biophysical data submitted, the clinical and commercial products appear comparable. However, differences were noted between the products from these 2 manufacturing processes in both animal and human PK Additional clinical safety data was requested to support licensure of the commercial product. Panitumumab drug product manufacturing has also undergone manufacturing changes ranging from facility changes, concentration and vial size. Panitumumab concentration was increased from —o 20 mg/mL with the implementation of the CHO clinical manufacturing process. Vial size increased from — 10 mL to accommodate the larger clinical dose. Other than concentration of panitumumab, the formulation and excipients have remained the same throughout development. Clinical drug product used in the pivotal trial was produced at Amgen Thousand Oaks (ATO), while commercial drug product will be manufactured at —

It was felt that the post-marketing commitments described in Section 1.2.3 above will provide sufficient additional information to assure the continued safety of the product.

3.2 Animal Pharmacology/Toxicology

For a complete review and evaluation of the non-clinical data submitted in support of this application, please see the review by Dr. Anne Pilaro. From her report:

"Panitumumab (ABX-EGF, AMG 954; VECTIBIX™) was evaluated for pharmacologic activity in human tumor cell lines *in vitro* and in human tumor xenografts in nude mice, and for toxicity and pharmacokinetics in nude mice and cynomolgus monkeys. Tissue binding studies demonstrated that ABX-EGF bound with moderate to strong intensity to surface epidermal growth factor receptor (EGFr) in samples of both human and cynomolgus monkey skin, tonsil, breast, and prostate, and in urothelium of the ureter and urinary bladder, and uterine endometrium and cervical squamous

epithelium in monkeys. Treatment of tumor-bearing nude mice with panitumumab alone or in combination with several different biologic or chemotherapy regimens resulted in delayed tumor growth in human colon, epidermoid, breast, or pancreatic cancers. Where effective, combination therapy with panitumumab and selected chemotherapy or biologic anti-tumor treatments resulted in approximately additive, but not synergistic effects. Pharmacokinetic profiles of panitumumab in cynomolgus monkeys following initial, i/v injections of 7.5, 15, 30, or 60 mg/kg doses showed linear, dose-related increases in C_{max} and AUC_{0-t}, dose-related decreases in clearance with a concomitant increase in apparent elimination half-life, and steady state volumes of distribution approximately equal to the plasma space. Steady state, as evidenced by peak and trough serum ABX-EGF levels was achieved in repeat dose studies following approximately 5 to 6 doses of panitumumab. With repeated administration for 4 to 26 weeks, the dose-related decreases in clearance and increases elimination half-life were slightly higher than following the initial dose; however, the C_{max} and AUC_{0-last} were only slightly (< 2-fold) increased over the initial, observed values. Therefore, the toxicokinetic evaluations confirmed that exposure to ABX-EGF was continuous over the duration of these studies with little accumulation of drug. Although group mean values for C_{max} and AUC_{0-last} were frequently not different for the same dose levels of ABX-EGF over the study durations, anti-panitumumab antibodies developed in several monkeys in all repeat-dose studies, resulting in decreased ABX-EGF exposure in these individual animals, and in some cases, reversal of some of the panitumumab-related toxicities. Severe dermatologic and gastrointestinal toxicities were noted at all dose levels in cynomolgus monkeys treated weekly with 7.5, 15, 30, or 60 mg/kg panitumumab for 4, 13, or 26 weeks. These doses correspond to approximately 1.25 to 10-fold greater than the proposed human dose of 6 mg/kg ABX-EGF administered every two weeks, and approximately 3 to 24-fold higher than the proposed 2.5 mg/kg/week panitumumab dose, when adjusted for body weight. Observed toxicities included decreases in body weight and food consumption, decreases in serum calcium, phosphate, and magnesium, and dose-dependent clinical signs consisting of soft or watery stool, alopecia, skin rash, erythema, flaking and/or dryness, suppurative dermatitis, erosions, sloughing, and ulcerations, and in several studies, early mortalities secondary to the severity of the skin lesions. These changes occurred with increased frequency and severity as both the dose and duration of ABX-EGF increased, and only partially reversible following discontinuation of panitumumab treatment. Panitumumab treatment inhibited ovarian function in non-pregnant female monkeys, and was abortifacient, although not teratogenic when administered to pregnant animals from GD20 through GD48, throughout organogenesis."

The non-clinical findings were consistent with toxicities observed in the clinical development program. The sponsor has agreed to a Phase 4 commitment to assess the role of EGFr in post natal lung, gastrointestinal, neurologic, bone or pancreatic development in humans (Section 1.2.2). With this, the non-clinical review team recommended approval.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

As agreed to at the Type C meeting held on May 24, 2005, Amgen submitted the clinical data electronically in eCTD format. Study reports and SAS data sets were provided for all

patients enrolled on studies of:

- Panitumumab monotherapy in subjects with mCRC:
  - 20020408
  - 20025405
  - 20030167
  - 20030194
  - 20030250,
- Panitumumab monotherapy in subjects with other solid tumors:
  - 20025408
  - 20030110
  - 20040116
  - 20020374
  - 20020375
- Panitumumab in combination with chemotherapy:
  - 20025404-part 1, 20025404-part 2 (lung)
  - 20025409-part 1, 20025409-part 2 (mCRC)

Provision of CRS:

- All CRFs were submitted for studies of panitumumab monotherapy conducted in/including mCRC subjects, and/or supportive of PK in the target indication:
  - 20020408, 20030167, 20030250, 20025405, 20030194, 20030251, 20030138, 20040116, 20020375
- CRFs were provided for all subjects enrolled on other studies who died on study or withdrew from study due to an adverse event

- No CRFs were submitted for:
  - monotherapy studies conducted in subject populations different from the one in the target indication:
    - 20030110, 20020374, 20025408
  - studies of panitumumab in combination with chemotherapy:
    - 2002504 part 1 and part2, 20025409 part 1 and part2
  - Studies of panitumumab in Japanese subjects
    - 20040192

— submitted digitalized images obtained on all subjects and used to assess response on study 20020408. Digitalized radiographs were also provided on the subset of study participants crossed to study 20030194 on the basis of a local assessment of disease progression where progression was not confirmed on central review. For these subjects, CRFs documenting the Independent Radiology Review Committee (IRC) assessment of eligibility based on prior treatment failure and of the IRC's blinded assessment of disease response were provided for review, as needed.

4.2 Tables of Clinical Studies

The studies included in this submission are delineated in Table 2 below:

Table 2. List of Clinical Studies in Support of the Application

STUDY	TITLE	PANIT. TREATED		SAFETY	EFFICACY
		mCRC	Total		
Monotherapy					
mCRC					
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	229	229	X	X
20030194	A Multicenter Open-Label Single Arm Clinical Trial to Determine the Safety of ABX-EGF Extended Therapy in Subjects with Metastatic Colorectal Cancer	174	174	X	X
20030167	A Phase 2 Multicenter, Single-arm Clinical Trial of ABX-EGF Monotherapy in Subjects with Metastatic Colorectal Cancer Following Treatment with Fluoropyrimidine, Irinotecan, and Oxaliplatin Chemotherapy	91	91	X	X
20030250	A Phase 2 Multicenter Single Arm Clinical Trial of ABX-EGF Monotherapy in Subjects with Metastatic Colorectal Cancer Wholse Tumors Express Low or Negative EGFr Levels by Immunothistochemistry Following Treastmenw with Fluoropyrimidine, Irinotecan, and Oxaliplatin Chemrotherapy	88	88	X	X
20025405	An Open Label Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of ABX-EGF in Subjects with Metastatic Colorectal Cancer	148	148	X	X
Solid Tumors					
20020375	A Multi-Center, Open-Label Clinical Trial to Determine the Safety of ABX-EGF as Continued Treatment for Patients Who Have Benefited From and Tolerated Prior ABX-EGF Treatment	2	11	X	
20040116	An Open Label, Maintenance Dosing, Clinical Trial of ABX-eGF in Patients with Renal, Prostate, Pancreatic, Nonsmall-cell Lung, Colorectal, or Esophageal Cancer, to Follow Clinical Trial ABX-eG-9901(20030138)	20	20	X	
20030138	An Open Label, Multiple Dose, Dose-rising Clinical Trial of the Safety of ABX-EGF in Patietns With Renal, Prostate, Pancreatic, Nonsmall-cell Lung, Colorectal, or Esophageal Cancer	39	96	X	
20040192	A Phase 1 Clinical Sutyd of ABX-EGF (Panitumumab)	10	12	X	

	Evalaution of the Safety and Pharmacokinetics of ABX-EGF In Japanese Subjects with Advanced Solid Tumors				
30030251	An Open-Label Clinilcal Trial Evaluating the Safety and Pharmacokinetics of Two Dose Scheduels of Panitumumab in Subjects With Advanced Solid Tumors	10	55	X	
20025408	A Clinical Trial of the Safety and Efficacy of ABX-EGF as Second Line Treament for Advanced Non-small Cell Lung Cancer (crossover study for 20025404)	-	9	X	
20030110	A Clinical Trial Evaluating the Safety and Efficacy of ABX-EGF in Patinets with Hormone-resistant Prostate Cancer with or without Metastases	-	33	X	
20020374	A Two-part, Multiple Dose Clinical Trial Evalauting the Safety and Effectiveness of ABX-EGF in Patinets with Renal Carcinoma	-	195	X	
Combination Therapy					
20025409	A Clinical Trial of the Safety and Efficacy of ABX-EGF in Combination with Irinotecan, Leucovorin, and 5-Fluorouracil in Subjects with Metastatic Colorectal Cancer	43	-	X	
)25404	A Two Part, Multiple Dose Clinical Trial of the Safety and Efficacy of ABX-EGF in Combiation with Paclitaxel and Carboplatin in Patients with Advanced Non-small Cell Lung Cancer	-	131	X	

4.3 Review Strategy

The clinical review was focused on the data submitted for the pivotal study 20020408 in order to confirm the primary endpoint of PFS and from 10 additional studies of panitumumab monotherapy to assess safety. Electronic data sets, CRF and data from the independent endpoint review committee (RadPharm) were used to verify the sponsor's analysis and claims. Throughout the review process, consistency between SAS data set entries and CRFs was examined.

In addition to the statistical, pharm/tox and product reviewers, the Panitumuamb review team included personnel from Division of Scientific Investigations (see section 4.4 below), Facilities Inspection, Office of In-vitro Diagnostics (for EGFr testing kit), and DDMAC.

4.4 Data Quality and Integrity

FDA's Division of Scientific Investigation (DSI) conduct audits the 4 sites which accrued the largest number of subjects to study 20020408 (Table 17). This included sites: 1102, Brussels, Belgium (21 subjects), 1103, Gent, Belgium (63 subjects), 1104, Brussels, Belgium (23 subjects), and 1401, Milan, Italy (34 subjects). In total these 4 sites accounted for 30% of the study population of study 20020408. No FDA 483's were issued. The submitted data from the sites inspected appeared acceptable (see Appendix 10).

4.5 Compliance with Good Clinical Practices

The sponsor asserts that all studies were conducted in accordance with the Principles of Food and Drug Administration (FDA) and International conference on Harmonization (ICH) Good Clinical Practice (GCP- regulations/guidelines. The protocols and their amendments were approved by independent Ethics Committees and by the Authorities according to the country-specific laws.

4.6 Financial Disclosures

Financial disclosures were provided for investigators on the following studies: 20020408, 20025405, 20030167, 20030194 and 20030250. For the pivotal trial, 20020408, Amgen provided a list of all clinical investigators with no arrangements or financial interests to disclose. One clinical investigator, — disclosed financial arrangements/interests during the period of study conduct with Amgen. One additional sub-investigator, — had no documented financial disclosure status, but the site confirmed that this sub-investigator had no financial interests to disclose.

COMMENT: There is minimal potential for bias of clinical study results for study 20020408 based on the financial interests of these investigators. The endpoint of study 20020408 required radiological documentation. The results were central reviewed by the independent Review Committee.

5. CLINICAL PHARMACOLOGY

For a complete review and evaluation of the clinical pharmacologic and pharmacokinetic data submitted in support of this application, please see the review by Dr. Angela Men.

The clinical pharmacology team noted that Vectibix™ used in the clinical pharmacologic and pharmacokinetic studies submitted by the sponsor was manufactured from a — CHO

Process. The to-be-marketed product (from the — CHO process) was deemed by the clinical pharmacology review team to be pharmacokinetically comparable to the clinical trial product (from — CHO process). With the Phase 4 Commitments delineated in Section 1.2.2 and agreed to by the Sponsor, they found data submitted under BLA125147 to be acceptable from the Clinical Pharmacology perspective, to support approval.

5.1 Pharmacokinetics

From Dr. Men's review:

"Following a single dose administration of panitumumab as a 1-hour infusion, the area under the concentration time curve (AUC) increased in a greater than dose proportional manner. Clearance (CL) decreased and half-life increased with increasing of doses. As the dose of panitumumab increased from 0.75 to 9 mg/kg, the clearance decreased from 30.6 to 4.6 mL/day/kg and the half-life increased from 0.8 day to 6.5 days. However, at doses above 2.0 mg/kg, the AUC of panitumumab increased in an approximately dose proportional manner. The concentration-time profile was best described by a 2-compartmental PK model with linear and nonlinear clearance pathways, likely to be mediated by the reticuloendothelial system (RES) and EGFr, respectively.

Following the recommended dose regimen (6 mg/kg Vectibix™ given once every 2 weeks as a 1-hour infusion), panitumumab concentrations reached steady-state levels by the third infusion with mean (±SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 μg/mL, respectively. Panitumumab peak and trough concentrations were comparable across studies. The mean (±SD) AUC was 1306± 374 μg•day/mL and the elimination half-life was approximately 7.5 days after 3rd dose of Vectibix™ administration".

5.2 Pharmacodynamics

A statistically significant prolongation in PFS was observed in patients receiving panitumumab compared to those receiving BSC alone. There were 19 partial responses observed in patients randomized to panitumumab, for an overall response rate of 8% (95% CI: 5.3%, 12.5%). The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks).

5.3 Exposure-Response Relationships

The clinical pharmacology team review noted the following:

- An exposure-response relationship could not be established because of the low overall response rate and the limited PK data.

- Integument/eye toxicity and panitumumab exposure: Using logistic regression, the clinical pharmacology reviewer assessed the relationship between panitumumab dose and the incidence of integument/eye toxicities within 28 days of panitumumab treatment. A plateau in the incidence of integument/eye toxicity was observed at 2.5 mg/kg QW. Panitumumab exposure was correlated with the incidence and duration of integument/eye toxicity but not with the duration of severe integument/eye toxicity. There was no correlation between the duration of integument/eye toxicity and C_{trough} of panitumumab identified.

- The potential relationship between EGFr expression and panitumumab exposure or the clinical response was assessed. The intensity of EGFr membrane expression in tumor cells had no effect on the PK of panitumumab. In the randomized controlled trial, exploratory univariate analyses were conducted to assess the correlation of EGFr expression and efficacy. PFS and ORR did not correlate with either percentage of positive cells or the intensity of EGFr expression.

6. INTEGRATED REVIEW OF EFFICACY

The integrated review of efficacy described in this section is based on a single multinational, randomized controlled trail of 463 patients with EGFR-expressing metastatic carcinoma of the color or rectum (mCRC) who had progressed on or following treatment with regimen(s) containing a fluoropyrimidine, oxaliplatin and irinotecan [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 (20020480)]. The basis for accelerated approval is an improvement in progression-free survival in patients treated with panitumumab.

6.1 Indication

The indication sought is: —

The approval recommendation is for the following indication: —

6.1.1 Methods

This review is focused on the data submitted by Amgen for the pivotal trial, Study 20020408, which is described in detail in this section. Electronic data sets, Case Report Forms, and results of summary data from the IRC eligibility and endpoint reviews were used to verify the applicants' analyses and claims. Consistency between the SAS dataset, Case Report Forms, and summary data from the IRC for a randomly selected 10% subset of all subjects and all subjects identified as responders was verified. Particular attention was focused on confirming documentation of protocol-specified prior therapy, documentation of disease progression during or within 6 months following the most recent prior chemotherapy regimen as required for eligibility, and verification of dates of disease progression as documented by the IRC.

Data from the four additional single armed studies (20030194, 20030250, 20030167, and 20025404) are summarized in tabular format in this section. A detailed description of these supporting trials is included in Section 10.1.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for study 20020408 was progression free survival (PFS) defined as the time from randomization date to the date of the first observed disease progression by central review or to death. Survival time and best objective response rate over time were co-secondary endpoints. Duration of response, time-to response, time to disease progression, time to treatment failure, duration of stable disease and patient-reported outcomes (PRO) were secondary outcomes of interest.

Efficacy for this study was verified by an Independent Radiology Review Committee (IRC) which provided efficacy evaluations for all subjects enrolled on the study. The IRC consisted of 14 independent radiologists. Two radiologists were assigned at random to review all images for a particular patient. Readers were blinded to the assigned treatment arm and to the local assessment. Each radiologist identified target and non-target lesions at baseline and followed these lesions at each subsequent time point. Neither radiologist knew which target/non-target lesions had been selected for review by the other assigned reader. Changes in the size of lesions were evaluated according to the RECIST criteria. Readers were provided with relevant clinical information including radiation therapy history, procedures performed on study, adverse events and cytology reports of fluid collection. The results of the two readers were compared for the following key variables: 1) best overall response, 2) date of first response, and 3) date of progression. If the two initial readers did not agree on any of these three key variables, a third, independent radiologist blinded to the identity of the two previous readers, adjudicated the readings. A Board-Certified medical oncologist independently reviewed each subject's clinical information (including adverse event reports, cytology and biopsy reports, reports of procedures performed on each subject during study, radiation therapy history and lesions found by the investigator on physical examination). The medical oncologist reviewed the

results of the independent radiology review and determined the overall response at each time point and the best overall response for the subject. In both the radiology review and the oncology review, a Sequential Locked Read Paradigm was followed. Assessments made at prior time points were locked and could not be altered. The IRC charter defined operating procedures for image submission, processing, reading, data handling and quality control.

COMMENT: During a teleconference between Amgen and FDA held on December 6, 2004, FDA agreed that a robust and durable improvement in PFS found in the pivotal trial could support the approval of panitumumab for the treatment of metastatic CRC after failure of stand chemotherapy. However, FDA clarified that an advantage in overall survival would be required for regular approval. Please refer to Section 2.5 for a discussion of the regulatory history of the endpoint.

6.1.3 Study Design

6.1.3.1 Study 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"

Study sites:
The study was being conducted at 81 sites in Western, Eastern and Central Europe, Canada, Australia and New Zealand.

Study period:
Date first patient enrolled: January 16, 2004
Date last patient enrolled: March 16, 2005
Date of data cutoff: June 20, 2005
32 subjects were still receiving treatment at the time of the data cutoff.

Objectives:
Primary:
To assess whether panitumumab 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:
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 outcome and safety of patients treated with panitumumab plus BSC compared with BSC alone as third or fourth line therapy in subjects with metastatic colorectal cancer.

Study design:

The overall study design is summarized in the Figure 1 (reproduced from \\cbsap58\m\eCTD_Submissions\STN125147\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\colorectal-cancer\5351-stud-rep-contr\20020408, p1850.):

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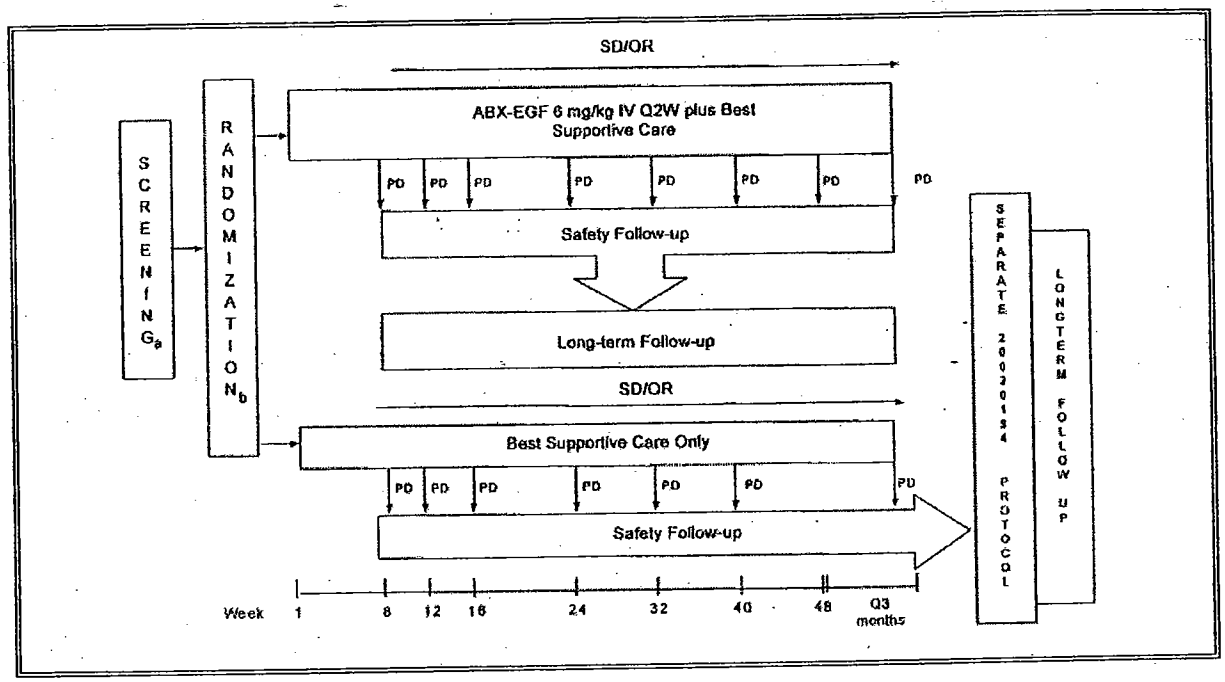
Figure 1. Design of Pivotal Trial (20020408)



This study was a multinational, open-label, randomized, observational controlled trial of 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum (mCRC). Patients were required to have progressed on or following treatment with a regimen(s) containing a fluoropyrimidine, oxaliplatin and irinotecan. All patients were required to have EGFR expression defined as at least 1+ membrane staining in ≥1% of tumor cells by the DakoCytomation EGFR PharmDx test kit. Patients were randomized 1:1 to receive panitumumab at a dose of 6 mg/kg given once every two weeks plus best supportive care (BSC) [n=231] or BSC alone [n=232] until investigator-determined disease progression, intolerable side effects, or other reason for discontinuation. Randomization was stratified based on ECOG performance status (0-1 vs. 2) and geographic region (Western Europe, eastern/central Europe, or other). Upon investigator-determined disease progression, patients in the BSC alone arm were permitted to receive panitumumab (6 mg/kg every 2 weeks) in an open-label extension study (20030194). All subjects were being followed for survival approximately every 3 months for up to 48 months from randomization.

COMMENT: Because of the high incidence and characteristic appearance of skin toxicity associated with panitumumab, a blinded study was not deemed feasible.

Study population:

Inclusion criteria:

- Competent to comprehend, sign, and date and IEC/IRB-approved informed consent form

- Man or woman 18 years of age or older
- Metastatic colorectal carcinoma
- ECOG performance status 0, 1, or 2
- Documented evidence of disease progression during or following treatment with fluoropyrimidine, irinotecan, and oxaliplatin. Radiographic documentation of disease progression during or within 6 months following the most recent chemotherapy regimen is required. Time interval between documented tumor progression and study entry must not exceed 6 months.

COMMENT: Subject eligibility and enrollment were determined by the investigator. Eligibility was confirmed by an Independent Eligibility Review Committee (IERC) composed of two board-certified radiologists and one board-certified medical oncologist. One radiologist and the oncologist reviewed the imaging and clinical information for each participant to document radiographic progression following the most recent chemotherapy and prior treatment for metastatic disease determined whether the subject met the protocol-defined criteria for prior metastatic therapy which included: 1) 5FU (any dose intensity over any period of time); 2) Irinotecan ≥ 65 mg/m2/week over any period of ≥8 consecutive weeks; and 3) Oxaliplatin ≥ 30 mg/m2/week over any period of ≥6 consecutive weeks. The treatment arms were balanced in the percent of enrolled subjects who met the above protocol-defined eligibility criteria (panitumumab: 179/231(77%) vs. BSC: 173/232(75%).

- 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
- Subject with history of other primary cancer 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
- Tumor expressing EGFr by immunohistochemistry (positive in ≥ 1% of evaluated tumor cells (based on evaluation conducted at a central laboratory)

COMMENT: The protocol originally required EGFr expression in ≥ 10% of evaluated tumor cells. The protocol was amended to include patients with EGFr expression in ≥ 1% of evaluated tumor cells based on information in the Erbutux™ label (Amendment 2, June 7, 2004; 99 patients enrolled).

- Hematologic function:
  - ANC ≥ 1.5 x 10^9 cells/L
  - Platelet count ≥ 100 x 10^9 /L

- Renal function:
  - Creatinine < 2.0 mg/dL
- Hepatic function:
  - AST ≤ 3-x ULN (if liver metastasis ≤ 5 x ULN
  - ALT ≤ 3 x ULN (if liver metastasis ≤ 5 x ULN
  - Bilirubin ≤ 2 x ULN

Exclusion criteria:

- Any disorder that compromises the ability of the subject to give written informed consent and/or comply with study procedures
- Symptomatic brain metastases requiring treatment
- Use of systemic chemotherapy or radiotherapy within 30 days before randomization
- Any 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, irinotecan, and oxaliplatin for colorectal carcinoma in accordance with specified regimens (leucovorin and levamisole were not considered as chemotherapy in this exclusion criterion)
- Unresolved complication that in the opinion of the investigator, did 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 ad for 6 months after the last ABX-EGF infusion
- Male subjects 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 was pregnant or breast feeding
- Unwilling or unable to comply with study requirements
- 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
- Allergic to the ingredients of the study medication or to *Staphylococcus* protein A

Randomization:

Eligible patients were randomized in a ratio of 1:1 to receive panitumumab plus BSC or BSC alone. Subjects were randomized through an Interactive Voice Response System (IVRS) and were stratified by ECOG performance status (0 or 1 versus 2) and by region (Western Europe versus Central and Eastern Europe versus Rest of World).

Treatment plan:

Patients randomized to the panitumumab arm were to receive panitumumab without routine premedication at a dose of 6 mg/kg (based on actual baseline body weight) in a minimum of 100 mL normal saline every other week, over 60 – 90 minutes (depending on volume). Patients on the panitumumab arm also received best supportive care (BSC) which included: antibiotics, analgesics, radiation therapy for pain control limited to bone metastases only, corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery or any symptomatic therapy as clinically indicated at the discretion of the investigator according to institutional norms.

Patients randomized to the BSC arm received BSC as defined above. Antineoplastic therapy was excluded.

COMMENT: Protocol 20030194 was opened (March 4, 2004; 28 patients enrolled in protocol 20020408) as an incentive to increase subject enrollment in protocol 20020408 and to permit follow-up of participants randomized on the BSC on a defined protocol. Patients randomized to the BSC arm of protocol 20020408 with disease progression assessed on local review were allowed to receive panitumumab on protocol 20030194, an open label, single arm study.

Dose modification and delays:

Panitumumab was to be administered on the same day of the week (+/- 3 days) every other week and was to continue until investigator-determined disease progression, intolerable side effects, or other reason for study discontinuation. If a dose was not administered within three days of the scheduled dose, it was considered missed and the next dose was given at the time of the next regularly scheduled dose.

Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 2.0. The definition of infusional toxicity and skin toxicity which was graded using a modified version of the CTCAE, version 3.0 dermatology/skin grading criteria is described in detail in section 7.1.3.3.

- Infusion reactions:
  Patients who developed "any serious infusion reaction" during the panitumumab infusion were to have the infusion stopped. Continuation of dosing was based on the severity and resolution of the event and was considered at the joint discretion of the investigator and the sponsor.
- Skin-related toxicity and panitumumab dose modification:

Subjects who developed severe skin toxicity (Grade 3 or above in the modified CTCAE version 3.0 dermatology/skin grading criteria or who met any of the criteria below had the next dose of panitumumab held:

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

Panitumumab dosing was re-evaluated according to the algorithm in Table 3 below:

Table 3. Dose Modification Schema for Panitumumab in Study 20020408

REINSTATE AT 50% IF:	Skin toxicity improves to ≤ grade 2 after withholding 1 or 2 doses of panitumumab and patient is symptomatically improved
Increase Dose If:	Toxicities do not recur and escalate each additional dose of panitumumab in 25% increments of the starting dose until the recommended starting dose is reached
Discontinue Dose If:	Toxicity does not resolve after withholding 1 or 2 doses of panitumumab or if toxicity recurs or becomes intolerable at 50% of original dose.

Panitumumab dosing was discontinued for any grade 3 or 4 major organ toxicity.

Concomitant Therapy:

- The use of any concomitant medication deemed necessary to provide BSC was allowed including: antibiotics, analgesics, radiation therapy for palliation of bone metastases, corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated.
- The use of topical or oral antibiotics to treat skin-related toxicities was at the investigators discretion.
- Hypomagnesemia was to be treated as clinically indicated according to local practice.
- Panitumumab was to be administered without premedication. If a reaction occurred during or after any infusion, premedication could be used for subsequent infusions.
- Subjects were to be withdrawn from study if they received any of the following:
  - Investigational agents
  - Anti-EGFr targeting agents (other than panitumumab)
  - Experimental or approved anti-tumor therapies
  - Radiotherapy (except for palliation of bone metastases)

Study schedule:

The study schedules are shown in Tables 4 – 7
\\cbsap58\m\eCTD_Submissions\STN125147\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\colorectal-cancer\5351-stud-rep-contr\20020408, pages 1923 – 1925).

Table 4. Study 20020408: Schedule of Assessments (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[a,b] and weight[d]	x		x		x		x		x		x		x		x		x	
Electrocardiogram	x																	
ECOG performance status	x		x				x				x				x			
Hematology[c]		x	x				x				x				x			
Chemistry[c]		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									
Carcinoembryonic antigen		x								x				x				x
Serum for EGFr signaling analysis[d] (BSC group at week 1 only)			x				x				x				x			
Pharmacokinetics[e,f]									x									
CT Scans / chest X-ray / tumor response[g]	x									x				x				x

EGFr = epidermal growth factor receptor, ECOG = Eastern Cooperative Oncology Group, BSC = best supportive care, CT = computed tomography, NCCN/FACT = National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy, DLQI92 = Dermatology and De Novo "Bother" Life Quality Index 92

[a] could have been done any time before randomization
[b] blood pressure, resting pulse, respiration rate, and temperature within 30 minutes before and approximately 30 minutes after the start of the panitumumab infusion, upon completion of the infusion, and approximately 30 minutes after the infusion
[c] within 72 hours of randomization, when applicable; could have been performed at a local laboratory
[d] must have been completed/recorded before panitumumab infusion
[e] serum sample drawn within 30 minutes before panitumumab infusion
[f] serum sample drawn 15 minutes after panitumumab infusion
[g] CT scans of abdomen and pelvis and chest X-ray or chest CT (chest CT must have been obtained at baseline; chest CT must have been obtained if chest X-ray was abnormal), and all other sites of disease

Table 5. Study 20020408: Assessments (Screening through Week 16) (Cont'd)

	Screening		Week															
Study Procedures	- 28 Days	-7 Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
NCCN/FACT and DLQI92			x		x		x		x		x				x			
EORTC-QLQ-C30 and EUROQOL EQ-5D			x				x				x				x			
Panitumumab infusion (panitumumab group only)			x		x		x		x		x		x		x		x	
Adverse event/ skin toxicity assessments[a]			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			

EGFr = epidermal growth factor receptor, ECOG = Eastern Cooperative Oncology Group, BSC = best supportive care, CT = computed tomography, NCCN/FACT = National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy, DLQI92 = Dermatology and De Novo "Bother" Life Quality Index 92

[a] could have been done anytime before randomization
[b] blood pressure, resting pulse, respiration rate, and temperature within 30 minutes before and approximately 30 minutes after the start of the panitumumab infusion, upon completion of the infusion, and approximately 30 minutes after the infusion
[c] within 72 hours of randomization, when applicable; could have been performed at a local laboratory
[d] must have been completed/recorded before panitumumab infusion
[e] serum sample drawn within 30 minutes before panitumumab infusion
[f] serum sample drawn 15 minutes after panitumumab infusion
[g] CT scans of abdomen and pelvis and chest X-ray or chest CT (chest CT must have been obtained at baseline; chest CT must have been obtained if chest X-ray was abnormal), and all other sites of disease

Table 6. Study 20020408: Schedule of Assessments (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		
ECOG performance status	x				x				x				x				x				x				x				x			
Physical examination	x				x				x				x				x				x				x				x			
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																									
Carcinoembryonic antigen								x[f]								x[f]								x[f]							x	
Serum for EGFr signaling analysis[a]	x								x								x							x								
Pharmacokinetics[c]							x																									
CT scans/ chest X-ray/ tumor response[e]								x[f]								x[f]								x[f]							x	
NCCN/FACT and DLQI92	x				x				x				x				x				x				x				x			
EORTCQLQC30 and EUROQOL EQ5D	x				x				x				x				x				x				x				x			
Panitumumab 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			

EGFr = epidermal growth factor receptor, ECOG = Eastern Cooperative Oncology Group, CT = computed tomography, NCCN/FACT = National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy, DLQI92 = Dermatology and De Novo "Bother" Life Quality Index 92

[a] blood pressure, resting pulse, respiration rate, and temperature within 30 minutes before and approximately 30 minutes after the start of the panitumumab infusion, upon completion of the infusion, and approximately 30 minutes after the infusion
[b] must have been completed/recorded before panitumumab infusion
[c] serum sample drawn within 30 minutes before panitumumab infusion
[d] serum sample drawn 15 minutes after the panitumumab infusion
[e] CT scans of abdomen, pelvis and chest X-ray or chest CT (chest CT was to be obtained if chest X-ray was abnormal)
[f] complete or partial response must have been confirmed no less than 4 weeks after the criteria for response were first met, carcinoembryonic antigen at the time of tumor assessment

Table 7. Study 20020408: Schedule of Assessments (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
Hematology[b]	x				x				x				x
Chemistry[b]	x				x				x				x
Serum for immunogenicity testing[c]												x[e]	x[g]
Carcinoembryonic antigen													x
Serum-EGFr signaling analysis (BSC group at follow-up only)[b]													x
Pharmacokinetics													x
CT Scans/ chest X-ray/ tumor response[d]												x[e]	x
NCCN/FACT and DLQI92	x				x				x				x
EORTCQLQC30 and EUROQOL EQ5D	x				x				x				x
Panitumumab 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

EGFr = epidermal growth factor receptor, ECOG = Eastern Cooperative Oncology Group, CT = computed tomography, NCCN/FACT = National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy, DLQI92 = Dermatology and De Novo "Bother" Life Quality Index 92

[a] blood pressure, resting pulse, respiration rate, and temperature within 30 minutes before and approximately 30 minutes after the start of the panitumumab infusion, upon completion of the infusion, and approximately 30 minutes after completion of the infusion; weight at safety follow-up visit
[b] must have been completed/recorded before panitumumab infusion
[c] serum sample drawn within 30 minutes before panitumumab infusion
[d] CT scans of abdomen, pelvis and chest X-ray or chest CT (chest CT was to be obtained if chest X-ray was abnormal)
[e] complete or partial response must have been confirmed no less than 4 weeks after the criteria for response are first met, carcinoembryonic antigen at time of tumor assessment
[f] must have occurred 4 weeks after last treatment in panitumumab plus BSC group and within 4 weeks after disease progression in BSC group
[g] if positive for anti-panitumumab antibodies at safety follow-up, the subjects was to be followed every 3 months until value became negative or reaches baseline value

COMMENT: Vital signs were monitored 30 minutes prior to, during, and 30 minutes following each panitumumab infusion. This resulted in a limited window of opportunity to systematically monitor for infusion reactions.

Endpoint assessment:

Tumor assessment:
The CT scans of the abdomen and pelvis and chest X-ray (chest CT was obtained if Chest X-ray was abnormal) were collected, digitalized and sent to [redacted] at the following study-defined intervals:

- Within 28 days of first panitumumab infusion
- At symptomatic progression
- In the absence of symptomatic progression: 8, 12, 16, 24, 32, 40, and 48 weeks following the first panitumumab, and every 12 weeks thereafter, or until documentation of progression
- Additional scans were required to confirm response no less than 4 weeks after the response criteria were first met.

Modified RECIST criteria were used for assessing tumor response. Patients were required to have at least one unidimensionally measurable lesion with the longest diameter (LD) of ≥20 mm by CT, MRI or spiral CT. Up to 10 target lesions could be selected (from outside radiation ports) with the sum of the longest diameter (SDL) for all target sessions calculated at baseline and follow-up. Other (non-target) lesions were recorded and measured over the course of therapy. Responses were categorized according to Table 8 and Table 9 below.

Table 8. Criteria for Evaluation of Target and Non-Target Lesions

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 a 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 a 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
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 ≥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

Table 9. Overall Response Evaluation for All Combination of Tumor Responses

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			

Special Laboratory Variables:

EGFr staining:
EGFr membrane expression in the subject's tumor samples was determined at a central laboratory using the DakoCytomation EGFR pharmDx™ kit. Test results were expressed as a percentage of total cells with positive membrane staining, the highest membrane staining intensity score (0=none, 1+=weak, 2+=moderate, or 3+=strong), the percentage of cells with membrane staining at the highest staining intensity, complete or incomplete membrane staining and the percentage of tumor cells with cytoplasmic staining.

Anti-panitumumab antibodies:
Serum was assayed for the presence of anti-panitumumab antibodies in both the treatment and BSC groups at weeks 1 (baseline) 7, 23, and at the safety follow-up (4 weeks after the final panitumumab dose. In subjects receiving panitumumab, serum was drawn within 30 minutes prior to the panitumumab infusion. In seropositive subjects, additional samples were drawn every 3 months until return to seronegative or to baseline levels.

Two validated assays were used to screen for anti-panitumumab antibody. The first assay was a bridging enzyme-linked immunoabsorbent antibody (EELISA) which included an acid dissociation sample preparation step to reduce interference from excess serum panitumumab. The second assay was a cell-based assay for the detection of neutralizing

panitumumab activity. Prior to June 9, 2005, all samples testing positive in the ELISA screen were tested in the bioassay for the presence of neutralizing antibody. After June 9, 2005, only samples testing positive in both the screening and immunodepletion assays were tested in the bioassay for the presence of neutralizing antibody.

Efficacy endpoints:

Primary:

- Progression-free survival (time from randomization to the date of the first observed disease progression or death)

Secondary:

- Co-secondary endpoints:
  - Survival (time from randomization to death); and
  - Best objective response over time (best disease status from randomization through the end of the study)
- Other endpoints of interest:
  - Duration of response (time from the first response to either disease progression or death due to disease progression)
  - Time to response (time from randomization to first partial or complete response, subsequently confirmed $\geq$ 4 weeks after the criteria for response were first met)
  - Time to disease progression (time from randomization to disease progression or death due to disease progression)
  - Time to treatment failure (time from randomization to the time a decision was made to withdraw from the treatment phase for any reason)
  - Duration of stable disease (defined for subjects whose best response was stable disease as the time from randomization to disease progression or death due to disease progression)
  - Patient reported outcomes

Statistical and analytical plan:

Analysis sets:

The following analysis sets were identified prior to the data cutoff and data base lock:

- All enrolled (ITT): All consented and enrolled subjects analyzed according to assigned treatment group. This analysis set was used for the primary analysis of all efficacy endpoints.
- Adjudicated Prior Failures: All consented and randomized subjects determined by the Independent Eligibility Review Committee to have met the eligibility criteria for prior treatment and radiographic evidence of progressive disease. Subjects were analyzed according to randomized treatment assignment. This data set was used for the secondary analysis of all efficacy endpoints.
- Per Protocol: Subjects from the Adjudicated Prior Failures analysis subset who did not have selected, important, predefined protocol deviations thought to have potential impact on the efficacy analysis, including:
  - Violation of the following inclusion criteria:

- Competent to comprehend/sign informed consent
- Pathologic diagnosis of CRC
- Metastatic CRC
- ECOG 0, 1 or 2
- Unidimensional measurable disease per RECIST(not previously irradiated and ≥ 20 mm)
- At least 2 but no more than 3 prior mCRC chemotherapy regimens

o Violation of exclusion criteria:

- Disorders that compromise ability to give written consent or comply with study procedures
- Received investigational agent, anti-EGFr targeting agent, or experimental anti-tumor therapies

o Other:

- Screening scan missing
- Missing scan before progressive disease response
- Missed or unevaluable scan and tumor response is different just before and after missing scan
- Treated but not randomized

This analysis set was used for sensitivity analysis of progression-free and overall survival.

Statistical methodology and analysis:

- Sample Size determination: Median progression-free survival for BSC alone was assumed to be 2.5 months. The sample size goal was to achieve at least 90% power for a 2-sided 1% significance level test given a hazard ratio (panitumumab plus BSC: BSC of 0.67). With the primary analysis was to be performed on the All Enrolled (ITT) analysis set, it was estimated that a total of 430 randomized subjects would be required to achieve the progression event target of 362 events (progression or death) with a follow-up of 8 weeks.

- General methods: Continuous variables were summarized using descriptive statistics. For discrete variables, the frequency and percent distribution were summarized in frequency tables. PFS was analyzed at the 5% significance level using a log-rank test stratified by baseline ECOG performance status and geographic region. If the log-rank test for PFS was significant, the co-secondary endpoints of survival and best objective response rate were to be simultaneously analyzed. To control for multiple testing, survival was to be analyzed at the 4% significance level and response rate at the 1% significance level. The primary analysis for PFS and OR and an interim analysis for survival were to be analyzed when the target of 362 events was reached with the primary survival analysis done after the last subject achieved 1 year of follow-up. Other efficacy endpoints were analyzed descriptively with point estimates and 95% confidence intervals.

  The time-adjusted AUC values for the PRO scales were analyzed for weeks 8 to 16 with an analysis of covariance used to estimate between group treatment differences with main effects for treatment group, baseline PRO scale score, baseline ECOG

performance status and geographic region. Summary statistics were calculated for all PRO scale scores and the change from baseline for each visit was compared by treatment group.

Amendments to protocol:

Major amendments to the protocol are shown in Table 10. below:

Table 10. Major amendments to Protocol 20020408

VERSION	DATE	ENROLLED	KEY PROTOCOL MODIFICATIONS
0	12SEP03	0	Original protocol issued
1	25OCT03	0	• IRC Charter/Endpoint review using mod. RECIST • Serum samples to be collected for HAHA • Mod. To skin toxicity grading; guidelines for suspension of treatment with skin toxicity
1	4MAR04	28	• Protocol 20030194 opened. Allowed cross-over of patients in BSC arm.
2	7JUN04	99	• Changes to Study Design: – Definition of BSC clarified – Subjects allowed to remain on therapy until progression • Eligibility – Required EGFr expression in ≥ 1% of evaluated tumor cells – Requirements for prior therapy documentation of treatment failure clarified – Exclusion of patients with interstitial pneumonia, pulmonary fibrosis
3	1FEB05	382	• Changes to SAP: – Primary analysis set changed from APF to ITT – Timing of analysis changed to event based – Primary analysis to adjust only for stratification factors
4	26APR05	463	• Expand biomarker analysis

6.1.3.2 Supporting Efficacy Studies

Four uncontrolled monotherapy trials were submitted by the sponsor in support of efficacy data from the pivotal trial, 20020408. These trials, 20030194, 20030267, 20030250 and 20025405 are summarized in Table 11. These trials either were not felt

to meet the criteria detailed in 21 CFR 314.126, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm) as adequate and well-controlled studies or were not felt to be designed to provide a reasonable assessment of benefit in the population for which licensure was sought:

20030194(ongoing):

This study was an open-label, single arm extension study which permitted subjects originally randomized to the BSC arm of the pivotal trial, 20020408, to receive panitumumab (6 mg/kg IV) every 2 weeks until disease progression, intolerable side effects or withdrawal. Patients entering Study 20020408 were required to have radiographic evidence of disease progression during or following treatment with fluoropyrimidine, irinotecan, and oxaliplatin. Eligibility was confirmed by an independent review committee. However, progression in this study, assessed by the RECIST criteria was not confirmed by central review.

20030167(ongoing):

This study is an open-label, single arm study of patients with EGFr-expressing (≥10%) mCRC who have failed therapy with fluoropyrimidine, irinotecan and oxaliplatin treated with panitumumab (6 mg/kg IV) every two weeks. Response to therapy, assessed using the WHO criteria, was based on a central review. However, only 39(42%) of subjects met the protocol-defined criteria for prior therapy failure.

20030250(ongoing):

This study is comparable to study 20030167 but enrolled subjects with tumors with a lower level of EGFr expression (< 10%). Only 23(26%) of subjects met the protocol-defined criteria for prior therapy failure.

20025405 (completed):

This study is an open-label, single arm study of weekly panitumumab (2.5 mg/kg IV) in subjects with EGFr-expressing (≥10%) mCRC who had failed therapy with a fluoropyrimidine containing regimen plus either irinotecan, oxaliplatin or both. Subjects were treated until disease progression, intolerable side effects or withdrawal. In this study, radiographs were reviewed in a post-hoc centralized independent review. However, collection and documentation of prior failure and chemotherapy dose intensity was done retrospectively and was unavailable for many patients.

Table 11. Studies submitted in support of the efficacy of Panitumumab.

	20030194	20030267	20030250	20025405
N	175	93	88	148
Analysis Subset (n)	Mod. ITT (174)	APF (39)	APF(23)	ITT(148)
Prior Therapy	FU, I & O	FU, I & O	FU, I & O	FU, I and/or O
Endpoint	OR (RECIST)	OR(WHO)	OR(WHO)	OR(RECIST)
Review	Local	Central	Central	Local/Central
EGFr Level	≥ 1%	≥ 10%	< 10%	≥10%
Vectibix™ Dose/sched.	6 mg/kg/2w CHO	6 mg/kg/2w CHO	6 mg/kg/2w CHO	2.5 mg/kg/w Hybridoma
ORR (%) (95%CI)	10* (5.8,15.2)	8 (1.6,20.9)	13 (2.8,33.6)	9 (5.2,14.4)
* Includes 1 patients with low disease burden assessed to be a CR.				

Despite differences in study design and small sample sizes, these uncontrolled studies consistently show response rates of 8-10%.

6.1.4 Efficacy Findings

6.1.4.1 Patient Disposition, Demographic and Baseline Characteristics

Between January 16, 2004 and March 16, 2005, 463 subjects were enrolled (231 subjects randomized to the panitumumab plus BSC arm; 232 subjects randomized to the BSC alone arm).

Subjects were enrolled in 81 sites in Western, Eastern and Central Europe, Canada, Australia and New Zealand. Thirty-six per cent of patients were enrolled at Belgian sites, 20% at Italian sites, 9% at Australian sites and 6% at Spanish sites. Enrollment at the 4 highest accruing centers (1102- Brussels, Belgium (21 subjects); 1103- Gent, Belgium (63 subjects); 1104- Brussels, Belgium (23 subjects); and 1401- Milan, Italy (34 subjects)) accounted for 30% of the study population. Subjects were predominantly Caucasian (99%) and male (63%).

Enrollment was stratified according to ECOG performance status (0, 1, or ≥ 2) and by geographic region (Western Europe, Central/Eastern Europe, and Rest of World). The distribution of patients by stratification factors was similar between arms and is shown in Table 12.

Table 12. Study 20020408: Enrolled Subjects by Stratification Factors

REGION/ ECOG PS	PANIT. PLUS BSC 231 (100%)	BSC ALONE 232 (100%)	TOTAL
W. Europe			
0 -1	155	150	305
2 or 3	23	30	53
C. E. Europe			
0-1	17	17	34
2 or 3	3	2	5
Rest of World			
0-1	29	28	57
2 or 3	4	5	9
Total	231	232	463

The distribution of subjects in the panitumumab plus BSC and the BSC Alone arms were similar with respect to gender, age and race (Table 13).

Table 13. Study 20020408: Demographic Data

	PANIT. PLUS BSC (N = 231) N(%)	BSC ALONE (N = 232) N(%)	TOTAL (N = 463) N%)
Gender			
Male	146 (63)	148 (64)	294 (63)
Age			
Median (range)	62.0(27,83)	63.0(27,82)	62.0(27,83)
≥ 65	94 (42)	91 (39)	187 (40)
Race			
White	229 (99)	228 (98)	457 (99)

The baseline disease characteristics of subjects enrolled in study 20020408 is shown in Table 14.

Table 14. Study 20020408: Disease Characteristics

	PANIT. PLUS BSC (N = 231) N(%)	BSC ALONE (N = 232) N (%)	TOTAL (N = 463) N(%)
Primary site			
Colon	153 (66)	157 (68)	310 (67)
Rectum	78 (34)	75 (32)	153 (33)
ECOG PS			
0	107 (46)	80 (34)	187 (40)
1	94 (41)	115 (50)	209 (45)
2	29 (13)	35 (15)	64 (14)
3	1 (0)	2 (1)	3 (1)
Number of disease sites			
1	64 (28)	53 (23)	117 (25)
2	97 (42)	108 (47)	205 (44)
3	45 (19)	51 (22)	96 (21)
4	23 (10)	13 (6)	36 (8)
5	2 (1)	5 (2)	7 (2)
Metastatic sites – n (%)			
Liver	178 (77)	194 (84)	372 (80)
Lung	147 (64)	139 (60)	286 (62)
Lymph nodes	52 (23)	66 (28)	118 (25)
Abdomen	37 (16)	29 (17)	76 (16)
Mo. Since metastatic diagnosis			
Median			
(Range)	18.9 (5.2,129.2)	19.3 (4.6,68.6)	19.1 (4.6,129.2)
CEA > normal n (%)	212 (92)	214 (92)	426 (92)
Prior metastatic regimens			
1-2	147 (64)	144(62)	290(63)
3-4	81(35)	87(38)	169(37)
≥5	3(1)	1(0)	4(0)

COMMENT: While the two groups were generally similar, subjects randomized to the panitumumab plus BSC arm tended to have a lower ECOG PS, fewer disease sites, less frequent liver involvement, and fewer prior metastatic regimen, all of which could bias outcome in favor of the panitumumab arm. The median number of prior metastatic regimens in both arms was 2.4.

The EGFr expression of subjects' tumors is shown in Table 15.

Table 15. Study 20020408: EGFr Expression Level

	PANIT. +BSC 231 (100%)	BSC ALONE 232 (100%)	TOTAL 463 (100%)
Percent of cells with positive staining			
<1%	2(<1)	1(<1)	3(<1)
1-9%	57(25)	57(25)	114(25)
10-20%	65(28)	75(32)	140(30)
>20 – 35%	14(6)	28(12)	42(9)
>35%	93(40)	71(30)	164(35)
Percent of cells with membrane staining			
<1%	1 (<1)	0(0)	1 (<1)
1-9%	54(23)	50(22)	104(22)
10-20%	64(28)	80(34)	144(31)
>20 – 35%	12(5)	24(10)	36(8)
>35%	100(43)	78(34)	178(38)
Maximum staining intensity			
0	2(<1)	0(0)	2(<1)
1+	60(26)	78(34)	138(30)
2+	122(53)	113(49)	235(51)
3+	47(20)	41(18)	88(19)

Most subjects had a high level of EGFr expression with 74% having ≥ 10% positive staining, 77% having ≥ 10% of cells with membrane staining, and 70% having a maximum staining intensity of 2+ or 3+. The two arms were similar in the distribution of percent staining, percent of cells with membrane staining, and maximum staining intensity.

The disposition of subjects is described in Table 16. A total of 1,040 subjects were screened for participation in study 20020408. EGFr screening data was available on 1,007; 297(29%) of those with available screening data were found to be ineligible because of low level EGFr staining (< 1%). At the time of data cutoff, 401 subjects had either central radiologic disease progression or had died.

Table 16. Study 20020408: Subject Screening and Randomization

	PANIT. PLUS BSC	BSC ALONE	TOTAL
Subjects screened			1,040
Total Screened with EGFr data			1,007(97)
Membrane staining < 1%			297(29)
Subjects randomized n (%)	231 (100)	232 (100)	463 (100)
Received study drug	229(99)	0(0)	229 (49)
Did not receive study drug	2(1)	232 (100)	234 (51)

6.1.4.2 Protocol Deviations

The Division of Scientific Investigations (DSI) conducted bioresearch monitoring clinical investigator inspections at the four highest accruing sites participating in Study 20020408 from May 8, 2006 to May 25, 2006. The sites inspected are listed in Table 17 below. These four sites combined accrued 30% of all subjects enrolled in the pivotal trial. All four sites were in Western Europe. The inspector concluded that sufficient documentation was available to assure that the subjects audited met the eligibility criteria and received the assigned study treatment, that adverse events were adequately reported, and that the primary and secondary study endpoints were assessed in accordance with protocol requirements. No FDA-483s were issued. For additional details of the DSI inspection, please see the Clinical Inspection Summary submitted by J. Lloyd Johnson, Good Clinical Practice Branch II, DSI.

Table 17. Bioresearch Monitoring Clinical Investigator Inspections, Study 20020408

NAME	CITY	COUNTRY	INSPECTION DATE	EIR RECEIVED	CLASS
Alain Hendlisz (Site 1102)	Brussels	Belgium	May 8 – May 9, 2006	June 28, 2006	NAI*
Yves Humblet (Site 1104)	Brussels	Belgium	May 10 – May 12, 2006	June 28, 2006	NAI
Marc Peeters (Site 1103)	Gent	Belgium	May 15 – 19 2006	June 30, 2006	NAI
Salvatore Siena (Site 1401)	Milano	Italy	May 22 - 25, 2006	July 3, 2006	NAI
*NAI = No deviation from regulations. Data acceptable					

Major protocol violations were pre-specified. Overall, the rate of protocol violations was low. Those violations thought to have a potential impact on outcome assessment are summarized in Table 18 below. The rate of pre-specified protocol violations was higher in the panitumumab arm because of those violations associated with panitumumab dosing and infusion. Most violations involved antibody assessment. Other important protocol violations involved failure to meet protocol specified criteria for disease progression and

prior chemotherapy when reviewed by the independent review committee. The number of subjects for whom prior failure could not be confirmed was low, 2% and 0% in the panitumumab and BSC arms respectively. One subject (111804001) in the panitumumab plus BSC arm received a single dose of cetuximab 104 days prior to study entry. In general, the two study arms were balanced with respect to protocol violations. To assess the potential impact of protocol violation on study outcomes, pre-specified sensitivity analyses of the subset of ITT subjects will only adjudicated prior failures, and another subset of patients without major protocol violations (The per-protocol analysis subset) were performed.

Table 18. Study 20020408: Protocol Deviations

CATEGORY	DEVIATION	PANIT. PLUS BSC (N = 231)	BSC ALONE (N = 232)
Eligibility	Received > 3 prior chemotherapy regimens (after Amendment 2)	0 (0)	1 (0)
	Received ≤ 2 prior chemotherapy regimens (after Amendment 2)	1 (0)	0 (0)
	Prior EGFr targeting agents	1 (0)	0 (0)
	Index lesion(s) previously irradiated	0 (0)	2 (1)
	Prior therapies that did not have protocol specified washout times	6 (3)	10 (4)
	Prior chemotherapy criteria not per protocol	12 (5)	7 (3)
	Radiographic evidence of disease progression is > 6 months	4 (2)	1 (0)
	Prior radiographic evidence of disease progression not done	2 (1)	2 (1)
	EGFr membrane staining below protocol specified criteria of ≥10% of tumor cells (before Amendment 2)	5 (2)	6 (3)
	EGFr membrane staining below protocol specified criteria, ≥1% (after Amendment 2)	1 (0)	0 (0)
	EGFr expression cannot be determined	0 (0)	2 (1)
	Screening procedures or assessments done before informed consent	1 (0)	0 (0)
	Screening ECOG performed prior to informed consent	7 (3)	6 (3)
	New primary tumor discovered at Baseline	0 (0)	1 (0)
Screening Lab Tests	Study-specific tests drawn prior to informed consent or not done per protocol	6 (3)	7 (3)
Study Drug	Delivered dose too high (> 10% of planned dose)	2 (1)	-
	Delivered dose too low (< 10% of planned dose)	2 (1)	-
	Dose not held per protocol	1 (0)	-
	Dose not re-instated per protocol	10 (4)	-
	Start and/or stop time for infusion is unknown	31 (13)	-
	Weight changed by >10% and dose was not adjusted	7 (3)	-
	Study drug not discontinued as per protocol	1 (0)	-
	Infusion duration not per protocol	1 (0)	-
	Baseline weight not done, unable to determine correct dose	1 (0)	-
Antibody Samples	Baseline sample not done	6 (3)	7 (3)
	Follow-up sample collected < 21 days from last dose	29 (13)	3 (1)
	Sample taken after the start of investigational product	1 (0)	0 (0)
	End of study sample not collected	87 (38)	69 (30)
Disease Assessment	Missed on-study disease assessments	2 (1)	0 (0)

Provided by the sponsor: \\cbsap58\m\eCTD_Submissions\STN125147\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\colorectal-cancer\5351-stud-rep-contr\20020408, p143

COMMENT: The number of study participants with significant protocol violations was small and similar across treatment group and is unlikely to impact the efficacy or safety analysis.

At the data cut-off date, 87% of subjects on the panitumumab plus BSC and 99% of the subjects on the BSC arm had ended treatment. The primary reason for ending treatment in both arms was disease progression. No subjects on the panitumumab treatment arm ended treatment because they met a protocol specified study withdrawal criteria (due to toxicity) and no patients on the panitumumab treatment arm withdrew consent for study participation (Table 20).

Table 19. Patient Disposition

	BSC ALONE	PANIT. PLUS BSC	TOTAL
Number of subjects ending treatment	202 (87)	229 (99)	431 (93)
Disease Progression			
Death	151 (75)	194(85)	345 (80)
Adverse event	14 (7)	11(5)	25 (6)
Protocol specified criteria	12(6)	5(2)	17(4)
Consent withdrawn	0(0)	0(0)	0(0)
	0(0)	4(2)	4(1)

6.1.4.3 Analysis of Tumor Response

COMMENT: For additional details of the statistical analysis, please refer to the review by Kallappa M. Koti, Ph.D., Statistical Reviewer.

The efficacy claim is based on the Sponsor's report of a highly statistically significant improvement in PFS ($p< 0.0001$) in the panitumumab plus BSC arm compared to the BSC alone arm (For the panitumumab plus BSC and the BSC alone arm, the comparisons for the median and mean PFS were 8 vs. 7.3 weeks and 13.7 vs. 8.6 weeks respectively). The Sponsor claims a reduction in risk of disease progression of 0.46 in the panitumumab treated arm.

The primary analysis data set was the All Enrolled (ITT) data set which included all randomized subjects who signed informed consent. Two subjects (111107004 and 111405010) randomized to the panitumumab plus BSC arm were included in the ITT population but died of disease progression within 1 day of randomization and did not receive study drug. Tumor assessment according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) was done at 8, 12, 16, 24, 32, 40, and 48 weeks and every 3 months thereafter. Tumor assessment was also done at the time of symptomatic disease progression.

COMMENT: The protocol-specified primary analyses of progression-free survival, overall response rate, and response duration were based on events confirmed by the IRC that was masked to treatment assignment. However, upon locally assessed disease progression, subjects randomized to the BSC alone arm were permitted to receive panitumumab (6

mg/kg IV every 2 weeks) on the open-label single arm study, 20030194. If a subject was assessed to have progressed locally but disease progression was not confirmed by the IRC, subsequent tumor assessments on Study 20030194 were submitted to the IRC for ongoing review. In these discrepant cases, subjects were censored at the time of centrally determined progression on study 20030194.

Primary endpoint: Progression-free survival (PFS):

The analysis of PFS for Study 20020408 is shown in Table 21 and the Kaplan-Meier curves for PFS are shown in Figure 2 below. There was a highly statistically significant difference in PFS favoring the panitumumab plus BSC arm. However the difference in the median PFS between arms was only 5 days and the difference in mean PFS of 37 days.

Table 20. Study 20020408: PFS in the All Randomized (ITT) Study Population

		PANIT. PLUS BSC	BSC ALONE
Progressed	Total #	231	232
	N (%)	193 (84%)	208 (90%)
Censored	N (%)	38 (16%)	24 (10%)
PFS (days)	Median	56	51
	95% CI	(55, 59)	(50, 54)
	Mean (sd)	96.4 (5.3)	59.7 (3.75)
	Min, Max	0, 357	0, 337

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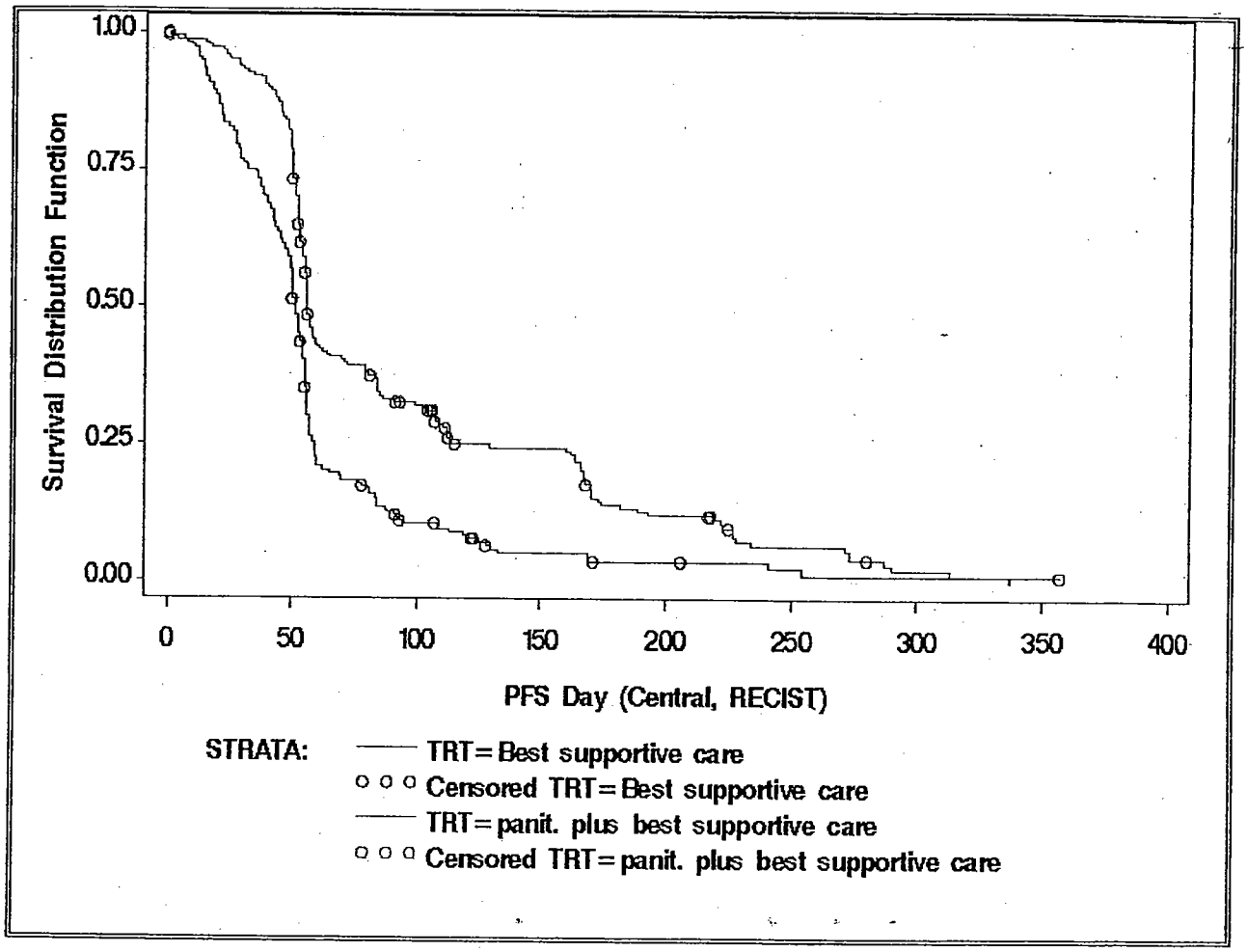
Figure 2. Kaplan-Meier Curves for PFS for Study 20020408 by Treatment Group



The difference observed in PFS was consistent across all pre-specified analysis subsets as shown in Table 22.

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Table 21. 20020408: PFS in Analyses Subsets*

	PROGRESSED/TOTAL		MEDIAN (95% CI)		MEAN (SD; MIN,MAX)	
Population	Panit. Plus BSC	BSC Alone	Panit. Plus BSC	BSC Alone	Panit. Plus BSC	BSC Alone
All Enrolled(ITT)	193/231	208/232	56 (55,59)	51 (50,54)	96 (5.3;0,357)	60 (3.8;0,337)
Adjud. Prior Failure	150/179	153/173	56 (54,58)	52 (50,55)	94 (6.0;0,357)	62 (4.7;0,335)
Per Protocol	142/171	147/166	56 (54,58)	52 (50,55)	93 (6.3;0,357)	63 (4.8;0,337)

*Stratified log-rank test p-values for comparisons between treatment groups are < 0.0001 for all pre-defined population subsets.

As can be seen from Figure 2, a large number of subjects progressed prior to the first scheduled study assessment at week 8. A total of 88 subjects; 9(4%) of those randomized to the panitumumab arm and 79(34%) of those randomized to the BSC arm underwent an unscheduled assessment prior to Week 8. Given the unblinded nature of the study, differential assessment of progression in the two study arms represents a major potential source of bias. Moreover, in a disproportionate number of subjects in the BSC arm, a local assessment of progressive disease which was not confirmed on central review, led to study termination (Table 23.).

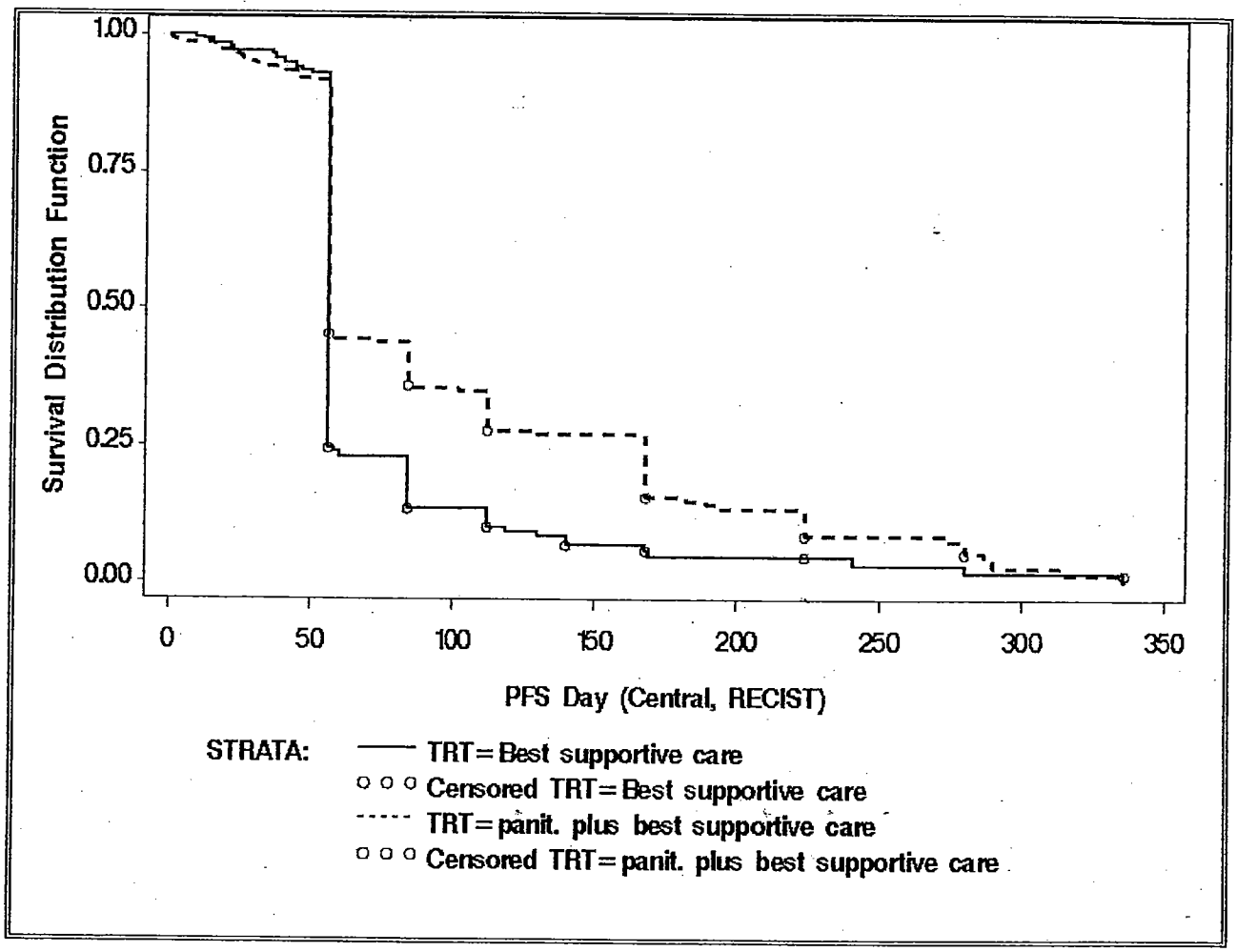
Table 22. Unscheduled Assessment Prior to Week 8

	PANT. PLUS BSC 231(100)	**BSC ALONE 232(100)**
Total Unscheduled Assessments	9 (4)	79(34)
Discrepant Readings Local=PD Central=other	0(0)	17(22)

To evaluate the potential impact of bias based on the timing of unscheduled tumor assessments, a post-hoc sensitivity analysis was conducted in which events of disease progression by central review were moved to the day of the closest scheduled assessment time in both treatment arms. This adjustment was not performed for deaths. The time-

adjusted Kaplan-Meier curve for PFS is shown in Figure 3. below and still shows a consistent treatment benefit (log rank test p-value < 0.0001):

Figure 3. PFS in Study 20020408 Adjusted for Early Assessment



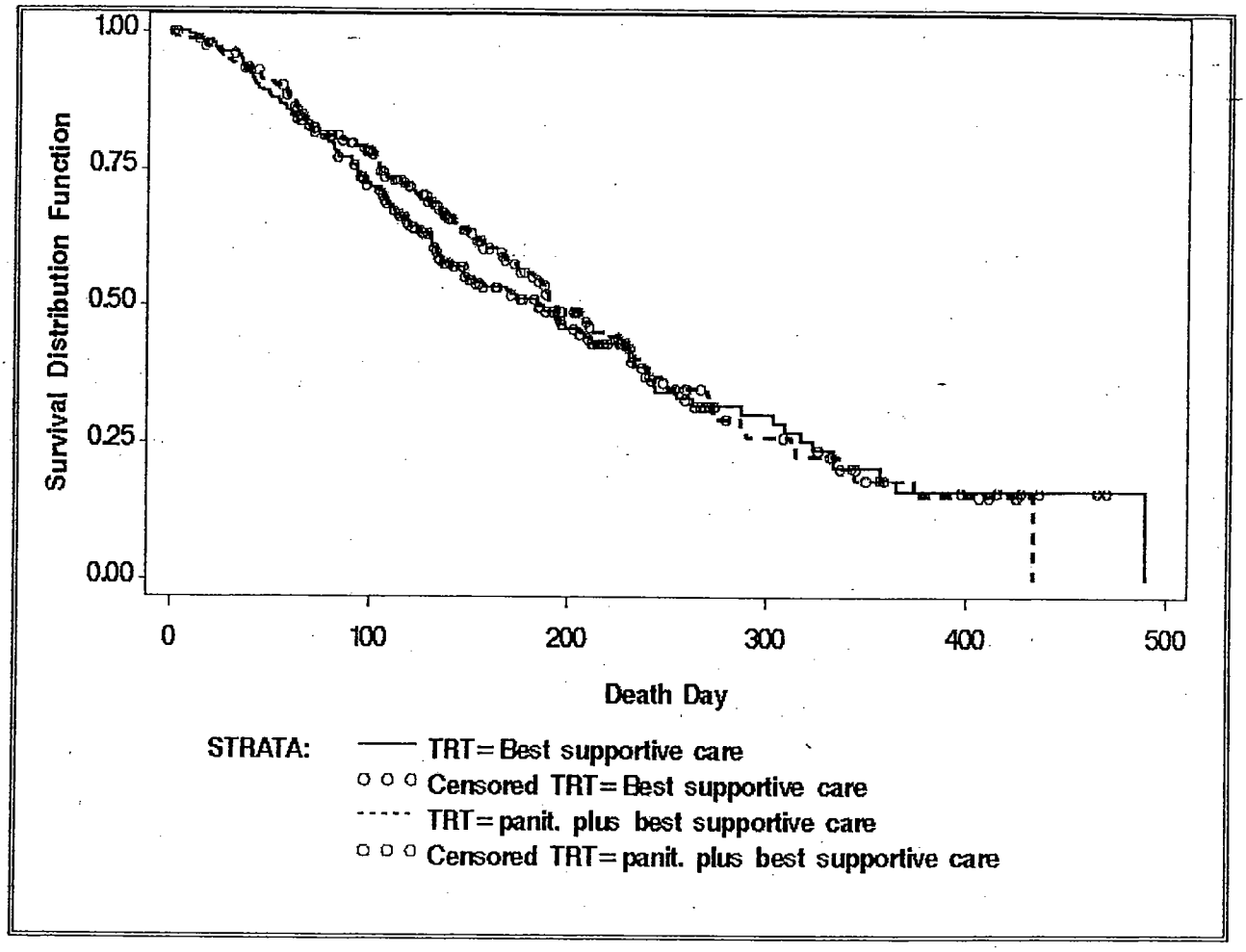
Secondary endpoints:

In the interim survival analysis, no difference was observed in survival between the two treatment arms as shown in Table 24. The Kaplan-Meier survival curve for overall survival is shown in Figure 4 below:

Table 23. Study 20020408: Overall Survival

		PANIT. PLUS BSC	BSC ALONE
Survival Dead Censored	Total # N (%) N (%)	231 119 (51.5%) 112 (48.5%)	232 131 (56.5%) 101 (48.5%)
Survival (days)	Medain (95% CI)	193 (174, 233)	184 (148, 228)
	Mean (sd) Min, Max	215 (10.9) 0, 434	>218 0, 490
Hazard ratio (95% CI)	0.987 stratified (0.768, 1.267)		
Stratified Log-rank test	P-value = 0.6041		

Figure 4. Overall Survival for Study 20020408



Moreover, additional follow-up time will not change the results of the interim analysis.

Nineteen partial responses were observed, all in the panitumumab treatment arm. No complete responses were observed. The difference in response rates between arms was highly statistically significant (Table 25).

Table 24. Study 20020408: Objective Response Rates

	ND	PD	PR*	SD	UE	TOTAL
BSC alone	25	156	0	24	27	232
Panit. Plus BSC	31	113	19	64	4	231
Total	56	269	19	88	31	463

ND: Not done; UE: Unevaluable
* p-value < 0.0001 (for PR)

Table 25. 20020408: Efficacy Endpoints All Enrolled Analysis Set

CENTRAL ASSESSMENT	**PANITUMUMAB PLUS BSC** (N = 231)		**BSC ALONE** (N = 232)
Objective tumor response			
Subject responding – n (%)	19 (8)		0 (0)
Rate (95% CI)- %	8.23 (5.02, 12.55)	8.2 (4.5, 12.7)	0.0 (0.0, 1.6)
Difference in rates (95% CI)			
Odds ratio (99% CI) stratified by IVRS, ECOG and region		NE (3.9, NE)	
p-value		< 0.0001	
Duration of response (weeks)			
Median time (95% CI)	17.0 (16.4, 25.3)		NE (NE, NE)
Minimum, Maximum	4, 40		NE, NE
Time to response (weeks)	19 (100)		NE (NE)
N (%)	8.9 (2.7)		NE (NE)
Mean (SD)	7.9		NE
Median	7.1, 10.6		NE, NE
Q_1, Q_3	6.7, 15.4		NE, NE
Minimum, Maximum			
Time to disease progression (weeks)	8.0 (7.9, 8.7)		7.3 (7.1, 7.7)
Median time (95% CI)	0, 51		0.48
Minimum, Maximum			

The median duration of response among responders in the panitumumab treatment group was 17 weeks.

PFS in special/subgroup populations:

Table 26. 20020408: PFS in Special/Subgroup Populations*

POPULATION	PROGRESSED TOTAL (% PROGRESSED)		MEDIAN (DAYS) (95% CI)		LOG-RANK TEST
	Panit. Plus BSC	BSC Alone	Panit. Plus BSC	BSC Alone	p-value
Age					
< 65	114(84)	129(91)	56	49	<0.0001
≥ 65	79(82)	79(87)	57	55	0.0016
Sex					
Male	121(83)	132(89)	57	51	<0.0001
Female	72(85)	76(90)	56	50	<0.0001
Disease Site					
Colon	126(82)	141(90)	56	50	<0.0001
Rectum	67(86)	67(89)	57	54	0.0003
Lines of prior therapy					
1-2	121(83)	132(92)	55	51	<0.0001
≥ 3	69(84)	75(86)	70	51	0.0003

The analysis performed by the FDA statistical reviewer confirmed the Sponsor's claim that the improvement observed in PFS in response to panitumumab was consistent across the following subgroups: age, sex, disease sites and number of prior lines of chemotherapy.

As shown in Table 27, there was no correlation between EGFr expression status and PFS.

Table 27. 20020408: PFS by EGFr Expression Level*

EGFR EXPRESSION	PROGRESSED TOTAL (% PROGRESSED)		MEDIAN (DAYS) (95% CI)		LOG-RANK-TEST
	Panit. Plus BSC	BSC Alone	Panit. Plus BSC	BSC Alone	p-value
% cells with positive staining					
1-9%	57(72)	57(88)	59(53,80)	50(42,54)	0.0003
≥ 10%	172(87)	174(90)	56(55,58)	51(50,54)	<0.0001
Max. staining intensity					
0, 1+, 2+	182(82)	190(88)	56(55,61)	51(50,54)	<0.0001
3+	47(87)	41(95)	56(51,83)	48(36,55)	0.0132

Patient-reported outcomes:

At least one post-baseline PRO assessment was obtained on 207(90%) of subjects on the panitumumab arm and on 184(79%) of subjects on the BSC Alone arm. Due to the unblended nature of the data and the disproportionate amount of missing data on subjects on the BSC Alone arm, analysis of the primary PRO assessment, time adjusted AUC for EUROQOL EQ-5D, which favored the panitumumab arm were not considered to be interpretable.

COMMENT: Analysis of PRO data is considered exploratory, incomplete, and potentially biased and is not considered sufficiently robust to support a marketing claim.

6.1.5 Clinical Microbiology

Panitumumab is not an antimicrobial, therefore this section is not applicable.

6.1.6 Efficacy Conclusions

Study 20020408 is a randomized phase 3 clinical study conducted in patients with refractory, metastatic colorectal cancer who had failed irinotecan- and oxaliplatin-containing regimen(s). There has been no effective therapy found for this patient population.

The inability to conduct a blinded study due to the characteristic nature of the skin toxicity

associated with panitumumab and early study termination and subsequent panitumumab treatment of subjects randomized to the BSC Alone arm based on the assessment of an unblinded local investigator are inherent sources of bias which may have lead to the inability to detect a survival advantage of panitumumab, if one existed.

Potential existed for an over-reporting and attribution of adverse events to the treatment drug compared to the control group given BSC alone and for premature study termination of patients on the BSC arm allowing them to cross-over to receive a potentially active drug on study 20030194 (see 20020408 study report page 204).

Stringent criteria were employed to validate prior therapy and prior treatment failure which was confirmed for 75% of the ITT population. Based upon IRC determination of disease progression, a statistically significant prolongation in PFS was observed in patients receiving panitumumab compared to those receiving BSC alone. There were 19 partial responses observed in patients randomized to panitumumab, for an overall response rate of 8% (95% CI: 5.3%, 12.5%). The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks).

The modest effect size is to be expected in this heavily pre-treated patient population with uniformly poor prognosis provides is to be expected and provides sufficient evidence of efficacy of panitumumab in the indicated population. The improvement in PFS is sufficient grounds for approval of this drug under accelerated

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review was performed separately using data provided by the sponsor in the 120 day safety update for the randomized, controlled study (20020408) and for the following pre-defined ISS study groups:

- Subjects with mCRC receiving panitumumab monotherapy (mCRC Monotherapy Set; n=789). This subset included subjects from the studies shown in Table 28.
- Subjects receiving panitumumab in combination with other chemotherapy regimens (All Combination Therapy Set; n=174)
- Subjects from studies with defined interval assessments of serum magnesium levels (Hypomagnesemia Subset; n = 812)

Table 28. Subjects in the mCRC Monotherapy Dataset by Study

STUDY	N
20020408	229
20025405	148
20030138	39
20030167	148
20030194	176
20030250	157
20030251	10
20040192	13
Total	920

For study 20020408, a review of case report forms and narratives for all subjects dying during or within 30 days of study and for all subjects with serious adverse events was conducted. Case narratives were reviewed for subjects dying during or within 30 days of study for all other studies in the mCRC Monotherapy Set

Based on the safety review detailed in this section, the most common adverse events were skin rash, hypomagnesemia, paronychia, fatigue abdominal pain and diarrhea. The most serious adverse events seen with panitumumab were pulmonary fibrosis, dermatologic toxicity complicated by infection and death, infusion reactions, abdominal pain, nausea and diarrhea.

7.1.1 Deaths

7.1.1.1 Deaths on study 20020408

Table 29 summarizes deaths in all subjects who died on study or within 60 days of the end of study treatment up to the data cut-off. Up to the time of the data cut-off, there were 117 deaths in the panitumumab plus BSC arm including those that occurred during long-term follow-up of study 20020408. A total of 133 deaths occurred among patients randomized to the BSC Alone arm, including 83 deaths that occurred among patients who subsequently received panitumumab on study 20030194.

Table 29. 20020408. Deaths on or within 60 Days of Study, by Study Arm

	PANIT. TREATED			
		Randomized to BSC		
	Panit. Plus BSC (N=229)	BSC Crossover to 20030294 (N=174)	BSC Without Crossover (N=60)	All BSC (N=234)
Deaths to Cut-off (n)	117(51)	83(48)	50(83)	50(21)
Deaths within 30 days of end of treatment	44(19)	43(25)	34(57)	34(15)
Deaths > 30 days of end of treatment	73(32)	40(23)	16(27)	16(7)

COMMENT: Because a large number of subjects randomized to the BSC Alone arm were treated with panitumumab on study 20030194 within the short-and long-term follow-up phase of study 20020408, a direct comparison between study arms is confounded. Subjects on the BSC Alone arm who were found to be ineligible for enrollment on study 20030194 had a lower performance status and rapidly progressive disease. For that reason, the death rate observed in this subset is not representative of the randomized group.

Case narratives and case report forms for deaths occurring within 30 days of the end of treatment for all subjects on studies 20020408 and 20030194 were reviewed. The cause of death attributions by the Sponsor and the FDA reviewer are shown in Table 30. In all cases, the FDA reviewer concurred with the sponsor on the attribution of the cause of death.

Table 30. FDA's Attribution of the Cause of Death

CAUSE OF DEATH	PANIT. PLUS BSC		BSC CROSSOVER TO 20030294*		BSC WITHOUT CROSSOVER*	
	Sponsor	Reviewer	Sponsor	Reviewer	Sponsor	Reviewer
On study/within 30 days	44	44	43	43	34	34
Progression/complication	40	40	40	40	34	34
Other	4	4	3	3	0	0
*Deaths within 30 days of receiving last panitumumab infusion on 20030294 or from decision to end study participation on 20020408 if not crossed-over.						

The cause of death for all subjects by study arm is listed in Table 31.

Table 31. Attribution of Deaths on Study 20020408

CAUSE OF DEATH	PANIT. PLUS BSC (N=229)	BSC ALONE (N=234)
All deaths up to data cut-off	117(51)	133(57)
Disease Progression	113(49)	131(56)
Acute Respiratory Failure	1(0)	0(0)
Gastrointestinal hemorrhage	1(0)	0(0)
Cardiopulmonary failure	0(0)	1(0)*
Hepatic Failure	1(0)	0(0)
Sepsis	1(0)	0(0)
Systemic mycosis	0(0)	1(0)*
Cerebrovascular accident	0(0)	1(0)*
*Occurred following panitumumab administration.		

COMMENT: As anticipated in this study population with advanced, metastatic disease, most deaths were found to be related to disease progression. Two deaths attributed to other causes in the BSC Alone arm occurred in panitumumab-treated subjects after enrollment onto study 20030194. Case-synopses of deaths not directly attributed to disease progression are included below.

Case Narratives, Deaths:

Panitumumab plus BSC group:
111103010 was a 55-year-old white woman CRC metastatic to liver, lung and lymphatics who discontinued panitumumab after the third infusion due to disease progression. Eleven days following the third panitumumab infusion, she presented with mild vomiting, moderate dyspnea, a swollen abdomen and severe constipation and was hospitalized the next day. An echogram of the abdomen revealed severe hepatomegally with liver metastases and suspected thrombosis in the portal vein. She was treated during hospitalization with anti-emetics, laxatives and oxygen. The constipation and dyspnea improved but the hepatomegally persisted. She was discharged home 2 weeks later for palliative care and died 4 days after hospital discharge (29 days after the last panitumumab dose).

111105018 was a 50-year-old white woman with rectal cancer with metastases to bone, lung, liver, muscle and lymphatics and past history of hypertension. While hospitalized for bowel obstruction and one day after receiving the 1st panitumumab infusion the subject developed sepsis. Antibiotics were initiated and the subject underwent a colostomy. Three days after the onset of septicemia, she developed grade 4 coma and was transferred to the ICU. Blood culture was positive for E. coli. The coma resolved 3 days after onset and was

reported to be due to epilepsy related to morphine. Five days after resolution of the comma, during port-a-cath placement, the subject developed a cardiopulmonary arrest. Other associated AEs included gastrointestinal bleeding, anemia, hematuria, and edemia. Five days later, during insertion of a central catheter, the subject developed cardiopulmonary arrest. She recovered from the cardiopulmonary arrest but subsequently died from E. coli sepsis.

111107007, a 63 year-old white man with colon cancer metastatic to liver, lung, peridcardium, and lymphatics was hospitalized on the day of the 4th panitumumab infusion with neutropenia, severe lung infection, hepatic decompensation, hypoproteinemia and general deterioration. He was treated with antibiotics, bronchodilators, and diuretics. Panitumumab was permanently discontinued due to lung infection. Sixteen days after the 4th panitumumab infusion, the subject developed gastrointestinal hemorrhage associated with disease progression and died. Death was not considered panitumumab-related.

111408012, a 70-year-old white woman with colon cancer metastatic to lung, liver, adrenals, and lymphatics, had a mild fever on the day of the first panitumumab infusion. Two weeks later, the patient was hospitalized with a moderate epileptic seizure. CT scan ruled out brain metastases. The subject was treated with conticosteroids and barbiturates. The subject remained in the hospital, developed acute respiratory failure and died 21 days after the single panitumumab infusion.

BSC alone group:
133104006, a 64-year-old white woman with colon cancer metastatic to liver and lymphatics had disease progression after 59 days on the BSC alone arm and crossed over to receive panitumumab. She was noted to have fungal stomatitis around the time of the first infusion. Fifteen days after the first infusion, the subject had severe rectal ulcer hemorrhage and panitumumab was withdrawn. The subject also developed systemic mycosis and died of systemic mycosis approximately 6 weeks after the single infusion of panitumumab.

115004007, a 66-year-old white woman with colon cancer metastatic to liver and lung had disease progression after 51 days on the BSC alone arm and crossed-over to receive panitumumab. On 20020408, the patient had moderate nausea, mild vomiting, constipation, fever, severe pain and moderate hypokalemia. Two days after the second panitumumab infusion, the subject was hospitalized with confusion and expressive aphasia. Cerebrovascular accident was diagnosed with abnormal ECG. An abnormal ECG result was also noted after 3 days with a normal sinus rhythm of 68 and a prolonged QT interval for this rate and non-specific ST-T abnormalities. Chest X-ray performed the same day showed no signs of acute cardiac disease or congestive heart failure. Treatment included phenytoin and lorazepam. Progressive disease became apparent with hepatic enlargement and abdominal distension. The subject died due to the cerebrovascular event 10 days after the second panitumumab infusion.

111708009, a 60-year-old white man with colon cancer, liver and lymphatics, had disease progression after 40 days on the BSC alone arm. On the day of the second panitumumab

infusion, the subject developed life-threatening jaundice and hepatotoxicity, severe abdominal pain and choluria. The patient died of cardiopulmonary failure attributed to disease progression 28 days after the second dose of panitumumab.

REVIEWER'S COMMENTS REGARDING DEATHS ON STUDY: The cross-over of patients initially randomized to the BSC Alone arm of the randomized, controlled study effectively precluded a valid comparison between subjects who received panitumumab therapy and those who received BSC Alone. A review of the CRFs and patient narratives of deaths occurring on study or within 30 days of treatment for studies 20020408 and 20030194 validated the sponsor's attribution of the cause of death.

7.1.1.2 Deaths occurring in the mCRC Safety Subset

Deaths occurring in the mCRC Monotherapy Set reported to the Agency in the 120 day safety update were reviewed. There were 523 deaths that occurred among the 920 subjects in the mCRC safety subset occurring on study or within 30 days of the last panitumumab administration. The MedDRA preferred term for the fatal Adverse Event is listed for the remaining deaths in Table 32 below.

Table 32. mCRC Monotherpay Set – Non-Progression Deaths

CAUSE OF DEATH (BY MEDDRA PT)	MCRC SUBSET (N=920)
All deaths within 30 days of last panitumumab dose – n(%)	140(15)
Disease Progression	125(14)
Acute Respiratory Failure	2(0)
Cardiac Arrest	1(0)
Cerebrovascular accident	1(0)
Gastrointestinal hemorrhage	1(0)
Hepatic failure	1(0)
Intestinal perforation	1(0)
Myocardial infarction*	1(0)
Pleural effusion	1(0)
Pneumonia	1(0)
Pulmonary edema	1(0)
Respiratory distress	1(0)
Sepsis	1(0)
Small intestinal obstruction	1(0)
Unknown	1(0)

*A second fatal event of cerebrovascular accident was also reported by the investigator in this subject.

COMMENT: Most deaths were due to disease progression or were disease associated. There was little evidence of panitumumab-related cardiac or pulmonary mortality.

7.1.2 Other Serious Adverse Events

In the randomized trial, the percentage of subjects experiencing any AE was high in both arms. All subjects enrolled on the panitumumab arm experienced an adverse event. The incidence of SAEs, Grade 3-4 AEs and AEs resulting in study withdrawal were all higher in the panitumumab arm.

The percentage of AEs, SAEs, Grade 3-4 AEs and AEs resulting in study withdrawal was similar across the panitumumab treated safety subgroups.

Table 33. Study 20020408: Overall Incidence of Adverse Events

SUBJECTS WITH:	STUDY 20020408		MCRC SAFETY SET (N=920)
	Panit. Plus BSC (n= 229)	BSC Alone (n=234)	
Any AE	229(100)	204(87)	920(100)
Any SAEs	99(43)	61(26)	357(39)
Grade 3 - 4 AEs	128(56)	67 (20)	520(57)
AEs resulting in study withdrawal	13(6)	6(3)	94(10)

Two of the 232 subjects initially randomized to receive panitumumab on study 20020408 died after randomization but prior to receiving study drug. For the safety analysis, these two subjects were considered with patients randomized to the control arm. For subjects initially enrolled onto the BSC Alone arm of study 20020408 who subsequently received panitumumab on study 20030194, only AEs occurring prior to crossover were attributed to study 20020408.

7.1.2.1 Overview of Other Serious Adverse Events on Study 20020408

The verbatim term for all clinical adverse events reported on case report forms were assigned a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 8.0, mapped to the appropriate system organ class. Adverse events

were graded using NCI CTC version 2.0 with the exception of selected dermatologic/skin adverse events, which were graded using a modified version of the CTCAE version 3.0).

A serious adverse event was defined as any event regardless of assessment causality that: is fatal, life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, is a persistent or significant disability or a congenital anomaly/birth defect.

The incidence of SAEs in study 20020408 by randomization arm is shown in Table 34. All SAEs occurring in ≥ 4 subjects (1.75%) in either arm is shown.

Table 34. SAEs in Study 20020408 by Randomization Arm

SERIOUS ADVERSE EVENT	BSC N=234(%)	PANIT. PLUS BSC N=229(%)
COLORECTAL CANCER METASTATIC/ COLORECTAL CANCER	25(10.7)	45(19.7)
GENERAL PHYSICAL HEALTH DETERIORATION	7(3.0)	12(5.2)
ABDOMINAL PAIN	7(3.0)	8(3.5)
INTESTINAL OBSTRUCTION	4(1.7)	8(3.5)
HEPATIC FAILURE	4(1.7)	7(3.1)
DYSPNOEA	5(2.1)	6(2.6)
CONSTIPATION	0(0)	5(2.2)
ASCITES	2(0.9)	4(1.8)
ASTHENIA	2(0.9)	4(1.8)
DEHYDRATION	1(0.4)	4(1.8)
JAUNDICE	4(1.7)	4(1.8)
VOMITING	5(2.1)	4(1.8)
TOTAL	66	107

Metastatic colorectal cancer or colorectal cancer was the most frequently reported serious adverse event in both study arms. General physical health deterioration, intestinal obstruction, hepatic failure, ascites, asthenia and dehydration were all more commonly reported among subjects randomized to the panitumumab arm.

COMMENT: With the exception of dehydration, the constellation of commonly reported SAEs suggests disease progression. It is likely that eligible subjects on the BSC Alone arm with early evidence of disease progression were taken off study and treated with panitumumab before developing SAEs related to disease progression.

7.1.2.2 Overview of Other Serious Adverse Events in the mCRC Dataset

Table 35. Subject Incidence of Serious Adverse Events

PREFERRED TERM	ALL SUBJECTS (N-920)
Subjects with any adverse even – n (%)	44(5)
Hypomagnesemia	7(1)
Dehydration	4(0)
Hypersensitivity	4(0)
Dyspnea	3(0)
Hypocalcemia	3(0)
Infusion related reaction	2(0)
Pulmonary embolism	2(0)
Acute myocardia infarction	1(0)
Asthenia	1(0)
Back pain	1(0)
Cardiomyopathy	1(0)
Catheter site infection	1(0)
Cellulitis	1(0)
Cerebrovascular accident	1(0)
Chills	1(0)
Colonic fistula	1(0)
Deep vein thrombosis	1(0)
Dermatitis acneiform	1(0)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

As shown in Table 33 in Section 7.1.2, AEs resulted in termination of dosing in 13(6%) of subjects on the panitumumab study arm and 6(3%) of subjects on the BSC arm in study 20020408. In the mCRC Monotherapy Safety Dataset, 94 (10%) of subjects withdrew due to an AE.

7.1.3.2 Adverse events associated with dropouts

The adverse event leading to study withdrawal in Study 20020408 by study arm are listed in Table 36.

Table 36. AEs Leading to Study Withdrawal, 20020408

PANITUMUMAB PLUS BSC				
ID	Sex/Age	Panit. Cycle	AE	Serious
111001002	M/69	1	Infusion reaction	Yes
111102011	M/65	2	Intestinal obstruction	Yes
111102024	F/35	1	Abdominal pain	No
111102028	F/57	1	General deterioration	Yes
111103044	M/55	9	Coma	Yes
111103082	F/67	2	Depressed consciousness	Yes
111104005	F/51	15	Renal Failure	Yes
111104015	M/64	6	General deterioration	Yes
111105017	M/82	1	Asthenia	No
111107007	M/63	4	Lung infection	Yes
111107015	M/49	3	Pelvic Mass	Yes
111405003	M/63	2	DVT/PE	Yes
115006002	M/68	2	Dermatitis, acneiform	No
BSC Alone				
ID	Sex/Age	Panit. Cycle	AE	Serious
111101001	F/72	NA	Dyspnea	No
111103028	M/64	NA	Vomiting	Yes
111405005	M/66	NA	Supraventricular Arrhythmia Septic Shock Wound infection	Yes Yes Yes
111408016	F/71	NA	General deterioration	Yes
111412002	M/58	NA	Jaundice	Yes
113005002	M/61	NA	Spinal cord compression	Yes

COMMENT: One subject on study 20020408 withdrew a moderate infusion reaction (mild chills, coldness and tachycardia 5 minutes after the start of the initial panitumumab infusion for which he was premedicated). This case is described in more detail in section 7.1.3.3 below. One subject was withdrawn for grade 3 skin toxicity two weeks following the second panitumumab dose. Subject 111105017 developed severe asthenia on the day of the 1st panitumumab infusion and experienced moderate anorexia one day later. Subject 111107007 was hospitalized with neutropenia, a severe lung infection, hepatic decompensation, hypoproteinemia and degradation of general status. Panitumumab was discontinued due to the lung infection. Patient 1111405003 was discontinued due to a

DVT/PE. In all other cases, the adverse event associated with study withdrawal was clearly linked to disease progression.

Events leading to permanent discontinuation among subjects in the mCRC Monotherapy Set are listed in Table 37 below:

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Table 37. AEs Leading Study Withdrawal in ≥ 2 Subjects

PREFERRED TERM	920 (100%)
Subjects with any adverse event – n(%)	112(12)
Colon cancer metastatic	10(1)
Dermatitis acneiform	9(1)
Colon cancer	7(1)
Colorectal cancer	6(1)
Erythema	6(1)
General physical health deterioration	4(< 1)
Intestinal obstruction	4(< 1)
Paronychia	4(< 1)
Rash	4(< 1)
Ascites	3(< 1)
Skin exfoliation	3(< 1)
Spinal cord compression	3(< 1)
Abdominal pain	2(< 1)
Asthenia	2(< 1)
Colorectal cancer metastatic	2(< 1)
Convulsion	2(< 1)
Dyspnea	2(< 1)
Hepatic failure	2(< 1)
Hyperbiliruinemia	2(< 1)
Jaundice	2(< 1)
Malignant neoplasm progression	2(< 1)
Myocardial infarction	2(< 1)
Nausea	2(< 1)
Pleural effusion	2(< 1)
Pruritis	2(< 1)
Pneumonia	2(< 1)
Pulmonary embolism	2(< 1)
Rectal cancer metastatic	2(< 1)
Respiratory distress	2(< 1)
Vomiting	2(< 1)

COMMENT: Most events leading to permanent discontinuation from study are likely related to disease progression or are disease-associated. Among the remaining events,

skin and nail-associated AE most commonly led to permanent discontinuation of panitumumab.

7.1.3.3 Other significant adverse events

Skin toxicity:

For purposes of skin toxicity assessment in study 20020408, all skin, nail, eye, or hair disorders were recorded as adverse events. Pre-specified MedDRA Version8.0 terms were examined. Any treatment-emergent adverse event indicative of a skin, nail, eye or hair disorder that occurred with a 5% or higher incidence in the panitumumab arm compared to the BSC arms were considered to be integument and eye toxicity. These specific terms were used to scan the mCRC database.

In addition, pre-specified terms agreed with the FDA during the review of the Cetuximab license application for skin toxicites were also used to scan the database. These terms included: acneiform rash, acne, maculopapular rash, pustular rash, rash, exfoliative dermatitis, and dry skin.

Skin toxicities were graded based on a modification of the CTCAE Version 3.0 shown in Table 38 below:

Table 38. Study 20020408 – Skin Severity Grading Schema

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.

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Subjects with any integument/eye toxicity and integument/eye toxicity of grade 3 or greater as defined in Table 39 are shown below.

Table 39. I/E Toxicity, Study 20020408 and mCRC Safety Database

	20020408		MCRC N=920
	Panit. Plus BSC N=229	BSC Alone N=234	
Any IE (Grade 1-4)	206(90)	21(9)	842(92)
Any IE (Grade 3-4)	34(15)	0(0)	117(13)

COMMENT: Approximately 90% of subjects in the pivotal trial and in the mCRC Safety dataset had integument/eye toxicity. Approximately 15% of subjects had severe integument/eye toxicity.

A total of 42 subjects met the modified CTCAE criteria for any grade 3 or 4 integument/ eye toxicity or reported otherwise intolerable integument/eye toxicity. The disposition of these subjects is detailed in Table 40.

Table 40. Study 20020408 – Dose Modifications in Subjects with I/E Toxicity

	PANIT. PLUS BSC (N = 42)
Dose withheld	16(38)
Dose withheld and reinstated	12(29)
Dose withheld and reinstated, returned to full dose	10(24)
Dose withheld and reinstated and withheld again	2(<1)

COMMENT: in the pivotal study, a panitumumab dose was withheld due to integument/eye toxicity. In some cases, dose was withheld for a toxicity perceived to be intolerable by the subject that did not meet the criteria for Grade 3 or 4 toxicity. In all but two cases, panitumumab dosing was resumed at full or reduced dose.

Table 41. I/E AEs in ≥ 10% of Subjects - Between Group Difference of ≥ 10%

ADVERSE EVENT	PAN. PLUS BSC 229(100%)	BSC ALONE 234(100%)	DIFFERENCE %
All Integument and eye	90	9	81
Erythema	65	1	64
Acneiform dermatitis	57	1	56
Pruritus	57	2	55
Skin exfoliation	25	0	25
Paronychia	25	0	25
Rash	22	1	21
Skin fissures	20	0	20
All eye toxicity	15	2	13
Acne	13	0	13
Dry Skin	10	0	10

Table 42. AEs in 5-9% - Between Group Difference > 5%

ADVERSE EVENT	PAN. PLUS BSC 229(100%)	BSC ALONE 234(100%)	DIFFERENCE %
Nail disorder	9	0	9
Mucosal inflammation	6	1	5
Stomatitis	7	1	6
Growth of eyelashes	6	0	6

In the randomized controlled clinical trial, Integument/eye toxicities were reported in 90% of patients receiving panitumumab. Toxicity was severe (NCI-CTC grade 3 and higher) in 16% of patients. In the pivotal study, severe integument/eye toxicities occurring in > 1% of subjects were classified under the verbatim terms: dermatitis acneiform (7%), erythema (5%), pruritis (2%), and skin exfoliation (2%).

Using the composite definition of acneiform rash, based on pre-defined MedDRA version 8.0 preferred terms, 125(55%) of subjects in the panitumumab arm and 2(1%) of subjects in the BSC arm had adverse events. Acneiform rash was graded as severe in 12(5%) of subjects in the panitumumab arm and was described by the verbatim terms: skin exfoliation (2%), pustular rash (1%), acne (1%) and rash (1%). In all other cases, acneiform rash was graded as mild or moderate. Chelitis was identified in 6(%) subjects, all in the panitumumab arm. These events were graded as mild or moderate.

Ocular toxicities occurred in 34 (15%) subjects in the panitumumab arm and 5 subjects (2%) on the BSC arm. The most commonly occurring events were (in the panitumumab and BSC arms, respectively): conjunctivitis (4% and 1%), ocular hyperemia (3% and 0%), and increased lacrimation (2% and <1%).

Stomatitis/oral mucositis were defined using the following MedDRA version 8.0 terms: stomatitis, mucosal inflammation, aphthous stomatitis, mouth ulceration, mucosal dryness, and mucosal ulceration. According to this definition, stomatitis/oral mucositis was reported in 31(14%) subjects in the panitumumab arm and 4(2%) subjects in the BSC arm. One subject, 111304003, developed severe mucosal inflammation 4 weeks following the last panitumumab. This subject had been taken off study for disease progression and had started another chemotherapy regimen.

Nail toxicities were identified in 78(34%) of subjects in the panitumumab arm. No nail toxicities were identified in the BSC arm. Nail adverse events included paronychia (24%), nail disorder (9%), onchorrhexis, nail bed infection, nail bed inflammation, nail discoloration, nail discomfort, and oncholysis (all <1%).

Integument/eye-related toxicities that were infectious in nature were seen in 72(31%) subjects in the panitumumab arm and 5(2%) subjects in the BSC arm. The most frequently reported events (in the panitumumab and BSC arms, respectively) were: paronychia (24% and 0%), pustular rash (4% and 0%), folliculitis (2% and <1%), and eye infections (2% and 0%), and impetigo (1% and 0%). Five subjects (2%), all in the panitumumab arm, had severe events including paronychia and pustular rash.

Median time to the development of integument/eye-related toxicity was 12 days; the time to most severe skin/eye- related toxicity was 15 days after the first dose of panitumumab; and the median time to resolution after the last dose of panitumumab was 43 days. Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage were reported.

Infusional Toxicity:

Infusional toxicity is anticipated with infusions of proteins/antibodies. Three separate and progressively more conservative approaches to the identification of infusion reactions were used in this application:

- Infusion Reaction (AE): Adverse events identified as allergic reaction, hypersensitivity, infusion reaction, or anaphylaxis by the investigator on the case report form attributed to drug exposure.
- Infusion Reactions (First Dose): This included infusion reactions occurring with the first panitumumab dose defined as any reported allergic reaction, anaphylactoid reaction, grade 3 or 4 chills per NCI CTC Version 2.0, fever, or dyspnea, occurring within 24 hours of the first panitumumab dose that were not otherwise designated as either anaphylactoid or allergic reaction. This definition has been used in FDA review of other monoclonal antibodies.
- Infusion Reaction (Any Dose): Infusion reaction defined using 40 pre-specified

terms indicating any signs and symptoms of potential infusion reaction defined per CTCAE Version 3.0 as "allergic reaction/hypersensitivity" and "cytokine release syndrome/acute infusion reaction" and coincident with any panitumumab infusion, starting the day of the infusion and resolving within 24 hours. These terms are listed in Table 43 below.

Table 43. Infusion Reaction Terms Based on NCICTCAE, V 3.0

allergic reaction	fatigue	myalgia
anaphylaxis	fever	nausea
angioedema	flushing	pruritus
arthralgia	headache	rash
asthenia	hives	rigors
bronchospasm	hypersensitivity	sweating
chills	hypertension	tachycardia
cough	hypotension	tumor pain
desquamation	infusion reaction	urticaria
diaphoresis	itching	vomiting
dizziness	joint pain	welts
drug fever	lethargy	wheals
dyspnea/dyspnoea	malaise	
edema/oedema	muscle pain	

Study 20020408

No subject in study 20020408 had an adverse event reported by the investigator as "infusion reaction" or "infusion-related reaction". One subject (111001002) discontinued panitumumab after the first infusion because of a serious adverse event of "moderate hypersensitivity" considered related to panitumumab by the investigator. An infusion-associated adverse event ("severe hypertension") in a second subject was graded as severe.

Using the Infusion Reaction (First Dose) definition, 10/229(4%) subjects treated with panitumumab in study 20020408 experienced infusion reactions of which 2(1%) were grade 3. Using the Infusion Reaction (Any Dose) definition, 12/229(5 %) subjects had an infusion and reactions occurred as late as the 13th panitumumab infusion.

mCRC Safety Subset

A review data from all subjects with mCRC (n=920) who received panitumumab monotherapy identified 9 subjects (1%) with investigator reported infusion reactions of which 4 were reported as grade 3 and none were considered life-threatening (grade 4). Using the FDA definition limited to the first infusion, 17 (1.8%) subjects had an infusion reaction including 3 (0.3) subjects that had an infusion reaction graded as ≥ grade 3. Using the broadest definition, 94/920 (10.2%) had infusion reaction occurring coincident with any panitumumab infusion, of which 8(0.9%) were ≥ grade 3. Overall, infusion reactions have resulted in treatment discontinuation in 2 subjects.

Monotherapy Safety Subset

A review of data from all subjects treated with panitumumab monotherapy (n=1293) permitted the most in depth exploration of the association of dose- and cell line- and infusion reactions. The infusion rate was highest among subjects treated at panitumumab doses lower than 6.0 mg/kg ($\chi^2 = 16$; $p<0.0003$).

Table 44. Monotherapy Dataset, Infusion Reactions (Any Infusion) by Dose

DOSE	N	SUBJECTS WITH A REACTION TO ANY PANIT. INFUSION N(%)
< 6.0 mg/kg	447	74(17)
6.0 mg/kg	796	71(9)
9.0 mg/kg	50	4(8)
Total	1293	149(12)

However, most subjects treated with doses of < 6.0 mg/kg received the hybridoma-derived product; most subjects who received higher panitumumab doses received the CHO-derived product (Table 45).

Table 45. Monotherapy Dataset, Distribution of Dose by Cell Line Type

DOSE	TOTAL 1293(100%)	HYBRIDOMA 455(100)	CHO 838(100%)
< 6.0 mg/kg	447	441	6
6.0 mg/kg	796	7	789
9.0 mg/kg	50	7	43
Total	1293	455	838

Infusion reactions were significantly more common with the CHO-derived product (Table 46).

Table 46. Monotherapy Dataset, Infusion Reactions (Any Infusion) by Cell Line

CELL LINE	N	SUBJECTS WITH A REACTION TO ANY PANIT. INFUSION N(%)
Hybridoma	455	78(17)
CHO	838	71(8)
Total	1293	149(12)
$X^2 = 21$, $p < .0001$; 2-Tail, Fisher's Exact		

To date, panitumumab administration has not resulted in any fatal potential infusion reaction.

Pulmonary Toxicity:

Pulmonary toxicity was defined according to CTCAE Version 3.0 category of pulmonary/upper respiratory and selected MedDRA version 8.0 preferred terms corresponding to these events. Subjects with evidence of pulmonary fibrosis or interstitial pneumonitis were excluded from study 20020408. Adverse events related to pulmonary toxicity were reported in 59 subjects (26%) in the panitumumab arm and in 46 subjects (20%) in the BSC arm. Pulmonary adverse events are listed in Table 47.

Table 47. Pulmonary AEs Identified in Study 20020408

	PANIT. PLUS BSC (N=229)	BSC ALONE (N=234)	BETWEEN ARM DIFFERENCE %	MCRC SAFETY DATABASE (N=920)
Any Pulmonary Toxicity	59(26)	46(20)	6	271(29)
Dyspnea	33(14)	31(13)	1	146(16)
Cough	31(14)	17(7)	7	127(14)
Pleural effusion	4(< 1)	1(< 1)	2	18(2)
Productive cough	1(< 1)	1(< 1)	0	18(2)
Pneumonia	1(< 1)	1(< 1)	0	8(1)
Respiratory failure	1(< 1)	1(< 1)	0	6(1)
Acute respiratory failure	1(< 1)	0(0)	0	3(< 1)
Pneumonia, atypical	1(< 1)	0(0)	0	1(< 1)
Pneumonia, bacterial	0(0)	1(< 1)	0	2(< 1)
Pulmonary edema	0(0)	1(< 1)	0	1(< 1)

The difference between treatment groups was primarily a result of the incidence of cough.

The incidence of pulmonary events in the mCRC Safety Database closely paralleled that in the pivotal trial.

Because of the interest in pulmonary fibrosis observed early in clinical trials of panitumumab as a potential class-associated toxicity and observed with both proteins and small molecules that affect EGFr signaling pathways, the larger safety database (All Treated Safety Database) which includes all panitumumab-treated subjects (mCRC and all other solid tumor types; monotherapy and panitumumab in combination with chemotherapy) was screened for adverse events which identified "pulmonary fibrosis" as the MedDRA preferred term. This search identified two cases:

Study 20025404; Subject4152 (Death Attributed to Pulmonary Fibrosis):

Subject with past medical history significant for hypertension and rheumatoid arthritis, and idiopathic pulmonary fibrosis (confirmed by open lung biopsy in 2002) and treated intermittently with steroids and imuran was diagnosed with metastatic (hepatic, adrenal glands pelvis and spine) NSCLC in August 2003 while undergoing evaluation for a lung transplant. The subject was subsequently enrolled in ABX-EGF study 20025404. At study baseline the subject's pulmonary fibrosis was reported to be stable. The subject received the first two weekly doses of ABX-EGF with cycle 1 chemotherapy (carboplatin and paclitaxel) and after the 3rd and 4th weekly doses of study drug, complained of increased shortness of breath. The 4th dose of ABX-EGF was administered on 14 October 2003 and the 5th dose was held because of a grade 2 skin rash. On — the subject reported worsening shortness of breath and he was unable to get out of bed. The subject was hospitalized and treated with intravenous steroids and antibiotics, bronchodilators, and oxygen. Chest CT scan results confirming worsening pulmonary fibrosis revealed pulmonary lesions and severe bilateral interstitial changes with thickening of the interlobular septa and diffuse ground glass opacities predominantly in the dependent lungs; no pulmonary embolism was seen. Comparatively, the baseline scan on 29 August 2003 showed patchy fibrotic changes present throughout both lungs and a scan on 19September 2003 showed patchy interstitial changes through both lungs with areas of partially calcified pleural thickening bilaterally, right greater than left. The subject remains hospitalized and the event remains ongoing. Study drug was discontinued. CT of the abdomen after 2 cycles of chemotherapy and 4 doses of ABX-EGF revealed an interval response to treatment with a decrease in size and count of suspected lesions in the liver. The Investigator reported the event of severe hypoxia as a worsening of the subjects underlying pulmonary fibrosis, and indicated that in his opinion, study drug probably contributed to the worsening because there is a documented, although rare, incidence of pulmonary fibrosis with other epidermal growth factor inhibitors. On 28 October-2003, the subject was withdrawn form study. On — , the subject died; cause of death is not provided. Other suspected causes of this event reported were the subject's underlying disease and concurrent illness.

Adverse Event – Pulmonary Fibrosis:

Study 20040116; Subject 351062 – (75-year-old white male with advanced renal cell carcinoma; 6.0mg/kg panitumumab Q2W, hybridoma-derived panitumumab), with a history that included a lung resection to remove metastases, experience mild pulmonary fibrosis considered possibly related to panitumumab 8 days after the 11th dose (4 doses were given in Study 20030138). After receiving the 12th dose of panitumumab, the subject withdrew from the study because of the pulmonary fibrosis graded as mild, which was ongoing at the time of withdrawal.

An additional pulmonary death was identified in the All Treated Safety Database. The etiology and drug-relatedness of this fatal adverse event is not clear. This event is described below:

Other Pulmonary Death, possibly drug related:

Study 20030167; Subject 121124006 – Subject with colon cancer and metastatis to the lungs developed a productive cough approximately 6 weeks post initiation of panitumumab and approximately 1 week after the last dose of study drug was hospitalized for hypoxia and pulmonary infiltrates (— A chest x-ray revealed diffuse bilateral pulmonary infiltrates, and suspect pulmonary nodules in the right lung including a possible 3 centimeter mass or nodule in the medial right lung base, oxygen saturation was 75% on room air from a baseline in the low 90's. Treatment with oxygen and levofloxacin was initiated. The study drug was withheld. The following day, oxygen saturation was 90% on oxygen at 4 liters/min; respiratory rate was 22/min. A prolonged INRE was noted (value not reported). Video swallow study revealed a paralyzed epiglottis with poor retroflexion of the epiglottis; however, there was no evidence of frank aspiration. Echocardiogram showed left ventricular ejection fraction of 50-55%. The subject was discharged 3 days after admission (— . The subject expired at home 4 days later on — — The death certificate listed the cause of death as sudden death, due to or as a consequence of pulmonary edema and diabetes mellitus. The investigator reported that there was a reasonable possibility that the hypoxia and pulmonary infiltrates may have been caused by study drug; he further reported the probably etiology as an infection, hemorrhage or toxicity from study drug. No autopsy was performed. The death certificate listed the cause of death as sudden death due to or as a consequence of pulmonary edema and diabetes mellitus with colon cancer listed as condition contributing to death but not related to the cause of death. The investigator reported that there was a reasonable possibility the pulmonary infiltrates may have been caused by study drug. He further reported that although the cause of death remains somewhat unclear', there was a reasonable possibility the sudden death may have been caused by study drug. CT scan of the chest revealed enlargement of multiple pulmonary nodules up to 2.8 x2.3 cm in size consistent with increasing metastatic disease, and a 3 cm metastatic lesion in the right hepatic lobe; bilateral pulmonary infiltrates or edema were noted, right greater than left. The investigator subsequently concluded that he did not know if the patient had pulmonary infiltrates or edema since these conditions were indistinguishable on CT scan and no autopsy was done; however, if there was edema, he concluded, it was non-cardiogenic in nature.

COMMENT: The two cases of pulmonary fibrosis and the fatal pulmonary event of unclear etiology are described in the WARNINGS: Pulmonary Fibrosis *section of the panitumumab label.*

Cardiac Toxicity:

Cardiac toxicity was defined according to CTCAE Version 3.0 categories of "cardiac arrhythmia" and "cardiac general" (excluding vascular and pulmonary events" consistent with other FDA labeled antibodies. MedDRA Version 8.0 preferred terms corresponding to these events were considered to be cardiac toxicity for purposes of analysis (Table 48).

Table 48. AEs Considered to be Associated with Cardiac Toxicity

Event	Source	Event	Source
acute myocardial infarction	CTCAE v 3.0	palpitations	CTCAE v 3.0
angina	CTCAE v 3.0	pericardial effusion	CTCAE v 3.0
arrhythmia	CTCAE v 3.0	pericarditis	CTCAE v 3.0
arterial flutter	CTCAE v 3.0	premature ventricular contraction	CTCAE v 3.0
artrioventricular heart block	CTCAE v 3.0	prolonged QTc interval	CTCAE v 3.0
atrial fibrillation	CTCAE v 3.0	restrictive cardiomyopathy	CTCAE v 3.0
bigeminy	CTCAE v 3.0	right ventricular dysfunction	CTCAE v 3.0
cardiac infarction	CTCAE v 3.0	shock	CTCAE v 3.0
cardiac ischemia	CTCAE v 3.0	sinus bradycardia	CTCAE v 3.0
cardiac left ventricular funtion decreased ejection fraction	CTCAE v 3.0	sinus tachycardia	CTCAE v 3.0
cardiac tamponade	CTCAE v 3.0	supraventricular tachycardia	CTCAE v 3.0
cardiac troponin I, increased G1-4	CTCAE v 3.0	suproventricular arrhythmias	CTCAE v 3.0
cardiac troponin T, increased G1-4	CTCAE v 3.0	syncope	CTCAE v 3.0
cardiopulmonary arrest	CTCAE v 3.0	trigeminy	CTCAE v 3.0
cardiovascular arrhythmia	CTCAE v 3.0	valvular heart disease	CTCAE v 3.0
conduction abnormality	CTCAE v 3.0	vasovagal episode	CTCAE v 3.0
congestive heart failure	CTCAE v 3.0	ventricular arrhythmia	CTCAE v 3.0
cor pulmonale	CTCAE v 3.0	ventricular tachycardia	CTCAE v 3.0
left ventricular diastolic dysfunction	CTCAE v 3.0	Wenckebach	CTCAE v 3.0
left ventricular systolic dysfunction	CTCAE v 3.0	orthostatic hypotension	CTCAE v 3.0
myocarditis	CTCAE v 3.0	heart murmur (s3 gallop)	trastuzumab label
nodal syncope	CTCAE v 3.0	reduced ejection fraction	trastuzumab product information
nodal/junction arrhythmia/dysrhythmia	CTCAE v 3.0	left ventricular dysfunction	bevacizumab label
non-specific T wave changes	CTCAE v 3.0		
hypotension	CTCAE v 3.0		

NOTE: G1-4 = increased between grades 1 and 4 in severity.

Cardiac events were uncommon in both the panitumumab and BSC arm. None were considered treatment related by the investigators. Two deaths occurred in the panitumumab arm including 1 event of cardio-respiratory arrest (subject 111105018_ and severe pericarditis and supraventricular tachycardia (subject 111212002). The first subject subsequently died and is discussed in section 7.1.1. Neither event was associated with altered magnesium or calcium level. One severe event of supraventricular arrhythmia (111405005) occurred in the BSC arm.

Based upon the observation of myocardial degeneration in a 1-month primate toxicology study and the cardiac toxicity observed with Herceptin, an antibody that inhibits a receptor (HER2) closely related to EGFr, all subjects enrolled into early panitumumab studies (20030138, 20040116, 20030110, 20025404 and the initial portions of studies 20025405, 20025409, 20020374, 20020375 and 20030167) were monitored for cardiac toxicity. Monitoring included MUGA scans measuring left ventricular ejection fraction (LVEF), and assessment of cardiac enzymes, troponin T and cPK-MB at specified time points before and after dosing. Cardiac monitoring results are available on 331 panitumumab-treated subjects who met defined protocol eligibility criteria: normal LVEF < 45% and no history of myocardial infarction in the year preceding enrollment. The analysis of cardiac monitoring on subjects with normal baseline cardiac function indicated no change in LVEF or cardiac enzymes with panitumumab therapy. These findings were interpreted to indicate lack of evidence of cardiac toxicity associated with panitumumab and the cardiac monitoring in subsequent studies was not required.

Only one of the 14 subjects with serious cardiac events did not have a reported prior history of cardiac disease or risk factors for CAD (diabetes, hypertension, etc.) (Table 49). For this subject, the events were not considered related to study drug. No subject in the mCRC Monotherapy Set had a cardiac adverse event of grade 3 or higher. Only three subjects (0.4%) had an adverse event of congestive cardiac failure; none of these were considered treatment related.

Table 49. Serious Cardiac AEs, mCRC Safety Database

Subject No.	Study ID.	Preferred Term	Age (Yrs)	Other Cardiovascular History/Risk Factors
5131	20025405	Cardiac arrest	76	Hypertension, hyperlipidemia, peripheral vascular disease, diabetes mellitus
111101032	20020408	Tachycardia	79	Hypertension
111002008[a]	**20020408**	**Cardiomyopathy**	**66**	**Hypertension, cor hypertonicum, cardiac decompensation, left bundle branch block**
111105018	20020408	Cardiorespiratory arrest	50	Hypertension
111212002	20020408	Pericarditis Supraventricular tachycardia	52	Tachycardia, atrial fibrillation
121128002	20030167	Atrial fibrillation Cardiac failure congestive	63	Coronary artery disease, atrial fibrillation, cardiac congestive failure, hypertension, diabetes mellitus, hyperlipidemia
131105007	20030194	Atrial fibrillation	66	Atrial fibrillation, hypertension, hyperlipidemia
131401059	20030194	Blood pressure decreased Syncope	43	None
131405001	20030194	Atrial fibrillation	72	Atrial fibrillation, hypertension, ischemic cardiomyopathy
135001010	20030194	Angina pectoris	55	Thrombophlebitis
140012003	20030250	Myocardial infarction	76	Diabetes mellitus, hyperlipidemia, hypertension, recent deep vein thrombosis, supraventricular tachycardia
141156001	**20030250**	**Myocardial infarction**	**64**	**Hypertension, diabetes mellitus**
141160001	20030250	Unstable angina	74	Angina pectoris, coronary artery disease, coronary stent, diabetes mellitus, hypertension, renal failure
141167001	20030250	Acute myocardial infarction	53	Hypertension, embolism

*History of tachycardia and atrial fibrillation; on treatment with flecainide
**History of angina pectoris

COMMENT: Based on this review, there does not appear to be a strong association between panitumumab monotherapy and cardiovascular toxicity.

Diarrhea:

In study 20020408, diarrhea was more common in the panitumumab arm (21%) than in the BSC arm (11%). One subject (111103022) in the panitumumab arm also had infectious diarrhea. Diarrhea was considered treatment related in 19(8%) subjects. Four subjects (all in the panitumumab arm) had diarrhea or infectious diarrhea that was graded as severe. No subject discontinued panitumumab due to diarrhea or infectious diarrhea.

In the mCRC Monotherapy set, diarrhea occurred in 244(27%) subjects. Only 1 subject had a serious adverse event of diarrhea that was considered treatment-related. No subject discontinued treatment or withdrew from study because of diarrhea.

Of note, in the one study (20025409) in which panitumumab was given in combination with irinotecan, bolus 5-fluorouracil, and leucovorin (IFL), the incidence of NCI-CTC grade 3-4 diarrhea was 58% and was fatal in 1 patient. In a study of 24 patients receiving panitumumab plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhea was 25%.

COMMENT: The increased risk of diarrhea when used in combination with irinotecan is described in the WARNINGS: Diarrhea *section of the panitumumab label.*

7.1.4 Other Search Strategies

A safety review was done comparing the safety profile of those subjects treated with the — CHO-derived product and the to-be-marketed — CHO product. While the number of subjects treated with the product is limited (69 patients), this product was shown to be pharmacologically comparable to the — CHO-derived product. There did not appear to be differences in the safety profile of the two products with respect to the overall number of adverse events, the number of serious adverse events or skin toxicities.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Key variables were coded using composite of MedDRA Version 8.0 terms. These were selected to be consistent with those used with other approved monoclonal antibodies.

These are shown in Table 50 below:

Table 50. Definition of Composite AEs of Interest

ADVERSE EVENT	DEFINITION/MEDDRA PREFERRED TERMS
Acneiform Rash	acneiform rash, acne, maculopapular rash, pustular rash, rash, exfoliative dermatitis, and dry skin.
Infusion Reaction (First Infusion)	allergic reaction, anaphylactoid reaction, grade 3 or 4 chills per NCI CTC Version 2.0, fever, or dyspnea, occurring within 24 hours of the first panitumumab dose that were not otherwise designated as either anaphylactoid or allergic reaction.
Infusion Reaction (Any Infusion)	any reported Infusion reaction defined using 40 prespecified terms indicating any signs and symptoms of a potential infusion reaction defined per CTCAE Version 3.0 definition of "allergic reaction/hypersensitivity" and "cytokine release
Hypomagnesemia (laboratory)	As defined in CTCAE Version 3.0
Hypomagnesemia (Adverse Event)	As defined as any treatment-emergent adverse event of low magnesium, decreased magnesium, or hypomagnesemia using the MedDRA Version 8.0 preferred terms corresponding to these events
Cardiac	Defined according to CTCAE Version 3.0 categories of "cardiac arrhythmia" and "cardiac general" (excluding vascular and pulmonary events" and according to selected MedDRA version 8.0 preferred terms corresponding to these events.
Pulmonary	Defined according to CTCAE Version 3.0 category of pulmonary/upper respiratory and selected MedDRA version 8.0 preferred terms corresponding to these events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The definitions of the above predefined composite variables was discussed with the FDA during the Type C meeting held with the Applicant on May 24, 2005 and were deemed to be appropriate.

7.1.5.3 Incidence of common adverse events

Study 20020408:

The incidence of adverse events, regardless of relationship to study treatment which occurred in ≥ 10% of subjects with a between group difference of ≥ 5% is shown in Table 51 below. Adverse events which occurred in ≥ 10% of subjects with a between group difference of ≥ 5% are shown in Tables 52 and 53. The most common adverse events were integument/eye toxicity which occurred in 90% of subjects treated on the panitumumab arm as well as paronychia. Fatigue, abdominal pain, nausea, vomiting and diarrhea were also more common in the panitumumab arm as were dry skin, other nail disorders, stomatitis and mucosal inflammation.

7.1.5.4 Common adverse event tables

Table 51. I/E AEs ≥ 10%- Between Group Difference ≥ 10%

ADVERSE EVENT	PAN. PLUS BSC 229(100%)	BSC ALONE 234(100%)	DIFFERENCE %
All integument and eye	209(90)	21(9)	81
Erythema	148(65)	2(1)	64
Acneiform dermatitis	131(57)	2(1)	56
Pruritus	131(57)	5(2)	55
Skin exfoliation	57(25)	0	25
Paronychia	56(25)	0	25
Rash	50(22)	2(1)	20
Skin fissures	45(20)	1(< 1)	19
Fatigue	59(26)	34(15)	15
All eye toxicity	34(15)	5(2)	13
Acne	29(13)	0	13
Constipation	48(21)	21(9)	10
Diarrhea	84(21)	26(11)	10

Table 52. AE ≥ 10% - Between Group Difference 5-9%

ADVERSE EVENT	PAN. PLUS BSC 229(100%)	BSC ALONE 234(100%)	DIFFERENCE %
Abdominal Pain	57(25)	39(17)	8
Nausea	53(23)	37(16)	7
General deterioration	25(11)	9(4)	7
Vomiting	43(19)	28(12)	7
Cough	31(14)	17(7)	6
Peripheral edema	27(12)	13(6)	6
Dry Skin	22(10)	0	10

Table 53. Other Non-I/E AEs > 5% - Between Group Difference 5-9%

ADVERSE EVENT	PAN. PLUS BSC 229(100%)	BSC ALONE 234(100%)	DIFFERENCE
Nail disorder	20(9)	0	9
Stomatitis	16(7)	2(1)	6
Growth of eyelashes	14(6)	0	6
Mucosal inflammation	14(6)	2(1)	5

Adverse events occurring with a frequency of 5% or higher in the mCRC Safety Database are listed in Table 54 below:

Table 54. mCRC Safety Database – AEs ≥ 5%

ADVERSE EVENT	N=920	%
DERMATITIS ACNEIFORM	487	52.93
ERYTHEMA	484	53
PRURITUS	481	52
RASH	337	37
FATIGUE	316	34
NAUSEA	276	30
DIARRHOEA	245	27
SKIN EXFOLIATION	225	24
ANOREXIA	205	22
ABDOMINAL PAIN	200	22
VOMITING	199	22
CONSTIPATION	186	20
PARONYCHIA	186	20
DRY SKIN	152	17
DYSPNOEA	150	16
SKIN FISSURES	145	16
PYREXIA	132	14
COUGH	128	14
OEDEMA PERIPHERAL	115	13
BACK PAIN	111	12
ASTHENIA	104	11
STOMATITIS	86	9
INSOMNIA	76	8
WEIGHT DECREASED	71	8
ANXIETY	70	8
ABDOMINAL PAIN UPPER	67	7
COLORECTAL CANCER	63	7
HEADACHE	61	7
NAIL DISORDER	61	7
ACNE	60	7
RASH PUSTULAR	60	7
ARTHRALGIA	59	6
PAIN IN EXTREMITY	57	6
HYPOMAGNESAEMIA	55	6
COLORECTAL CANCER METASTATIC	53	6
DEPRESSION	53	6
ANAEMIA	52	6
CONJUNCTIVITIS	47	5
DEHYDRATION	47	5
DYSPEPSIA	47	5
CHILLS	46	5

COMMENT: The adverse event profile of panitumumab monotherapy administered to patients with mCRC in the pivotal trial did not reveal any unexpected findings from what was observed with the related approved pharmacologically related agents in this class (See Section 2.4 and the current Erbitux™ US Package Insert. The frequencies of common adverse events found in the mCRC Safety Database were consistent with those found in the pivotal trial.

7.1.5.5 Identifying common and drug-related adverse events

Serious adverse events occurring in study 20020408 are shown in Table 55. Of the 10 serious adverse events occurring on the panitumumab arm, only hypersensitivity was considered to be panitumumab-related by the investigator. Infusion reaction/hypersensity and acneiform dermatitis are well defined toxicities associated with cetuximab therapy and likely to be class-associated toxicities. Serious adverse events occurring on the BSC arm are included for comparison.

Table 55. Study 20020408: Serious AEs

PANITUMUMAB PLUS BSC					
Subject	Sex/Age	Infusions	Adverse Event	Related	Serious
111001002	M/69	1	Hypersensitivity	Yes	Yes
111102011	M/65	2	Intestinal obstruction	No	Yes
111102028	F/57	1	General deterioration	No	Yes
111103044	M/55	9	Coma	No	Yes
111103082	F/67	2	Depressed consciousness	No	Yes
111104005	F/51	15	Renal Failure	No	Yes
111104015	M/64	6	General deterioration	No	Yes
111107007	M/63	4	Lung infection	No	Yes
111107015	M/49	3	Pelvic Mass	No	Yes
111405003	M/63	2	DVT/PE	No	Yes

BSC ALONE				
Subject	Sex/Age	Adverse Event	Related	Serious
111103028	M/64	Vomiting	No	Yes
111405005	M/60	Supraventricular Arrhythmia	No	Yes
		Septic Shock	No	Yes
		Wound infection	No	Yes
111408016	F/71	General deterioration	No	Yes
111412002	M/58	Jaundice	No	Yes
113005002	M/61	Spinal cord compression	No	Yes

7.1.5.6 Additional analyses and explorations

No additional analysis or explorations were done.

7.1.6 Less Common Adverse Events

No unexpected or unusual less common adverse events were identified, except as noted above.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Since all subjects entered into the panitumumab mCRC studies had metastatic disease and had failed prior treatment with fluoropyrimidine, irinotecan and/or oxaliplatin for metastatic colorectal cancer at study entry, a number of these subjects would be expected to have altered baseline blood/bone marrow and hepatic function. The eligibility criteria for the mCRC monotherapy studies stipulated that the levels for absolute neutrophil counts and platelet counts were to be within normal limits or no more than grade 1 (NCICTCAE Version 2.0). Additionally, it was specified that aspartate aminotransferease (AST) and alanine aminotransferease (ALT) level could be no greater than 3 x the upper limits of normal (ULN) or no more than 5 x ULN if the subject had liver involvement. Bilirubin could be no more than 2 x ULN and creatinine could be no more than 2.0 mg/dL. There were no other restrictions for metabolic or laboratory dysfunction.

Laboratory assessments of serum chemistries, including magnesium and calcium levels, complete blood counts, and urinalysis, were collected at protocol-specified time points in each of the studies. The investigators were instructed to report clinically significant laboratory abnormalities (defined as those needed alterations in medical care) as adverse events. These were graded according to the CTCAE Version 2.0. Anti-panitumumab antibodies were also measured at regular intervals (please refer to 6.1.3.1 for details of the study monitoring plan for 20020408).

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

Drug-control comparisons were limited to evaluation of differences between the panitumumab and BSC arms of the pivotal trial, 20020408.

7.1.7.3 Standard analyses and explorations of laboratory data

The incidence of Grade 3 or 4 laboratory values in study 20020408 were analyzed. Severity was graded according to the NCICTCAE Version 2.0.

Table 56. Grade 3 or 4 Laboratory Abnormalities

LABORATORY TEST	PANIT. PLUS BSC N=229		BSC 234	
	N	%	N	%
Anemia	4	3	1	0
Total Neutrophils	1	0	0	0
Neutropenia (ANC)	1	0	0	0
Lymphocytopenia	13	6	12	5
Alk. Phosphatase	15	7	14	6
AST	10	4	3	1
ALT	6	3	4	2
Bilirubin	13	5	8	3
Low albumin	1	0	0	0
Low Magnesium	8	4	0	0
High Potassium	4	1	3	1
Low Potassium	4	2	2	1
Low Sodium	9	4	5	2
Low Calcium	2	1	0	0
Low Phosphorus	9	4	2	1

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The incidence of hematological, chemistry and electrolyte abnormalities were similar in both treatment groups (results not shown). Overall the incidence of grade 3 or 4 laboratory

toxicities was low, except for lymphocytopenia, alk. phasphatase, and bilirubinemia. Except for magnesium levels (Section 7.1.7.4), no consistent differences were observed.

7.1.7.4 Additional analyses and explorations

Because of the known occurrence of hypomagnesemia with the other pharmacologically-related agent in this class, particular attention was focused on alterations in magnesium, calcium and potassium levels, both in the pivotal trial and in a subset of subjects enrolled in studies in which routine monitoring for magnesium was done (Hypomagnesemia Analysis Set). These studies enrolled a total of 812 subjects evaluable for toxicity.

Table 57. Studies with Routine Monitoring of Serum Magnesium

STUDY	N
20020408	229
20030167	148
20030194	176
20030250	157
20030251	84
20040192	18
Total	812

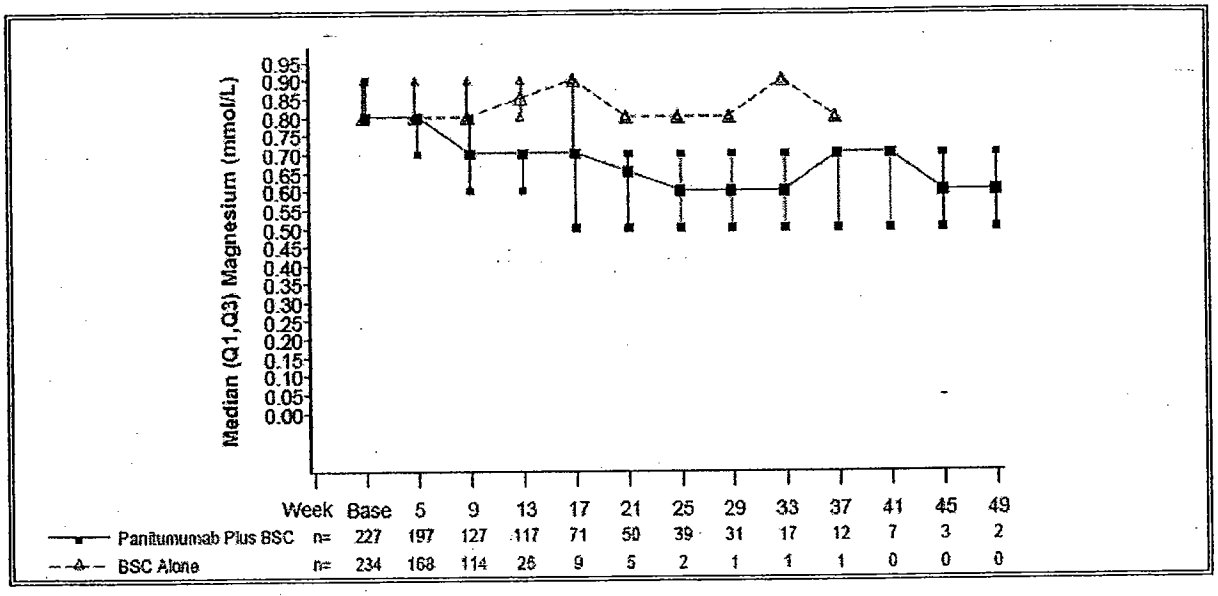
In study 20020408, 38% of subjects in the panitumumab arm and 2% of subjects in the BSC arm experienced hypomagnesemia. Three percent of subjects in the panitumumab arm and no subjects in the BSC arm experienced Grade 3 or 4 hypomagnesemia.

Table 58. Study 20020408, Hypomagnesemia by CTCAE Toxicity Grade

TOXICITY GRADE (NCICTCAE V. 2.0)	PANIT. PLUS BSC N=229(%)	BSC ALONE N=234(%)
1 (LLN to 0.5 mmol/L)	70(31)	5(2)
2 (<0.5 to 0.4 mmol/L)	9(4)	0
3 (<0.4 to 0.3 mmol/L)	6(3)	0
4 (<0..3 mmol/L)	2(1)	0

The median magnesium levels by arm over time (as provided by the Sponsor) are shown in Figure 5 below:

Figure 5. Study 20020408, Median Magnesium Levels (mmol/L) Over Time



\\cbsap58\m\eCTD_Submissions\STN125147\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\colorectal-cancer\5351-stud-rep-contr\20020408 , page 246

Two subjects in the panitumumab arm had grade 4 hypocalcemia; both had concurrent hypomagnesemia (grade 1). No subject in the BSC arm had grade 3 or 4 hypocalcemia. Nine subjects (4%) in the panitumumab plus BSC arm and 2 subjects (1%) in the BSC alone arm had grade 3 hypophosphatemia.

The Applicant reviewed the incidence of hypomagnesemia in the Hypomagnesemia Analysis Set (See \\cbsap58\m\eCTD_Submissions\STN125147\0015\m2\27-clin-sum, section 2.1.5.5.1, pages 135 – 147). Based on the analysis of 812 subjects monitored for changes in magnesium levels, the overall incidence of hypomagnesemia adverse events (defined as any treatment-emergent adverse event of low magnesium, decreased magnesium, or hypomagnesemia using the MedDRA Version 8.0 preferred terms corresponding to these events) was 8%. Nineteen subjects (29%) had a worst grade of hypomagnesemia of severe; 5 received IV magnesium treatment.

No subject discontinued treatment due to hypomagnesemia.

7.1.7.5 Special assessments

No other special assessments were conducted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs assessed in the clinical studies included systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Height and weight were assessed at baseline, and weight was recorded prior to each infusion.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs were consistently measured for the following studies: 20020408, 20030194, 20030250 and 20030167. Data from the controlled trial will be considered in this review.

7.1.8.3 Standard analyses and explorations of vital signs data

The incidence of treatment-emergent, clinically meaningful changes in vital signs was assessed. Clinically meaningful changes were defined as:

- Temperature: Any post-infusion value $\geq 38^{\circ}C$
- Blood pressure (systolic/diastolic), heart rate, respiration rate: Any pre- to post-infusion increase or decrease $\geq 30\%$ in magnitude

Any vital sign scheduled to be taken within 30 minutes prior to the start of a panitumumab infusion was considered a "pre-infusion vital sign measurement. Any vital sign value taken during or after a panitumumab infusion and on the same day as a panitumumab infusion is considered a post-infusion vital sign measurement. However, vital signs were routinely measured at screening, just prior to the start of each infusion, during infusion and at the end (or within 30 minutes following) infusion.

In study 20020408, vital sign adverse events were similar in both study arms.

Table 59. Study 20020408, % Reporting Vital Signs AEs during Study by Study Arm

VITAL SIGN AE	PANIT. PLUS BSC (N=229)	BSC ALONE (N=234)
Pyrexia	14	13
Hypertension	3	0
Tachycardia	2	1
Any Serious VS AE	1	3

7.1.9 Electrocardiograms (ECGs)

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7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Early in development, due to the known association of Herceptin, an antibody that inhibits HER2, a receptor closely related to EGFr, with cardiotoxicity, ECG and echocardiograms were routinely performed at baseline and prior to each cycle. This data was reviewed at the transition from the hybridoma- to the CHO- derived product. The assessment was made that the and CHO-derived product were comparable in terms of cardiotoxicity and that neither product was associated with cardiotoxicity. In study 20020408, cardiac monitoring was limited to the baseline screening and was repeated as clinically indicated.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

This is to be done in the post-marketing setting. See Section 1.2.2.

7.1.9.3 Standard analyses and explorations of ECG data

See Section 7.1.9.2.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.10 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of panitumumab has been evaluated using two different screening

immunoassays for the detection of anti-panitumumab antibodies; an acid dissociation bridging enzyme linked immunosorbent assay (ELISA) (detecting high-affinity antibodies) and Biacore® biosensor immunoassay (detecting both high and low-affinity antibodies).

The incidence of binding antibodies to panitumumab (excluding predose and transient positive patients) as detected by acid dissociation ELISA was 2/612 (< 1%) and as detected by the Biacore® assay was 25/610 (4.1%).

For patients whose sera tested positive in screening immunoassays, an in vitro biological assay was performed to detect neutralizing antibodies. Excluding predose and transient positive patients, eight of the 604 patients (1.3%) with postdose samples and 1/350 (< 1%) of the patients with follow-up samples tested positive for neutralizing antibodies.

There was no evidence of altered pharmacokinetic profile or toxicity profile between patients who developed antibodies to panitumumab as detected by screening immunoassays and those who did not.

7.1.11 Human Carcinogenicity

No carcinogenicity studies were required. Such studies are not informative for protein products. In addition, such studies are typically not required for drugs intended to treat patients with advanced cancer.

7.1.12 Special Safety Studies

None additional special safety studies were required.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Panitumuamb has no expected risk of abuse or withdrawal phenomena.

7.1.14 Human Reproduction and Pregnancy Data

There are no studies of panitumumab in pregnant or lactating women. Such studies are not typically required for drugs intended to treat patients with advanced cancer.

7.1.15 Assessment of Effect on Growth

There is no information on the use of this drug in children. The indication supported by this application occurs almost exclusively in adults. Future phase one and two studies of panitumumab in pediatric solid tumors will incorporate assessments of the effect of panitumumab on growth.

7.1.16 Overdose Experience

The highest per-infusion dose administered in clinical studies was 9 mg/kg administered every 3 weeks. There is no experience with overdosage in human clinical trials

7.1.17 Postmarketing Experience

This is the original application for this drug and therefore there is no post-marketing experience.

7.2 Adequacy of Patient Exposure and Safety Assessments

The number of patients exposed to panitumumab, the extent of exposure and the safety assessments were adequate to evaluate the safety of Vectibix™

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

A description of the studies submitted in support of the application is included in Section 10.1.1, Overview of the clinical studies.

7.2.1.1 Study type and design/patient enumeration

Refer to section 4, Sources of Clinical Data and Section 6, Review of Trials by indication, Study Design and Results.

7.2.1.2 Demographics

Refer to section 4, Sources of Clinical Data and section 6, Review of Trials by Indication, Study Design and Results.

7.2.1.3 Extent of exposure (dose/duration)

In study 20020408, the median weight-adjusted cumulative dose was 26.1 mg/kg. The median number of infusions per patient was 5. The distribution of infusions per patient is described in Table 61 below:

Table 60. Drug Exposure on study 20020408

	N = 229
Median duration of therapy (range)	56 days (1, 421)
Median number of infusions/patient (range) $\leqslant 4$ 5 – 8 9 – 12 13 – 16 $\geqslant 16$	5 infusions (1, 26) 50 22 13 11 4
Median weight-adjusted cumulative dose (range)	26.1 mg/kg (0.19 – 151.34)
Median average weight-adjusted dose delivered (range)	6.0 mg/kg (0.19 -6.56)

The exposure on studies other than the pivotal trial was similar; subjects received panitumumab from at doses of 2.5 mg/kg/week, 6.0 mg/kg every two weeks, and 9.0 mg/kg every 3 weeks.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary clinical data sources used to evaluate safety.

7.2.2.1 Other studies

Not applicable, since there are no other studies beyond those described in the primary source of safety data, the biologic license application itself.

7.2.2.2 Postmarketing experience

There is no post marketing experience with panitumumab.

7.2.2.3 Literature

See Section 7.2.2.2.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience with panitumumab in clinical development is adequate to allow a decision on licensing/approval for marketing. Data on the — product which was felt to be pharmacologically equivalent to the — product is limited. There is currently no data to suggest that the safety profile of the — product differs from that of the — product used in the pivotal study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The development program of panitumumab was appropriate to evaluate the toxicity of panitumumab in the target population. Additional non-clinical data is needed concerning the likely toxicity in children.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing planned and conducted in the clinical studies supporting the application was adequate to comprehensively evaluate the safety of panitumumab.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No formal drug-drug interactions studies were conducted in the development of

panitumumab. This product is a biologic, which does not undergo metabolism and excretion in the same ways as small molecules do.

No apparent drug-drug interaction was observed when panitumumab was administered concomitantly with antibiotics or analgesic medications. Although the variety of antibiotics and analgesics used precludes a more robust analysis of any potential interactions.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Formal drug-drug interaction studies should be conducted with irinotecan/other antineoplastics that may be routinely combined with panitumumab.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data for review of safety was adequate. Please refer to previous comments made in this section 7.2.

7.2.9 Additional Submissions, Including Safety Update

All data related to the safety of panitumumab are contained within this application. Amgen submitted the 120-Day Safety Update on August 1, 2006. The incremental data, including AEs, SAEs, additional clinical, laboratory and immunogenicity from all studies ongoing at the time of BLA submission have been included in the safety analysis.

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

7.3.1 Infusion Reactions:

In the randomized, controlled clinical trial of Vectibix™ monotherapy, 4% of patients experienced infusion reactions and in 1% reactions were severe (NCI CTC Grade 3-4). Across all clinical studies, the incidence of infusion reaction was 1%, approximately half of which were graded as severe.

Comment: Although fatal infusion reactions were not reported with Vectibix™, there is insufficient data to conclude that the rate or severity of infusion reactions with Vectibix™

differs substantially from other agents in the class. Likewise, there is insufficient data to estimate the risk of infusion reactions with Vectibix™ in individuals who have experienced a severe infusion reaction when treated with cetuximab.

7.3.2 Immunogenicity:

The immunogenicity of panitumumab has been evaluated using two different screening immunoassays for the detection of anti-panitumumab antibodies; an acid dissociation bridging enzyme linked immunosorbent assay (ELISA) (detecting high-affinity antibodies) and Biacore® biosensor immunoassay (detecting both high and low-affinity antibodies). The incidence of binding antibodies to panitumumab as detected by acid dissociation ELISA was <1% (2/612) and as detected by the Biacore assay was 4.1% (25/610).

COMMENTS: Immunogenicity testing has not extensively been done with the to-be-marketed product and is a Phase 4 commitment.

7.3.3 Hypomagnesemia:

In the randomized, controlled, clinical trial, of Vectibix™ monotherapy, median magnesium levels decreased by 0.1mmol/L in the panitumumab arm; hypomagnesemia requiring oral or intravenous electrolyte repletion (NCI-CTC Grade 3 or 4) occurred in 2% of patients. Hypomagnesemia occurred 6 weeks or longer after the initiation of panitumumab. In some patients hypomagnesemia was associated with hypocalcemia.

COMMENT: Hypomagnesemia appears to be a toxicity associated with agents of this class. The Vectibix™ includes a warning that patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of panitumumab therapy.

7.3.4 Dermatologic Toxicity:

Dermatologic toxicities, including but not limited to dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures, were reported in 88% of patients and were severe (NCI-CTC grade 3 and higher) in 11% of patients receiving Vectibix™ monotherapy. Severe dermatologic toxicities were complicated by infection including sepsis, septic death, and abscesses requiring incisions and drainage.

COMMENT: Because protocols for the prophylaxis and treatment of dermatologic toxicities were not standardized in clinical development, the optimal approach to the prevention and management of dermatologic toxicities has not been determined. The following warning for dermatologic toxicity has been included into the Vectibix™ PI: "Withhold or discontinue Vectibix and monitor for inflammatory or infectious sequelae in

patients with severe dermatologic toxicities". Protocols for assessment of the management of dermatologic toxicities are Phase 4 commitments.

7.3.5 Pulmonary:

Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix™. Of these two cases, one occurring in a patient with underlying idiopathic pulmonary fibrosis who received panitumumab in combination with chemotherapy resulted in death from worsening pulmonary fibrosis after 4 doses of panitumumab. The second case was characterized by dyspnea within 8 days following the initial dose, persistent symptoms and CT evidence of pulmonary fibrosis following the 11th dose of panitumumab as monotherapy. An additional patient died with bilateral pulmonary infiltrates with hypoxia, after X doses of Vectibix™.

COMMENT: Patients with a history of interstitial pneumonitis, pulmonary fibrosis, evidence of interstitial pneumonitis, or pulmonary fibrosis were excluded from most clinical studies of Vectibix™. Therefore, the estimated risk in a general population which may include such patients is uncertain. The Vectibix™ PI includes the warning that Vectibix™ therapy should be discontinued in patients developing interstitial lung disease, pneumonitis, or lung infiltrates.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Data from the pivotal trial, 20020408, was used to assess the relative frequency of adverse events based on the occurrence of events in the comparator arm. This approach was limited due to the early cross-over of subjects initially randomized to the BSC arm at the time of clinical or radiologic disease progression to receive panitumumab on the open label trial, 20030194.

To confirm observations made in the pivotal trial and to explore for the incidence of rare adverse events, data across the following subgroups was pooled:

- Subjects with mCRC receiving panitumumab monotherapy (mCRC Monotherapy Set; n=789).
- Subjects receiving panitumumab in combination with other chemotherapy regimens (All Combination Therapy Set; n=174)

- Subjects from studies with defined interval assessments of serum magnesium levels (Hypomagnesemia Subset; n = 812)

The studies included in these data subgroups are delineated in Section 10.1.

The incidence of deaths, serious adverse events, events leading to termination of panitumumab administration, as well as other adverse events were similar across all pooled subsets (See Sections 7.1.1, 7.1.2; Tables 33, 46, and 54)

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7.4.1.2 Combining data

The numerator events and denominators for the selected studies were combined. No formal weighting methods were used.

7.4.2 Explorations for Predictive Factors

No predictive factors for treatment adverse events due to age, sex, or race were identified in this analysis.

7.4.2.1 Explorations for dose dependency for adverse findings

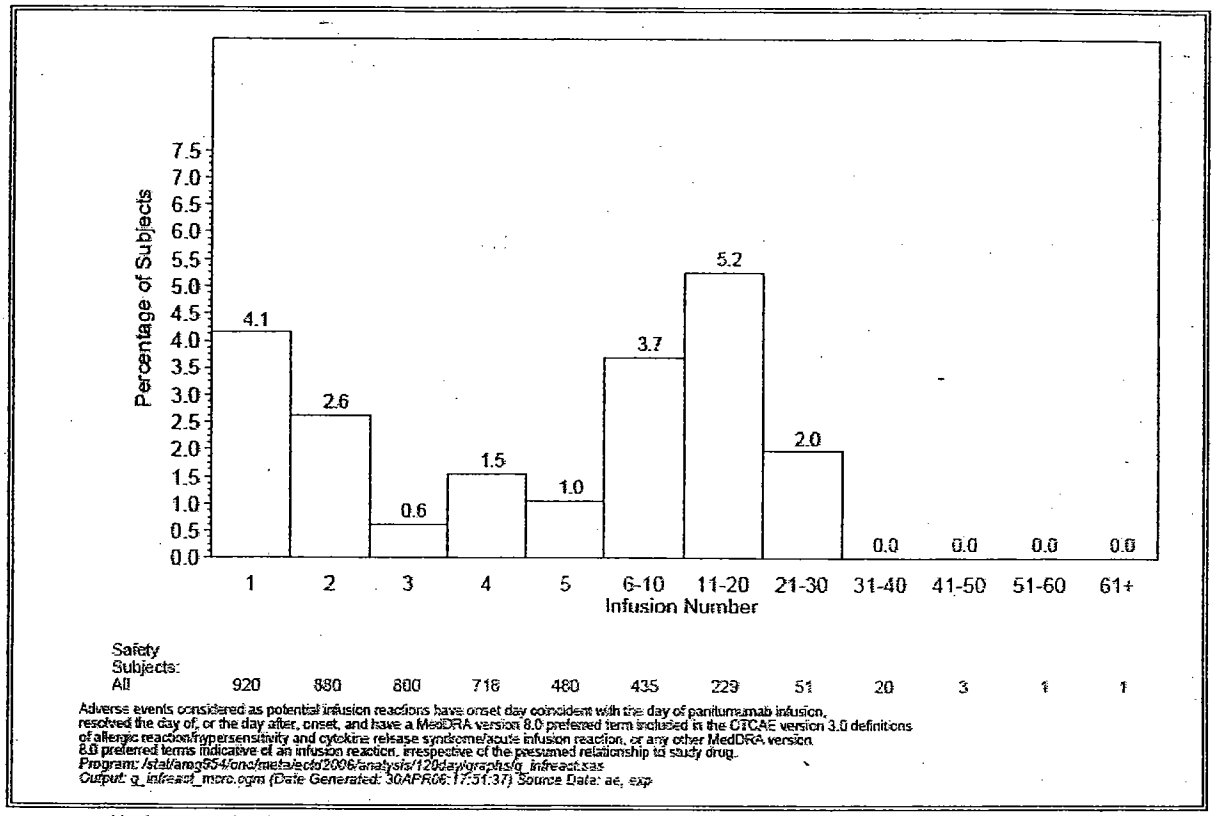
It is of note that the no DLT was determined in the dose-escalation trials which ranged from 0.25 mg/kg/week to 9.0 mg/kg every 3 weeks. The recommended dosing was based on non-clinical assessments of EGFr-receptor saturation.

7.4.2.2 Explorations for time dependency for adverse findings

Infusion Reactions:

The incidence of infusion reactions using the CTCAE defined criteria for infusions occurring with any panitumumab infusion occurring in the Monotherapy Subset are shown in Figure 6 below (provided by the Sponsor).

Figure 6. mCRC Dataset, % with Infusion Reactions by Infusion Number



COMMENT: While the rate of infusions was highest with the initial infusion, reactions were observed after prolonged panitumumab therapy. Only 2 reactions resulted in termination of study drug; one of which occurred with the first dose, the second on the 49th dose.

Integument/Eye Toxicity:

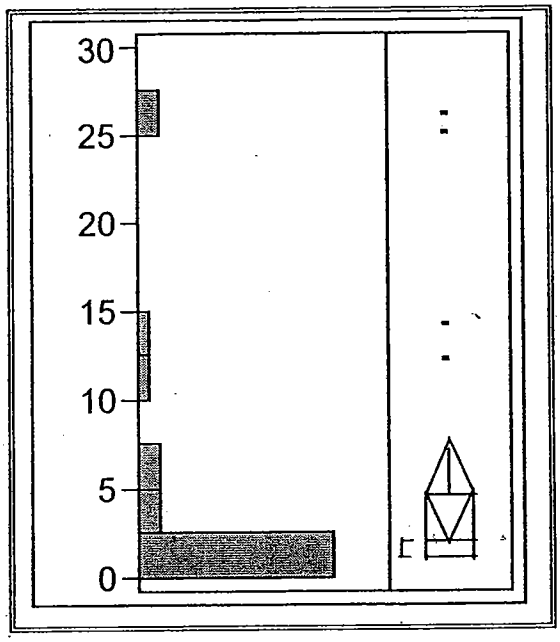
Because of the uniformity of skin toxicity assessment in the pivotal trial and the high incidence of this adverse event, exploration for time dependency in the development of Grade 3 or 4 integument/eye toxicities was conducted. Grade 3 and 4 toxicities appeared early in the course of panitumumab therapy with most patients developing grade 3 or 4 integument/eye toxicity with the first dose. The median time to first grade 3 or 4 integument/eye toxicity was 6 days (95% CI: 5,7) while the median time to first toxicity of any grade was 10 days (95% CI: 9,11). However, since both the cumulative weight adjusted dose and the duration of exposure were higher among those subjects developing grade 3 or 4 toxicity, this would appear to suggest a dose response relationship among those subjects not developing early integument/eye toxicity (Table 62).

Table 61. Study 20020408, Dose and Duration of Treatment and I/E Toxicity

	GRADE 3 OR 4 INTEGUMENT/EYE TOXICITY (N=229)		
		Y(N=30)	N(N=199)
Cum. Weight-Adj. Dose (mg/kg)	Mean (95% CI)	62.9(50,76)	42(37,47)*
Duration of exposure (days)	Mean (95% CI)	154(121,187)	90(77,103)*
*test for difference in means p< 0.01			

Figure 7 below shows the first onset of Grade 3 or 4 toxicities by number of panitumumab infusions in study 20020408.

Figure 7. 20020408, Onset of Grade 3 or 4 I/E Toxicity by Infusion Number



COMMENT: Most subjects treated on study 20020408 progressed within a relatively short time period. The apparent association between weight-adjusted dose and duration of therapy may suggest that skin toxicity may increase with protracted panitumumab therapy and should be carefully monitored in trials of earlier stage disease.

7.4.2.3 Explorations for drug-demographic interactions

Adverse events were analyzed by age, sex, and race. There were no obvious drug-demographic interactions.

7.4.2.4 Explorations for drug-disease interactions

No drug-disease interactions were noted in the review of safety of panitumumab.

7.4.2.5 Explorations for drug-drug interactions

See discussions above, under Section 7.2.6.

7.4.3 Causality Determination

Skin toxicity, infusion reactions and hypomagnesemia are causally related to panitumumab and appear to be a class effect.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dose of panitumumab is 6 mg/kg administered over 60 minutes as an intravenous infusion every 14 days. Doses higher than 1000 mg should be administered over 90 minutes.

Data presented do not support the safety or efficacy of —

8.2 Drug-Drug Interactions

There were no formal drug-drug interactions studies performed. Please refer to Sections 1.3.5 and 7.2.6 for the reviewer's comments.

8.3 Special Populations

Clinical studies done to support the panitumumab application include studies of adult patients with solid tumors, predominantly mCRC. Within this population, pharmacokinetic analysis was performed to explore the potential effects of selected covariates on Vectibix™ pharmacokinetics. Results suggest that age (26-85 years), gender, race (15% non-White), mild to moderate renal dysfunction, mild to moderate hepatic dysfunction, and EGFR membrane staining intensity (1+, 2+, 3+) in tumor cells had no apparent impact on the pharmacokinetics of panitumumab.

Evidence of the safety and efficacy in other age categories and racial/ethnic populations could be gathered from post-marketing studies or surveillance in registries.

No formal pharmacokinetic studies of panitumumab have been conducted in patients with renal or hepatic impairment.

8.4 Pediatrics

No studies have been performed in the pediatric age group. Amgen has submitted a draft protocol and plans to study the pharmacokinetics of panitumumab in a pediatric population with EGFr-expressing solid tumors as a post-marketing commitment.

8.5 Advisory Committee Meeting

An Advisory Committee meeting was not considered necessary for this product.

8.6 Literature Review

The applicant conducted a review of the literature and submitted an extensive reference section under each part of the BLA. The FDA conducted a search of the literature and reviewed the submitted references. Trials submitted by the applicant in support of the BLA have been presented in abstract form at national and international meetings.

8.7 Postmarketing Risk Management Plan

Required Phase 4 Commitments are outlined in Section 1.2.2. No additional formal risk-management plan was deemed necessary.

8.8 Other Relevant Materials

No other materials are deemed relevant to this review.

9. OVERALL ASSESSMENT

9.1 Conclusions

Panitumumab monotherapy plus BSC provided a statistically significant improvement in time to progression when compared to BSC alone in the treatment of patients with EGFr-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

9.2 Recommendation on Regulatory Action

This reviewer recommends accelerated approval of VECTIBIX™ for the following indication:

> VECTIBIX™ monotherapy is indicated for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regiments

As documented in this review confirmation of clinical benefit is required to support regular approval for this indication. In addition, a clear pattern of adverse events emerged from the application, allowing for an assessment of the risk-benefit profiles, and allowing for development of a label with adequate directions for use, under 21CFR § 201.5.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk management will be primarily handled by pharmacovigilance and post-marketing reports of safety information (in periodic or expedited reports).

9.3.2 Required Phase 4 Commitments

Required Phase 4 Commitments are outlined in Section 1.2.2.

9.3.3 Other Phase 4 Requests

The additional Phase 4 requests are outlined in Section 1.2.3.

9.4 Labeling Review

9.4.1 Review of Package Insert

There were several labeling negotiations with the applicant and the final version of the label is attached. FDA recommended the following major changes in content and format of the originally proposed physician package insert:

1. Boxed Warnings:
    - Addition of a Boxed Warnings section for infusion reactions. Dermatologic toxicity. Severe infusion reactions were observed with Vectibix™ and, based on cxpcricncc with othcr monoclonal antibodies severe reactions may result in death. The recommended management of severe infusion reactions is interruption of dosing.
    - Addition of a Boxed Warnings section for dermatologic toxicity. Dermatologic toxicities were included because of the risks of sepsis. The recommended management of severe dermatologic toxicities is interruption of dosing.

    Inclusion of a Boxed Warnings was felt appropriate because of the serious nature of the toxicities and because appropriate physician intervention is necessary to manage and prevent more serious sequelae, which can be best highlighted in Boxed Warnings.

2. Description
    - Characterization of formulation changed from —— to mass (mg) units
3. Clinical Pharmacology:
    - Section re-organized for consistency with ordering of information in other product labels for monoclonal antibodies

- Removed statements regarding [redacted] because data supporting these statements deemed not reliable.

4. Human Pharmacokinetics

- Information regarding [redacted] replaced with statement that pharmacokinetics are greater than dose proportional at lower doses and become dose-proportional at doses above 2 mg/kg.
- Summary statistics for PK properties modified based on the analysis and conclusions by Dr. Men, OCP reviewer.

5. Clinical Studies

- Removed table providing [redacted] replaced with a figure of the K-M curve for PFS based on IRC-determined events.
- Removed references to [redacted]
- Removed statements regarding [redacted]
- Removed [redacted]

6. Indications:

- Revised to [redacted]
- Addition of "EGFR-expressing" qualifier to indication statement, because only patients with evidence of EGFR-expression in tumor were enrolled in the pivotal study. This subgroup represents only 70% of patients with metastatic colorectal cancer.

7. Warnings/Precautions:

- Addition of non-clinical data in the WARNINGS: Dermatologic toxicities subsection to include information on the severe dermatologic toxicities and deaths in monkeys treated with panitumumab.
- Added WARNINGS subsection on Infusion Reactions because of the severe nature of a limited number of events which suggest the potential for fatal events and because risks of serious events can be minimized by appropriate management.

- Title of WARNINGS subsection on [redacted] changed to Pulmonary Fibrosis, to provide greater clarity on description of events
- Added WARNINGS subsection on Electrolyte [redacted] because risks of serious events can be minimized by appropriate management.
- Title of WARNINGS subsection on [redacted] changed to Diarrhea to provide greater clarity on description of events and to provide clarification of the scope of the events (also occurs at increased incidence in patients receiving panitumumab monotherapy)
- Title of PRECAUTIONS subsection [redacted] changed to Photosensitivity to provide greater clarity on description of events
- Added PRECAUTIONS subsection on EGF Receptor Testing for consistency with and to include important information on text kit qualification when such a kit is necessary for selection of patients for whom the product is indicated.
- PRECAUTIONS: Information for Patients subsection strengthened to include instruct physicians to counsel patients regarding risks of pulmonary fibrosis and embryofetal lethality and to counsel patients regarding risks of, and need to adhere to laboratory monitoring for, electrolyte depletion.
- Modification of PRECAUTIONS: Drug Interactions subsection for accuracy regarding lack of formal testing and to remove misleading statements regarding [redacted]
- Modification to PRECAUTIONS: Carcinogenesis subsection for accuracy and to remove potentially misleading statements regarding [redacted]
- Modifications to the PRECAUTIONS section of the label, including revision of the language regarding potential impairment of fertility by panitumumab, and to the Pregnancy subsections based on non-clinical studies.

8. Adverse Reactions:
   - Modified Table in ADVERSE REACTIONS section to limit data to the randomized trial, so that data on comparator arm can be included.
   - Deleted [redacted] and placed the information for each category of adverse reactions in discrete subsections under WARNINGS or PRECAUTIONS.
9. Dosage and Administration:
   - Removed references to [redacted]
   - Streamlined Dose Modifications subsection for clarity and include separate subsection of directions for dose modification in the event of infusion reactions.

9.4.2 Review of Other Labeling Elements

PACKAGE AND CARTON LABELING
No comments.

TRADE NAME REVIEW

After review of the proposed trade name " for the , panitumumab under IND 8382, and in consultation with the Division of Drug Marketing, Advertising and Communication (DDMAC), the Division of Medication Errors and Technical Support (DMETS) and the Division of Therapeutic Biologic Oncology Products rejected that trade name. The objection was based on the . An alternative trade name proposed by Amgen, "VECTIBIX™', was reviewed by DDMAC, DMETS and by this Division, and was found to be acceptable

MEDICATION GUIDE OR PATIENT PACKAGE INSERT
Vectibix™ is not intended to be self-administered. A Medication guide or Patient Package Insert is not necessary.

9.5 Comments to Applicant

No additional comments to Amgen.

10. APPENDICES

10.1 Review of Individual Study Reports

The recommendation of approval of Vectibix™ is primarily based on the pivotal study 20020408. This has been extensively discussed in the previous sections of this review. Synopses of other studies submitted to the BLA can be found at \\cbsap58\m\eCTD_Submissions\STN125147\0002\m2\27-clin-sum pages 2-89.

10.1.1 Overview of the clinical studies:

The organization of studies submitted to support the safety and efficacy of panitumumab is shown below in Figure 8. A summary of studies providing clinical efficacy data is included in Table 63.

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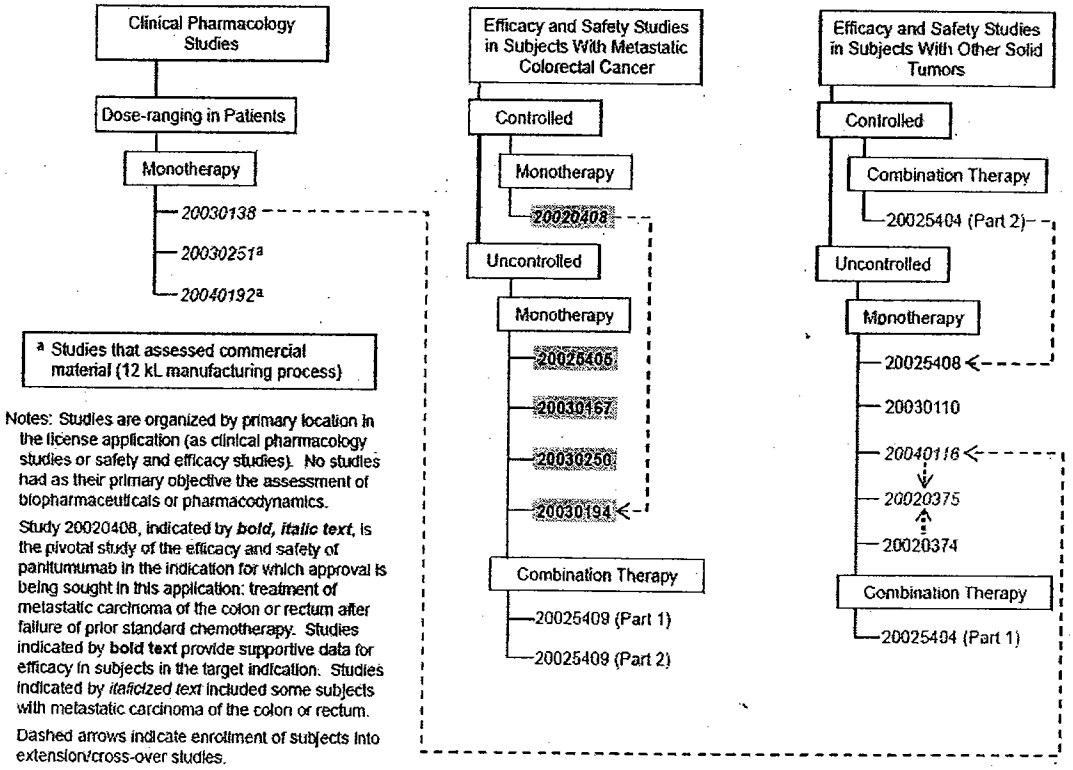
Figure 8. Organization of the Panitumumab Clinical Studies



Notes: Studies are organized by primary location in the license application (as clinical pharmacology studies or safety and efficacy studies). No studies had as their primary objective the assessment of biopharmaceuticals or pharmacodynamics.

Study 20020408, indicated by ***bold, italic text***, is the pivotal study of the efficacy and safety of panitumumab in the indication for which approval is being sought in this application: treatment of metastatic carcinoma of the colon or rectum after failure of prior standard chemotherapy. Studies indicated by **bold text** provide supportive data for efficacy in subjects in the target indication. Studies indicated by *italicized text* included some subjects with metastatic carcinoma of the colon or rectum.

Dashed arrows indicate enrollment of subjects into extension/cross-over studies.

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Table 62. Studies Providing Clinical Efficacy Data

Type of Study	Protocol No.	Location of Study Report	Primary Endpoint	Study Design	Test Product/ Dosage/Route Regimen/ Manufacturing Process	Number of Subjects Enrolled/Enrollment Status	Disease/EGFr status	Duration of Treatment	Type of Report/Type of Analysis
Controlled Study									
Monotherapy									
Efficacy	20020408		PFS	Open-label, randomized (panitumumab: BSC, 1:1)	Panitumumab 6 mg/kg IV every 2 weeks; CHO	463 (complete)	mCRC; disease progression during or after prior fluoropyrimidine, irinotecan and oxaliplatin, ≥ 1%EGFr+ per Amendment 2 (≥ 10% before amendment)	Until disease progression, intolerance or other reason (death, withdrawal, etc)	Full report, primary analysis (interim analysis for survival)
Uncontrolled Studies									
Monotherapy									
Safety	20030194		Safety	Open-label, single arm extension of 20020408 BSC arm upon PD per investigator's assessment	Panitumumab 6 mg/kg IV every 2 weeks; CHO	175 (ongoing)	mCRC progressing on BSC arm of 20020408/EGFr status from 20020408 BSC arm baseline	Until disease progression, intolerance or other reason (death, withdrawal, etc)	Full report, interim analysis

BSC = best supportive care; CHO = Chinese hamster ovary; EGFr = epidermal growth factor receptor; mCRC = metastatic colorectal cancer; PFS = progression-free survival; PD = progressive disease

Type of Study	Protocol No.	Location of Study Report	Primary Endpoint	Study Design	Test Product/ Dosage/Route Regimen/ Manufacturing Process	Number of Subjects Enrolled/Enrollment Status	Disease/line of therapy/EGFr status	Duration of Treatment	Type of Report/Type of Analysis
Efficacy	20025405		Objective tumor response	Open-label, single arm	Panitumumab 2.5 mg/kg IV every week; hybridoma	150 (complete)	mCRC; failed therapy with a fluoropyrimidine plus either irinotecan or oxaliplatin or both, ≥10% EGFr+	Until disease progression, intolerance or other reason (death, withdrawal, etc)	Full report, primary analysis
Efficacy	20030167		Objective response through week 16, duration of response (co-primary)	Open-label, single arm	Panitumumab 6 mg/kg IV every 2 weeks; CHO	93 (ongoing)	mCRC; failed therapy with fluoropyrimidine, irinotecan, and oxaliplatin, ≥10% EGFr+	Until disease progression, intolerance or other reason (death, withdrawal, etc)	Full report, interim analysis
Efficacy	20030250		Objective response through week 16, duration of response (co-primary)	Open-label, single arm	Panitumumab 6 mg/kg IV every 2 weeks; CHO	88 (ongoing)	mCRC; failed therapy with fluoropyrimidine, irinotecan, and oxaliplatin; < 10% (including <1%) EGFr+	Until disease progression, intolerance or other reason (death, withdrawal, etc)	Full report, interim analysis

BSC = best supportive care; CHO = Chinese hamster ovary; EGFr = epidermal growth factor receptor; mCRC = metastatic colorectal cancer; PFS = progression-free survival; PD = progressive disease

10.2 Line-by-Line Labeling Review

There were several negotiations with the applicant and the final version of the label reflect the agreed upon changes to the originally submitted package insert. Because of the several iterations of the package insert during the process of labeling negotiations both the original applicant submitted version of the package insert and the final accepted version of the package insert are attached here. The substantive changes are noted in section 9.4.

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32 Page(s) Withheld

_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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