CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

STN/BLA 125084

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	BLA STN # 125084 / 0 / 001
Drug Name:	Cetuximab: Initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2
Indication(s):	Metastatic colorectal adenocarcinoma (CRC) expressing EGFR
Applicant:	Imclone Systems, Incorporated
Date(s):	Submission date: August 12, 2003
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Keywords: EGFR (epidermal growth factor receptor), CRC (colorectal cancer), BOND (Bowel Oncology with Cetuximab Antibody) trial, IRC (Independent Review Committee)

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1. EXECUTIVE SUMMARY

BLA STN #125084 / 0 / 001 is an original biologics application for the treatment of advanced colorectal cancer (CRC) with combination therapy consisting of the study agent, cetuximab, plus irinotecan. Major evidence presented by the sponsor included one pivotal randomized controlled study (i.e., BOND study) of the cetuximab/irinotecan combination versus cetuximab monotherapy and two supportive uncontrolled studies, one using the combination and the other using cetuximab alone. The two uncontrolled trials constituted supportive evidence and did not receive statistical review. They are discussed in the clinical review. This application was submitted under the accelerated approval mechanism.

1.1 Conclusions and Recommendations

No problematic statistical issues were identified for the pivotal trial (BOND) reviewed. This reviewer's analyses of the major efficacy endpoints, based on the electronic database provided, confirm the sponsor's reported statistical findings. The estimated objective tumor response rate was 22.9% in the cetuximab plus irinotecan treatment group vs. 10.8% in the cetuximab monotherapy group based on analysis of the ITT population (defined as all patients as randomized). The objective tumor response rates in secondary pre-study CRC treatment populations, including the most stringent irinotecan refractory subgroup, were similar to the ITT population. In all of the pre-study CRC treatment subpopulations analyzed, the lower 95% confidence limit for combination therapy groups exceeded 12.5%, the value regarded as clinically relevant in the study protocol. In the ITT population, the median time to progression (TTP), a secondary endpoint, was statistically significantly longer in the combination therapy group vs. the monotherapy group. And, for the most stringent irinotecan refractory subgroup, this statistically significant TTP improvement was also demonstrated. The randomized study reviewed provides statistical support for the sponsor's efficacy claim.

1.2 Brief Overview of Clinical Studies

Three clinical studies constitute the major evidence for this original BLA submission, one controlled randomized study and two uncontrolled studies. The pivotal study is the randomized controlled trial (#EMR 62 202-007), designated as BOND (BOWEL ONCOLOGY WITH CETUXIMAB ANTIBODY). This was an open-label, randomized, multi-center, Phase II study of cetuximab alone or in combination with irinotecan in patients with metastatic colorectal adenocarcinoma expressing the epidermal growth factor receptor (EGFR) and progressing on a defined irinotecan-based regimen. Eligible patients had to have documented disease progression (PD) after at least 6 weeks of treatment with a defined irinotecan-containing regimen. In Part 1 of the study, patients were randomized 2:1 to cetuximab in combination with the same dose of irinotecan to which they became refractory (Arm A: 218 patients) or to cetuximab monotherapy (Arm B: 111 patients). Randomization was balanced on previous treatment, Karnofsky Performance Status (KPS), and study site (all European). All patients were to be treated with study medication until PD or occurrence of unacceptable toxicity. Patients who failed cetuximab monotherapy on Arm B could continue cetuximab in combination with the same irinotecan

regimen to which they had become refractory in Part 2 of the study. Tumor response and time to progression (TTP) were evaluated every 6 weeks for the first 24 weeks and every 3 months thereafter. Assessments were made by the investigator and by an independent review committee (IRC). The study's **primary objective** was to determine the **objective confirmed response rate** of the combination of cetuximab plus irinotecan and of cetuximab as a single agent in patients with metastatic colorectal cancer (CRC) who were progressive on the irinotecan-containing regimen. **Secondary objectives** were: (a) to assess differences in efficacy between the two treatment groups (b) to determine TTP, time to treatment failure (TTF), duration of response (DR), and survival (c) to determine the percentage of patients who were progression free at 3 and 6 months (d) to evaluate the safety and toxicity of cetuximab in combination with irinotecan and as a single agent (e) to evaluate population pharmacokinetic parameters and (f) to determine response rate and disease control rate in Part 2 of the study. The primary analysis was performed for the ITT population i.e., all patients as randomized. Further analysis populations included the IRC-PD group defined as those patients refractory within 30 days after the last course of a previous irinotecan-containing therapy and assessed by the IRC. The ITT-Oxali population comprised those ITT patients pre-treated with oxaliplatin. The IRC-PD Oxali population comprises those IRC-PD patients pre-treated with oxaliplatin. Finally, the per-protocol population was also analyzed. Objective confirmed tumor response rates were compared using a 2-sided Fisher's exact test and a Cochran Mantel-Haenszel test to adjust for the randomization balancing factors. The difference in response rates between groups and its 95% CI were computed. Differences in TTP and overall survival were assessed via the logrank test, hazard ratios, and their CI's. All statistical tests were carried out at a 2-sided $\alpha = .05$ level of significance.

The first study conducted, submitted in the initial application which received a RTF designation, was an uncontrolled Phase II study, #IMCL CP02-9923, in patients with EGFR-positive, metastatic CRC that was refractory to irinotecan. These patients received cetuximab/irinotecan combination therapy. The third study, #IMCL CP02-0147, was also uncontrolled and was conducted in 57 patients with metastatic CRC that was refractory to irinotecan. These patients received cetuximab monotherapy.

The focus of this statistical review will be solely on the controlled BOND study. Refer to the clinical review for discussion of the two uncontrolled studies.

1.3 Statistical Issues and Findings

There were no outstanding statistical issues for the pivotal BOND study. This reviewer's analyses of the major efficacy endpoints, based on the electronic database provided, confirm the sponsor's reported statistical findings. The estimated objective tumor response rate was 22.9% in the cetuximab plus irinotecan treatment group vs. 10.8% in the cetuximab monotherapy group based on analysis of the ITT population. The objective tumor response rates in secondary pre-study CRC treatment populations, including the most stringent irinotecan refractory subgroup, were similar to the ITT population. In all of the pre-study CRC treatment subpopulations analyzed, the lower 95% confidence limit for combination therapy groups exceeded 12.5%, the value

regarded as clinically relevant in the study protocol. In the ITT population, the median time to progression (TTP), a secondary endpoint, was statistically significantly longer in the combination therapy group vs. the monotherapy group. And, for the most stringent irinotecan refractory subgroup, this statistically significant TTP improvement was also demonstrated.

2. INTRODUCTION

2.1 Overview

General Background on Study Agent and CRC Disease Indication: Cetuximab, the subject of this original BLA, is a chimeric monoclonal antibody that was specifically designed to block the human epidermal growth factor receptor (EGFR) for the treatment of colorectal cancer (CRC) and several other cancer types that express EGFR. Its development program was carried out jointly by three partners, ImClone, Bristol-Myers Squibb (BMS), and Merck KGaA. CRC is the fourth most common form of cancer worldwide and remains a leading malignancy both in terms of incidence and mortality. Approximately 35% to 40% of stage II/III patients will experience recurrence of metastatic or locally invasive disease. The majority of these recurrences in patients who have undergone a complete CRC resection occur within 3 to 5 years of surgery. Inoperable metastatic CRC is incurable. For many years, 5-fluororuracil (5-FU) was the sole cytotoxic agent with significant activity in advanced CRC and has remained the main treatment for CRC. Several attempts have been made to increase the efficacy of this drug by biochemical modulations with compounds such as folinic acid (FA) or by increasing tumor exposure to the drug via protracted continuous infusions. Although these techniques increased the efficacy of 5-FU in terms of response rate by 2- to 3-fold, survival remained disappointing and rarely exceeded a median duration of 10 to 12 months. New drugs for metastatic CRC have recently been introduced, including irinotecan and oxaliplatin. Both of these have different mechanisms of action from 5-FU. However, until very recently, there were no approved standard treatment options for patients failing irinotecan with or without 5-FU/FA. In the European Union irinotecan is approved for first- or second-line treatment of metastatic CRC and oxaliplatin is approved, in combination with 5-FU/FA, for first-line treatment of metastatic CRC. In the United States oxaliplatin received conditional approval (under the accelerated mechanism) with 5-FU/FA for second line treatment of CRC (i.e., patients previously treated for advanced CRC with disease recurrence or progression during or within 6 months of completion of first line therapy with the combination of 5-FU/LV and irinotecan) and first line approval for use with 5-FU/FA was granted on January 9, 2004. The EGFR expression rate in CRC is estimated to be between 25 and 77% in the literature. High expression has been associated with more aggressive disease and poor prognosis. Preclinical studies have shown that cetuximab shows antitumor activity in EGFR-positive tumors, including colon tumors.

The clinical justification for the use of cetuximab in combination with irinotecan was based on experience in a phase II study sponsored by ImClone (IMCL CP02-9923) in patients with EGFR-positive, metastatic CRC that was refractory to irinotecan. In this trial, patients were treated with cetuximab and continued to receive the same irinotecan regimen on which they had previously progressed. Based on investigators' assessments, 19% of patients who were progressive on an

irinotecan-containing regimen showed a response to the combination of irinotecan and cetuximab. Preliminary clinical experience also suggested that cetuximab may also have activity as a single agent. In another ImClone trial, IMCL CP02-0141, 57 patients with metastatic CRC that was refractory to irinotecan were treated with cetuximab alone, yielding a response rate of 11% according to investigators. Refer to the clinical review for a comprehensive discussion of these two uncontrolled studies. The response rates of cetuximab in irinotecan-refractory CRC both in combination with irinotecan and as a single agent provided the rationale for investigating the effectiveness of cetuximab in both of these settings.

The initial BLA submission for cetuximab received a refuse to file (RTF) action on December 28, 2001. This submission was based primarily on one uncontrolled study of the combination of cetuximab plus irinotecan, Study #IMCL CP02-9923. Reasons for the RTF decision were: (1) insufficient data to isolate the contribution of irinotecan to the efficacy of the combination, cetuximab + irinotecan (2) insufficient data to confirm that patients enrolled in CP02-9923 were refractory to irinotecan and (c) insufficient data to support the proposed dose and schedule of 400/250 mg/m^2. The present submission consists of that study, a study of cetuximab alone, #IMCL CP02-0141, and the pivotal phase II controlled BOND study, #EMR 62 202-007. The focus of this statistical review will be solely on the BOND study. This study was amended three times and enrolled patients from 56 study centers in 11 European countries (Austria, Belgium, France, Germany, Italy, the Netherlands, Norway, Spain, Switzerland, Sweden, and the United Kingdom). This study's sponsor was Merck KGaA, Darmstadt, Germany. Data management and statistical analysis were conducted by the department of Biostatistics and Data Sciences at Merck KGaA. Eligible patients were randomized to study medication by a central randomization service, [redacted] Expression of the epidermal growth factor receptor (EGFR) in tumor tissue was evaluated centrally at a center in Germany. [redacted] was primarily responsible for providing the technical facilities and organizing the independent review of the radiologic images obtained by CT or MRI. They also provided the study sites with instructions on imaging procedures, organized the collection of scans, and forwarded the scans and relevant clinical data to the Independent Review Committee (IRC) for central, independent evaluation. The IRC consisted of 3 radiologists and 1 oncologist who were blinded to the treatment arm. They evaluated the CT or MRI scans and assessed the tumor response. Another radiologist assessed the quality of the pre-study scans before they were sent to the IRC.

2.2 Data Sources

All of the relevant study reports and electronic data were loaded onto CBER's Electronic Document Room (EDR). The electronic data sets comprised raw and derived SAS transport data sets for the three studies. SAS programs for the major efficacy and safety analyses were also provided electronically.

3. STATISTICAL EVALUATION

The statistical analyses performed on the pivotal BOND study were initially specified in the study protocol. Further details of the planned statistical analyses were provided in the statistical analysis plan that was finalized on April 2, 2003 prior to database closure. Statistical analyses were performed by the sponsor using data collected until the clinical cut-off date of November 15, 2002. Survival data were analyzed using a data cut-off of January 31, 2003. All data tabulations, summarizations, and analyses used SAS, Version 8.2 software.

3.1 Evaluation of Efficacy

3.1.1 Bond Study

3.1.1.1 Design

This open-label, randomized multi-center, Phase II study consisted of the following periods:
Prescreening: Evaluation of EGFR status on tumor tissue (first informed consent). Only patients with EGFR-positive tumors were to attend the screening visit.
Screening: Assessment of EGFR-positive patients with documented PD on a defined irinotecan regimen for study eligibility, randomization of eligible patients to study medication (second informed consent). Patients who were eligible for randomization to study treatment had to have documented PD after being treated for at least 6 weeks with one of the following irinotecan-based regimens as their most recent chemotherapy treatment (including a maximum of two dose reductions):

Irinotecan 125 mg/m^2 weekly for 4 consecutive weeks, followed by 2 weeks rest, as a single agent or in combination with 5-FU/FA
Irinotecan 180 mg/m^2 every 2 weeks in combination with 5-FU/FA
Irinotecan 350 mg/m^2 every 3 weeks as a single agent

Patients were allowed into the study if they had progressed during or within 3 months after the last course of one of the above therapies. Patients whose dose of irinotecan was reduced due to toxicity in accordance with recommendations could also be included, if they tolerated the lower dose.
Treatment Period: Treatment with study medication until PD or unacceptable toxicity
Follow-up Period: Assessment of survival status

Study Amendments: This study was amended three times. The original protocol (issued June 18, 2001) stated that the study planned to randomize a target of 225 patients with metastatic colorectal adenocarcinoma whose tumors expressed the EGFR. It was estimated that approximately 400 patients would have to be pre-screened for EGFR positivity in order to recruit 225 EGFR-positive patients. After discussion with the Swedish regulatory authority, however, the protocol was amended (**Amendment 1, March 19, 2002**) to increase the sample size, requiring a total of 500 patients to be screened in order to randomize 300 EGFR-positive patients resulting in 225 patients who satisfied a stricter definition of irinotecan refractoriness.
Amendment 2 was issued on **July 23, 2002** when all patients had been randomized to study

medication. The most important changes were: (a) The IRC review was to be performed using the modified WHO criteria instead of the RECIST. The FDA advised that the WHO criteria (in particular the bi-dimensional measurement of lesions) should be used. WHO criteria were adopted for the IRC in order to optimize comparability of the US and European studies. The RECIST criteria were, however, retained for the investigators' assessments because evaluation had already started in approximately half of the patients. (b) EGFR expression was to be presented as percentage of positive cells instead of degrees of positivity (1+, 2+, or 3+) because this was more exact. A clear score to differentiate the EGFR categories was not available when the study was started. **Amendment 3 (August 15, 2002)** was issued when all patients had been randomized to study medication and was designed to reflect changes in the analysis of the immunogenicity of cetuximab. An additional blood sample was scheduled at the end-of-study visit, which was postponed from 4 weeks to 6 weeks after the last dose of cetuximab, in order to determine HACA and cetuximab levels.

Source of Product: At the start of the phase II study, pilot-scale material from ImClone's pilot plant was planned for use for the entire trial. In order to meet increasing demands for clinical trials, ImClone transferred the manufacturing process to Lonza Biologics (USA). In the course of the scale up, minor process changes became necessary. However, a set of physicochemical characterization studies demonstrated comparability of the ImClone and Lonza materials and processes. After the sample size augmentation, the trial used the intermediate-scale (IS) material produced at Lonza.

Randomization: Eligible patients were randomized in a ratio of 2:1 to treatment Arm A (cetuximab in combination with irinotecan) or Arm B (cetuximab monotherapy). The time between randomization and first infusion of cetuximab was not to exceed 3 days. Each center called the IVRS central randomization service. Randomization was performed via a minimization dynamic allocation method with the following stratification factors: (a) Karnofsky Performance Status (KPS) at two levels (60 to 70 vs. 80 to 100) (b) previous treatment at three levels (patients coming from first line treatment vs. patients coming from second or subsequent treatment line with prior oxaliplatin vs. patients coming from second or subsequent treatment line without prior oxaliplatin) and (c) study center (56 centers). The sponsor states that this method may use a probability of assignment other than 0.66 and 0.33 to maintain a 2:1 ratio of treatment groups overall and within levels of each stratification factor. The sponsor provided simulation results [redacted], which demonstrated very good performance for the chosen method.

Study Objectives: The **primary objective** of this study was to determine the objective confirmed tumor response rate of the combination of cetuximab plus irinotecan and of cetuximab as a single agent in patients with metastatic colorectal cancer who were progressive on an irinotecan-containing regimen. The **secondary objectives** were as follows:

- To assess the difference in efficacy between the two treatment groups
- To determine time to progression (TTP)
- To determine time to treatment failure (TTF)
- To determine the percentage of patients who were progression-free at 3 and 6 months

- To determine the duration of response (DR)
- To determine the overall survival time (OS)
- To evaluate the safety and toxicity of cetuximab in combination with irinotecan and of cetuximab as a single agent
- To evaluate population pharmacokinetic parameters
- To determine response rate and time to progression in Part 2 of the study
- To investigate the inhibition of the EGFR signaling pathway in patients randomized to receive cetuximab monotherapy (Arm B) and giving additional consent to participate in these pharmacodynamic investigations (This objective was added in local Amendment 1 and was only applicable to the Belgian centers, but due to late approval of this amendment, these additional investigations were not performed)
- To determine if the activity demonstrated by cetuximab plus irinotecan could be maintained even if irinotecan was withdrawn (This objective was included in the protocol but no analyses were performed because of the small number of patients involved)

Treatment Period: All patients were to be treated with study medication until PD or occurrence of unacceptable toxicity. The concomitant use of 5-FU/FA was not allowed. Patients were to be assessed by the investigator for side effects every week. CT or MRI evaluation for the assessment of tumor response was to be performed at baseline, weeks 6, 12, 18, and 24 and thereafter every 3 months. **Tumor response was also evaluated by the IRC.** The treatment period was divided into 2 parts:

Part 1:

- **Arm A:** Patients were to be treated with cetuximab in combination with the same irinotecan regimen (i.e., dose and frequency) to which the patient became refractory. Patients who benefited from the combination therapy but developed unacceptable toxicity to irinotecan were allowed to continue on cetuximab as a single agent.
- **Arm B:** Patients were to be treated with cetuximab monotherapy. Patients who failed this treatment were eligible for Part 2 of the study.

Part 2: Patients who failed cetuximab monotherapy in Arm B of Part 1 could continue cetuximab treatment in combination with the same irinotecan regimen (i.e., dose and frequency) to which they had become refractory. Irinotecan was to be reintroduced within 2 weeks after documentation of PD on cetuximab monotherapy. Cetuximab was to be continued as weekly therapy without an initial dose whereby therapy could be interrupted for up to 2 weeks after documentation of PD on cetuximab as a single agent.

Follow-up Period: Survival status of all patients who discontinued study treatment was to be assessed every 6 weeks.

Doses Used in the Study: The selected cetuximab dose regimen (initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2) was established in early phase I and II studies and

showed first signs of efficacy and an acceptable tolerability profile. The selected irinotecan regimens are the recommended dosages for the treatment of patients with advanced CRC.

Blinding: This was an open-label study. However, the IRC was blinded with regard to center, patient, and treatment group during their review of radiological scans and clinical data for evaluation of tumor response. They were not presented with information on efficacy as reported by the clinical investigator. Finally, the IRC was not blinded with regard to whether the scans were taken before or during the study.

Description of Efficacy Variables: The **primary analysis of efficacy** is based on the assessment of **the best (objective) overall confirmed tumor response** as determined by the IRC. Best response is classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE). WHO, rather than RECIST criteria, were used at FDA's request. The **primary target variable of objective response rate** is defined as the number of patients whose best overall response was CR or PR relative to the number of patients belonging to a particular study population. The primary analysis was performed on the ITT population, defined as all randomized patients. The **secondary target variable of disease control rate** is defined as the number of patients whose best overall response was CR, PR, or SD relative to the number of patients belonging to the study population of interest. Only patients with measurable disease (i.e., at least one measurable lesion) at baseline were to be enrolled in this study. All measurable lesions representative of all involved organs up to a maximum of five lesions per organ and ten lesions in total were to be identified as target lesions and recorded and measured at baseline. **Target lesions** were selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements.

Tumor Assessment Performed by the IRC: The Independent Review Committee (IRC) was established in order to provide an objective, unbiased independent review of the eligible patient population based on refractoriness to prior irinotecan therapy, as well as patient benefit as shown by response to either cetuximab plus irinotecan or to cetuximab alone. The IRC consisted of three independent, board-certified radiologists or national equivalent (readers) and an oncologist who were responsible for the following assessments:

- Assessment of pre-study scans and clinical data (details of prior irinotecan therapy) to establish whether the patient had a pre-study status of PD or a pre-study status of non-PD
- Assessment of on-study scans and clinical data (patient listings of AE's, physical examination, concomitant medications and laboratory safety variables) to determine the primary efficacy endpoint of best overall response, date of first response, date of response confirmation, date of progression, and date of last tumor assessment. The clinical data presented during independent review did not include lesion measurements or response assessments as reported by the clinical investigators.

The IRC was blinded with regard to institution, patient, and treatment group. In the original protocol, the IRC was to assess tumor responses according to the RECIST criteria. In Amendment 2, however, it was decided that the IRC should base their evaluation on the modified WHO criteria so that the results would be consistent with those of other studies being conducted with cetuximab in the U.S.

Study Populations:

Intention-to-Treat Population (ITT): defined as all patients who were randomized into the study.

IRC-PD Population: All ITT patients with an objective confirmed irinotecan-refractory status as assessed by the IRC, i.e.:

- Progressed on prior irinotecan, as determined by the IRC
- Progressed within 30 days after the last irinotecan treatment course, i.e., pre-study scans documenting progressive disease
  - For the 125 mg/m^2 weekly schedule: within 51 days of the last dose of prior irinotecan treatment
  - For the 350 mg/m^2 every 3 weeks schedule: within 51 days of last dose of prior irinotecan treatment
  - For the 180 mg/m^2 every 2 weeks schedule: within 44 days of last dose of prior irinotecan treatment
  - For the "other not defined" schedule or if the schedule was missing: within 31 days of last dose of prior irinotecan treatment, i.e., 30 days after last dose
- Pre-study comparison scan: The scan assigned at baseline for the prior irinotecan regimen was performed either less than or equal to 6 weeks (42 days) prior to the first dose of the most recent irinotecan therapy or performed after first dose at least four weeks prior to the date of the scan used to assess progression
- Pre-study comparison scan/pre-scan documenting PD: At least a 4-week interval between the 2 scans covering at least 1 course (cycle) of irinotecan therapy, i.e.:
  - For the 125 mg/m^2 weekly schedule: $\geq$ 4 doses of irinotecan
  - For the 350 mg/m^2 every 3 weeks schedule: $\geq$ 1 dose of irinotecan
  - For the 180 mg/m^2 every 2 weeks schedule: $\geq$ 1 dose of irinotecan
  - For the "other not defined" schedule or if the schedule was missing: $\geq$ 2 doses of
  - irinotecan
- Minimum irinotecan dosing: received adequate pre-study irinotecan, i.e.:
  - For all schedules, received at least 1 cycle of irinotecan, and
  - For a weekly irinotecan schedule with less than 2 cycles, received at least 4 irinotecan doses
- Received any dose of cetuximab

ITT Oxali Population: All ITT patients with prior oxaliplatin therapy

IRC-PD Oxali Population: All IRC-PD patients with prior oxaliplatin therapy

Per Protocol Population: All IRC-PD patients who
- Did not fulfill one or more of the criteria for major protocol violations

- Had adequate study medication compliance, i.e., patients who received at least 50% of the scheduled cetuximab treatment (number of infusions divided by weeks of cetuximab treatment)
- Had received at least 6 weeks of cetuximab treatment, except in case of death or PD (IRC) within the first 6 weeks after start of cetuximab treatment

NOTE: The IRC-PD population is a subset of all patients who were assigned a pre-study PD status by the IRC and fulfilled all the criteria as given above. Besides other restrictions, it included only those patients who had progressed within 30 days after the last pre-study irinotecan treatment course and thus fulfilled the stricter criterion of refractoriness asked for by the Swedish regulatory authority.

3.1.1.2 Endpoints and Results

The primary analyses of efficacy were based on the ITT population. The main assessments of the efficacy endpoints of response, duration of response, time to response, and TTP were based on data independently determined by the IRC according to the modified WHO criteria for Part 1 of the study. The best overall response, date of progression, date of response, date of response confirmation, and date of last on-study tumor assessment were based on the IRC determinations. Note that investigator assessments were considered as supportive results.

Description of Primary Efficacy Variable:

The **primary analysis** of efficacy is based on the assessment of the **best (objective) overall confirmed tumor response** as determined by the IRC. The primary target variable is the **objective response rate**, i.e., the rate of complete and partial responses. The **disease control rate**, a secondary target variable, is based on achieving a complete response (CR), a partial response (PR), or stable disease (SD). Point estimates and 2-sided Clopper-Pearson exact 95% CI's were calculated. In order to assess differences in efficacy between the two treatment groups, objective response rates and disease control rates for Part 1 of the study were compared via Fisher's exact test. In addition, Cochran Mantel-Haenszel (CMH) tests were performed for response rates in order to adjust for the randomization balancing factors, i.e., Karnofsky Performance Score (KPS) at two levels (< 80 vs. ≥ 80) and line of treatment (first line, second or subsequent line with oxaliplatin, second or subsequent line without oxaliplatin). Treatment comparisons were performed at the .05 2-sided α-level. The objective response rates are presented for various patient subsets based on demographic variables, disease characteristics, variables that characterize previous treatment and EGFR status, the baseline status of selected safety laboratory variables, and the on-study occurrence of skin reactions and acne-like rash. Overall response rates and disease control rates were also calculated for the investigator's assessment of response, based on RECIST criteria. The agreement between IRC and the investigator's assessment was presented.

Description of Secondary Variables:

The **duration of response (in months) (or DR)** in those patients with a confirmed CR or PR was defined as the time from first assessment of CR or PR to the first time disease progression was documented or death within 60 days after last tumor assessment or randomization (whichever occurred first). If a patient did not progress or the death date was beyond 60 days after last tumor assessment and randomization, the duration of response was censored on the date of last known tumor assessment. These dates were based on the IRC assessment.

The **time to response (in months) (or TTR)** in those patients with a CR or PR was defined as the time from the first dosing day of cetuximab until the assessment of CR or PR (based on IRC).

The **duration of disease control (in months) (or DDC)** was defined as the time from the first dosing day of cetuximab to the first time disease progression was documented or death within 60 days after the last tumor assessment or randomization (whichever occurred first) in those patients who achieved a best response of CR, PR, or SD. If a patient did not progress or the death date was beyond 60 days after the last tumor assessment or randomization, the duration was censored on the date of last known tumor assessment. The required dates were taken from the IRC assessment.

Time to progression (in months) (or TTP) was defined as the time from randomization until the first observation of disease progression or death due to any cause within 60 days after the last tumor assessment or randomization (whichever occurred first). If a patient had no IRC progression date or the death date was beyond 60 days after the last tumor assessment and randomization, TTP was censored on the date of the last tumor assessment or randomization. A patient who had not received study treatment and who had neither progressed nor died was censored on the day of randomization (Day 1).

Time to treatment failure (in months) (or TTF) for Part 1 is defined as the time from randomization until the first occurrence of one of the events defining treatment failure, i.e., first PD date according to the investigator's assessment or treatment discontinuation due to AE's, PD, withdrawal of consent, or death within 60 days of last tumor assessment or randomization (whichever occurred first). If a patient did not fail treatment (was still on randomized treatment), TTF was censored on the date of the last known disease assessment. A patient who did not receive study treatment and who did not progress or die was censored on the day of randomization.

Survival time (in months) is defined as the time from the day of randomization to death. For patients who were alive at the survival cut-off date of January 31, 2003, survival was censored at the last recorded date that the patient was known to be alive or on January 31, 2003 (whichever was the earlier calendar date). Survival from the start of the most recent pre-study irinotecan regimen was calculated similarly.

Progression-free rates at 3, 6, 9, and 12 months (IRC assessment) and the 3-, 6-, 9-, 12-, 18-, and 24-month survival rates were calculated based on Kaplan-Meier estimates. TTP (by IRC) and survival were tabulated for the same patient subsets that were considered for presentation of the

objective response rate. TTP was also presented for the subgroup of responders, i.e., those patients with confirmed CR or PR according to the IRC. Hazard ratios and associated 95% CI's were presented for TTP (IRC) and survival time. These ratios were based on proportional hazards adjusting for the following strata used for randomization: KPS and previous treatment line. In addition, the logrank test was used to compare the two treatment arms.

Note: No formal statistical hypotheses were tested for secondary variables.

Determination of Sample Size: This study was designed to enroll 225 patients: 150 to be treated with cetuximab in combination with irinotecan and 75 with cetuximab monotherapy. The ratio of 2:1 was chosen for randomization as it was expected that a much smaller response rate would be obtained for cetuximab monotherapy than for combination therapy with irinotecan. Discussions with the Swedish Medical Products Agency, while the study was already running, revealed that a patient population that fulfilled the more restrictive inclusion criteria of being progressive at most one month after end of irinotecan treatment course would be considered truly refractory to irinotecan. At the time this information was received, about 70% of the 208 patients already enrolled fulfilled that criterion. Therefore, the sample size was increased to a total of 300 patients in order to insure that the study objectives could be met for the subset of patients who enrolled at most one month after failure of irinotecan treatment. Although this increase was made to achieve sufficient power for a subgroup, it was also justified for the primary ITT population because it led to more precise estimation of the response rate and narrower CI's. Moreover, it increased the chance of distinguishing the effect of the combination therapy from that of monotherapy. This was desirable because evidence from another study indicated that the response rate under cetuximab monotherapy was higher than expected at the time when this study was planned. An exact test for a single proportion at a 2-sided 0.05 alpha-level would have the following power in the combination treatment group based on a sample size of 200 patients:

Expected Response under H_0	12%	11%	10%	9%	8%
Expected Response under H_1	19%	19%	19%	19%	19%
Power (n = 200)	78%	88%	94%	98%	99%

With 200 patients receiving combination treatment and 100 patients receiving monotherapy, the following confidence limits (Clopper-Pearson) would be obtained for the specified potentially observed response rates:

	Combination Treatment (n = 200)				Monotherapy (n = 100)			
# Resps	30	34	38	42	5	7	9	11
Resp Rate	0.15	0.17	0.19	0.21	0.05	0.07	0.09	0.11
CI	0.104-0.207	0.121-0.229	0.138-0.251	0.156-0.273	0.016-0.113	0.029-0.139	0.042-0.164	0.056-0.188

A statistical comparison between the two treatment groups would have power of about 80% if the response rates in the two treatment groups were 19% and 7%, respectively (based on Fisher's exact test). However, this comparison remained a secondary objective. (per Amendment 1)

Pooling of Study Centers: Efficacy analyses were performed for the ITT population, the IRC-PD population, the ITT oxali population, and the IRC-PD oxali population. Selected variables were also presented for the per-protocol population. **Data** were **pooled across centers** to provide overall estimates of the treatment effects. Due to the large number of centers (56) participating in this study and the small number of patients recruited in many centers, the primary target variable was presented by country, whereby small countries were pooled.

Missing Data Handling: Unless otherwise specified, missing data were not replaced. Analyses were performed considering all observed data. If either the day or month of a date was missing, the missing value was imputed as the midpoint within the smallest known interval for the purpose of efficacy evaluations. Missing observations were presented in tables as a separate category. Unless otherwise stated the calculation of proportions includes the missing category. The last measurement prior to randomization served as the baseline measurement. If such a value was missing, the last measurement prior to the first cetuximab administration was used.

General Methods: Continuous variables were summarized using descriptive statistics. Qualitative variables were summarized by means of counts and percentages in terms of frequency tables. Two-sided Clopper-Pearson exact 95% CI's were calculated for response and disease control rates. Time-to-event variables were presented using Kaplan-Meier probabilities and curves with associated statistics, i.e., the median and two-sided 95% CI. Selected data for Part 2 of the study were summarized separately using the same definitions and methods as for Part 1.

Efficacy Analyses for Part 2 of the Study:

Descriptive statistics were provided for best overall response according to investigator's assessment. The overall response rate was defined as the rate of patients with confirmed CR or PR in Part 2 relative to the number of patients treated in Part 2. The disease control rate was defined as the number of patients whose best response was CR, PR, or SD in study period 2 relative to the number of patients in Part 2. The determination of response in Part 2 was done using the progression scan from Part 1 as a baseline. Two-sided Clopper-Pearson exact 95% CI's were calculated. No formal statistical hypotheses were tested for the Part 2 variables.

Efficacy Results:

Patient Disposition: Patients were enrolled at 56 study centers in 11 European countries: 6 in Austria, 4 in Belgium, 7 in France, 6 in Germany, 8 in Italy, 5 in the Netherlands, 1 in Norway, 6 in Spain, 2 in Switzerland, 2 in Sweden, and 9 in the United Kingdom. 577 patients were pre-screened for EGFR status. 474 (82.1%) of these patients were EGFR positive and were screened for protocol eligibility. 329 patients were randomized to study medication: 218 to the combination arm of cetuximab with irinotecan (Arm A) and 111 to cetuximab monotherapy (Arm B). In both groups, 1 patient was randomized, although they were not EGFR positive. 147 screened patients were EGFR-positive but were not included in the trial. This was because screening for EGFR expression was performed quite early during previous treatment with irinotecan to identify those patients in advance who could potentially be enrolled in this study. After having progressed on this therapy, it became obvious that these patients did not fulfill all

inclusion criteria at the time of randomization. Recruitment status is summarized by country in the following sponsor's table:

Table 1: Recruitment by Country

Country	Pre-screened N = 577	Safety Population N = 327	ITT Group N = 329	IRC-PD Group N = 206
Austria	39	24	24	16
Belgium	136	88	90	49
France	76	47	47	33
Germany	54	24	24	17
Italy	120	61	61	29
Netherlands	15	6	6	5
Norway	11	8	8	6
Spain	50	30	30	21
Sweden	3	3	3	1
Switzerland	15	10	10	9
United Kingdom	58	26	26	20

Distribution of the patients between the two treatment arms in the ITT group was similar with regard to the randomization balancing factors indicating that stratification was successful. Stratification was also successful in the IRC-PD, ITT-oxali, IRC-PD oxali, and per-protocol populations. Two patients in Arm A were randomized but did not receive any study medication. The remaining 327 randomized patients received treatment with cetuximab in combination with irinotecan or as monotherapy. Four patients were randomized to the combination arm, but received only 1 dose of cetuximab as a single agent due to a severe hypersensitivity reaction. For efficacy evaluation these patients were analyzed as randomized; in the safety population they were analyzed together with the other patients of the monotherapy group. The distribution of cetuximab manufactured by the pilot process and the IS (Lonza) process were similar between the two treatment arms. In Parts 1 + 2 of the study, 132 (40.1%) patients received pilot-scale material alone, 109 (33.1%) received IS (Lonza) material alone, and 86 (26.1%) patients received both types.

Patient Discontinuations: 279 (84.8%) patients discontinued from or completed Part 1 of the study after randomization and before the data cutoff on November 15, 2002. The main reason for discontinuation or completion in both treatment groups was PD. A higher proportion of monotherapy patients discontinued due to PD (82.0% vs. 61.5% of combination therapy patients) until the cutoff date. The percentage of withdrawals due to AE's and deaths was higher in the combination therapy group than in the monotherapy group, which can be explained by the longer observation period. 54 patients who had PD under monotherapy in Part 1 elected to participate in Part 2 before data cutoff and were given combination therapy (Part 2 cohort). 40 of these patients discontinued from the study (35 due to PD, 3 due to AE's, 1 death, 1 withdrawal of consent).

Protocol Deviations: Patients with major protocol violations were excluded from the per-protocol population. However, patients with minor protocol deviations were regarded to be fully evaluable for efficacy and therefore form part of the per-protocol population. Patients with protocol deviations were analyzed in the ITT population. Pre-randomization deviations were more frequent in the monotherapy group than in the combination therapy group: 13 (11.7%) vs. 15 (6.9%) patients. This was largely due to a higher incidence of patients who did not have one of the specified irinotecan treatments as their most recent chemotherapy (monotherapy 6 (5.4%) vs. combination therapy 4 (1.8%). The frequency of post-randomization deviations was comparable in the two treatment groups: combination therapy 9.2% vs. monotherapy group 8.1%. Major protocol deviations were only reported in 3 patients. One patient in each treatment group had no evidence of positive EGFR expression and 1 patient in the monotherapy group had no evidence of metastatic CRC at baseline. None of the patients in the combination therapy group had a first on-study dose of irinotecan that was significantly higher than the last pre-study dose.

Patient Groups Analyzed: The following sponsor's table summarizes patient counts for the 7 analysis populations by treatment arm:

Table 2: Number of Patients in Study Populations

Population	Combination Therapy		Monotherapy		Total	
	n	% of ITT	n	% of ITT	n	% of ITT
Screened					577	
ITT	218	100.0%	111	100.0%	329	100.0%
Safety	212	97.2%	115	103.6%	327	99.4%
IRC-PD	135	61.9%	71	64.0%	206	62.6%
ITT oxali	135	61.9%	71	64.0%	206	62.6%
IRC-PD oxali	84	38.5%	46	41.4%	130	35.9%
Per protocol	122	56.0%	66	59.5%	188	57.1%

Demographic and Other Baseline Characteristics: Of the 577 pre-screened patients, 353 (61.2%) were male and 223 (38.6%) were female. The median age of the screened patients was 59 years (Range: 26 – 84) and the majority were Caucasian (98.6%). Age, race, and gender characteristics of the IRC-PD, ITT oxali, and IRC-PD oxali populations were similar to those of the ITT population. The distribution of KPS values was similar for the two treatment groups. About one-third of patients had a value between 60 and 80, one-third had a value of 90, and one-third had a value of 100. The proportion of patients with a KPS of 100% was higher in the monotherapy patients who entered Part 2 than in the overall monotherapy group (42.6% vs. 29.7%).

EGFR Staining: Staining results of the tumor biopsies are presented in the following sponsor's table:

Table 3: EGFR Staining Characteristics of Tumor Biopsies

EGFR Staining Characteristics	Combination Therapy N = 218		Monotherapy N = 111		Total N = 329	
	No. pts.	%	No. pts.	%	No. pts.	%
% pos cells:						
0%	1	0.5%	1	0.9%	2	0.6%
> 0 - < 10%	93	42.7%	40	36.0%	133	40.4%
10 - < 20%	23	10.6%	22	19.8%	45	13.7%
20 - < 30%	18	8.3%	10	9.0%	28	8.5%
30 - < 40%	21	9.6%	6	5.4%	27	8.2%
≥ 40%	62	28.4%	32	28.8%	94	28.6%
Max staining:						
Faint / barely	53	24.3%	21	18.9%	74	22.5%
Weak to Mod	89	40.8%	55	49.5%	144	43.8%
Strong	75	34.4%	34	30.6%	109	33.1%
Missing	1	0.5%	1	0.9%	2	0.6%

The distribution of EFGR staining was similar for both treatment groups. In just over half of the patients (i.e., 178 or 54.1%) the percent of positively stained cells was < 20%. Maximal staining intensity was faint in 22.5% of patients, weak to moderate in 43.8%, and strong in 33.1%.

IRC Documentation of Disease Progression and Tumor Assessment: According to the IRC assessment, PD on the most recent pre-study irinotecan treatment was based on radiologic progression in the majority of cases (83.0%). In 5.2% of patients, PD was assessed clinically, and in 11.9% the IRC did not diagnose PD. Reasons for progression were similar in the two treatment groups. There were no major differences between treatment groups with regard to the number of metastatic sites or the localization, measurability, and size of the index lesions.

Previous Anti-cancer Treatment: The frequencies of the major categories of cancer pre-treatment were similar in the two treatment arms. All patients had previous irinotecan therapy, but 294 (89.4%) had received additional chemotherapies (not including the most recent therapy with irinotecan), 59 patients (17.6%) had radiotherapy, and 18 patients (5.5%) had some other type of therapy. The number of prior treatment lines for metastatic disease as assessed by medical review by the sponsor was also similar in the two treatment arms.

Analyses of Tumor Response

Primary Analysis of Objective Response Rate and Disease Control Rate in the ITT Group

The primary analysis of efficacy was based on analysis of the best overall response in the ITT population as assessed by the IRC. The primary target variable is the confirmed objective response rate (i.e., confirmed CR or PR). The following sponsor's table summarizes analytic findings for objective response rate and disease control rate (i.e., confirmed CR, PR, or SD) along with 95% CI's.

Table 4: Summary of Best Overall Response in ITT Group (IRC Assessment)

Response	Combo Arm (N = 218)		Mono Arm (N = 111)		Δ in Proportions	
	n	%	n	%	%	p-value*
Best Response						
CR	0	0	0	0		
PR	50	22.9	12	10.8		
SD	71	32.6	24	21.6		
PD	68	31.2	59	53.2		
Not evaluable	29	13.3	16	14.4		
Obj. Response	**50**	**22.9**	**12**	**10.8**	**12.1**	**0.0074**
95% CI		**17.5, 29.1**		**5.7, 18.1**	**4.1, 20.2**	
Disease Control	121	55.5	36	32.4	23.1	0.0001
95% CI		48.6, 62.2		23.9, 42.0	12.1, 34.0	

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

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

Reviewer's Comments: The medical reviewers reviewed all scans and other relevant documentation for determination of tumor response and were in 100% accord with the IRC's assessments. This reviewer confirmed all statistical analyses summarized in the above sponsor's table as well as the CMH stratified analysis.

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Analyses of Objective Response Rate and Disease Control Rate in Secondary Groups (IRC Assessment)

The following sponsor's table summarizes objective response rates in secondary populations based on the IRC assessments of tumor response.

Table 5: Summary of Objective Response Rates in Secondary Populations

Population	Combo therapy		Monotherapy		Δ in proportions	
	n / N	%	n / N	%	%	p-value*
IRC-PD Obj Resp Rate 95% CI	34/135	**25.2**	10/71	**14.1**	**11.1** 0.2, 22.0	0.075
ITT oxali Obj Resp Rate 95% CI	30/135	**22.2**	6/71	**8.5**	**13.8** 4.2, 23.3	0.013
IRC-PD oxali F Obj Resp Rate 95% CI	19/80	**23.8**	5/44	**11.4**	**12.4** -0.8, 25.6	0.104
Per Protocol Obj Resp Rate 95% CI	34/122	**27.9**	10/66	**15.2**	**12.7** 1.0, 24.5	0.070

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

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

In the IRC-PD 2-cycle subset, objective tumor response was consistent with the results observed in the ITT population. The objective response rate was 25.8% with a 95% CI of (18.5, 34.1) for the combination arm and 14.5% with a 95% CI of (7.2, 25.0) in the monotherapy arm. The difference in response rates in favor of combination therapy was 11.3% with a 95% CI of (0.1, 22.4). The Fisher's exact test p-value for testing if this difference is significantly different from zero was p=0.074 and the p-value for the stratified Cochran Mantel-Haenszel test was p=0.068. This study was not powered to detect statistically significant differences for the secondary analysis populations.

Reviewer's Comment: This reviewer confirmed all of the statistical analyses summarized in the above sponsor's table.

Disease Control Rates: The disease control rates in all secondary populations were similar to those in the ITT population. Rates in the combination therapy group ranged from 50.4% to

60.7%. Rates in the monotherapy group ranged from 30.4% to 34.8%. The difference in proportions between the two treatment arms ranged from 19.4% to 25.8%. Statistical significance was reached for all populations in favor of the combination therapy arm.

Reviewer's Comment: This reviewer confirmed the disease control rate analytic findings. However, it should be borne in mind that the disease control endpoint is less robust than objective response since its definition includes stable disease (SD), a category much less precise than CR or PR.

Analysis of Investigator Assessment of Objective Response and Disease Control Rates in the ITT Population: The objective response rates in the ITT population according to the investigators' assessments were similar to the results as assessed by the IRC, i.e., 20.2% vs. 22.9% in the combination therapy group, 13.5% vs. 10.8% in the monotherapy group. The disease control rate according to the investigators' assessments was higher than that assessed by the IRC, i.e., 62.8% vs. 55.5% in the combination therapy group, 47.7% vs. 32.4% in the monotherapy group. In the majority of patients (236 or 71.7%), there was agreement between the investigaor and IRC assessment of best overall response. In terms of confirmed CR and PR, the IRC found a worse result than the investigator for 12 patients (including one patient with a change from CR to PR). In 14 patients the IRC found a better result (change from SD to PR).

Reviewer's Comment: Analyses of investigators' assessments should only be considered supportive.

Analysis of Duration of Response (IRC Assessment): The median duration of response in the ITT population was longer in the combination therapy arm than in the monotherapy arm: 5.7 months (95% CI: 4.2, 7.6) vs. 4.2 months (95% CI: 2.8, 5.5). Results for the three other populations were as follows (combination therapy vs. monotherapy):

- IRC-PD: 4.2 months (95% CI: 3.8, 7.3) vs. 4.1 months (95% CI: 2.8, 5.5)
- ITT oxali: 5.7 months (95% CI: 4.2, 7.3) vs. 4.3 months (95% CI: 2.8, 5.5)
- IRC-PD oxali: 5.6 months (95% CI: 4.2, 7.3) vs. 4.2 months (95% CI: 2.7, 6.5)

Reviewer's Comment: This reviewer confirmed the descriptive analyses of Kaplan-Meier probabilities and the reported medians with associated 95% CI's.

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

- **IRC-PD:** 1.4 months (95% CI: 1.3, 2.6) vs. 1.4 months (95% CI: 1.3, 2.7)
- **ITT oxali:** 1.4 months (95% CI: 1.3, 2.7) vs. 1.4 months (95% CI: 1.3, 2.4)
- **IRC-PD oxali:** 1.4 months (95% CI: 1.3, 2.6) vs. 1.4 months (95% CI: 1.3, 2.7)

The protocol specified that the tumor measurements would occur every 6 weeks and these findings show that a response was already observed in the majority of responders.

Reviewer's Comment: This reviewer confirmed the descriptive analyses of Kaplan-Meier probabilities and the reported medians with associated 95% CI's.

Time to Progression (IRC Assessment): The median TTP in the ITT population was longer in the combination therapy arm than in the monotherapy arm: 4.1 months (95% CI: 2.8, 4.3) vs. 1.5 months (95% CI: 1.4, 2.0). This difference in TTP was statistically significant (logrank, $p < 0.0001$). The estimated hazard ratio was 0.54 (95% CI: 0.42, 0.71). This indicates a reduction in risk for progression of disease of 46% for a patient in the combination therapy group compared to a patient in the monotherapy group at a given time point. The following reviewer's Figure 1 presents the Kaplan-Meier plot for TTP (in months) for both treatment groups:

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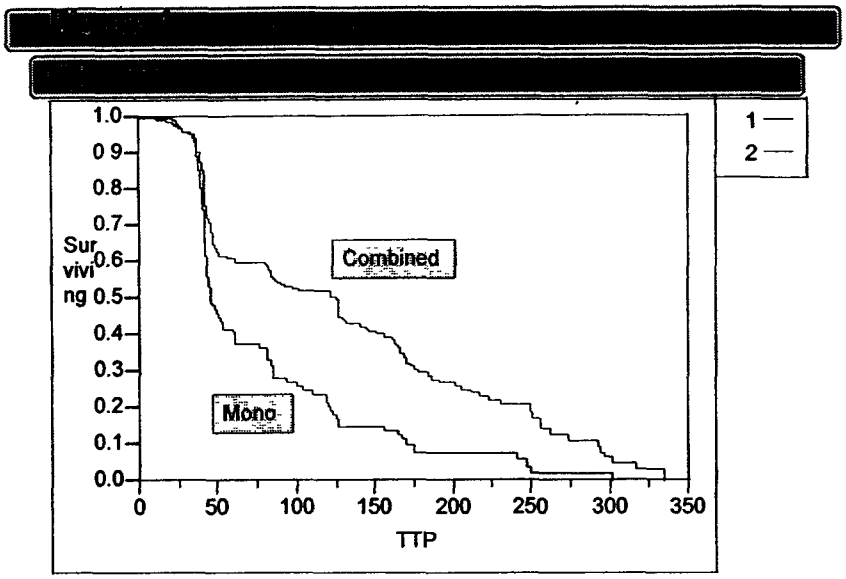


Time to event: TTP

Censored by

Grouped by RGROUP

Group	N Failed	N Censored	Mean	Std Error
1	152	66	134.389	7.29905
2	92	19	81.9764	6.77388
Combined	244	85	116.849	5.53874

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
1	126	84	132	44	206
2	46	44	61	41	105
Combined	83	51	98	43	171

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	26.2841	1	<.0001
Wilcoxon	19.3795	1	<.0001

Note: This reviewer's plot uses days, not months, as the time unit.

Reviewer's Comment: The sponsor's TTP analyses were confirmed. In addition, this reviewer performed a stratified logrank analysis to adjust for the effect of the randomization stratification factors. The stratified test also yielded a highly statistically significant result of $p < .0001$.

The median TTP values in the analysis subsets are summarized in the following sponsor's table:

Table 6: TTP Analysis Populations (IRC)

Population	Combo Therapy		Monotherapy		HR (CI)[1]	p-value[2]
	n/ N	Median[3]	n/ N	Median		
ITT	152/218	4.1	92/111	1.5	0.54 (0.42, 0.71)	< 0.0001
IRC-PD	97/135	4.0	62/71	1.5	0.52 (0.37,0.73)	0.0001
ITT oxali	96/135	3.2	61/71	1.5	0.56(0.40,0.78)	0.0003
IRC-PD oxali	62/84	2.9	43/46	1.5	0.48(0.31,0.72)	0.0004
Per Protocol	93/132	4.0	60/66	1.5	0.50(0.36,0.71)	<0.0001

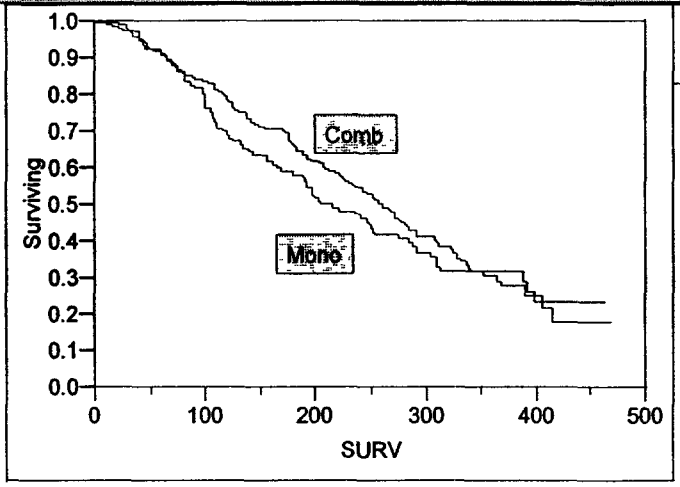
[1] Hazard ratio and associated 95% CI
[2] p-value based on logrank test
[3] Medians are reported in months

TTP in the IRC-PD oxaliplatin-failure population was in favor of the combination therapy arm. Median TTP was 2.9 months with the combination and 1.5 months with monotherapy. The estimated hazard ratio of 0.48, 95% CI of (0.31, 0.72), was statistically significantly different from 1.0 in favor of the combination arm (p=0.0004, stratified logrank test). Similar results were observed in the IRC-PD 2-cycle population. The median TTP was 4.0 months with combination therapy and 1.5 months with monotherapy. The estimated hazard ratio of combination:monotherapy was 0.52 with a 95% CI of (0.37, 0.73), which was statistically significant in favor of the combination therapy arm (p=0.0001, stratified logrank test).

Reviewer's Comment: This reviewer confirmed the sponsor's TTP analytic findings in the treatment subsets.

Survival Time: Evaluation of survival was based on data collected up until January 31, 2003. 215 (65.3%) of the 329 ITT patients had died up to this point (140 in the combination therapy group and 75 in the monotherapy group). The median survival time from randomization in the ITT population was longer in the combination therapy group than in the monotherapy group: 8.6 months, 95% CI of [7.6, 9.6] vs. 6.9 months, 95% CI of [5.6, 9.1]. The difference between the two groups via the logrank test was not statistically significant (p = 0.48). The estimated hazard ratio was 0.91 with associated 95% CI of [0.68, 1.21]. This estimate indicates a slightly reduced risk of death for patients on the combination therapy arm vs. those on the monotherapy arm at a given timepoint. The following reviewer's Figure 2 shows the Kaplan-Meier plot for survival in each of the treatment groups:

Figure 2



Time to event: SURV

Censored by

Grouped by RGROUPC

Group	N Failed	N Censored	Mean	Std Error
CETUXIMAB	75	36	233.317 Biased	12.8591
CETUXIMAB+IRINOTECAN	140	78	253.785 Biased	9.16914
Combined	215	114	248.264 Biased	7.56079

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
CETUXIMAB	216	169	276	107	400
CETUXIMAB+IRINOTECAN	262	227	286	138	407
Combined	251	218	276	122	400

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.5068	1	0.4765
Wilcoxon	1.7303	1	0.1884

Note: This reviewer's plot uses days, not months, as the time unit.

Reviewer's Comment: This reviewer confirmed the sponsor's survival analytic findings.

3.2 Evaluation of Safety

Safety will not be discussed in this review. Refer to the detailed clinical safety review for a comprehensive assessment of all safety data.

4. FINDINGS IN SPECIAL SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The age, gender and race characteristics of the two treatment groups are summarized in the following table:

Table 7: Age, Gender, and Race Characteristics by Treatment Arm (ITT)

Characteristics	Combo Therapy	Monotherapy	Total	Part 2 Cohort*
	N = 218	N = 111	N = 329	N = 54
Age (years)				
Median	59	58	59	58.5
Range	26 – 82	39 – 84	26 – 84	39 – 80
Age Categories				
< 65	155 (71.1%)	78 (70.3%)	233 (70.8%)	39 (72.2%)
≥ 65	63 (28.9%)	33 (29.7%)	96 (29.2%)	15 (27.8%)
Gender				
Males	143 (65.6%)	63 (56.8%)	206 (62.6%)	36 (66.7%)
Females	75 (34.4%)	48 (43.2%)	123 (37.4%)	18 (33.3%)
Race				
Caucasian	214 (98.2%)	109 (98.2%)	323 (98.2%)	53 (98.1%)
Black	2 (0.9%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Asian	2 (0.9%)	2 (1.8%)	4 (1.2%)	1 (1.9%)

- The Part 2 cohort comprises the patients who progressed on cetuximab monotherapy and continued on combination therapy in Part 2 of the study. Age for this cohort refers to that at study baseline.

Age characteristics for the two treatment groups were comparable. The study population contained a higher proportion of males than females. All but six patients were Caucasian. Age, race, and gender characteristics of the IRC-PD, ITT oxali, and IRC-PD oxali populations (not shown) were similar to those of the ITT population.

Analytic findings for the primary efficacy endpoint for key demographic subgroups are presented in the following table:

Table 8: Objective Tumor Response Rates in Patient Demographic Subgroups (ITT) by IRC Assessment

Subgroup	Combination Therapy N = 218		Monotherapy N = 111	
	n / N (%)	95% CI	n / N (%)	95% CI
< 65 years	36 / 155 (23.2%)	16.8, 30.7	7 / 78 (9.0%)	3.7, 17.6
≥ 65 years	14 / 63 (22.2%)	12.7, 34.5	5 / 33 (15.2%)	5.1, 31.9
Men	36 / 143 (25.2%)	18.3, 33.1	10 / 63 (15.9%)	7.9, 27.3
Women	14 / 75 (18.7%)	10.6, 29.3	2 / 48 (4.2%)	0.5, 14.3
KPS < 80	4 / 25 (16.0)	4.5, 36.1	1 / 15 (6.7%)	0.2, 31.9
KPS ≥ 80	46 / 193 (23.8%)	18.0, 30.5	11 / 96 (11.5%)	5.9, 19.6

Reviewer's Comment: This reviewer confirmed the sponsor's findings.

4.2 Other Special/Subgroup Populations:

Analytic findings for the primary efficacy endpoint are presented for additional important subgroups in the following table:

Table 9: Objective Tumor Response Rates in Key Patient Subgroups (ITT) by IRC Assessment

Subgroup	Combination Therapy N = 218		Monotherapy N = 111	
	n / N (%)	95% CI	n / N (%)	95% CI
# Prior Trt Lines				
1	7 / 41 (17.1%)	7.2, 32.1	5 / 27 (18.5%)	6.3, 38.1
2	20 / 79 (25.3%)	16.2, 36.4	5 / 41 (12.2%)	4.1, 26.2
3 or more	23 / 98 (23.5%)	15.5, 33.1	2 / 43 (4.7%)	0.6, 15.8
Previous oxali	30 / 135 (22.2%)	15.5, 30.2	6 / 71 (8.5%)	3.2, 17.5
No previous oxali	20 / 83 (24.1%)	15.4, 34.7	6 / 40 (15.0%)	5.7, 29.8
Most recent irinotecan				
125 mg/m^2 weekly	5 / 33 (15.2%)	5.1, 31.9	4 / 20 (20.0%)	5.7, 43.7
180 mg/m^2 every 2 weeks	29 / 124 (23.4%)	16.3, 31.8	5 / 54 (9.3%)	3.1, 20.3
350 mg/m^2 every 3 weeks	15 / 57 (26.3)	15.5, 39.7	2 / 31 (6.5%)	0.8, 21.4
Time since previous irinotecan course				
≤ 30 days	20 / 105 (19.0%)	12.0, 27.9	4 / 58 (6.9%)	1.9, 16.7
> 30 days	30 / 111 (27.0%)	19.0, 36.3	8 / 53 (15.1%)	6.7, 27.6
# metastatic sites				
1	30 / 102 (29.4%)	20.8, 39.3	10 / 62 (16.1%)	8.0, 27.7
2	15 / 78 (19.2%)	11.2, 29.7	2 / 27 (7.4%)	0.9, 24.3
3 or more	1 / 9 (11.1%)	0.3, 48.2	0 / 6 (0.0%)	0.0, 45.9
EGFR % positive cells				
0 to ≤ 10%	25 / 109 (22.9%)	15.4, 32.0	4 / 56 (7.1%)	2.0, 17.3

> 10% to ≤ 20%	4 / 20 (20.0%)	5.7, 43.7	5 / 16 (31.3%)	11.0, 58.7
> 20 to ≤ 35%	6 / 27 (22.2%)	8.6, 42.3	0 / 7 (0.0%)	0.0, 41.0
> 35%	15 / 62 (24.2%)	14.2, 36.7	3 / 32 (9.4%)	2.0, 25.0
EGFR Staining				
Faint / barely	11 / 53 (20.8%)	10.8, 34.1	1 / 21 (4.8%)	0.1, 23.8
Weak to moderate	22 / 89 (24.7%)	16.2, 35.0	7 / 55 (12.7%)	5.3, 24.5
Strong	17 / 75 (22.7%)	13.8, 33.8	4 / 34 (11.8%)	3.3, 27.5
Acne-like Rash				
None	8 / 48 (16.7%)	7.5, 30.2	2 / 27 (7.4%)	0.9, 24.3
Any	42 / 170 (24.7%)	18.4, 31.9	10 / 84 (11.9%)	5.9, 20.8
Grade 3 or 4	13 / 22 (59.1%)	36.4, 79.3	1 / 4 (25.0%)	0.6, 80.6
Skin Reaction				
None	2 / 32 (6.3%)	0.8, 20.8	0 / 18 (0.0%)	0.0, 18.5
Any	48 / 186 (25.8%)	19.7, 32.7	12 / 93 (12.9%)	6.8, 21.5
Grade 3 or 4	16 / 29 (55.2%)	35.7, 73.6	2 / 6 (33.3%)	4.3, 77.7

Reviewer's Comment: This reviewer confirmed the sponsor's analytic findings.

The combination therapy shows consistently higher response rates as compared to monotherapy. Several baseline and on-study factors were found to correlate with objective tumor response. Higher response rates in both treatment arms were observed in male patients, in patients with only one metastatic site (vs. 2 or more sites), in patients with KPS ≥80 (vs. < 80), and in patients with more severe skin reactions (vs. none or less severe reactions. Lower response rates were observed in patients who received 125 mg/m^2 weekly irinotecan in the combination therapy group (this schedule is common in certain countries, including the U.S.). The sponsor states that gender, KPS, number of metastatic sites, and elevated alkaline phosphatase are predictive factors for a more favorable outcome that have already been reported in other CRC studies. Also, the correlation between severity of skin reactions and tumor response was found in earlier studies with cetuximab.

Patients with more than 30 days since their most recent irinotecan treatment had a higher response rate than patients with a duration of less than 30 days. The two EGFR expression factors (i.e., percentage of EGFR-positive cells and maximal staining intensity) did not appear to have an impact on tumor response rates in this study population with EGFR-positive, metastatic CRC. In the remaining subgroups, there were no clear relationships between the investigated factors and tumor response rates.

Finally, results for subgroup analyses in the IRC-PD population were similar to those in the ITT population. Differences were not regarded to be clinically relevant and can probably be explained by the smaller number of patients in this analysis population.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This application's source of major evidence consisted of one randomized pivotal study. It also included two non-randomized supportive studies. The focus of this statistical review was solely on the randomized BOND study. The clinical review discusses the supportive uncontrolled studies. For the BOND study, pre-planned statistical analytic approaches were adhered to by the sponsor. This reviewer uncovered no problematic statistical issues and confirmed the sponsor's major efficacy analytical findings.

5.2 Conclusions and Recommendations

This reviewer confirmed the sponsor's major efficacy analyses for the pivotal BOND study. No problematic statistical issues were uncovered. The estimated objective tumor response rate was 22.9% in the cetuximab plus irinotecan treatment group vs. 10.8% in the cetuximab monotherapy group based on analysis of the ITT population. The objective tumor response rates in secondary pre-study CRC treatment populations, including the most stringent irinotecan refractory subgroup, were similar to the ITT population. In all of the pre-study CRC treatment subpopulations analyzed, the lower 95% confidence limit for combination therapy groups exceeded 12.5%, the value regarded as clinically relevant in the study protocol. In the ITT population, the median time to progression (TTP), a secondary endpoint, was statistically significantly longer in the combination therapy group vs. the monotherapy group. And, for the most stringent irinotecan refractory subgroup, this statistically significant TTP improvement was also demonstrated. The randomized study reviewed provides statistical support for the sponsor's efficacy claim. The randomized study provides statistical support for the sponsor's efficacy claim.

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