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

FDA CLINICAL BRIEFING DOCUMENT FOR THE ONCOLOGIC DRUG ADVISORY COMMITTEE SEPTEMBER 13, 2005 MEETING

NDA NUMBER:	**21-743/S-003**
DRUG NAME:	**Tarceva™ (erlotinib) Tablets**
INDICATION:	**Advanced/Metastatic Pancreatic Cancer**
APPLICANT:	**OSI Pharmaceuticals Inc**
CLINICAL REVIEWER:	**Adrian Senderowicz, M.D**.
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1 EXECUTIVE SUMMARY:

OSI Pharmaceuticals, Inc., seeks the following indication: Erlotinib in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

OSI Pharmaceuticals, Inc has submitted a single, multi-center (US and international), double-blinded, placebo controlled, randomized, phase 3 study of erlotinib plus gemcitabine (EG) versus gemcitabine/placebo (PG) as first-line chemotherapy for locally advanced or metastatic pancreatic carcinoma. This study will be referred as PA.3 in this review. No other well-controlled supportive trial was submitted in this application.

The primary endpoint of the trial was overall survival. Secondary endpoints were progression-free survival, quality of life, response rate and response duration. The trial had 80 % power to demonstrate a 33% improvement in survival (i.e. from median 6.8 months with gemcitabine alone to median 8.8 months for the combination treatment (hazard ratio of ~ 0.75). A total of 450 patients would be accrued to achieve the required number of deaths (N = 381) for the final analysis. Thus, the primary analysis for this study was overall survival when 381 deaths occurred.

A total of 569 patients were randomized to receive EG or PG. Patients were enrolled from 140 sites: 59 centers in the US, 25 centers in Canada, and 56 in the rest of the world. Stratification factors were ECOG PS (0/1 vs 2) and extent of disease (locally advanced vs. metastatic). Out of a total of 569 patients, 521 patients were randomized in the 100 mg group cohort (261 patients in the EG group and 260 in the PG group). Because of the small numbers for the 150 mg groups (total 48: 24 patients in each EG and PG), this ODAC briefing document will discuss the 100 mg group only.

Forty-nine % of patients in the EG group were male. In contrast, 56 % of patients in the PG arm were males. Fifty-two % of patients in the EG arm and 53 % of patients in the PG arm were younger than 65 years of age. Most patients had ECOG PS 0/1: (84% vs. 83 %, respectively). Most patients had advanced local disease (71 % vs 71%). Finally, a similar % of patients had pain intensity score > 20 (53% vs 53%, respectively). Of note, pathological confirmation of adenocarcinoma of pancreas was missing or inconclusive in some cases.

Although the primary survival analysis was to be performed after 381 deaths, the analysis was performed when 484 deaths occurred, an excess of 100 deaths over the original number planned for this analysis. An updated survival database (cutoff June 2005) with 504 deaths was subsequently submitted to the FDA. The median overall survival for the 100 mg group (504 deaths), estimated from univariate Kaplan-Meier curves, was 6.37 months (95% CI: 5.84 to 7.33) in the EG arm and 5.95 months (95% CI : 5.09 to 6.70), in the PG arm, a difference of ~ 12 days in favor of the EG group (p= 0.0596, unadjusted log-rank test). When the median overall survival was analyzed at 381 events, as planned in the protocol, similar results were obtained: medians 6.47 months (95% CI: 5.95 to 7.36) and 5.95 (95 % CI: 5.09 to 6.70) with a p value of p 0.062 (unadjusted log-rank

test). Moreover, the hazard ratio (HR) for overall survival in the 100 mg erlotinib/gemcitabine arm relative to the placebo arm (504 deaths), estimated from a univariate Cox model, was 0.84 (95% CI 0.70 to 1.007, p = 0.06). In the 100 mg dose cohort (381 events), the HR was 0.83 (CI 95%: 0.67 to 1.01, p = 0.063). Multivariate Cox model was constructed that included treatment and both of the protocol specified covariates, namely ECOG PS and extent of disease. The adjusted HR for overall survival in the 100 mg EG arm relative to the PG arm (504 deaths) was 0.81 (95% CI: 0.68 to 0.97, p = 0.02). In the 100 mg cohort (381 events), the adjusted HR was 0.79 (95 % CI: 0.65 to 0.97, p = 0.026). The adjusted analysis was specified in the protocol as the primary analysis.

Secondary objectives were analyzed as well:

a) median PFS for 100 mg group, estimated from univariate Kaplan-Meier curves, was 3.81 months for EG (95 % CI: 3.58 to 4.92) and 3.55 months (95 % CI: 3.22 to 3.75) for PG (adjusted HR: 0.76 , 95% CI: 0.63 to 0.92, p =0.004). Although statistically significant, the median PFS represents a difference of only 10 days.
b) Tumor response was assessed according to RECIST criteria by the investigators in patients with measurable disease. There was no statistical difference between EG and PG arms. One complete response (CR) and 22 partial responses (PRs) in the 100 mg EG arm and a similar number (3 CRs and 18 PRs) were observed in the PG arm, for overall objective response rates of 8.6% and 8.0%, respectively (p=0.869); and
c) Symptoms and functioning concerns commonly reported by cancer patients and determined to be components of health-related quality of life were measured using the EORTC QLQ-C30 Version 3.0. In the EG group, a statistically significant worsening in diarrhea (p <0.001) was accompanied by other decrements that approached statistically significance including cognitive functioning, social functioning, dyspnea, nausea/ vomiting and loss of appetite. These data were consistent with the worse adverse event profile of EG arm described below.

The EG arm was associated with a greater toxicity and discontinuations due to adverse events (AEs) as compared with PG group: The frequency of grade ≥ 3/4 AEs (70% vs 64 %) and serious AEs leading to discontinuation (31% vs 22%) were higher on the EG arm. Higher incidence of death during treatment or within 30 days of last treatment occurred in the EG group (33.2% vs 27.3 %). Of these patients, 7 % died due to complications of protocol treatment in the EG group while no patient died due to protocol treatment in the PG group. Thus, we can conclude that the combination group has higher incidence of toxic deaths compared with PG alone. Moreover, we believe that this is an underestimation of the incidence of drug induced death as the cause of death was unclear in several cases when there was tumor progression along with drug toxicity.

A greater incidence of severe AEs in the EG group (> 1.5 fold over PG) was observed in these categories (see table 28 and figure 21): stroke, cardiac ischemia/ infarction, stent occlusion, ARDS, pneumonitis, DVT, edema, arrhythmias, other infections, rash, diarrhea, ileus, pancreatitis, odynophagia/stomatitis, thrombocytopenia, neuropathy and renal insufficiency. Severe AEs that were statistically significantly different were (EG vs

PG) : stroke (N=6 vs 0, p=0.03), GI system as a whole (N=125 vs 9, p=0.02), ischemic events (N=15 vs 3, p=0.006), other infections (N=13 vs 2, p=0.006), rash (N=12 vs 3, p=0.03) and diarrhea (N=15 vs 5, p=0.03).

Moreover, stroke, peripheral neuropathy, arrhythmias, ileus, edema, pancreatitis, renal failure, thrombotic thrombocytopenic purpura (TTP) and stent occlusion are new and previously unrecognized toxicities in the erlotinib combination group in the PA.3. Since the dosing of gemcitabine was identical on the two arms; toxicity increases were likely due to the addition of erlotinib.

Notwithstanding the limitation of cross-study comparisons, the incidence of interstitial lung disease-like events (ILD) in PA.3 appears to be greater than in erlotinib monotherapy in NSCLC study BR.21 (2.3% vs. 0.8%).

An important caveat for this study is the lack of information in relation to hospitalization. Of note, the definition of Serious Adverse Event (SAE) includes" death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/ birth defect". The applicant did not capture the hospitalizations in this trial. Thus, the number of SAEs in this trial is a clear under representation of the true SAE incidence. These safety results suggest that the EG combination is significantly more toxic and is associated with decreased in quality of life, compared with the PG arm.

There are several relevant issues regarding this sNDA application. The first issue is, although some analyses showed statistically significant differences between the EG and PG arms, no clinically meaningful differences in response rate, duration of response, PFS or overall survival were observed. Second, some patients were considered ineligible by the FDA due to lack of pathological confirmation of the diagnosis. Reanalysis excluding these patients will lead to a different result. An analysis excluding these patients will be presented at the ODAC meeting. Third, the lack of a second supportive well-controlled clinical trial for this combination in patients with adenocarcinoma of pancreas. This is quite relevant as the difference in survival observed between the EG combination and PG is of marginal clinical importance while the combination has a significant increase in SAEs, death due to toxicity, discontinuation due to AEs and increase in withdrawing consent due to AEs.

2 Agency Approval Requirements

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers must demonstrate effectiveness by providing "substantial evidence." Substantial evidence was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations." With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. In 1997, the Food and Drug Administration Modernization Act stated that a single trial may suffice if other supportive

evidence exists such as evidence from other trials where the drug has been used in different age groups, at different doses, and in different regimens, or different modified release dosage forms. The 1998 Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products states, that to be considered, the single trial must be well-conducted, internally consistent, and demonstrates a compelling result. In general, the FDA has relied on a single adequate and well controlled efficacy study (along with supportive evidence) to support approval in cases in which a single multicenter study of excellent design and carefully conducted provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

3 Pancreatic carcinoma

Pancreatic carcinoma, if detected in an early stage, is usually curable surgically. However, locally advanced or metastatic disease usually is not resectable or curable and is almost uniformly fatal. Radiation therapy has a very limited role in the treatment of pancreatic carcinoma. For the treatment of locally advanced or metastatic disease, use of gemcitabine monotherapy is standard of care in the US. Of note, gemcitabine was approved for this disease based on a significant improvement in clinical symptoms with increase in overall survival (see below, section 3.1.1).

3.1 Approved Therapies for advanced/metastatic pancreatic carcinoma

At the present time, the Agency has approved only single agent gemcitabine for the treatment of advanced/metastatic adenocarcinoma of the pancreas. No combination therapies have been approved.

3.1.1 Gemcitabine

3.1.1.1 Gemcitabine monotherapy:

Gemcitabine is a nucleoside analog with activity against many solid tumors. In 1996, the FDA granted approval for gemcitabine for use in advanced and Metastatic Pancreatic Cancer. At that time, data from two clinical trials evaluated the use of gemcitabine in patients with locally advanced or metastatic pancreatic cancer. The first trial compared gemcitabine to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy (see Table 1 and Figure 1). A second trial studied the use of gemcitabine in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of gemcitabine was administered intravenously at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with gemcitabine. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was "clinical benefit response", which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status and weight change.

The first study was a multi-center, prospective, single blinded, two-arm, randomized, comparison of gemcitabine and 5-FU in 126 patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m^2 for 30 minutes. The baseline characteristics and results from this randomized trial are shown in Table 1. Of note, ~70% of patients in this trial had poor prognostic factors: KPS < 70 (ECOG 2) and metastatic disease. Patients treated with gemcitabine not only had statistically significant increases in clinical benefit response but also increase in survival, and time to disease progression compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 1. No confirmed objective tumor responses were observed with either treatment.

The second study, a supportive trial, was a multi-center, open-label study of gemcitabine in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median survival of 3.9 months.

Figure 1. Gemcitabine vs 5-FU in locally advanced/metastatic Pancreatic carcinoma

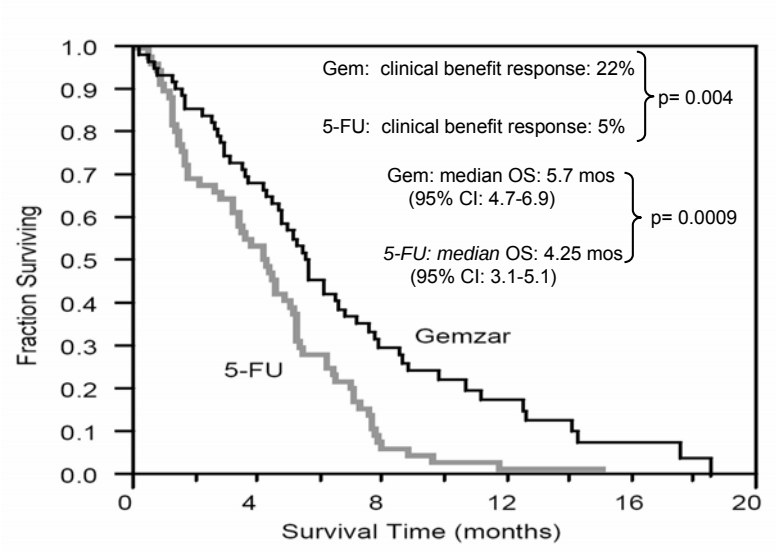


Table 1 Gemcitabine vs. 5-FU in Pancreatic Cancer. Baseline Characteristics and Antitumor activity

	Gemcitabine	**5-FU**	
Number of patients	63	63	
Male /Female	34 /29	34 /29	
Median age	62 years	61 years	
Range	37 to 79	36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS* ≤70	69.8%	68.3%	
Clinical benefit response	22.2%	4.8%	p = 0.004
	(Nc= 14)	(N = 3)	
Survival			p = 0.0009
Median	5.7 months	4.2 months	
6-month probability	(N = 30) 46%	(N = 19) 29%	
9-month probability	(N = 14) 24%	(N = 4) 5%	
1-year probability	(N = 9) 18%	(N = 2) 2%	
Range	0.2 to 18.6 months	0.4 to 15.1+ months	
95% C.I. of the median	4.7 to 6.9 months	3.1 to 5.1 months	
Time to Disease Progression			p = 0.0013
Median	2.1 months	0.9 months	
Range	0.1+ to 9.4 months	0.1 to 12.0+ months	
95% C.I. of the median	1.9 to 3.4 months	0.9 to 1.1 months	

*Karnofsky Performance Status, cN = number of patients, [b]Kaplan-Meier estimates. (source: Table 3, FDA revised label version 082598, page 8)

Reviewer's note: approx. 70 % of patients in this gemcitabine pivotal study have both metastatic disease and PS ≥ 2. In contrast, in the PA.3 study, ~ 60 % of patients had metastatic disease and only 17% had PS 2. This suggests that the population in this trial had worse prognostic factors at baseline compared with PA.3

3.1.2 Combinations of gemcitabine with other chemotherapeutic agents

3.1.2.1 Gemcitabine combinations:

Table 2 summarizes the data of the currently submitted study PA.3 and two other recently published Phase III studies comparing gemcitabine alone or combined with oxaliplatin or irinotecan (1-3). It also includes the study which led to regulatory approval of gemcitabine for first-line treatment of pancreatic cancer (gemcitabine vs. 5-FU) (4).

Louvet et al compared gemcitabine vs gemcitabine/oxaliplatin (Gemox). In this study (see table 2), there was a statistical significant difference in response rate, progression-free survival and clinical benefit in favor of Gemox with an increase in medina overall survival of 1.9 months. However, this increase was not statistically significant. In contrast, in PA3, there was no increase in response rate or improvement in clinical benefit but the increase in overall survival was statistically significant (HR: 0.81, similar to the Gemox trial). It is possible that the Gemox trial was underpowered as the number of patients enrolled in this trial were approx. half the number of patients enrolled in PA3 (see table 2). Other explanations for the lack in significant increase in OS in the Gemox arm are the per-protocol analysis in this report or that the HR was unadjusted for PS and extension of disease.

Recently, based on the small sample size for most locally advanced or metastatic pancreatic gemcitabine-combination trials, Liang H et al (5) performed a metaanalysis using all available randomized clinical trials (19 randomized clinical trials) with gemcitabine-based combination chemotherapy vs. gemcitabine alone in advanced or metastatic pancreatic cancer (from 1996 to 2004). The primary objective was to determine the 6-month and 1 year survival rates. Secondary objectives included objective response rate, PFS, TTP, clinical benefit response and overall toxicity. There was a significant improvement for gemcitabine-based combination group in median overall survival at 6 months (RD = 4%, p=0.02; RD, Risk difference= risk in the gemcitabine-based combination group - risk in the gemcitabine alone group) and 1 year (RD=3%, p=0.05), Also, there was an statistically significant increase in response rate (RD=5%, p=0.01) and PFS/ and TTP at 6 months (RD=10%, p<0.00001). Moreover, there was a trend in favor for the combinations for clinical response improvement (RD=7%, p=0.06). In contrast, the combination regimens were more toxic: WHO grade 3-4 toxicity was higher for gemcitabine-based combination group for neutropenia thrombocytopenia and nausea/vomiting. Thus, this important metaanalysis of gemcitabine-combination regimens along with recent reports (6, 7) suggests that combination gemcitabine chemotherapy may prolong overall survival.

Table 2 Efficacy Comparison of PA.3 Results With Other Trials Including Gemcitabine or Gemcitabine + Chemotherapy in Pancreatic Cancer

	PA. 3 Gemcitabine (1000 mg/m²) + 100 mg erlotinib versus Gemcitabine (1000 mg/m²) + placebo		**Gemcitabine (1000 mg/m2) versus 5-FU (600 mg/m²) (4)**		**Gemcitabine (1000 mg/m²) versus Gemcitabine (1000 mg/m2) + oxaliplatin (100 mg/m²) (2)**		**Gemcitabine (1000 mg/m²) versus Gemcitabine (1000 mg/m2) + irinotecan (100 mg/m²) (1)**	
	Gem N = 260	**Gem/Erl N = 261**	**5-FU N = 63**	**Gem N = 63**	**Gem N = 156**	**Gem/oxali N = 157**	**Gem N = 180**	**Gem/irinot N = 180**
Median survival (months)	5.95	6.38	4.41	5.65	7.1	9.0	6.6	6.3
95% CI	5.1 – 6.7	5.8 – 7.3					5.2 – 7.8	4.7 – 7.5
	p = 0.02* HR = 0.81*		p = 0.0025 HR = NA		p = 0.13** HR = 0.83		p = 0.789 HR = NA	
% 12-month survival	17	24	2	18	27.8	34.7	22	21
PFS/TTP (months)	(PFS) 3.55	(PFS) 3.81	(PFS) 0.92	(PFS) 2.33	(PFS) 3.7	(PFS) 5.5	(TTP) 3.0	(TTP) 3.5
95% CI	3.2 – 3.7	3.6 - 4.9					2.5 – 3.7	2.8 – 4.2
	p = 0.004*		p = 0.0002**		p = 0.04		p = 0.352	
% Response	8.0	8.6	0	5.4	16.7	28.7	4.4	16.1
95% CI	5.0 – 12.0	5.5 – 12.6					1.9 – 8.6	11.1 – 22.3
	p = 0.875		not significant		p = 0.02		p <0.001	

Note: NA = not available, * cox proportional adjusted for PS and disease status. **unadjusted cox proportional ratios
Source: (taken from applicant's table 13.1)

Reviewer's note: although several trials with combination gemcitabine and chemotherapy showed increase in response rate, in duration of response and in PFS with improvement in clinical benefit, the overall survival was not statistically significant. A possible explanation is that the studies were underpowered. A recent metaanalysis along with recent reports demonstrated that gemcitabine-combinations improve the overall survival compared with gemcitabine alone.

4 NDA Submission-Study PA.3

This supplemental NDA consists of only one study entitled "A Randomized Placebo Controlled Study of OSI-774 (Tarceva™) Plus Gemcitabine in Patients With Locally Advanced, Unresectable or Metastatic Pancreatic Cancer". This study will be referred to as PA.3 in this review. This study was submitted to support the efficacy claims for erlotinib for the indication of treatment of locally advanced or metastatic adenocarcinoma of the pancreas in combination with gemcitabine. PA3, was an international, multicenter, randomized, double-blind, active control, phase 3 trial comparing gemcitabine alone with gemcitabine and erlotinib in 569 patients with locally advanced/metastatic pancreatic carcinoma. No other supportive study was submitted in this sNDA.

The primary objective of PA3 was to compare overall survival in patients with locally advanced, unresectable or metastatic pancreatic cancer treated with erlotinib and gemcitabine (EG) or placebo and gemcitabine (PG). Secondary objectives included comparing PFS, quality of life using the EORTC QLQ-C30, response rates (CR, PR); response duration, the nature, severity, and frequency of toxicities, to correlate the expression of tissue EGFR levels (at diagnosis) with outcomes and response to treatment and to measure trough levels of erlotinib to define population pharmacokinetics of the 2 treatment arms.

The trial enrolled 569 patients who were randomized to either:

- Arm 1 group (EG): Erlotinib – 100/150 mg PO daily PLUS
  Gemcitabine 1000 mg/m^2 IV – Cycle 1 – Day 1, 8, 15, 22, 29, 36, and 43 of an 8-week cycle; Cycle 2 and subsequent cycles – Day 1, 8, and 15 of a 4-week cycle.

- Arm 2 (PG): Placebo 100 mg PO daily PLUS
  Gemcitabine 1000 mg/m^2 IV – At the same dose and schedule as listed for Arm 1.

The initial erlotinib dose proposed by the applicant was 150 mg (dose approved as monotherapy in patients with lung cancer). However, the applicant amended the protocol to assess the feasibility of 100 mg first. 521 patients were treated at 100 mg while only 48 (N = 24 in each arm) were treated at the 150 mg cohort. The number of patients in the 150 mg cohort of is too small to draw any definitive conclusions regarding the efficacy of this combination. Thus, in this report we will report only the safety and efficacy of 100 mg cohort.

4.1 Eligibility Criteria

The following criteria were to be met at baseline before randomization:

1. Histologically or cytologically confirmed diagnosis of adenocarcinoma of the pancreas that was unresectable, locally advanced or metastatic.

Reviewer's comments: Of note, the FDA review of the pathology reports/clinical information found some patients in the 100 mg cohort were ineligible for inclusion in this trial as the pathology reports were unable to support the diagnosis of adenocarcinoma of the pancreas (See section 5.1.1 for further information). In this review, all the efficacy analyses include all ineligible patients. However, FDA will present at ODAC (Sept, 13th, 2005) analysis excluding these patients as well.

2. Evidence of disease. Measurable disease at entry was not mandatory but to be considered evaluable for complete or partial response, patients had to have at least one measurable lesion as follows:

   X-ray, ultrasound, physical examination ≥ 20 mm
   Conventional CT scan ≥ 20 mm
   Spiral CT scan ≥ 10 mm
   Measurable lesions must have been outside a previous radiotherapy field if they were the sole site of disease, unless disease progression has been documented.

3. At least 18 years of age, able to sign informed consent, accessible for treatment follow-up

4. Could have received prior radiation treatment for management of local disease providing that disease progression had been documented, all toxicities had resolved, and the last fraction of radiation treatment was completed at least 4 weeks prior to randomization.

5. Could not have received prior chemotherapy, other than 5-FU (+/- folinic acid) or gemcitabine given concurrently with radiation treatment as a 'radiosensitizer'.

6. Investigations including chest X-ray, CT scan of abdomen, CT scan of brain (only if clinical suspicion of metastasis) and other scans as necessary to document all sites of study disease had to have been performed within 28 days prior to randomization. Negative scans performed within 35 days of randomization did not need to be repeated.

7. ECOG performance status of 0, 1 or 2.

8. Adequate hematological, renal and hepatic functions as defined by the following required laboratory values obtained within 14 days prior to randomization:

- Absolute granulocyte count $\geq 1.5 \times 10^9$/L (1,500 cells/mm^3)
- Platelet count $\geq 100 \times 10^9$/L (100,000/mm^3)
- Serum creatinine < 1.5 times the upper limit of normal
- Total bilirubin < 2.0 times the upper limit of normal
- ALT (SGPT) < 2.0 times the upper limit of normal and/or AST (SGOT) < 2.0 times the upper limit of normal. Note: If clearly attributable to liver metastasis, ALT (SGPT) and/or AST (SGOT) values < 5 times the upper limit of normal were permitted.

9. Negative serum or urine pregnancy test within 72 hours prior to randomization for WOCBP.

10. All North American (Canada and US) patients, as well as patients from other selected countries, had to be able and willing to complete the quality of life questionnaires. The baseline assessment had to be completed within 7 days prior to randomization. Exceptions could be granted on a patient-by-patient basis only if NCIC CTG gave approval prior to randomization.

11. Completed Pain Intensity Scale. If the scale was not available in the patient's language of literacy, a translator could be used.

12. All other investigations (except tissue collection) had to have been performed prior to randomization.

13. In accordance with NCIC CTG policy, protocol treatment was to begin within 5 working days of patient randomization

Exclusion Criteria

Patients with any of the following were not entered into the study:

1. History of malignancy in the last 5 years. Patients with prior history of *in situ* cancer or basal or squamous cell skin cancer were eligible.

2. Significant history of cardiac disease, e.g., uncontrolled high blood pressure, unstable angina, congestive heart failure, myocardial infarction within the previous year or cardiac ventricular arrhythmias requiring medication.

3. Serious active infection at the time of randomization or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment.

4. Known central nervous system metastases. CT scan of the brain was NOT required unless there was clinical suspicion of CNS metastases.

5. Any condition (eg, psychological, geographical, etc.) that did not permit compliance with the protocol.

6. Pregnant or lactating females.

7. WOCBP or sexually active males who were not employing adequate contraception (or practicing complete abstinence).

8. Treatment with any investigational drug within 2 weeks prior to randomization.

9. Any major surgery within 2 weeks prior to randomization

10. Ocular inflammation or infection had to be fully treated prior to entry to the trial. Any patients requiring ophthalmic surgery during the course of the trial were withdrawn from the study. Patients who continued to wear contact lenses could have had an increased risk of ocular adverse events. The decision to continue to wear contact lenses was discussed with the patient's treating oncologist and ophthalmologist.

11. Significant ophthalmologic abnormalities such as:
• Severe dry eye syndrome;
• Keratoconjuctivitis sicca;
• Sjögren's syndrome;
• Severe exposure keratopathy;
• Disorders that could increase the risk for epithelium related complications (eg, bullous keratopathy, aniridia, severe chemical burns, neutrophilic keratitis).

12. GI tract disease resulting in an inability to take oral medication such as uncontrolled inflammatory GI disease (eg, Crohn's disease, ulcerative colitis) or post surgical malabsorption characterized by uncontrolled diarrhea that results in weight loss and vitamin deficiency or requires IV hyperalimentation (however, use of pancreatic enzyme supplementation was allowed provided that the above criteria were not met).

13. History of allergic reactions attributed to compounds with similar chemical or biologic composition to erlotinib.

14. Prior treatment with inhibitors of EGFR of any kind.

15. Known to be HIV positive. Testing was not required in the absence of clinical signs and symptoms suggestive of HIV infection.

16. Patients requiring oral anticoagulants (coumadin, warfarin) were eligible provided there was increased vigilance with respect to INR. If medically appropriate and the treatment was available, the Investigator could also have considered switching these patients to LMW heparin, where an interaction with erlotinib was not expected.

Reviewer's note: items 11, 12 were amended since the original protocol. Item 16 was added since the original protocol. Items 10, 11 and 16 were added/modified due to known erlotinib toxicities and/or pharmacological interaction of erlotinib with anticoagulants.

4.2 Stratification

Once eligibility was confirmed, the interactive voice randomization System (IVRS) assigned a unique 3-digit patient ID number in order to receive erlotinib/gemcitabine or placebo/gemcitabine in a blinded fashion, based upon a computer generated randomization schedule

Patients were stratified according to the following criteria:

1. ECOG performance status = 0-1 vs. ECOG = 2
2. Locally advanced* vs distant metastases;
3. Center

* locally advanced was defined as unresectable pancreatic disease with or without regional lymph node involvement. Regional lymph nodes are: peripancreatic, hepatic artery, infrapyloric, subpyloric, celiac, superior mesenteric, pancreaticolienal, splenic, retroperitoneal, lateral aortic.

Reviewer's note: as per agreement with FDA (9/2004), "overall survival should be conducted using only randomized stratification factors (ECOG PS and extent of disease)". Thus, center was not used as randomization factor for analysis.

4.3 Screening and follow up Assessment

Most prestudy evaluations were obtained within 4 weeks of treatment (see Table 3). Within 14 days before randomization, patients with symptoms suggestive of corneal disease and/or abnormalities were examined for visual acuity, hyperemia, slit-lamp examination with fluorescein staining, and a Schirmer's test. Patients with ophthalmological abnormalities not considered clinically significant were eligible for study participation.

Table 3 Follow up and Timing of assessment performed during study

Required Investigations	Prestudy	Day 29 of Cycle 1 Day 1 of Cycle 2 Day 1 of subsequent cycles	Off Treatment	
			4 week Follow up	Every 12 weeks
Physical				
History, physical exam	✓	✓	✓	✓
Weight	✓	✓	✓	
Height	✓			
ECOG Performance Status	✓	✓	✓	
Prior therapy	✓			
Concomitant medications	✓	✓	✓	
Clinical tumor measurement	✓	Day 1 of cycle 2 Day 1 of cycle 4 then Day 1 of every 2 cycles.	✓	✓[7]
Hematology				
Hemoglobin WBC, granulocytes. Platelets INR	✓	✓[1,10]	✓	
Biochemistry				
Total bilirubin Serum creatinine Total protein ALT (SGPT) and/or AST (SGOT) Albumin	✓	✓[9]	✓	
Radiology				
CXR CT Abdomen Other scans to document all sites of disease[5] CT scan of brain[3]	✓	Day 1 of cycle 2 Day 1 of cycle 4 then Day 1 of every 2 cycles.	✓	✓[7]
Quality of Life				
EORTC QLQ C30	✓	✓	✓	✓[7,8]
Other Investigations				
ECG	✓	as clinically indicated	as clinically indicated	
Pregnancy test[2]	✓			
Tissue Block Collection	✓			
Ophthalmological examinations[6]	✓	as clinically indicated		
Pharmacokinetic sampling / AAG	✓	Prior to administration of both erlotinib and gemcitabine on days 8 and 43 of cycle 1 and day 1 of cycle 2		
Plasma sample	✓	Day 8 of cycle 1, Day 1 of cycle 2		
Toxicity				
Graded according to CTC V2.0	✓	✓	✓	✓[4]

1. Hemoglobin, WBC, granulocytes and platelets were done weekly on days of gemcitabine administration.
2. Only if WOCBP.
3. Only if clinical suspicion of metastases.
4. Ongoing or new toxicity that was definitely, probably or possibly related to protocol therapy.
5. Bone scans did not need to be repeated routinely except to confirm CR or PR (mandatory) or as clinically indicated.
6. Ophthalmological examinations were done at baseline only if patients presented clinical symptoms suggestive of corneal disease and/or abnormalities. It consisted of a visual acuity test, examination for hyperemia, slit-lamp examination with fluorescein staining and Schirmer's test.
7. Not required after tumor progression.
8. To be completed until PD. At least 1 Questionnaire was to be completed by all patients. Patients must have completed their final Questionnaire within 2 weeks of PD. If off treatment for PD, and QoL already completed within 2 weeks of date of PD, Questionnaire did not need to be completed at the 4-week visit. Canada, US and other selected countries only.
9. Total bilirubin and ALT (SGPT) and/or AST (SGOT) were done weekly for the first 7 weeks of Cycle 1 (ie, days 1, 8, 15, 22, 29, 36, and 43).
10. INR: Only for patients receiving warfarin while on protocol therapy. Was done twice a week, weekly for 3 weeks, then weekly or more often as clinically indicated.
Source: taken from applicant's table 9-5)

- ***Quality of Life Questionnaire***

QoL was measured using the EORTC QLQ-C30 Version 3.0(8). Initially, the NCIC stated that QoL would only be done in Canada and the US. However, the NCIC subsequently opened it up to any interested center. The questionnaire was completed within 7 days prior to randomization, every 4 weeks on therapy, at the 4-week post-treatment follow-up visit, and until PD. The form was completed during clinic visits before having any other evaluations or assessment of adverse events.

- ***Radiology and Disease Assessments***

Tumor lesions were measured within 28 days prior to randomization (35 days for negative tests) using radiological techniques (eg, CXR and CT scan of the chest and abdomen). A clinical assessment of any disease site was included in the physical examination, which was performed within 14 days of randomization. Assessments were repeated on Day 1 of Cycles 2 and 4, and then on Day 1 of every 2 cycles, at the 4-week post-treatment follow-up, and every 12 weeks thereafter unless disease progression had occurred. RECIST guidelines were used for all assessments. At every assessment and at relapse or disease progression, the date, and extent of disease in all target and non-target lesions were documented.

Bone scans were not repeated routinely except to confirm CR or PR (mandatory for positive scans only) or as clinically indicated.

4.3.1 Treatment

Gemcitabine was reconstituted and administered at the investigational site. Erlotinib/placebo was self-administered on an outpatient basis. Patients received either erlotinib or placebo at a fixed dose 100 or 150 mg taken orally once daily until PD or intolerable toxicity (see Table 4).

Patients were initially randomized to receive 100 mg erlotinib/placebo until a safety evaluation allowed for randomization of patients to receive (150 mg) erlotinib/placebo. Treatment could continue daily until PD or unacceptable toxicity.

Erlotinib/placebo and/or gemcitabine could be withheld or reduced for toxicity. Intrapatient dose escalation was not permitted for erlotinib/placebo but was permitted for gemcitabine.

Efficacy was evaluated by periodic assessments of survival and QoL scores. In addition, serial measurements of all disease sites were performed every 8 weeks, and tumor response was assessed using the RECIST (9).

Safety was assessed every 4 weeks by evaluating changes in hematology and biochemistry parameters, changes in physical examination, and by monitoring the incidence, severity, and relationship of adverse events to erlotinib/placebo and gemcitabine. Toxicity was graded using the NCI CTC, Version 2.0.

After discontinuing protocol treatment, patients were evaluated at Week 4, and survival status was assessed every 12 weeks until death.

Table 4 Study design

Patients were randomized to 1 of the following 2 arms:					
Arm	Agent(s)	Dose	Schedule	Route	Duration
1	Erlotinib	100 mg or 150 mg*	Daily	PO	Until unmanageable toxicity or progression. If toxicity related to oral or IV drug, non-causal study drug was to continue until unmanageable toxicity or progression.
	Gemcitabine	1000 mg/m2	Cycle 1 – Day 1, 8, 15, 22, 29, 36, and 43 of an 8-week cycle, Cycle 2 and subsequent cycles – Day 1, 8, and 15 of a 4-week cycle	IV	
2	Placebo	100 mg or 150 mg*	Daily	PO	
	Gemcitabine	1000 mg/m2	Cycle 1 – Day 1, 8, 15, 22, 29, 36 and 43 of an 8-week cycle, Cycle 2 and subsequent cycles – Day 1, 8, and 15 of a 4-week cycle	IV	

* Initially the applicant proposed 150 mg. However, initial safety assessments demonstrated that 100 mg erlotinib there was a considerable number of patients with severe transaminitis.

Reviewer's note: although erlotinib dose initially proposed by the applicant was 150 mg PO QD, the applicant initially assessed the safety of 100 mg erlotinib/gemcitabine. When this combination was deemed "safe", then, the applicant amended the protocol to treat some patients (N=48, 24 each arm) with 150 mg PO QD and gemcitabine.

4.3.1.1 Selection of doses in the study:

At initiation of the study, the tolerability of the combination of gemcitabine 1000 mg/m^2 IV weekly and erlotinib 100 or 150 mg daily had to be established. The plan was to evaluate an initial cohort of 8 to 16 patients randomized to erlotinib 100 mg or placebo at selected Canadian centers, with the possibility of dose escalation in a subsequent cohort to erlotinib 150 mg daily, depending upon the observed toxicity.

Evaluation of the 150 mg erlotinib dose was to be performed in the same manner using a cohort of 8 to 16 patients, if the 100 mg erlotinib dose was considered well tolerated. Patient treatment assignment information was blinded to OSI and NCIC CTG with appropriate rules in place for unblinding by the NCIC DSMC, if necessary.

A dose was considered safe if 0/8 or ≤ 1/16 patients in the combined dose arms had a DLT deemed related to study drug. Higher rates of DLT did not automatically render a dose unsafe but mandated closer consideration by NCIC CTG and OSI, and if necessary, unblinding by dose group or by patient, which involved the DSMC. Due to the known safety profile of gemcitabine, the relative likelihood of a relationship to study drug of the different toxicities was considered in the determination of a safe dose (eg, hematological toxicities had less impact as opposed to nonhematological toxicities). Hematological toxicities would only be considered a DLT if the incidence was higher than expected from the established gemcitabine data. A dose would be considered unsafe if ≥ 3/8 patients per treatment group experienced a DLT with the following exceptions when 3 DLTs were observed:

• 1 hematological and 2 nonhematological DLTs could result in continued evaluation of the 100 mg dose;
• 2 hematological and 1 nonhematological DLT could result in dose escalation to 150 mg.

These criteria assumed all the DLTs were in the erlotinib treatment arm and none in the placebo arm. The final decision was based on the difference in the rate of toxicities between the blinded arms or by patient, as determined by the DSMC.

The selection of the maximum daily dose of erlotinib of 150 mg in the study was based on safety and pharmacokinetic findings in Phase I trials. The most relevant of these was a single-agent dose escalation study in heavily pretreated patients with advanced solid tumors (OSI Study 248-004). In this study, diarrhea unresponsive to loperamide therapy was defined as the Phase I DLT at an erlotinib dose and schedule of 200 mg daily. Diarrhea was, however, well controlled at 150 mg daily with loperamide as needed.

The first safety evaluation in Study PA.3 took place on February 8th, 2002, after the initial 8 patients, from selected centers in Canada, had been treated for at least 4 weeks with erlotinib/placebo and gemcitabine. Since 1 drug-related transaminase increase and 1 febrile neutropenia were observed, the decision was made to expand the cohort to 16 evaluable patients. Following a second safety analysis of the first 16 patients treated in the study with erlotinib/placebo at 100 mg daily in combination with gemcitabine on March 27th, 2002, the applicant decided to expand the cohort to up to 50 patients due to transaminase elevations in3/16 patients in the combined treatment arms. One of these was considered a definite DLT while the 2 others were equivocal. An episode of febrile neutropenia was deemed consistent with the known safety profile of gemcitabine and therefore not considered a DLT. No individual patient unblinding was performed. At the same time, the decision was made to open enrollment in non-Canadian (international) sites at the 100 mg erlotinib/placebo dose. A third safety evaluation of the first 50 patients treated with 100 mg erlotinib/ placebo took place on 10 September 2002. Five patients in the combined arms were deemed to have a DLT, which was less than required for unblinded evaluation by the DSMC, and this dose was therefore considered tolerable. This resulted in opening accrual in selected Canadian centers at the 150 mg erlotinib/placebo dose.

A similarly rigorous safety evaluation of the 150 mg dose was performed on December 12th, 2002 in a subsequent cohort of 16 patients enrolled in selected Canadian centers. This safety evaluation concluded that the 150 mg dose was well tolerated. At that time, however, accrual to the study was so advanced (close to the target enrollment of 450) that enrollment at the 150 mg dose level was kept limited to Canadian centers. Hence, international centers continued enrollment in the 100 mg dose cohort only.

This approach lead to a final enrollment of 569 patients, 521 of whom received 100 mg and 48 of whom received 150 mg erlotinib/gemcitabine or placebo/gemcitabine.

Reviewer's note: Although the 100 mg erlotinib dose in combination with gemcitabine appears to be well tolerated, it is still unclear whether 150 mg is safe to be administered in combination with gemcitabine.

4.3.2 Efficacy Parameters

4.3.2.1 Primary Efficacy Parameter: Overall survival

The primary efficacy variable, overall survival, was determined from the time of randomization until death due to any cause. Patients who had not reached the event were censored at the last contact date.

4.3.2.2 Secondary efficacy study variables

- PFS was defined as the length of time from randomization to the first observation of disease progression or death due to any cause.
- Tumor response was determined using RECIST criteria.
- Response rate was calculated as the number of responders (CR + PR) divided by all patients who were evaluable for RECIST response.
- Duration of response was measured as the time that criteria for CR/PR were first met until the first date that recurrent or progressive disease or death was objectively documented.
- QoL was assessed by the EORTC QLQ-C30.

4.3.2.3 Missing and Incomplete Data

Baseline evaluations were those collected closest, but prior to, or on the first day of study medication, unless otherwise specified. When either day or month of a date was missing, the missing day and/or month was imputed by the midpoints within the smallest known interval. For example, if the day of the month was missing for any date used in a calculation, the 15th of the month was used to replace the missing day**. If the month and day of the year were missing for any date used in a calculation, the June 30th of the year was used to replace the missing month and day.**

4.3.3 Removal of Patients from Therapy:

Patients could withdraw from the study at any time for any reason. Investigators could discontinue patients for any of the following reasons:

- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree, and required discontinuation of protocol therapy
- Unacceptable toxicity, which was defined as toxicity (eg, diarrhea, rash) that was not controlled by optimal supportive care or was not tolerated due to symptoms, disfigurement, or interference with normal daily activities, regardless of severity. Patients experiencing toxicities that required a delay in scheduled dosing for ≥ 21 days had protocol therapy discontinued. In the event of unmanageable toxicity attributable to erlotinib/placebo alone, patients were to continue with single-agent gemcitabine until PD or unmanageable toxicity, and in the event of unmanageable toxicity attributable to gemcitabine alone, patients were to continue with single-agent erlotinib/placebo until PD or unmanageable toxicity.
- Tumor progression or disease recurrence
- Symptomatic progression
- Request by the patient
- Physician decision to discontinue for any reason
- Pregnancy
- If patients required ophthalmological surgery during the study, they were to be withdrawn.

The reason for study discontinuation was to be recorded on the CRF, and if possible, patients continued to have follow-up procedures after discontinuation. If PD was documented, any further treatment was at the Investigator's discretion. All randomized patients were to be followed every 12 weeks until death.

4.3.4 Statistical considerations:

Patients were randomized to receive either erlotinib or placebo in a 1:1 ratio. Patients were stratified at enrollment by center, extent of disease (locally advanced disease versus distant metastases), and ECOG PS (0 – 1 versus 2) using a dynamic minimization method.

The primary objective of the study was to compare overall survival between patients randomized to erlotinib or placebo, plus gemcitabine. The secondary objectives were to compare PFS, response rate, time to response, duration of response, toxicity and QoL between the 2 treatment arms. Tissue EGFR expression was correlated with clinical outcomes. Additional tissue and plasma correlative studies will be conducted in an exploratory fashion. Erlotinib trough levels were correlated with adverse events and response to treatment. Results of these plasma correlative studies are described in a separate pharmacokinetic report.

4.3.4.1 Sample size:

The sample size for this study was determined to compare the overall survival between patients in ARM1 and patients randomized to ARM2. The median survival of patients randomized to gemcitabine arm in NCIC PA.1 was 0.55 years. In order to have 90 % power to detect a 50 % improvement with the addition of erlotinib (i.e. a hazard ratio of 1.5), using a two-sided 5% level test, 256 deaths were needed to be observed before final analysis. If accrual of 470 patients could occur in 12 months, the required number of deaths (256) would be observed after following all patients for another 2 months. The estimated sample size would be 470 patients with 14 months as projected duration of the study.

Another trial of the same design (i.e. gemcitabine +/- erlotinib) in patients with unresectable or metastatic pancreatic adenocarcinoma was supposed to be done concurrent with this proposed trial. Although the conduct and statistical analysis of both trials would be independent of each other, a pooled analysis of the results of both studied was to be considered after study completion.

Reviewer's note: PA3 started on 11/29/2001 and last patient was randomized on 9/17/2004. The applicant amended the protocol on **12/17/2001** and changed the sample size from 470 to 800 patients (400 patients each group) to be accrued in 8 months. The sample size was modified based on the new assumptions that the median survival of the placebo group would be 6.6 months and the median survival of erlotinib would increase by 33% to 8.8 months (80% power, hazard ratio of ~ 0.75). At that time, the applicant decided to conduct only one trial instead of 2 trials for this disease. On **12/8/2002**, a new sample size readjustment occurred to target accrual of 450 patients. It was anticipated that after accrual of 450 patients in 9 months, the required number of deaths would be observed after following all patients for another 18 months (27 months projected duration of the study). Prolonging the overall follow-up of the study would provide the required number of events (N = 381) for the final analysis, maintaining the same statistical power

of the study (80%) in order to detect a 33% improvement in median survival with the addition of erlotinib to gemcitabine. Of note, the statistical analysis plan (SAP) was submitted to the agency on **August 2004**, 20 months after the last amendment was performed and only 1 month before study closure. The agency agreed that the primary statistical analysis should be the overall survival to be conducted when 381 deaths were observed using stratified log-rank test. Also, the agency agreed at that time that the factors planned to be used in this analysis were the two randomization factors (PS and extent of disease).

4.3.4.2 Interim analysis

Information regarding drug delivery and toxicity would be collected in a real time fashion on the first 16-20 patients randomized on the trials and considered evaluable for toxicity. If considered necessary and in any case where an unblinded review were required, safety data would be examined by the DSMB.

Reviewer's note: The applicant states that no interim efficacy analyses were planned or performed.

4.3.4.3 Efficacy Analysis

All randomized patients were included in all efficacy analyses (ITT analyses).

4.3.4.3.1 Survival

Overall survival was defined as the length of time from randomization until death due to any cause. Patients who were alive at the final analysis were censored at their last contact date. Kaplan-Meier curves of survival in each treatment arm were constructed, and 95% confidence intervals for the median survivals were computed using the method of Brookmeyer and Crowley (10). . In the primary analysis, the 2 treatment arms were compared using a stratified Log Rank test. All stratification factors (except center) were included as strata. This was a modification from the original analysis proposed in the statistical analysis plan (applicant's sNDA, Section 9.8.2). Since the stratified Log Rank test does not produce estimates of the effects of the stratification factors on survival, a multivariate Cox regression model was also constructed. The model contained the same stratification factors that were included in the stratified Log Rank test.

4.3.4.3.2 Progression-free Survival

Progression-free survival was a secondary endpoint defined as the time from randomization to the first observation of disease progression or death due to any cause. A patient who stopped treatment with study drug and went on to receive alternative therapy for pancreatic carcinoma prior to documentation of PD was censored on the date alternative therapy began. If a patient had not yet progressed or received alternative therapy and was still alive at time of database lock, the PFS was censored on the date of last disease assessment.

Kaplan-Meier curves of PFS in each treatment arm were constructed, and 95% confidence intervals for the median survivals were computed using the method of Brookmeyer and Crowley (10). In the primary analysis, the 2 treatment arms were compared using a stratified Log Rank test. All stratification factors (except center), were included as strata. Similar analysis to the ones performed for OS were conducted for PFS (see section 4.3.4.3.1)

4.3.4.3.3 Quality of Life/Symptoms

Patients' health-related quality of life (QoL) from date of randomization to the date of disease progression was assessed using EORTC QLQ-C30 instrument The EORTC QLQ-C30 is a self-administered cancer-specific questionnaire. It consists of both multi-item scales and single-item measures, including 5 functional domains: Physical, Role, Emotional, Cognitive and Social; 3 symptom domains: Fatigue, Nausea and Vomiting and Pain; 6 single symptom items: Dyspnea, Sleep, Appetite, Constipation and Diarrhea; and a global assessment domain(8). For each function domain and symptom item, a linear transformation was applied to standardize the raw score to the range from 0 to 100. All analyses in this section are exploratory and include all randomized patients who have at least one follow-up evaluation on QoL besides the baseline evaluation. No formal adjustment on p-values was made for the multiple tests.

The exploratory analyses of QoL endpoints were described in detail in the statistical analysis plan (applicant's sNDA, Appendix 16.1.9) and included compliance rates, cross-sectional analysis and a QoL response analysis.

The applicant indicated that patients were considered to have deteriorated for a given symptom if their score change from baseline on the domain/single item defining this symptom was 10 points or higher at any time-point after the baseline assessment. The applicant states that the value of 10 points on a 100 scale was chosen because previous studies have indicated that a 10% change of the highest possible score is considered clinically significant (11)

Quality of life response was calculated as follows for a functional domain: A change score of 10 points from baseline was defined as clinically relevant. Patients were considered improved if a score was reported 10 points or better than baseline at any time of QoL assessment. Conversely, patients were considered to have a worsened condition if a score was reported minus 10 points or worse than baseline at any time of QoL assessment without previous specified improvement. Patients whose scores were between 10-point changes from baseline at every QoL assessment were considered stable. The chi-square test was performed to compare distributions of data in these three categories between the two arms. Following the chi-square test, the Mantel-Haenszel chi-square test for trend was used to test if there was a trend that patients in one treatment arm had higher proportions in the better QoL categories than those on the other arm.

4.3.4.3.4 Tumor Response

All patients who had at least 1 measurable lesion at baseline and at least 1 tumor assessment after baseline were considered evaluable for response unless early progression was documented, in which case they were also considered evaluable for response (and

their best response was PD). Patients had their response classified as CR, PR, SD or PD according to the RECIST definitions. The response rate was estimated as the proportion of patients evaluable for response who met the criteria for CR or PR.

4.3.4.3.5 Response Duration

Response duration was defined as the time from the first objective assessment of CR/PR to the first documentation of PD or death among patients who had achieved a PR or CR. A patient who stopped protocol treatment and went on to receive alternative therapy prior to documentation of PD was censored on the date the alternative therapy began. The date of progression (or death, if progression was not documented before and no alternative therapy had been initiated) was considered as the event date for the duration of response. If a patient had not yet progressed or died, and if no secondary therapy had been initiated, the duration of response was censored on the date of last disease assessment. Duration of response was analyzed by constructing Kaplan-Meier curves, and computing 95% confidence intervals for the median duration of response using the method of Brookmeyer and Crowley (10).

4.3.5 Protocol amendments

The original study protocol dated 10 August 2001 was revised twice before starting date (11/29/2001). The protocol was subsequently amended 4 times. A summary of pertinent changes is presented in table 5.

Table 5 Pertinent protocol amendments

Type [Date]	Changes Made	Rationale
Revision 2 [16 OCT 2001]	Changed the starting dose of erlotinib/placebo from 150 mg to 100 mg. Removed all mention of 150 mg as the starting dose.	Data from an ongoing Phase 1b trial was not yet available to provide a basis for a 150 mg starting dose. The starting dose was changed to 100 mg to ensure that no patients were inadvertently given the wrong dose. No patients had been enrolled at the time of this revision.
	Changed the initial sample size for collection of drug delivery and toxicity information from 16-20 patients to 8-16 patients.	
Amendment 1 [17 DEC 2001]	Added that all patients will be randomized to 1 of the 2 schemas (100 mg or 150 mg erlotinib/placebo plus 1000 mg/m2 gemcitabine) depending on the results of the initial safety evaluation.	To allow 2 possible outcomes, starting doses of either 100 mg or 150 mg of erlotinib/placebo in the initial limited accrual safety phase of the trial.
	Added information from ongoing Phase 1b trial indicating that the combination of 150 mg erlotinib with 1000 mg/m2gemcitabine is tolerable.	
	Added availability of 150 mg erlotinib/placebo tablets.	
	Described in detail the initial limited accrual safety phase of the trial.	To provide a more detailed description of the initial limited accrual safety phase of the trial.
	Added that the initial limited accrual safety phase of the trial was limited to Canadian sites for enrollment	

Type [Date]	Changes Made	Rationale
	and evaluation of patients at 150 mg erlotinib/placebo until appropriate safety criteria were met, then expansion of enrollment at the 150 mg dose to all participating centers could occur.	
	Added QoL in US and selected countries.	PA.3 was originally designed and initiated to be conducted in conjunction with a second planned OSI Phase III study of similar design. However, due to anticipated logistical difficulties in recruiting two large Phase III studies in pancreatic cancer patients, OSI decided to combine the two studies into one. The planned second study was never filed to any regulatory agency and was never initiated. This amendment therefore reflects the decision to merge the second planned trial with this study and conduct a single trial with a larger patient population. The larger trial was also expanded to conduct pharmacokinetics sampling in all centers.
	Changed secondary objectives section to state "To measure trough levels of OSI-774 to define population pharmacokinetics" by removing "in a limited group of patients". Added that trough levels of OSI-774 and AAG would be performed at all centers, and added sampling times.	
	Changed planned sample size from 470 to 800 patients. Adjusted statistical analysis plan accordingly.	
	Added data from recent gefitinib trial in combination with gemcitabine and cisplatin.	To incorporate recent data from other trials into the background and rationale sections and add new toxicities to the sample patient consent form.
	Added data for DLTs that had occurred in the ongoing Phase 1b trials.	
	Added "The baseline assessment must be completed within 7 days of randomization."	To improve clarity of content.
	Added "If the pain intensity scale is not available in the patient's language of literacy, a translator may be used."	
	Revised and clarified ophthalmologic abnormalities and GI tract disorders.	
	Added "If a patient experiences several toxicities and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the next lowest level."	
	Added detail of plasma sample times and analytes.	
Amendment 2 [22 JAN 2002]	Added additional times for AST and ALT analyses.	Data from an ongoing Phase 1b trial demonstrated liver transaminase elevations in some patients treated with gemcitabine and erlotinib.

Type [Date]	Changes Made	Rationale
Amendment 3 [19 APR 2002]	Added information that erlotinib may have a possible interaction in patients receiving concurrent warfarin. Added additional safety monitoring for these patients.	Data from ongoing erlotinib trials demonstrated a possible drug interaction between erlotinib and warfarin.
	Added a dose modification table for elevated LFTs.	Data from an ongoing Phase 1b trial demonstrated liver transaminase elevations in some patients.
	Changed reporting responsibility of all serious adverse events at international centers from NCIC CTG to OSI.	Administrative reporting change.
Amendment 4 [16 DEC 2002]	Changed planned sample size from 800 to 450 patients, and changed follow-up time from 2.8 months to 18 months.	To reflect a decision to decrease the size of the patient population, but maintain the trial's scientific integrity by expanding the follow-up duration.
	Added monitoring and treatment information for suspected interstitial pneumonitis.	To address the possibility of the occurrence of pulmonary events.
	Added that serious adverse events are those defined in the protocol and which occurred within 30 days of last dose of study drug, irrespective of relationship.	To improve clarity of content.
	Updated sample informed consent with more current information on risks and side effects.	To provide most current safety information to sites and patients.

Source: applicant's table 9.6

4.3.6 Changes in the Planned Analyses

Analyses performed by the NCIC CTG for its internal reports and manuscripts and presentations differed from those performed by OSI for presentation in this Clinical Study Report and subsequent Summary Reports in the following ways. The statistical analysis plan stated: "A Kaplan-Meier curve for overall survival in each treatment arm will be displayed. The difference between the 2 treatment arms will be tested using the Log Rank test stratified by:

- ECOG performance status at randomization (0 – 1 versus 2);
- Extent of disease (locally advanced versus distant metastases;
- Pain score at baseline (≤ 20 versus > 20 versus missing on pain intensity scale).

Per discussion with the FDA 8/2004, agreement was reached that:

1. The primary analysis of stratified log-rank test of the primary endpoint, overall survival should be conducted using only randomized stratification factors (ECOG PS and extent of disease). Alternatively, the sponsor may choose unstratified log-rank test for the primary analysis.
2. If majority of the patients have missing pain intensity score, then any adjusted analysis using this factor will be misleading, because such an analysis would categorize the missing as another ordered category of the factor.

3. The analyses of secondary endpoints will be considered supportive only if the results of the primary analyses are positive.
4. Interpretability of the QoL analyses will depend on the missing pattern between the treatment arms, any imbalance in concomitant medication between the treatment arms, and whether missing at random can be assumed.
5. A 10 point change in the transformed scale is difficult to interpret with respect to the actual measured scale in the QoL analysis.
6. The instrument QLQ-C30 was developed for patient's report of overall health and wellbeing and not for any specific symptom

The protocol required 381 deaths to be observed for the final analysis. Prior to unblinding, in determining the data field cut-off date, a projection was made of when this number of events would be reached, based upon death rates observed at the time. However, the applicant underestimated the death rate in this trial, resulting in a field cut-off date of 484 events, an excess in more than 100 deaths from the initial proposal. Therefore, in agreement with the FDA, the primary statistical analysis was performed both at 484 events and censoring the survival analysis at the time 381 events were observed for the 100 mg cohort.

The NCIC CTG coded adverse events using NCI CTC, Version 2; each NCIC CTC term (or if no term was available, the Investigator verbatim) was converted using MedDRA Version 6.1 by OSI. The result was a more granular presentation of adverse events by OSI.

The statistical analysis plan stated: "Since the quality of life may not be assessed at the exact times as specified in the protocol, the following will be the scheme to determining the time frame of a QoL assessment: Baseline evaluation is the QoL questionnaire collected closest, but prior to, the date of randomization." Since several patients completed their initial questionnaires after randomization but before the start of study therapy, and this occurred with equal frequency in both treatment arms, all questionnaires completed before or on the first day of treatment were counted/accepted as "baseline" questionnaires in the analyses performed by OSI. The result of this different approach was that slightly fewer patients were included in the NCIC CTG analyses than in the OSI analyses.

OSI computed domain scores as recommended by the EORTC QLQ-C30 Scoring Manual. In particular, if at least 50% of the questions for a multiple-item domain were answered, the domain score was calculated. For two-item domains, the NCIC CTG required responses for both items before calculating the domain score, resulting in some missing scores. Therefore, OSI analyses could include more patients than the NCIC CTG analyses and there could be differences in the results.

EGFR protein expression was assessed by immunohistochemistry and was scored as negative, positive, or unknown. A positive EGFR expression was defined as having at least 10% of tumor cells staining for EGFR using the DAKO EGFR pharmDX™ kit. All assays and interpretations were made by LabCorp, blinded to patient identification, treatment assignment, and clinical outcome. Mutational status was not determined. At

the time of this report, no additional analyses on the paraffin-embedded tissue blocks were completed (eg, p-EGFR, p-ERK, presence of common mutations in EGFR). No analyses have been performed on plasma samples regarding EGFR, VEGF, PDGF, IL-1, IL-6, IL-8, TNF alpha, and IFN-γ.

The dose intensity of erlotinib/placebo as per the statistical analysis plan should have been described in "mg/week". However, since erlotinib/placebo is dosed daily, the dose intensity is described in "mg/day" which identifies more clearly the difference (if any) from the planned dose of 100 mg or 150 mg/day.

Information about hospitalizations and number of days hospitalized were not captured on the CRFs in a way to permit an accurate assessment of these events.

Reviewer's comments: the applicant was unable to capture hospitalizations in this trial. Thus, the assessment of Serious Adverse events (SAE) is compromised as hospitalizations or prolongation in hospitalizations were two 2 important factors in regulatory definition of SAEs. Moreover, as agreed with the FDA, "If majority of the patients have missing pain intensity score, then any adjusted analysis using this factor will be misleading, because such an analysis would categorize the missing as another ordered category of the factor". However, only 15 patients missed the pain assessment. Based on the known prognostic factor of pain intensity, this factor should be considered in the overall survival for this study.

5 Results

The planned sample size for this Phase III study, after Amendment 4 on December 16th, 2002, was 450 patients, with a follow-up time of 18 months. A total of 569 (521 patients in the 100 mg groups) patients with pancreatic adenocarcinoma were randomized across 140 study sites: 59 centers in the US, 25 centers in Canada, and 56 in the rest of the world. Thirty-six of the 176 initiated study sites did not enroll patients.

Among the 569 patients enrolled in the study, 285 patients were randomized to receive gemcitabine with erlotinib (261 patients in the 100 mg dose cohort and 24 patients in the 150 mg dose cohort) and 284 patients were randomized to receive gemcitabine with placebo (260 patients in the 100 mg dose cohort and 24 patients in the 150 mg dose cohort).

All randomized patients constituted the ITT population for the primary analysis of overall survival. The date of field cut-off was January 15th, 2004, and the date of data base lock for all analyses was September 17th, 2004. However, the FDA requested an updated database up to January 2005.

As of June 20th, 2005, disposition of patients in this trial is as follows:

- 551 (504 deaths in the 100 mg cohort) patients known to have died (8 patients died after January 1st, 2005)

- 18 patients alive at last follow-up (11 with last follow-up dates after January 1st, 2005). The 18 patients alive at last follow-up have the following dates of last follow-up (see Table 6).

Table 6 List of 18 patients alive at last follow up

Patient	Treatment	Dose	Status	Last FU	Survival (months)
SGKR0495*	Placebo	100	Lost to follow-up	17DEC2002	0.03
GRGT0656*	Placebo	100	Lost to follow-up	31JAN2003	0.03
DEFX0644**	Tarceva	100	Lost to follow-up	18FEB2003	0.66
CAMG0111	Tarceva	100	Lost to follow-up	07MAY2003	15.15
USQX0471	Tarceva	100	Alive	21NOV2003	11.40
ILIS0526	Tarceva	100	Alive	24MAR2004	14.78
USBY0418	Tarceva	100	Alive	17MAY2004	17.87
ILIQ0563	Placebo	100	Alive	15FEB2005	25.07
ILIQ0571	Tarceva	100	Alive***	18APR2005	27.07
ILIQ0552	Tarceva	100	Alive	25APR2005	27.47
BRRI0579	Placebo	100	Alive	12MAY2005	27.73
USQX0306	Placebo	100	Alive	19MAY2005	31.11
USYC0462	Tarceva	100	Alive	21MAY2005	29.50
DEFX0529	Tarceva	100	Alive***	27MAY2005	28.81
USYC0525	Tarceva	100	Alive	31MAY2005	29.04
BEBB0368	Placebo	100	Alive	07JUN2005	31.08
USQX0344	Tarceva	100	Alive	07JUN2005	31.34
CANL0574	Tarceva	150	Alive***	09JUN2005	28.78

Source: (applicant's letter , July 1st, 2005)
* Patient did not receive protocol treatment
** Patient received only 3 days of protocol treatment
*** Patient still receiving protocol treatment

All survival analyses in the Clinical Study Report for Study PA.3 were rerun using updated death dates and last follow-up dates (including dates after January 1st, 2005).

Reviewer's comment: Although the applicant planned to accrue 450 patients- in order to obtain 381 deaths, instead, the applicant accrued 569 patients, over 100 more patients than specified in the original protocol. Thus, the FDA primary efficacy analysis was determined at the time of 381 deaths in the 100 mg cohort. Based on the low number of patients treated at the 150 mg erlotinib, only patients treated at the 100 mg group will be considered for efficacy and safety (total of 521 patients).

5.1 Patient population

5.1.1 Protocol violations and patients ineligible for response:

The ITT population was the primary efficacy population. All patients who received any therapy constituted the safety population. The ITT population included 261 subjects in the 100 mg EGe group and 260 subjects in the PG group (total N = 521). The Safety Population of 515 included included 259 (99%) subjects in the 100 mg EG group and 256 (98.5%) subjects in the PG group.

Ten patients (4%) in the EG arm and 7 patients (2.7%) in the PG arm had protocol deviations. The most common deviations were elevated transaminase levels at baseline and the presence of another malignancy (see Table 7).

Table 7 Causes for ineligibility

	Gemcitabine+Erlotinib (N=261)		Gemcitabine+Placebo (N=260)	
	n	**(%)**	**n**	**(%)**
Reason for Ineligibility				
NO LFTS DONE	1	(<1)	0	(0)
BL CT >35 DAYS PRIOR TO RAND	0	(0)	1	(<1)
ELEVATED LFT'S	3	(1)	3	(1)
HAD OTHER PRIMARY MALIGNANCY	4	(2)	0	(0)
HX OF MALIGNANCY LAST 5 YRS	0	(0)	1	(<1)
PRE-BL CHEMO>RADS	0	(0)	1	(<1)
PSYCHOLOGICAL DISABILITY	0	(0)	1	(<1)
RADS & NO PROGRESSION	1	(<1)	0	(0)
SURGERY <14 D PRIOR TO RAND.	1	(<1)	0	(0)

Source: applicant's Table 10.5, section 10.2.1

Reviewer's note: On June 2005, the FDA requested the pathological reports for all patients in PA.3. In July 1st, 2005, the applicant submitted all relevant information along with a list of 9 patients deemed not eligible by the applicant. The FDA assessed the eligibility criteria for all 521 cases. Two FDA reviewers assessed the available pathology, surgical and radiological reports for all 521 patients. Both FDA reviewers assessed the cases in a blinded fashion (they were unaware of treatment group and antitumor response). After review, FDA requested further information from the applicant. The applicant submitted more information for some cases. All efficacy analysis in this review includes these patients. The FDA will present at ODAC (September 13th, 2005) analysis of efficacy excluding these ineligible patients.

In reconciling the kit numbers administered with the corresponding drug lot and agent, errors in drug lot dispensation were noted for 8 patients for some of the cycles (see Table 8).

For the safety analyses, patients were analyzed as per the treatment that they received. For the efficacy analyses, however, all patients were analyzed according to the treatment they were randomized to and not to treatment actually received.

Table 8 Treatment at Randomization Versus Treatment Received

	Gemcitabine+Erlotinib (N=261)		Gemcitabine+Placebo (N=261)	
Treatment Received	**n**	**(%)**	**n**	**(%)**
Erlotinib	258	(99)	1	(<1)
Placebo	1	(<1)	255	(98)
Never Treated	2	(<1)	4	(2)

Source: taken from applicant's table 10-6, section 10.2.2.1

5.1.1.1 Other Study Conduct Deviations

The only other study conduct deviation, as identified by NCIC CTG medical review, involved 1 patient (GBEG0547) who completed the baseline QoL Questionnaire only after randomization. The patient was included in the OSI QoL analyses because the baseline Questionnaire was completed before the start of protocol treatment.

Reviewer's note: in the efficacy analysis, 261 patients were randomized to the 100 mg EG group and 260 patients to the 100 mg PG group. However, these numbers will change if patients without confirmed pancreatic carcinoma are removed from the analysis. For safety purposes, 259 patients were treated in the 100 mg erlotinib and 256 in the placebo group.

5.1.2 Patient Demographics

Table 9 Demographic and Disease Characteristics (ITT) Part I

	Gemcitabine+Erlotinib (N=261)		Gemcitabine+Placebo (N=260)	
Characteristics	**n**	**(%)**	**n**	**(%)**
Gender				
Female	134	(51)	114	(44)
Male	127	(49)	146	(56)
Age (Years)				
18-39	1	(<1)	4	(2)
40-64	135	(52)	134	(52)
≥65	125	(48)	122	(47)
Race				
White	225	(86)	231	(89)
Black	8	(3)	5	(2)
Other	28	(11)	24	(9)
ECOG Performance Status				
0	82	(31)	83	(32)
1	134	(51)	132	(51)

	Gemcitabine+Erlotinib (N=261)		Gemcitabine+Placebo (N=260)	
2	44	(17)	45	(17)
Unknown	1*	(<1)	0	(0)
Pain Intensity Score				
≤20	119	(46)	119	(46)
> 20	133	(51)	135	(52)
Missing	9	(3)	6	(2)

* Patient USRW0582 had an unknown ECOG Performance Status at baseline, but was stratified as having a Performance Status of 0-1. Note: Unknown includes responses of 'Unknown' and missing.Pain Intensity classification was only collected at randomization and not at baseline. Source: applicant's table 11.3

Table 9-Part II

Characteristics		Gemcitabine + Erlotinib	Gemcitabine + Placebo
Age (Years)	n	261	260
	Median	64	63
	Range	37 - 84	36 - 92
Pain Intensity Score	n	252	254
	Median	22	22
	Range	0 - 100	0 - 100

Source: applicant's table 11.4

Reviewer's note: as will be discussed in section 5.2.1.1, there were more males in the PG group. Of note, male gender is a negative prognostic factor. This imbalance may explain, at least in part, the differences in overall survival and PFS in favor of the EG group.

Table 10 Summary of Previous Therapy for Pancreatic Cancer

	Gemcitabine+Erlotinib (N=261)		Gemcitabine+Placebo (N=260)	
	n	(%)	n	(%)
Previous Therapy				
Chemotherapy	19	(7)	23[a]	(9)
Surgery	260	(100)	258	(99)
Radiation	20	(8)	22	(8)
Hormonal Therapy	1	(<1)	0	(0)
Other Prior Therapy	2	(<1)	5	(2)

[a] 1 patient (USGN0262) received chemotherapy (cyclophosphamide and adriamycin) for a previous malignancy, described as a breast sarcoma, 10 years before starting the current protocol therapy, which accounts for the additional patient receiving chemotherapy compared with the number of patients receiving radiotherapy.
Source: applicant's table 11.10, Cancer History and Previous Therapy (section 11.2.2.3)

Table 11: Summary of Baseline Disease Characteristics

	Gemcitabine+Erlotinib (N=261)		Gemcitabine+Placebo (N=260)	
	n	**(%)**	**n**	**(%)**
Specimen Type *				
Histological	173	(66)	160	(62)
Cytological	86	(33)	98	(38)
Missing	2	(<1)	2	(<1)
Extent of Disease at First Diagnosis				
Resectable	19	(7)	21	(8)
Locally advanced/unresectable	75	(29)	81	(31)
Metastatic	167	(64)	158	(61)
Disease Status at Baseline				
Locally Advanced	61	(23)	63	(24)
Distant Metastasis	200	(77)	197	(76)
Time From Initial Diagnosis to Randomization (Months)				
<6	242	(93)	237	(91)
6 - 12	12	(5)	14	(5)
>12	7	(3)	9	(3)

Source: applicant's Table 11–13. ***Note: some patients did not have adequate documentation of adenocarcinoma of the pancreas. Analysis excluding those cases will be presented at ODAC.**

Table 9 through Table 11 summarize the main disease characteristics at baseline by treatment arm. Disease characteristics were well balanced between the 2 treatment arms. Approximately one third of the patients were diagnosed by cytology (FNA), as can be expected for this type of cancer. Many patients were entered in the study around the time of first diagnosis with a median time from initial diagnosis to randomization of approximately 1.0 month in each arm. Some patients did first undergo surgery with curative intent, hence the wide range in time from initial diagnosis to randomization.

The extent of disease for both groups appears well balanced. The majority of patients had measurable disease with at least 1 target lesion (94% in the EG arm and 92% in the PG arm). The majority of patients did not undergo a resection before entering the study, thus the pancreas was reported as a site of disease in approximately 90% of patients.

Reviewer's note: These numbers will change when patients with unconfirmed diagnosis of adenocarcinoma of the pancreas are removed from the analysis.

5.1.2.1 EGFR Expression at Baseline

Table 12 summarizes the EGFR protein expression by immunohistochemistry at baseline. Tumor samples were collected throughout the study from patients who gave written informed consent. Assays were performed and analyzed by a central laboratory in a blinded manner. A positive EGFR expression was defined as having at least 10% of

tumor cells staining for EGFR using the DAKO EGFR pharmDX™ kit. Pathology blocks or slides were available and the results were interpretable for 27% of the patients in the erlotinib arm and for 24% of the patients in the placebo arm. There were no significant differences in patient and disease characteristics between the patients for whom results were known and the patients for whom the results were unknown (see applicant's Table 14.2.15). It is unknown how many of the available samples are from the time of initial diagnosis or at a subsequent relapse.

In the EG arm, 16% of patients (representing 56% of the patients with known results) had a positive EGFR expression and 13% (44% of the patients with known results) had a negative expression, compared with 11% and 12% (representing 46% and 54% of the patients with known results) in the placebo arm (see Table 12).

Table 12 Summary of EGFR Expression

	Gemcitabine+Erlotinib (N=261)		**Gemcitabine+Placebo (N=260)**	
	n	**(%)**	**n**	**(%)**
EGFR Status				
Positive	41	(16)	29	(11)
Negative	34	(13)	32	(12)
Results Not Evaluable	6	(2)	13	(5)
Sample Not Available	180	(69)	186	(72)

Source: applicant's **Table 11–20**

Table 13 Patient Disposition

	Gemcitabine+Erlotinib (N=261)		**Gemcitabine+Placebo (N=260)**	
	n	**(%)**	**n**	**(%)**
Patients Never Treated	2	(<1)	4	(2)
Patients Off Erlotinib	251	(96)	252	(97)
Reasons Off Erlotinib				
Progressive Disease	121	(46)	149	(57)
Symptomatic Progression	41	(16)	36	(14)
Adverse Events	62	(24)	37	(14)
Intercurrent Illness	10	(4)	10	(4)
Patient Refusal	21	(8)	15	(6)
Death	25	(10)	21	(8)
Other	6	(2)	8	(3)
On Erlotinib	8	(3)	4	(2)

Note: Patient CAVC0149 in the 100 mg cohort of the erlotinib arm was never treated with study drug but had an off-study reason of 'Patient refusal'. Source adapted from applicant's table 10.4 and analysis of Patient.XPT SAS file. Adverse events requiring discontinuation were obtained from ADR.xpt SAS file: analysis of aewdraw subgroup "Withdrawn from Study due to AE".

Reviewer's note: analysis of patients that discontinued therapy due to death, toxicity, refusal and other causes will be analyzed in the safety section (section 5.3**).** Of note, 46% discontinue due to disease progression in the EG arm as compared to 57% in the PG arm. However, twice the number of patients discontinue due to drug toxicity in the EG group as compared to PG group (24% vs 14%).

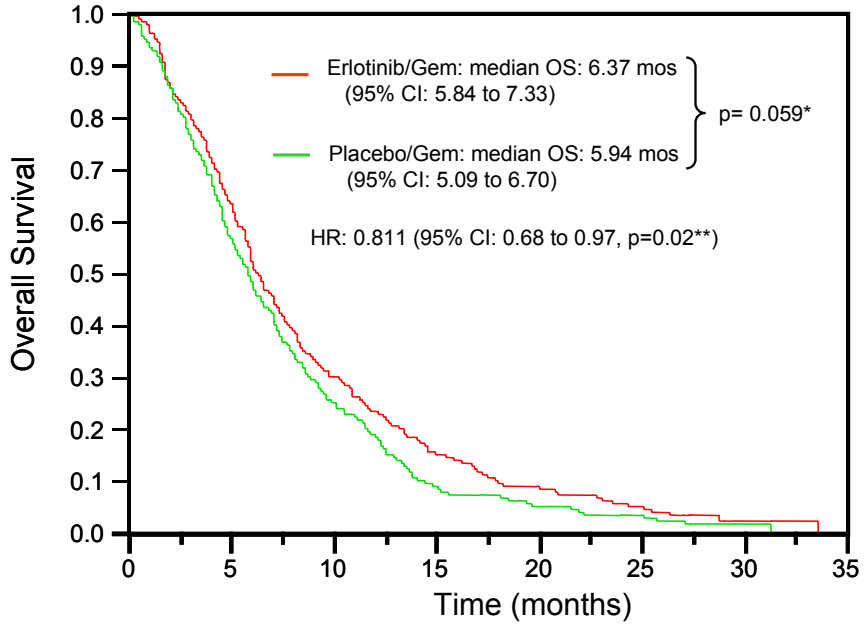
5.2 Efficacy

5.2.1 Overall Survival

The sponsor performed a survival analysis when 484 deaths occurred, an excess of more than 100 deaths over the original planned for this analysis (N=381). However, at the time of submission (June 2005), too many censored patients appeared in the database with no recent follow-up (85 patients). Therefore, because of the large number of censored patients with no recent follow-up, the FDA requested an updated analysis. The applicant agreed to update the efficacy database up to January 2005, but provided the update to June 2005. At that time, 551 (504 deaths in the 100 mg cohort) patients had died and 18 (17 patients in the 100 mg cohort) patients were alive at last follow-up. Because of the small numbers for the 150 mg groups (total 48: 24 patients in each EG and PG, respectively), this review will discuss the 100 mg group only.

An analysis performed by the FDA after 504 deaths revealed that the median overall survival (months), estimated from univariate Kaplan-Meier curves, was 6.37 in the EG arm and 5.95 in the PG arm, a difference of ~ 12 days in favor of the EG group (p= 0.0596, unadjusted log-rank test) (See Fig.2 and Table 14).

Figure 2. Kaplan Meier survival time curves for 100 mg patients (504 deaths)



* log-rank unadjusted; ** adjusted hazard ratio cox proportional model

When the overall survival was analyzed at 381 events, as planned in the original protocol, similar results were obtained: medians 6.47 months (95% CI: 5.95 to 7.36) and 5.95 (95 % CI: 5.09 to 6.70) with a p value of p 0.062 (unadjusted log-rank test, see Fig. 3).

Moreover, the hazard ratio (HR) for overall survival (504 deaths) in the EG arm relative to the PG arm, estimated from a univariate Cox model, was 0.84 (95% CI 0.70 to 1.007, p = 0.06).

For the 381 death analysis, the HR was 0.83 (CI 95%: 0.67 to 1.01, p = 0.063).

In addition, a multivariate Cox model was constructed that included treatment and both of the specified covariates, namely ECOG PS and extent of disease. The adjusted HR for overall survival in the EG arm relative to the PG arm was 0.81 (95% CI: 0.68 to 0.97, p = 0.02). In the 100 mg cohort (381 events), the adjusted HR was also 0.79 (95 % CI: 0.65 to 0.97, p = 0.026). The adjusted analysis was the protocol specified primary analysis.

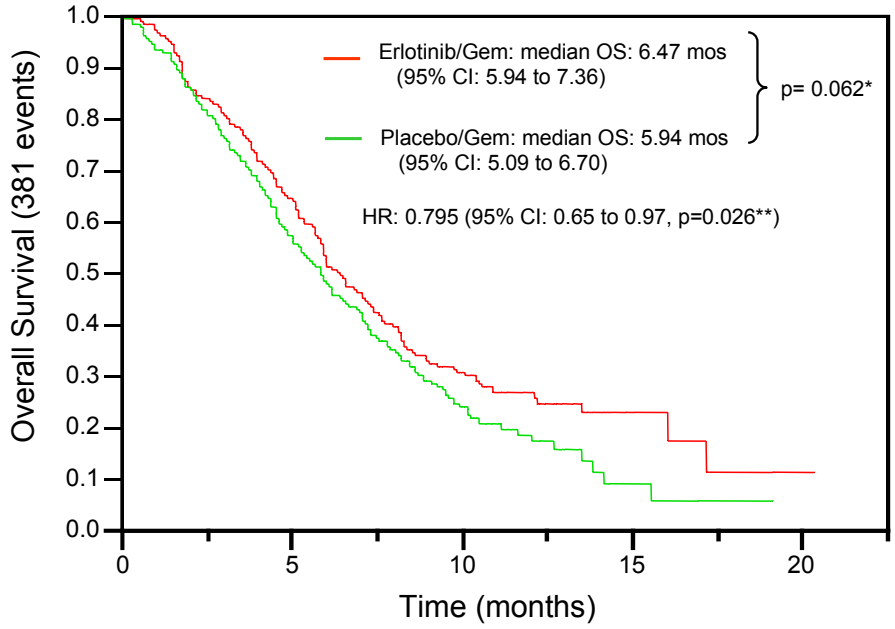
A summary of the different survival analysis is presented in figure 4.

Table 14: Survival time analysis (Intent-to treat population) in all patients treated at the 100 mg group after 504 deaths

Parameter	Erlotinib + gemcitabine (N = 261)	Placebo+ gemcitabine (N = 260)	Log-rank P value
Number (%)[a] of subjects who died	250 (95.8)	254 (97.7)	
Median survival time (mos)	6.37	5.94	0.0596*
95% Confidence interval	[5.84 – 7.32 mo.]	[5.09 –6.70 mo.]	

Survival time was defined as the time from the date of randomization to the date of death.
[a] Percentages were calculated by using N, the total number of subjects in the group, as the denominator.
* log-rank unadjusted. Source: jmp database

Figure 3. Kaplan Meier survival time curves 100 mg group (censored at 381st death)



* log-rank unadjusted; ** adjusted hazard ratio cox proportional model

Table 15 Survival time analysis (Intent-to treat population) for 100 mg cohorts censored at 381st death

Parameter	Erlotinib + gemcitabine (N = 261)	Placebo + gemcitabine (N = 260)	Log-rank P value
Number (%)[a] of subjects who died	183 (70.1)	198 (76.1)	
Median survival time (mos)	6.47	5.94	0.0622*
95% Confidence interval	[5.94 – 7.35 mo.]	[5.09 –6.70 mo.]	

Survival time was defined as the time from the date of randomization to the date of death.
[a] Percentages were calculated by using N, the total number of subjects in the group, as the denominator minus patients censored.. *Source:* crt databases, analysed by jmp 5.1.1.* log-rank unadjusted

Figure 4: Summary of different overall survival analyses using Cox proportional hazards model

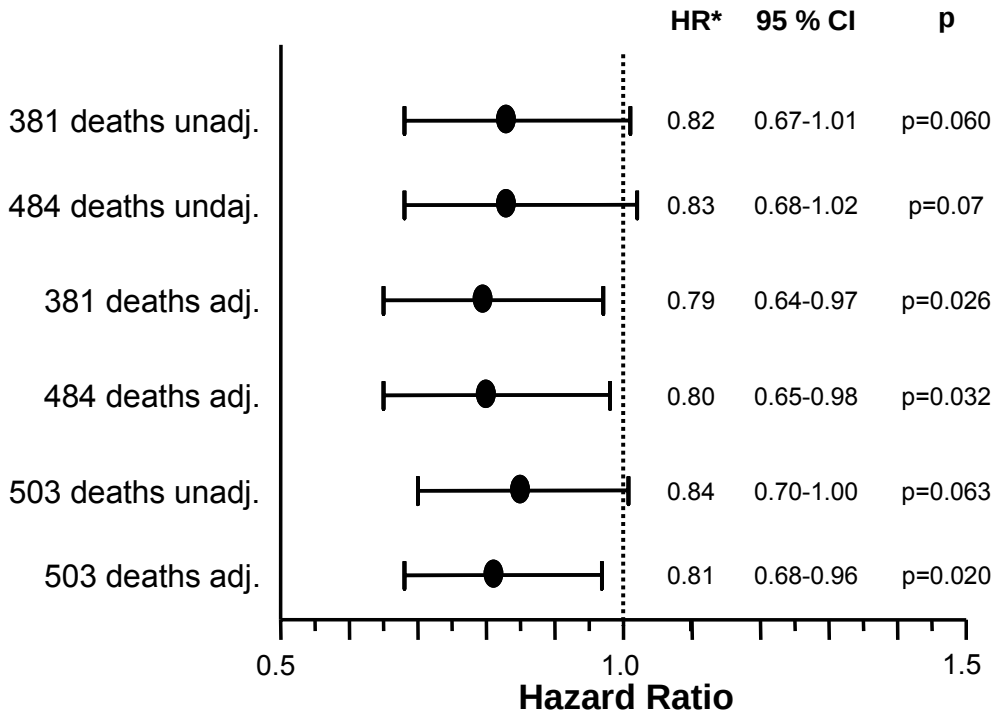


Figure 4. Forrest plot representation for overall survival by cox proportional hazards model for 100 mg group, censored at 381 events, unadjusted and adjusted for ECOG PS and disease status. Analysis occurred at 484 deaths (initial submission, 4/29/2005) and 504 deaths (updated submission, July 1st, 2005).

The primary multivariate analysis provided an opportunity to examine the prognostic effects of the stratification factors that were included in this analysis. In univariate analyses, both ECOG PS 2 and disease with distant metastases were associated with worse survival. In the multivariate analysis, after adjustment for the treatment effect, both factors remained statistically significant ($p < 0.001$, see Table 20).

Reviewer's note: the survival analyses presented by the applicant show that the median overall survival performed either in the entire population in the 100 mg groups or the population censored after 381 deaths is not statistically significant (Log-rank test).

When survival data are analyzed using Cox proportional hazard ratio, again, in either population, the unadjusted overall survival is not statistically significantly different.

However, when the Cox analyses are adjusted by the two stratification factors (performance status and disease status at randomization), as pre-specified in the Data Analysis Plan, the difference in overall survival between EG and PG is statistically significant.

As mentioned earlier, a significant number of cases were unable to be confirmed as adenocarcinoma of the pancreas. Re-analysis excluding these patients will be presented at the ODAC meeting.

5.2.1.1 Exploratory Analyses of overall survival analysis:

5.2.1.1.1 Survival by pretreatment characteristics

Table 16 Survival by pretreatment characteristics, univariate analysis

	Gemcitabine+Erlotinib N=261		**Gemcitabine+Placebo** N=260			
Pretreatment Characteristics	**N**	**Median Survival Months (95% CI)**	**N**	**Median Survival Months (95% CI)**	**Hazard Ratio* (95% CI)**	**Log-Rank p-value**
ECOG Performance Status at Baseline						
0-1	217	6.64	215	6.47	0.86	0.167
		(6.01, 7.69)		(5.72, 7.33)	(0.70, 1.06)	
2	44	4.73	45	3.22	0.60	0.023
		(3.55, 6.14)		(2.83, 4.47)	(0.38, 0.94)	
ECOG Performance Status as Randomized						
0-1	218	6.60	215	6.54	0.89	0.285
		(6.01, 7.69)		(5.88, 7.43)	(0.73, 1.10)	
2	43	5.16	45	3.22	0.49	0.002
		(4.07, 7.33)		(2.83, 4.40)	(0.31, 0.77)	
Disease Status at Baseline						
Locally Advanced	61	8.51	63	8.18	0.99	0.945
		(7.69, 10.58)		(7.06, 10.55)	(0.66, 1.48)	
Distant Metastasis	200	5.98	197	5.06	0.77	0.016
		(5.19, 6.57)		(4.47, 5.95)	(0.62, 0.95)	
Disease Status as Randomized						
Locally Advanced	77	8.21	75	7.33	0.93	0.706
		(7.00, 9.43)		(6.28, 9.69)	(0.65, 1.34)	
Distant Metastasis	184	5.98	185	5.29	0.77	0.021
		(5.29, 6.60)		(4.60, 6.05)	(0.62, 0.96)	
Pain Intensity Score						

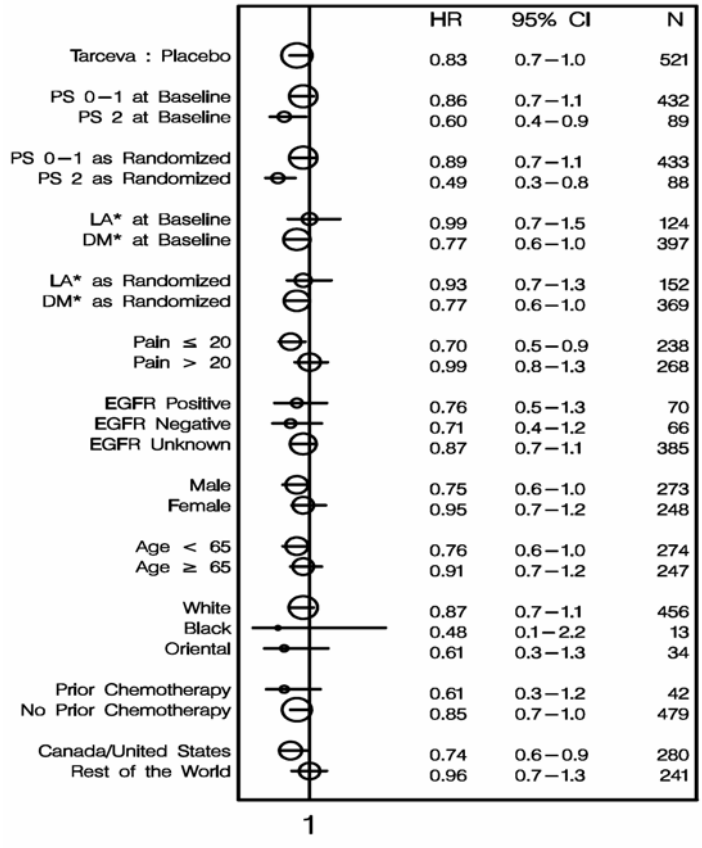
	Gemcitabine+Erlotinib N=261		**Gemcitabine+Placebo** N=260			
≤20	119	7.62	119	6.21	0.70	0.013
		(6.14, 9.33)		(5.52, 7.56)	(0.52, 0.93)	
> 20	133	5.75	135	5.11	0.99	0.937
		(4.90, 6.37)		(4.44, 6.60)	(0.77, 1.28)	
Unknown	9	9.03	6	5.68	0.49	0.243
		(1.87, 14.62)		(1.48, 11.86)	(0.15, 1.66)	
EGFR Status						
Positive	41	7.00	29	5.32	0.76	0.285
		(5.39, 7.79)		(2.86, 9.56)	(0.45, 1.27)	
Negative	34	6.47	32	5.93	0.71	0.191
		(5.16, 11.47)		(4.21, 8.25)	(0.42, 1.19)	
Unknown	186	6.24	199	6.01	0.87	0.202
		(5.82, 7.46)		(5.13, 6.97)	(0.70, 1.08)	
Gender						
Male	127	6.11	146	5.29	0.75	0.028
		(5.82, 7.46)		(4.27, 6.18)	(0.58, 0.97)	
Female	134	6.60	114	6.70	0.95	0.691
		(5.75, 8.28)		(5.91, 7.69)	(0.72, 1.25)	
Age						
< 65	136	6.60	138	6.18	0.76	0.038
		(5.95, 8.21)		(5.09, 7.23)	(0.58, 0.99)	
≥65	125	6.47	122	5.88	0.91	0.490
		(5.75, 7.36)		(4.73, 6.70)	(0.70, 1.19)	
Race						
White	225	6.37	231	5.93	0.87	0.179
		(5.85, 7.36)		(5.09, 6.70)	(0.71, 1.06)	
Black	8	10.17	5	9.46	0.48	0.336
		(7.79, 12.19)		(1.94, .)	(0.11, 2.20)	
Oriental	20	5.16	14	4.47	0.61	0.187
		(3.61, 8.57)		(2.69, 6.28)	(0.29, 1.29)	
Other	8	10.27	10	7.33	0.40	0.115
		(1.87, 13.57)		(4.34, 8.90)	(0.12, 1.31)	
Any Prior Chemotherapy						
Yes	19	8.38	23	4.47	0.61	0.133

	Gemcitabine+Erlotinib N=261		Gemcitabine+Placebo N=260			
		(4.24, 11.47)		(2.86, 7.85)	(0.32, 1.17)	
No	242	6.24	237	5.98	0.85	0.100
		(5.85, 7.20)		(5.29, 6.97)	(0.70, 1.03)	
Region						
Canada/United States	142	6.60	138	5.68	0.74	0.017
		(5.91, 8.02)		(4.70, 7.13)	(0.57, 0.95)	
Rest of the World	119	6.24	122	6.11	0.96	0.764
		(5.29, 7.36)		(5.09, 7.36)	(0.72, 1.27)	

Source: taken from applicant's table 11-24

A series of subsets formed by the values of the stratification factors at randomization and at baseline and pain intensity score, gender, age, race, any prior chemotherapy, EGFR status, and geographic location were examined in exploratory univariate analyses (Table 16). It is acknowledged that these are underpowered exploratory analyses, and no adjustments were made for the multiplicity of tests performed on these subsets.

Figure 5 Forrest plot for overall survival by pretreatment characteristics



*LA: locally-advanced, DM: distant metastasis. Source: applicant's Figure 11-6

Reviewer's note: Several subsets analyzed showed some trend for benefit in the EG arm. However, female, pain intensity ≥ 20, rest of the world and age (≥ 65 years) did not seem to benefit at all while patients with PS 2 seem to benefit the most. Interestingly, any potential survival benefit from EG does not seem to be related to EGFR expression status (in contrast to the NSCLC BR.21 study). However, caution must be applied because of the small number of patients in the groups with available EGFR status.

5.2.1.1.2 Therapies after tumor progression

Table 17 Progression Summary

	Gemcitabine+Erlotinib (N=261)		Gemcitabine+Placebo (N=260)	
	n	**(%)**	**n**	**(%)**
Patients who progressed *	225	(86)	232	(89)
Progression on study (1)	156	(60)	170	(65)
Progression during follow-up (2)	69	(26)	62	(24)
Patients who were censored *	36	(14)	28	(11)
Reason Censored				
Received anti-cancer therapy before documented progression (3)	26	(10)	19	(7)
Chemotherapy	23	(9)	17	(7)
Radiotherapy	5	(2)	4	(2)
Other	1	(<1)	3	(1)
Lost To Follow-Up	1	(<1)	1	(<1)
Not Progressed	9	(3)	8	(3)

(1) Radiological progression (not symptomatic) or death on-study without prior recording of disease progression
(2) Radiological progression after patient was taken off-study, either for symptomatic PD or other reason (toxicity, intercurrent illness etc.) or death after patient was taken off-study, without prior recording of disease progression
(3) Patients could have received more than 1 type of therapy. * cutoff date 9/17/2004. Source: Table 11–30

Table 18 summarizes the subsequent anticancer therapy (chemotherapy, EGFR inhibitors, hormonal therapy, or radiotherapy) received by treatment arm. Overall, in the EG arm, 102 patients (36%) received subsequent anticancer therapy compared with 92 patients (32%) in the PG arm. A total of 95 patients (33%) in the EG arm and 89 patients (31%) in the PG arm received further chemotherapy after discontinuing the study. Radiation was administered to 21 patients, 14 patients (5%) in the EG arm, and 7 patients (2%) in the PG arm.

Table 18: Type of Subsequent Chemotherapy

	Gemcitabine+Erlotinib (N=261)		Gemcitabine+Placebo (N=260)	
	n	**(%)**	**n**	**(%)**
Number of patients with any follow-up chemotherapy	88	(34)	82	(32)
Fluorouracil, 5-fluorouracil, adrucil	39	(15)	32	(12)
Gemcitabine	33	(13)	41	(16)
Capecitabine, xeloda	31	(12)	15	(6)
Calcium folate, leucovorin, folinic acid, cytovoru	13	(5)	13	(5)
Cpt-11, camptosar, irinotecan hydrochloride	13	(5)	15	(6)
L-folinic acid, l-leucovorin	13	(5)	11	(4)
Taxotere, docetaxel	11	(4)	11	(4)
Cisplatin, cddp, cisplatinum, platinol	9	(3)	19	(7)
Mitomycin-c, mutamycin	6	(2)	7	(3)
Oxaliplatin	4	(2)	6	(2)
Unknown Agent	4	(2)	2	(<1)
Taxol, paclitaxel	2	(<1)	1	(<1)
Carboplatin, paraplatin	1	(<1)	2	(<1)
Floxuridine, fudr	1	(<1)	0	(0)
Other novel anticancer	1	(<1)	0	(0)
Doxil, caelyx, liposomal doxorubicin	0	(0)	1	(<1)
Epirubicin, pharmarubicin	0	(0)	2	(<1)
Etoposide, vp-16, vepesid	0	(0)	1	(<1)
Mitoxantrone, novantrone	0	(0)	1	(<1)
Other chemotherapy agent	0	(0)	2	(<1)

Note: Patients could have received more than 1 type of chemotherapy.
Source: taken from sponsor's table 11–34

Table 18 summarizes the type of subsequent chemotherapy received by treatment arm. Different agents were used at various international sites. The most frequently used agents were 5-FU, gemcitabine, and capecitabine, and their use was relatively well balanced between the 2 treatment arms. It has to be noted however that in most cases, gemcitabine was reported as "subsequent therapy" to indicate the patient continued on gemcitabine as a single agent after stopping erlotinib/placebo.

To minimize the potential confounding effects of these anticancer therapies on overall survival, an exploratory analysis was performed in which survival times for patients who received these subsequent anticancer therapies were censored at the start of this therapy. The univariate Kaplan-Meier survival curve now demonstrate that there was no significant difference between EG and PG arms: EG median survival was 7.00 months compared with 5.98 months in the PG arm (HR = 0.80 [95% CI 0.64 to 1.01, p = 0.054]) (see applicant's table 14.2.26, section 14.2).

Reviewer's note: When the applicant censored patients before subsequent anticancer therapies, the univariate Kaplan-Meier Survival curve now shows a non-significant difference between EG and PG.

Table 19: Pretreatment characteristics that appeared significant from univariate analysis for worse overall survival

Pretreatment characteristics with worse overall survival	
Disease status	Metastasis
Pain intensity score	> 20
ECOG performance status	2
Gender	Male
age	< 65
Region	Rest of the world

Table 20: Multivariate analysis for overall survival

	Univariate	**Multivariate**		
Factors	**p-value**	**p-value**	**Hazard Ratio**	**(95% CI)**
Treatment Arm (Erlotinib : Placebo)	0.0539	0.0306	0.81	(0.66, 0.98)
ECOG Performance Status (2 : 0-1)	<0.0001	0.0005	1.57	(1.22, 2.02)
Extent of Disease (Distant : Local)	<0.0001	<0.0001	1.67	(1.31, 2.12)
Pain Score (> 20 : ≤20)	0.0036	0.0207	1.26	(1.04, 1.54)
Gender (Female : Male)	0.2267	0.1069		
Age (< 65 : ≥65)	0.2273	0.3654		
Race (White : Other)	0.8218	0.5343		
Any Prior Chemotherapy (No : Yes)	0.5010	0.3309		
Region (North America : Rest of the World)	0.4682	0.4176		
Baseline Albumin Grade (Ordinal)	<0.0001	0.0007	1.27	(1.11, 1.46)

(taken from applicant's table 11-26)

Since many of the potential prognostic factors may be correlated, exploratory multivariate analyses were performed that included each of the factors listed in table 20. Since EGFR status was only available for approximately 25% of patients, it was not appropriate to add this factor to this analysis. In addition, univariate analyses did not reveal any significant relationships between EGFR status and survival. Disease status and ECOG performance status at baseline were considered more representative of the patients' status for these exploratory analyses. Preliminary analyses indicated that

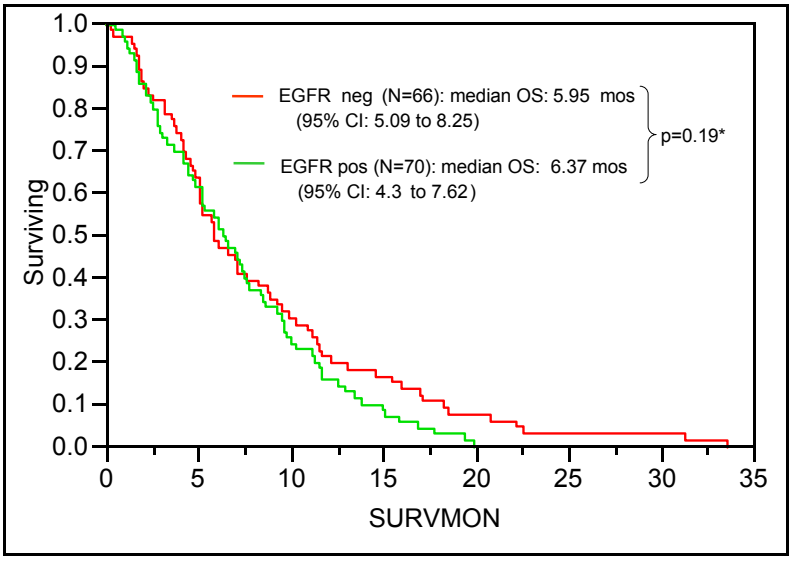
baseline albumin levels were associated with survival, so albumin CTC grade was included among the potential prognostic factors. Because baseline pain intensity scores were not available for 14 patients, baseline albumin levels were not available for 19 patients, and both items were not available for 1 patient, the multivariate analyses included 489 patients. Both forward stepwise selection and backward elimination with a level of significance of 0.1 used for entry or removal of variables (as specified in the statistical analysis plan) produced the same final model (taken from applicant's table 11-26).

The effect of erlotinib remained statistically significant, with an adjusted HR of 0.81 for the 100 mg dose cohort. Other factors that were significantly associated with survival included ECOG performance status, extent of disease, pain score and baseline albumin. Factors that were not associated with survival in this multivariate analysis included gender, age, race, prior chemotherapy, geographical region, and dose cohort. Of note, there were more males in the PG arm than in the EG group (see table 9).

5.2.1.1.3 Survival by expression of EGFR in tumor samples

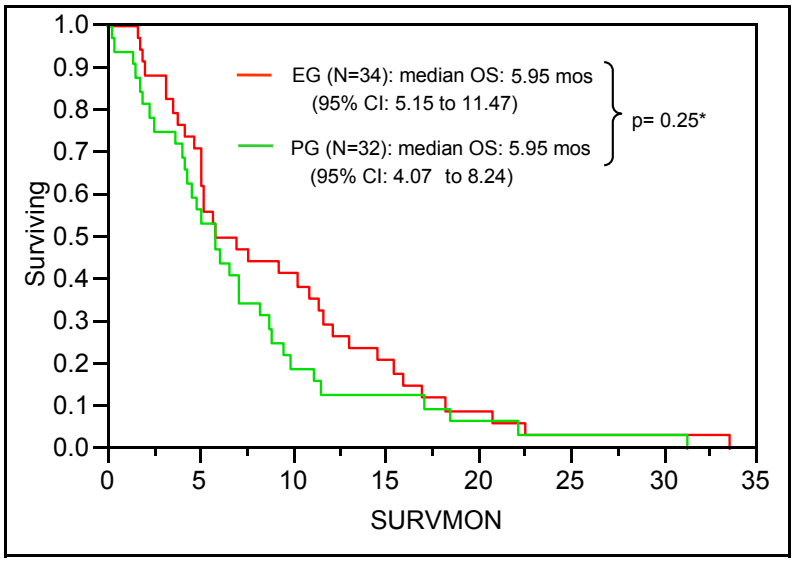
The expression of EGFR (target for erlotinib) was a predictive factor in the BR.21 trial NSCLC erlotinib monotherapy. In an exploratory analysis, the expression of EGFR in the PA.3 trial was correlated with overall survival in both treatment groups. It does not appear that EGFR expression as measured by IHC has a role in the prediction of overall survival for these patients.

Figure 6: Survival by EGFR expression of tumors, 100 mg cohorts



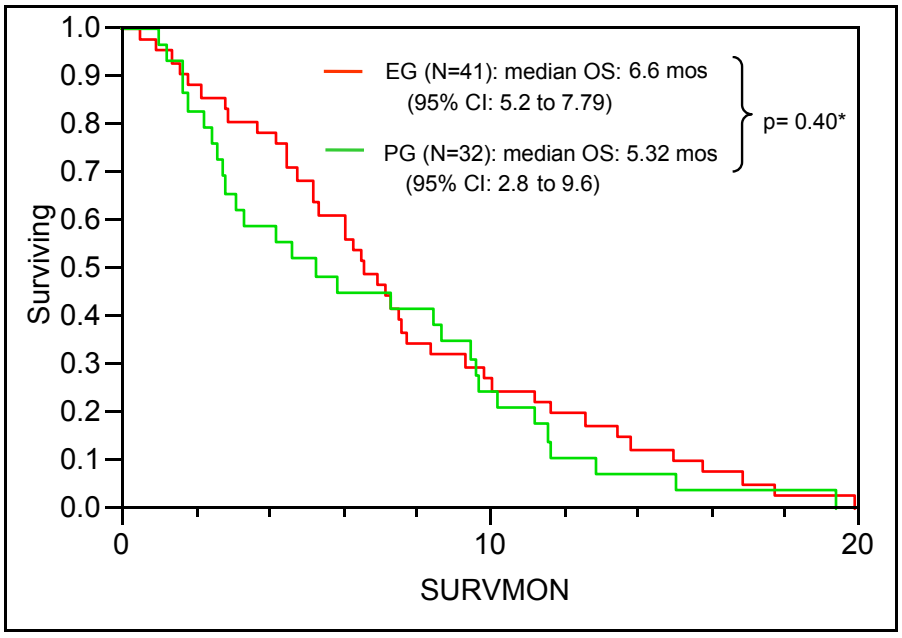
* unadjusted Log-rank test

Figure 7: Overall survival by treatment in patients with EGFR negative tumors



* unadjusted Log-rank test

Figure 8 Overall survival by treatment in patients with EGFR positive tumors



* unadjusted Log-rank test

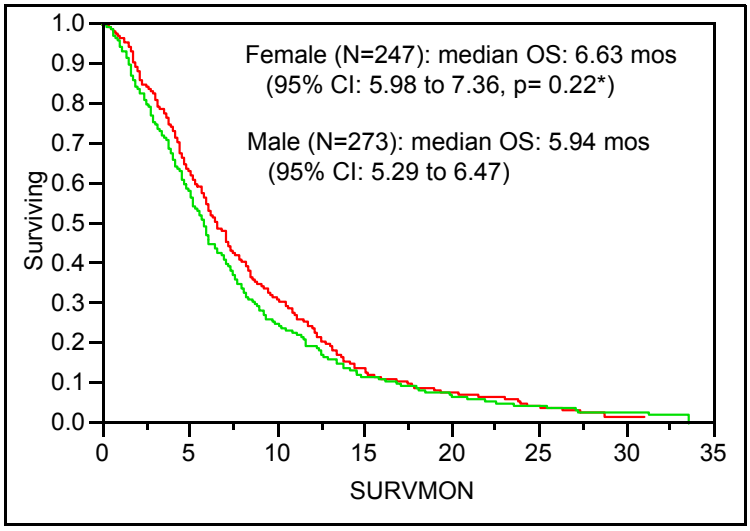
Reviewer's note: In contrast to the NSCLC BR.21 data, EGFR positive expression does not predict overall survival with EG.

5.2.1.1.4 Survival by Gender and Race

As shown in Fig. 9, in females, the median overall survival of females, 6.64 mos (5.98 to 7.36) is longer than the median survival of males , 5.95 months (5.29 to 6.4). However, the difference is not statistically significant (p=0.22). Of note, when the survival is also separated by treatment groups, in the PG group, females have a statistically significant increase in median overall survival than males, 6.70 months (5.89 to 7.69) vs. 5.29 months (4.27 to 6.11), with a p value of 0.04 (see Fig. 10).

Based on the lack of significant information regarding race, no analysis was provided for this variable.

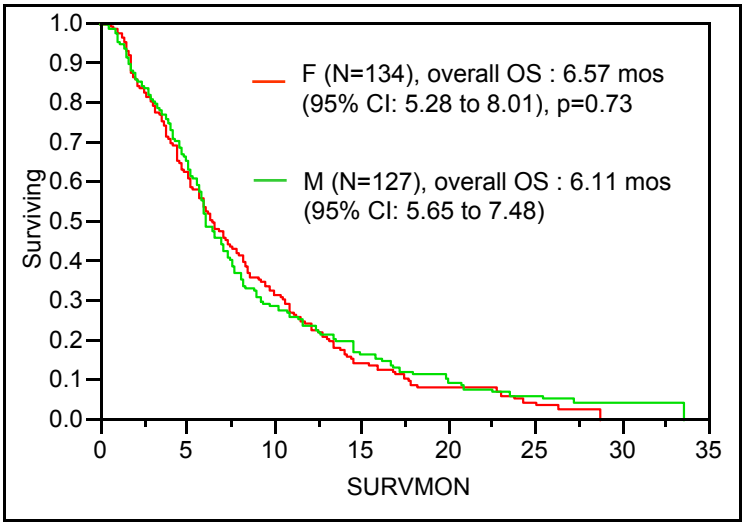
Figure 9 Survival by Gender



* unadjusted Log-rank test. F=female, M=Male

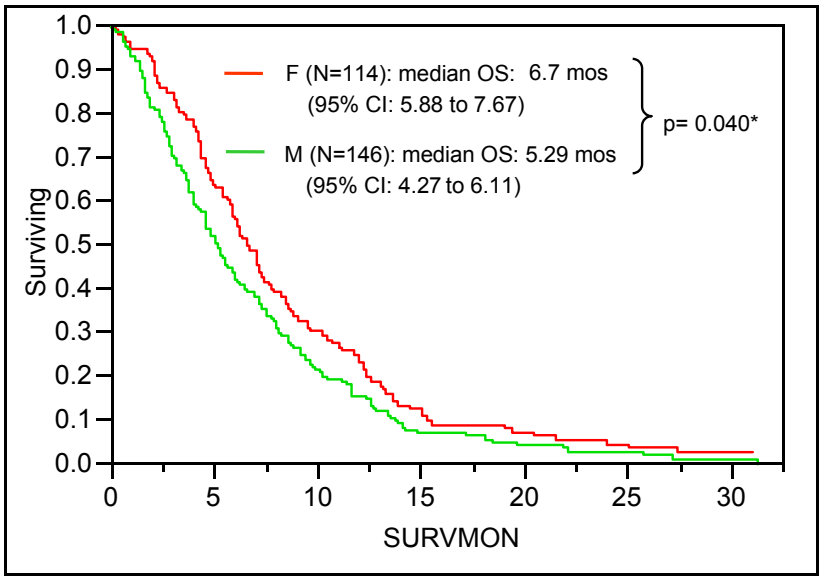
As shown in Fig. 9, females have a longer median overall survival, compared with males. However, the difference is not statistically significant.

Figure 10 Survival by Gender in patients treated with EG (N=261)



* unadjusted Log-rank test. F=female, M=Male

Figure 11 Survival by Gender in patients treated with PG (N=260)

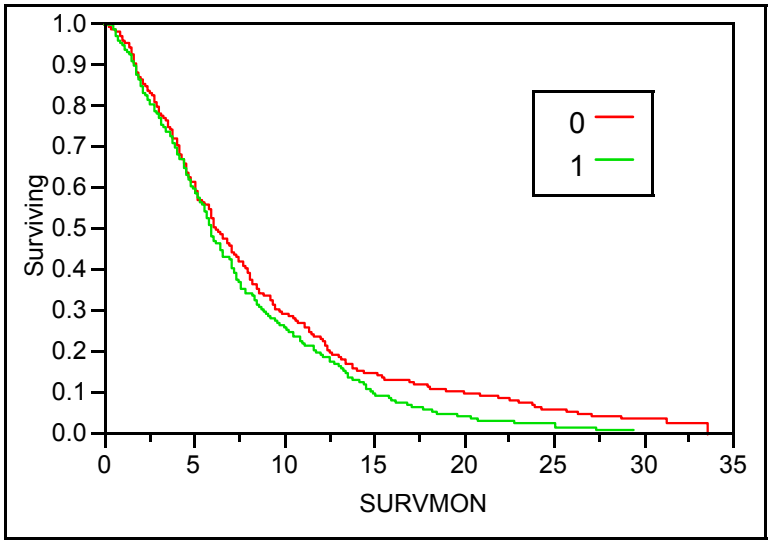


* unadjusted Log-rank test. F=female, M=Male

Reviewer's note: in the PG group, female patients has a significant increase in median overall survival

5.2.1.1.5 Survival by age

Figure 12: **Survival by age in 100 mg cohorts**

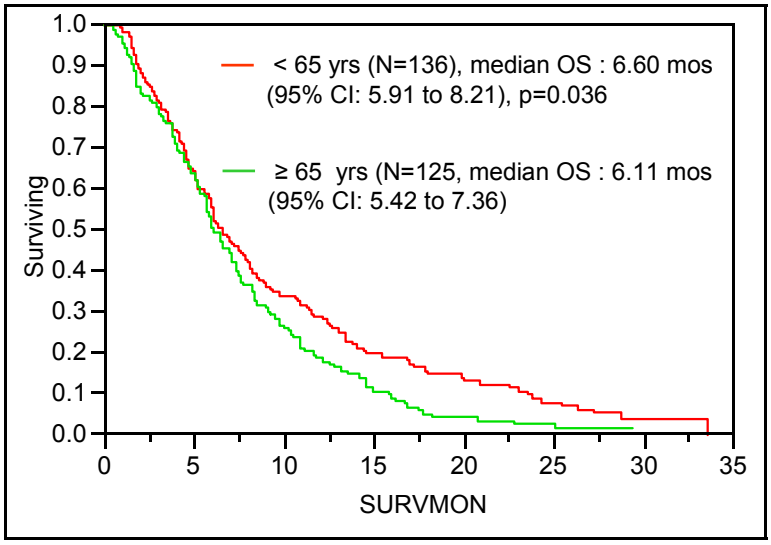


Note: < 65 years ("O") and ≥ 65 years old ("1").

As shown in figure 12, patients with < 65 years (N=274, depicted with the symbol "0"-red line) have better median overall survival than patients with ≥ 65 years (N=249, depicted with the symbol "1"-green line), median overall survival of 6.28 (5.65 to 7.23)

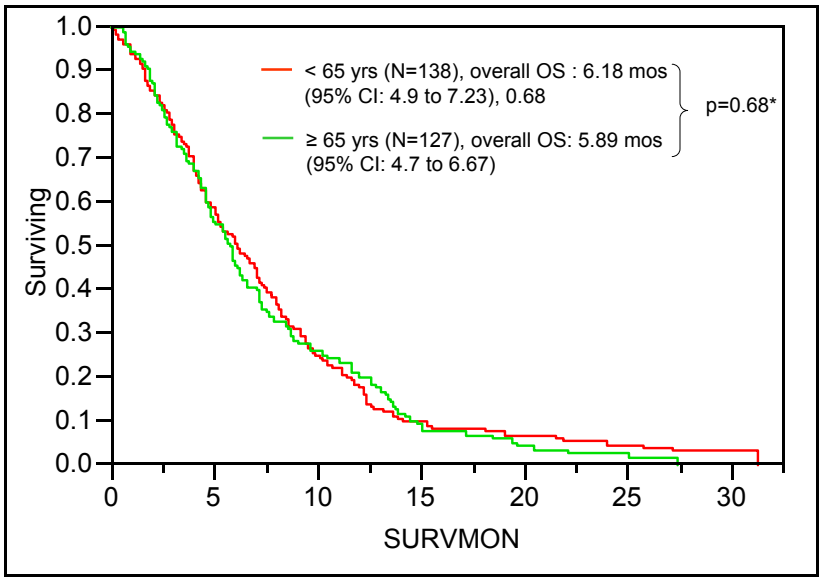
and 5.98 (5.42 to 6.64) with a p value of 0.06 (unadjusted Log-rank test). When assessed by treatment group, a significant difference can be seen only the EG group for the < 65 years : median overall survival of < 65 years is 6.60 mos (5.91 to 8.21) compared to ≥ 65 years, 6.11 mos (5.42 to 7.36), with a p value of 0.03, respectively.

Figure 13: **survival by age in patients treated with EG**



* unadjusted Log-rank test

Figure 14 Survival by age in patients treated with PG



unadjusted Log-rank test

Reviewer's note: To determine whether adjusting for prognostic factors of age, gender and pain intensity may have a role in overall survival of EG, the FDA performed an adjusted Cox proportional hazard model adjusting all these variables along with the 2 stratification factors (ECOG PS and extent of disease). The adjusted HR for EG over PG was 0.839 (95 % CI: 0.70 to 1.004, p=0.055), a non-significant difference. Thus, when

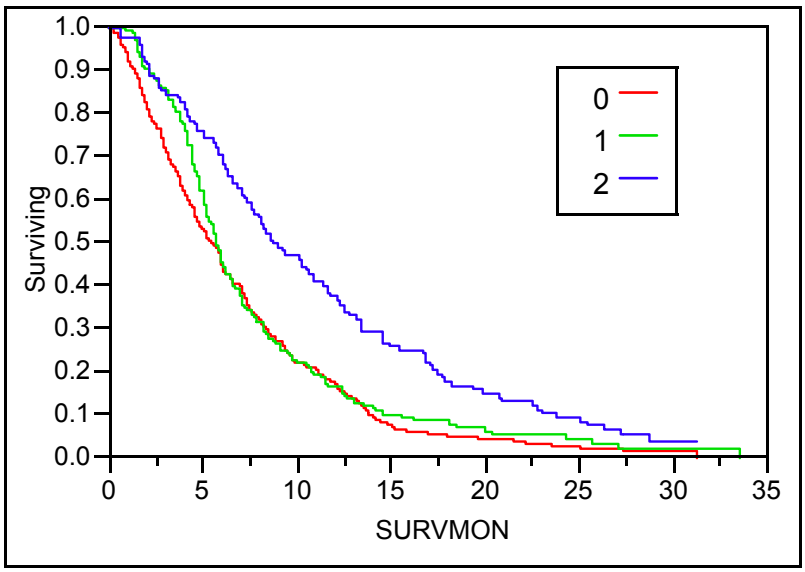
adjusting for known baseline imbalances, the marginal difference in overall survival between EG and PG became no longer statistically significant.

5.2.1.2 Survival by incidence of rash on therapy

In the BR.21 NSCLC pivotal study, patients who developed rash had longer OS compared with patients that did not have rash. Moreover, the higher grade of rash, the better increase in overall survival. (12). The agency studied this issue in the PA.3 study using OS data for the 100 mg group. Although patients with Grade 1 rash did not have any improvement of OS, patients with ≥ grade 2 had significant increase in OS when treated with EG.

As shown in Fig 15, group without rash (N=265, depicted with the symbol "0"-red line), Grade 1 (N=141, depicted with the symbol "1"-green line) and ≥ grade 2 rash (N=115, depicted with the symbol "2"-blue line). The median overall survivals (95% CI) were 5.45 months (4.63 to 6.11), 5.78 months (5.22 to 6.47) and 8.80 months (7.46 to 10.94), respectively with a p value of <0.0001 in favor of ≥ grade 2 rash group (comparing between group 0 "no rash" and group 2 "≥ grade 2 rash".

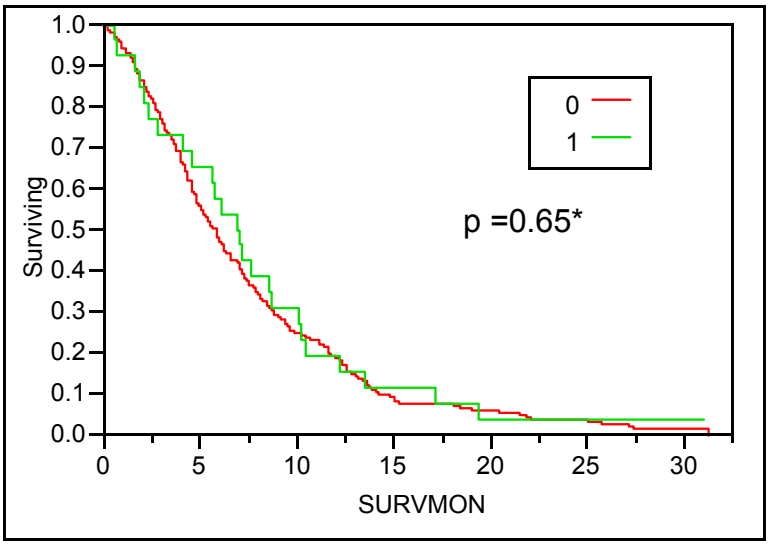
Figure 15 Survival by rash grade



Note: Group 0 (no rash), group 1 (grade 1 rash) and group 2 (≥ grade 2 rash). * unadjusted Log-rank test

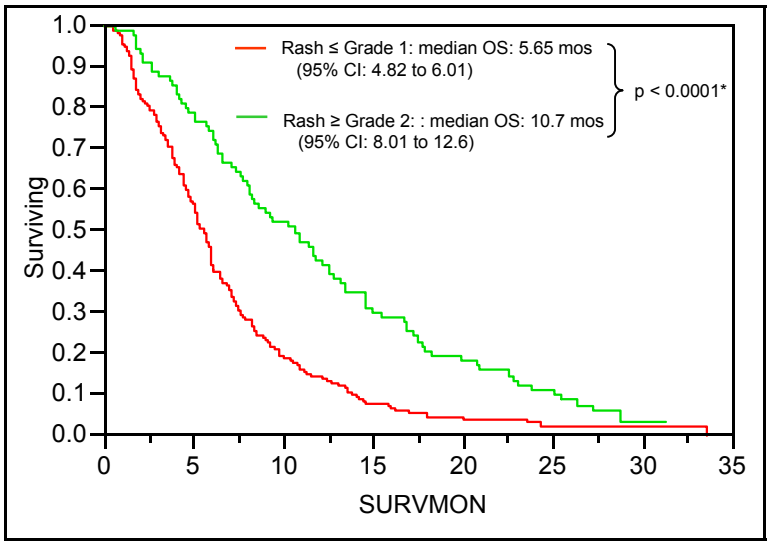
Fig 16 demonstrates the survival of patients in the arm PG (rash ≥ grade 2 or rash ≤ grade 1). Fig 17 demonstrate the survival of patients in the EG arm by rash status.

Figure 16 Survival by rash grade in PG arm



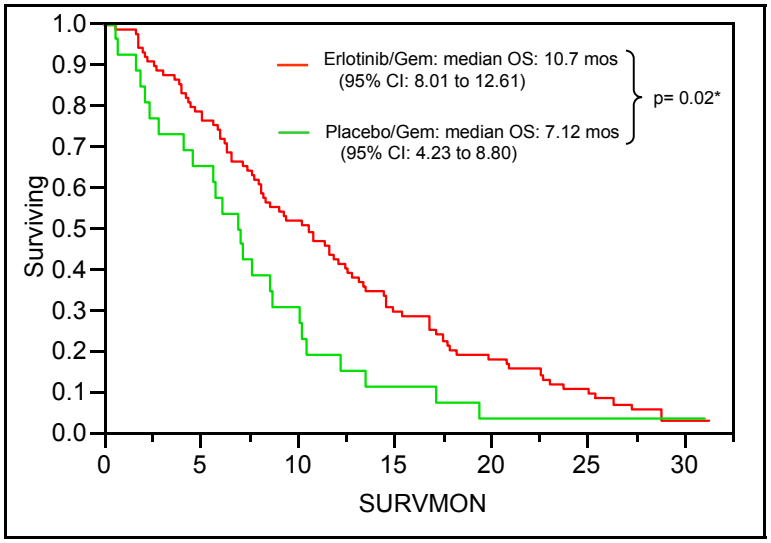
Note: group 0 (rash grade 0 and1) and group 2 (≥ grade 2). * unadjusted Log-rank test.

Figure 17 Survival by rash grade in EG arm



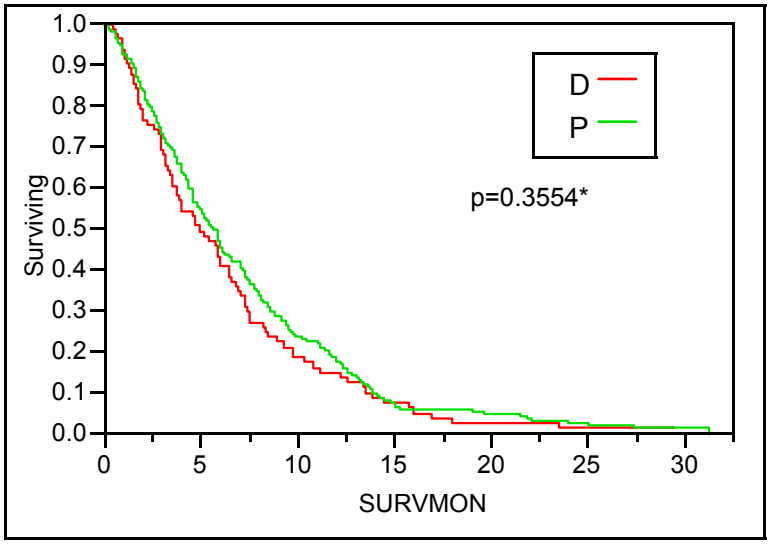
Note: * unadjusted Log-rank test

Figure 18 Survival by treatment in patients with rash ≥ grade 2



Note: group D (EG) and group P (PG). * unadjusted Log-rank test

Figure 19 Survival by treatment in patients without rash



Note: group D (EG) and group P (PG).

Table 21: Effect of rash in overall survival in PA.3

	Erlotinib/gemcitabine		Placebo/gemcitabine	
	Median survival (95 % CI)	N	**Median survival (95 % CI)**	N
Patients with no rash	4.99 (3.65 to 6.53)	82	5.72 (4.63 to 6.60)	183
Rash ≤ Grade 1	5.65 (4.83 to 6.01)	172	5.91 (4.93 to 6.60)	234
Rash ≥ Grade 2	10.68 (8.02 to 12.61)*	89	7.13 (4.23 to 8.80)	26

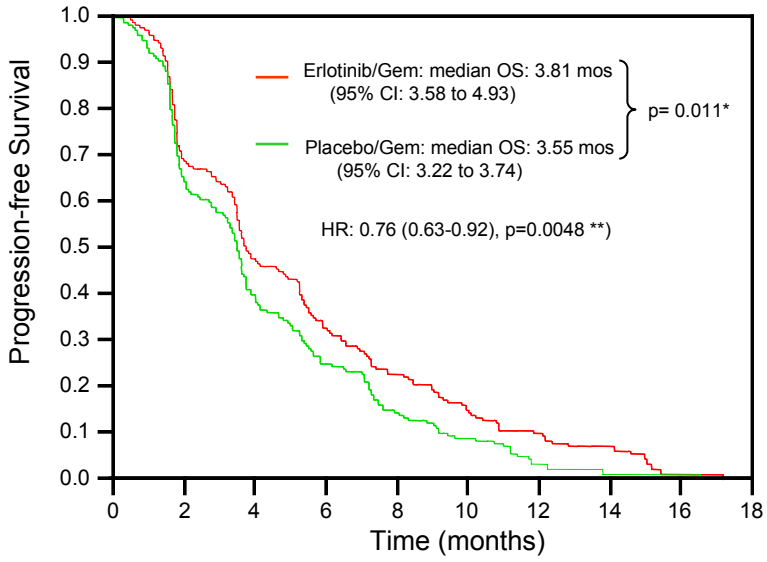
*p= 0.01

Reviewer's note: Patients with ≥ grade 2 rash benefit from EG. Moreover, patients with <grade 2 rash do not benefit from EG.

5.2.2 Progression-free survival:

PFS was a secondary endpoint defined as the time from randomization to the first observation of disease progression or death due to any cause. A patient who stopped therapy and went on to receive alternative therapy prior to documentation of PD was censored on the date alternative therapy began. If a patient had not yet progressed or received alternative therapy and was still alive at time of database lock, the PFS was censored on the date of last disease assessment.

Figure 20: **Kaplan-Meier curve for PFS 100 mg cohort**



* log-rank unadjusted; ** adjusted hazard ratio cox proportional model

Figure 20 represents the Kaplan-Meier PFS curves for patients in the 100 mg EG arm and PG arm. This is an ITT analysis. At the time of this report, ineligible cases due to lack of pathological confirmation were not excluded in this analysis. There was a statistically significant difference between the 2 treatment arms with respect to the

secondary endpoint PFS survival (unadjusted log-rank test, p-value=0.0119). The point estimate of the median progression-free survival was longer in the EG group, 3.81 mos (95% CI: 3.6-4.9) vs. 3.55 mos (95% CI: 3.2-3.7), a difference of 7.8 days. A total of 64 patients were censored (EG=36 and G=24)

Table 22 Progression-Free Survival Analysis (Intent-to-Treat Population)

Parameter	Erlotinib/gemcitabine (N = 261)	gemcitabine (N = 260)	Log-rank P value
Number (%)[a] of subjects with disease progression or death	225 (86.2)	232 (89.2)	
Median progression-free survival, mos	3.81	3.55	0.0119
95% Confidence interval	3.6-4.9	3.2-3.7	

Time to progression was calculated from the date of randomization to the date progression was first documented or the subject died. The last observation carried forward was used for missing data.
[a] Percentages were calculated by using N, the total number of subjects in the group, as the denominator.
[*Source: CRT database, patient.xpt, analyzed by jmp 5.1.1*

Cox proportional hazard model analysis for PFS demonstrated a hazard ratio (95 % CI) of 0.79 (0.66-0.95) with a p value of 0.012 when the analysis was unadjusted and a hazard ratio of 0.76 (0.63-0.92) with a p value of 0.0048 when the model was adjusted for PS and disease status.

Table 23: **Univariate and Multivariate Analyses for Progression-Free Survival**

		Univariate Analysis				Multivariate Analysis (1)		
Treatment Arm/Stratification Factors as Randomized	**N**	**Median PFS (Months)**	**Hazard Ratio (2)**	**(95% CI)**	**Log-Rank p-value**	**Hazard Ratio (2)**	**(95% CI)**	**Cox Regression p-value**
Treatment Arm					0.012			0.005
Placebo	260	3.55	0.79	(0.66, 0.95)		0.76	(0.64, 0.92)	
Erlotinib	261	3.81						
ECOG Performance Status					0.007			0.006
0-1	433	3.78	1.38	(1.09, 1.76)		1.40	(1.10, 1.79)	
2	88	3.22						
Disease Status					<0.001			<0.001
Locally Advanced	152	5.39	1.58	(1.28, 1.95)		1.58	(1.29, 1.95)	
Distant Metastasis	369	3.48						

Source: applicant's **Table 11–36**

5.2.3 Assessment of quality of life:

Results from the EORTC QLQ C-30 are presented in Table 24. Data are presented for each domain of the EORTC QLQ C30 including 5 functional subscales (physical, role, cognitive, emotional, and social), 8 symptom subscales (fatigue, pain, and nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation and diarrhea), a global health status question, and perceived financial impact of the disease. A statistically significant worsening in diarrhea ($p<0.001$) was accompanied by other decrements that approached statistically significance including cognitive functioning, social functioning, dyspnea, nausea/vomiting and loss of appetite. The global health status question did not demonstrate a statistically significant decrement in quality of life, but its results cannot support a "no decrement" conclusion because we do not know the clinical significance of the difference in response rates between treatment groups (32% of patients reporting quality of life worsening in the EG group compared to only 25% of the PG group).

Table 24 Results for QoL Response Analyses

	Gemcitabine+Erlotinib				Gemcitabine+ Placebo					
Domain/Item	N	Improved n (%)	Stable n (%)	Worsened n (%)	N	Improved n (%)	Stable n (%)	Worsened n (%)	Chi-Square p-value	Mantel-Haenszel p-value
Physical Functioning	205	48 (23)	97 (47)	60 (29)	200	38 (19)	94 (47)	68 (34)	0.438	0.201
Role Functioning	205	82 (40)	44 (21)	79 (39)	199	73 (37)	57 (29)	69 (35)	0.248	0.949
Emotional Functioning	205	85 (41)	60 (29)	60 (29)	201	76 (38)	78 (39)	47 (23)	0.111	0.779
Cognitive Functioning	205	63 (31)	60 (29)	82 (40)	201	63 (31)	77 (38)	61 (30)	0.075	0.203
Social Functioning	205	88 (43)	42 (20)	75 (37)	201	60 (30)	60 (30)	81 (40)	0.013	0.050
Fatigue	205	90 (44)	28 (14)	87 (42)	201	79 (39)	45 (22)	77 (38)	0.072	0.958
Nausea and Vomiting	205	62 (30)	69 (34)	74 (36)	201	41 (20)	90 (45)	70 (35)	0.028	0.264
Pain	205	117 (57)	45 (22)	43 (21)	202	102 (50)	58 (29)	42 (21)	0.264	0.420
Dyspnea	204	37 (18)	80 (39)	87 (43)	200	24 (12)	99 (50)	77 (39)	0.068	0.775
Sleep	203	91 (45)	61 (30)	51 (25)	200	72 (36)	64 (32)	64 (32)	0.154	0.055
Appetite	205	88 (43)	48 (23)	69 (34)	201	78 (39)	73 (36)	50 (25)	0.012	0.571
Constipation	204	74 (36)	77 (38)	53 (26)	201	61 (30)	89 (44)	51 (25)	0.343	0.484
Diarrhea	205	27 (13)	84 (41)	94 (46)	201	44 (22)	119 (59)	38 (19)	<0.001	<0.001
Financial	203	40 (20)	95 (47)	68 (33)	198	35 (18)	120 (61)	43 (22)	0.012	0.148
Global QoL	205	91 (44)	48 (23)	66 (32)	201	88 (44)	63 (31)	50 (25)	0.119	0.420

Source: taken from applicant's table 11–44.

Reviewer's note: A statistically significant worsening in diarrhea ($p<0.001$) was accompanied by other decrements that approached statistically significance including cognitive functioning, social functioning, dyspnea, nausea/vomiting and loss of appetite. The global health status question did not demonstrate a statistically significant decrement in quality of life, but its results cannot support a "no decrement" conclusion.

5.2.5 Objective antitumor responses

Table 25 Objective tumor responses

	Gemcitabine+Erlotinib (N=244)		Gemcitabine+Placebo (N=241)	
Response	**n**	**(%)**	**n**	**(%)**
Complete Response (CR)	1	(0.4)	2	(0.8)
Partial Response (PR)	20	(8.2)	17	(7.1)
Stable Disease (SD)	123	(50.4)	100	(41.5)
Progressive Disease (PD)	55	(22.5)	63	(26.1)
Missing	1	(0.4)	4	(1.7)
Inevaluable for Response or Not Assessed (IN/NA)	44	(18.0)	55	(22.8)

Source: (taken from applicant's table 11.46)

A total of 1 CR and 20 PRs, determined by RECIST criteria, were observed in the EG arm and a similar number, 2 CRs and 17 PRs, were observed in the PG arm, for an overall objective response rate of 8.6% (95% CI 5.4 to 12.9) in the EG arm and 7.9% (95% CI 4.8 to 12.0) in the PG arm, p = 0.869 (95% CI 5.5 to 12.6).

Reviewer's note: No differences were observed in objective response rates between EG and PG

5.2.6 Duration of Objective Response

No differences in duration of response or stable disease were observed between the 2 treatment arms (see Table 25). The overall median duration of the objective responses (CR and PR) in the EG arm was 23.9 weeks (95%: CI 16.3 to 31.9), ranging from 3.7 to 56.0+ weeks versus the placebo arm median duration of 23.3 weeks (95% CI: 16.1 to 32.4), ranging from 6.7+ to 65.3+ weeks (see applicant's Table 14.2.52, Section 14.2).

5.3 Safety Analysis

5.3.1 Dosing summary for erlotinib/gemcitabine

Erlotinib is a Human Epidermal Growth Factor Receptor Type 1 (HER1/EGFR) tyrosine kinase inhibitor, which was granted regular approval by FDA in November 2004 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. The recommended dose for this NSCLC indication is 150 mg orally administered once daily as a single agent.

The safety of 150 mg erlotinib PO QD was evaluated by study BR.21 (a placebo-controlled, randomized Phase III NSCLC study) where 485 patients receiving at least 1

dose of erlotinib were compared with 242 patients receiving placebo (see NDA 21-743 [NSCLC-July 29th, 2004].

The safety evaluation of erlotinib in combination with gemcitabline was primarily provided from Study PA3, " A Randomized Placebo Controlled Study of OSI-774 (Tarceva™) Plus Gemcitabine in Patients With Locally Advanced, Unresectable or Metastatic Pancreatic Cancer". In this study, a total of 569 were randomized to EG or PG arms. Of the 569 patients, 521 patients were randomized to received either 100 mg erlotinib (N=261) or placebo (N=260) and 48 patients were randomized to 150 mg EG or PG arms. Of those 521 patients, 259 patients received at least one dose of erlotinib/ gemcitabine and 256 patients received gemcitabine/placebo. Concurrently, an open label Phase Ib (OSI-774-155) study entitled "A Phase Ib Multicenter Trial to Determine the Safety, Tolerance and Preliminary Antineoplastic Activity of Gemcitabine Administered in Combination with Escalating Oral Doses of OSI-774 to Patient Cohorts with Recently Diagnosed, Gemcitabine-Naïve, Advanced, Pancreatic Carcinoma or Other Potentially Responsive Malignancies" was conducted with this combination in patients with various solid tumors including pancreatic carcinoma. Because of the different tumor types and the open label nature of this study, these studies were not pooled and analyzed.

Because no safety data were available for the combination of erlotinib and gemcitabine at the time of initiation of PA.3, the tolerability of the combination was assessed during an initial phase of limited accrual in selected Canadian centers during which patients were randomized to one of 2 arms: erlotinib 100 mg PO daily plus gemcitabine 1000 mg/m^2 IV or matching placebo PO daily plus gemcitabine 1000 mg/m^2 IV. Tolerability was assessed in a blinded fashion by reviewing cohorts of 8 – 16 patients for dose-limiting toxicity (DLT) during the first 4 weeks of therapy. Because of equivocal toxicities in some patients, the initial cohort was expanded to 50 patients. After the tolerability of erlotinib 100 mg in combination with gemcitabine was established, patient accrual at that dose level was opened to study sites worldwide, while limited accrual of 16 patients at selected Canadian centers evaluated the tolerability of erlotinib 150 mg in combination with the standard gemcitabine dose in a similar fashion. As stated by the applicant, after 16 patients were treated for at least 4 weeks, the 150 mg erlotinib dose was declared tolerable. Because of rapid accrual to the 100 mg cohort, however, only 48 patients were enrolled into the 150 mg cohort before the planned total accrual was accomplished.

A total of 6 randomized patients never received study drug: 2 patients randomized to receive erlotinib (2 in the 100 mg cohort) and 4 patients randomized to receive placebo (all in the 100 mg cohort). In addition, 2 patients did not receive the correct treatment as per randomization: 1 patient was randomized to placebo but received 100 mg of erlotinib during the second half of Cycle 1 and for 11 additional cycles of treatment, and one patient was randomized to the erlotinib arm but received placebo throughout the entire study. For the safety analyses, these 2 patients have been accounted for in the treatment group of what they actually received. An additional 6 patients received the incorrect treatment for short periods of time during the study. For the safety analyses, they have been accounted for in their randomized treatment groups. As a result, the safety

population for the 100 mg cohort used in the following analyses comprises 259 patients in the EG group and 256 patients in the PG group.

5.3.2 AEs and SAEs: overall summary of safety for the 100 mg cohort

Table 26: Overview of adverse events by treatment group: Safety Population

Category	Gemcitabine + Erlotinib (N=259)		Gemcitabine + Placebo N=256	
	n	(%)	n	(%)
Patients with at least one AE	256	(99)	248	(97)
Patients with at least one treatment-related AE	231	(89)	193	(75)
AEs Regardless of Causality by worst severity				
Grade 1	9	(3)	18	(7)
Grade 2	67	(26)	67	(26)
Grade 3	124	(48)	123	(48)
Grade 4	56	(22)	40	(16)
Treatment-Related AEs by worst severity				
Grade 1	46	(18)	59	(23)
Grade 2	106	(41)	79	(31)
Grade 3	67	(26)	48	(19)
Grade 4	12	(5)	7	(3)
Patients with at least one SAE	131	(51)	99	(39)
Patients with at least one treatment-related SAE	42	(16)	25	(10)
Patients who discontinued study due to treatment-related AEs	27	(10)	13	(5)
Patients with at least one severe (≥ grade 3) AE	180	(70)	163	(64)
Patients who died on treatment or within 30 days	86	(33)	72	(27)
Patients who died within 30 days due to a treatment-related AEs	5	(2)	0	(0)

(taken from applicant's table 12.36)

Reviewer's comment: The frequency of grade 4 AEs, serious AEs, grade ≥ 3 treatment-related AEs and AEs leading to discontinuation were all higher on the EG arm as compared with PG arm. Moreover, a greater number of patients died on treatment or within 30 days of therapy in the EG group (33%) as compared to PG (27%).

5.3.2.1 Deaths

The clinical database for Study PA.3 was initially locked on September, 17, 2004. At that time, 85 of the 569 patients who were randomized on this study were thought to be alive or lost to follow-up. In June 20th, 2005, an updated database revealed that a total of 551 patients died in this trial (out of a total of 569 patients). Moreover, 18 patients were found alive at last follow-up (see table 6). Last follow up ranged from December 2002 to June 2005. Of note, the cutoff date for this safety review is October 1st, 2004.

5.3.2.1.1 Death attributed to toxicity:

Death was attributed to toxicity from protocol treatment in 5 patients, all in the erlotinib arm of the 100 mg cohort (taken from applicant's table 12–42). The events resulting in death included 2 cases of pneumonitis, neutropenic and non-neutropenic sepsis in 1 patient each and 1 case of CNS bleeding. Moreover, 4 additional patients experienced serious drug-induced-related events with a fatal outcome, however, the Investigators attributed their death to other conditions or circumstances on the death form. This included 2 patients in the erlotinib arm who were noted to have lung infiltration and severe pneumonia, respectively, and 2 patients in the placebo arm who died from pneumonia, possible myocardial infarction or pulmonary embolus, and cancer death documented as drug-related, respectively.

Reviewer's note: The numbers are small but suggest an increase in the drug-toxicity associated with death in the EG group (N=5, 2.0%) as compared to PG (N=0, 0%)

Of note, the definition of Serious Adverse Event (SAE) (21 CRF 312. 32) "is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/ birth defect.". Unfortunately, the applicant did not capture the hospitalizations in this trial. Thus, the number of SAEs in this trial is a clear underrepresentation of the true SAE incidence.

5.3.2.1.2 Death in patients on therapy or within 30 days of last dose

Another important aspect of safety evaluation is the incidence of death on drug or within 30 days of last dose of drug. This represents a measure of drug toxicity (unless death is due to clear tumor progression).

A total of 521 patients were randomized to 100 mg erlotinib (N=261) or placebo (N-260). Of these patients, a total of 515 patients received at least one dose of either erlotinib (N=259) or placebo (N=256). A higher proportion of patients receiving 100 mg EG (N=86, 33.2%) died on study or within 30 days of last treatment comparing to placebo (N=70, 27.3 %). The factors associated with death within 30 days of drug administration is represented in table 27.

Table 27 Causes of death in patients that died within 30 days of last dose of treatment

	Erlotinib/Gem (N=86) %*	Placebo/Gem (N =72) %*
Toxicity due to protocol	2 (2.3)	0(0)
Combination Pancreatic cancer and protocol treatment	4 (4.7)	0(0)
Other primary malignancy	1(1.1)	0(0)
Pancreatic cancer progression	70 (81)	61(87.1))
Other reasons	9 (10.5)	10 (13.9)
Non-protocol treatment complication	0(0)	1(1.4)

*% of patients that died within 30 days of last dose

Reviewer's comment: In the EG group, a higher number of patients died on study or within 30 days of last dose due to either toxicity due to protocol drug or combination of pancreatic cancer and protocol treatment (7% versus 0% of all patients who died ≤ 30 days of drug administration).

5.3.2.2 Other Severe Adverse Events

The incidence of severe (≥ grade 3 NCI CTC) AE is presented in table 28. There does not seem to be a difference in the rate of severe AE's for most AEs. However, there is evidence that in the EG group there is higher incidence of several severe AEs including: stroke, cardiac ischemia/ infarction, stent occlusion, ARDS, pneumonitis, DVT, edema, arrhythmias, other infections, rash, diarrhea, ileus, pancreatitis, odynophagia/stomatitis, thrombocytopenia, neuropathy and renal insufficiency. The severe AEs that were statistically significantly different were stroke (p=0.03), GI system as a whole (p=0.02), ischemic events (p=0.006), other infections (p=0.006), rash (p=0.03), diarrhea (p=0.03). Moreover, pulmonary system as a whole, although not statistically significant, was leaning towards significance (p=0.09).

Table 28 Incidence of Patients with Severe Adverse Events (NCI CTC ≥ grade 3) Regardless of Causality

Adverse Event Preferred term	Erlotinib/Gem (N=259)	Placebo/Gem (N=256)
	N (%)	N (%)
Thrombotic		
Deep venous thromboses	6 (2.3)	5 (2)
Pulmonary embolism	9 (3.5)	3 (1.2)
Other thrombosis	17 (6.6)	18 (7)
Stent occlusion	5 (1.9)	1 (0.4)
TTP	2 (0.8)	0 (0)
Ischemic events		
Myocardial ischemia	7 (2.7)	3 (1.2)
Peripheral ischemia	1 (0.4)	0 (0)
Troponin elevation	1 (0.4)	0 (0)
Stroke (ischemic and hemorrhagic)	6 (2.3)	0 (0)

Adverse Event Preferred term	Erlotinib/Gem (N=259)	Placebo/Gem (N=256)
	N (%)	N (%)
Cardiovascular		
Congestive heart failure	2 (0.8)	3 (1.2)
Edema	12 (4.6)	5 (2)
Syncope	6 (2.3)	4 (1.6)
Arrhythmias	6 (2.3)	2 (0.8)
Hypertension	3 (1.2)	5 (2)
Hypotension	3 (1.2)	4 (1.6)
Pulmonary		
ARDS	3 (1.2)	0 (0)
Pneumonits	4 (1.5)	1 (0.4)
Hypoxia	1 (0.4)	1 (0.4)
Dyspnea	15 (5.8)	13 (5.1)
Pneumonia/Lung infiltration	13 (5.0)	6 (2.4)
Gastrointestinal		
Diarrhea	15 (5.8)	5 (2)
Abdominal pain	40 (15.4)	45 (17.6)
LFT elevation	19 (7.3)	15 (5.9)
Nausea/vomiting	23(8.9)	21 (8.2)
GI bleeding	15 (5.8)	8 (3.1)
Ileus	4 (1.5)	1 (0.4)
Pancreatitis	5 (1.9)	2 (0.8)
Odynophagia	3 (1.2)	0 (0)
Hematology		
Hemolytic anemia	2 (0.8)	0 (0)
Neutropenia	1 (0.4)	1 (0.4)
Thrombocytopenia	4 (1.5)	1 (0.4)
Bleeding disorders	3(1.2)	1 (0.4)
Metabolic		
Hyperglycemia	5(1.9)	10(3.9)
Hypoglycemia	2(0.8)	2(0.8)
Hyperkalemia	1(0.4)	1(0.4)
Hypokalemia	6(2.3)	4(1.6)
Hyponatremia	2(0.8)	4(1.6)
Hypercalcemia	1(0.4)	0(0)
Hypophosphatemia	0(0)	2(0.8)
Hypothyroidism	0(0)	2(0.8)
Constitutional symptoms		
Fatigue	42(16.2)	44(17.2)
Muscle weakness	0(0)	4(1.6)
Myalgia	3(1.2)	3(1.2)
Dehydration	9(3.5)	11(4.3)
Anorexia	19(7.3)	18(7)
Constipation	13(5)	19(7.4)
CNS		
Neuropathy	5(1.9)	1(0.4)
Depression	5(1.9)	3(1.2)

Adverse Event Preferred term	Erlotinib/Gem (N=259)	Placebo/Gem (N=256)
	N (%)	N (%)
Confusional state	3(1.2)	3(1.2)
Skin		
Rash	12(4.6)	3(1.2)
Infections		
Sepsis/bacteriemias	22(8.5)	22(8.6)
Other infections	13(5.0)	2(0.8)
Bone		
Bone pain	13(5.0)	9(3.5)
Aseptic necrosis bone	2(0.8)	1(0.4)
Others		
Renal failure	3(1.2)	0(0)

All patients that received at least one dose were eligible for this toxicity analysis. (EG: 256 and PG: 259)
Abbreviations: TTP: Thrombotic thrombocytopenic purpura. Source: CRF, XPT ADR database.

5.3.2.2.1 Incidence of Severe AEs by system.

1)Cardiovascular/circulatory system:

Ischemic events

Myocardial ischemia/infarction:

In the erlotinib group, 8 patients developed myocardial ischemia/infarction (incidence of 3.1 %). Two of these patients died due to a MI. In comparison, the PG group, 3 patients developed myocardial ischemia/infarction (incidence 1.2%) and only 1 died due to MI. The median time to onset of MI in the EG group was 72 days (21-123, 95 % CI). The earliest case was 13 days from drug initiation and the latest was 212 days after drug initiation. When compared both groups, using Fischer exact test, there was a statistically significant difference (p=0.006) between EG and PG arms.

Stroke:

Six patients in the EG group developed stroke (incidence: 2.3 %), four of them with a fatal outcome. One of these strokes was hemorrhagic. In comparison, in the PG group there was no stroke. The median time to stroke was 24 days (12-36, 95 % CI). The earliest case of stroke occurred by 2 days from drug initiation and the latest was 35 days after drug initiation, the differences were statistically significant (p=0.03).

Peripheral ischemia:

One patient developed peripheral ischemia in the erlotinib group (incidence: 0.4%)

In summary, 15 of patients had severe ischemic events in the EG group. In contrast, only 3 patients had severe ischemic events in the PG group. This difference is significant at the p 0.0066 (Fisher exact test, two-sided). Moreover, 6 patients developed stroke in the erlotinib group. This is unique as patients in the PG group did not develop this severe AE.

Venous thrombotic events:

Deep venous thrombosis (DVT)/other thrombosis and pulmonary embolism (PE):

Although the number of deep venous thrombosis and other thrombosis appear similar (23 in both EG and PG arms), a few more patients have higher incidence of pulmonary embolism in the EG group (9 versus 3 patients, respectively). Of note, 1 patient died of venous thromboses in PG group.

Stent occusion:

There was a significant increase in stent occlusion in the EG group as compared to PG (5 cases and 1 case, respectively)

Thrombotic thrombocytopenic purpura (TTP):

Two patients developed TTP in the EG group (0.8 %). Of note, TTP is a life-threatening disease with an estimated annual incidence of 3.7 cases per million.

Summary:

Although the incidence of DVT and other venous thrombosis are the same, the EG group had 3 times greater incidence of PE and 5 times greater incidence of stent occlusion. Moreover, two patients in the combined group developed TTP while no patient developed TTP in the placebo group.

Arrhythmias:

Patients in the EG group had 6 episodes of severe arrhythmia, including 2 sinus tachycardia, 2 atrial fibrillation, 2 undefined tachycardia and arrhythmia episodes, for an incidence of 2.3%. In contrast, the incidence in the PG group was much lower (0.8 %). Only 1 case of atrial fibrillation and 1 case of sinus tachycardia occurred in this group.

Congestive heart failure/peripheral edema:

Although similar number of patients have significant congestive heart failure, EG group has a higher incidence (more than 2 fold) of severe edema (4.6% vs 2 %, respectively).

Syncope:

A minimal increase in syncope was observed in the EG group (2.3% versus 1.6 %) , respectively.

Hypertension/hypotension:

A minimal increase in hypotension/hypertension was observed in the PG group.

In summary, cardiovascular AE appears worse for the EG group. Patients in the EG has higher incidence of peripheral edema, syncope and arrhythmias while patient in the PG group had higher incidence of hyper/hypotension. Of note, peripheral edema may be due to other causes such as liver or renal causes.

2)Sepsis/infections:

Although the number of sepsis episodes were quite similar among both groups (22 cases each group), the number of "other severe infections" were higher in the EG group (N=13 versus 2). The list of other severe infections included: 5 cholangitis, 3 cellulitis , 2 wound infections, 1 peritonitis, 1 salmonellosis, 1 urosepsis and 1 vaginal infection. In contrast, the PG had 1 episode of cholangitis and 1 wound infection. Three patients (1 neutropenic sepsis, 1 undefined sepsis and 1 cholangitis) and two patients died due to sepsis in the EG group and PG group, respectively.

In summary, patients in the EG had higher number of severe infections..

Pulmonary:

Thirteen patients in the EG group developed severe pneumonia (incidence: 5.0 %) while only eight patients developed pneumonia in the PG group (3.1%). Two patients with pneumonia died in the EG groups while no patient died due to pneumonia in the PG group.

Another significant adverse events is the interstitial lung disease (ILD). This adverse event was already reported in the lung pivotal study (BR.21). The incidence in that trial was approx. 0.8%. In this trial, the incidence was approx 3 times higher (2.3%). The difference is that in the BR.21 trial, patients were treated with higher erlotinib doses (150 mg). Moreover, those patients had lung cancer and some of them received chest irradiation. In contrast, patients in PA.3 trial have pancreatic carcinoma, received lower doses of erlotinib in combination with gemcitabine and no patient received chest irradiation.

A total of 7 patients developed serious ILD-like events, 6 patients in the EG arm (2.3%) and 1 patients in the PG arm (0.4%) (see table 29). 4 cases developed pneumonitis (EG=3 and PG=1). Three patient died due to IDL-like events in the EG groups while no patient died due to ILD-like event in the PG group. The median time to ILD-like event was 50 days (95 % CI: 17 to 63). The earliest case of ILD-like event occurred by 39 days from drug initiation and the latest case was 122 days after drug initiation. Overall, the incidence of serious ILD-like conditions in the EG arm is 2.3 % while the incidence of ILD-like in the PG group is 0.4 %. This incidence (2.3 %) is much higher than the one observed in the NSCLC BR.21 trial (0.8%).

Table 29 Patients with ILD-Like Serious Adverse Events Regardless of Causality

Patient ID	Group	MedDRA PT	Days to Onset	Outcome
AUQZ0321	EG	Pneumonitis	48	Died
ARAQ0642	EG	Pneumonitis	52	Died
USYH0372	EG	Pneumonitis	122	Recovered
USQB0488	EG	Pneumonitis	39	Recovered
USYR0233	EG	Lung infiltration	84	Recovered
SGKR0349	EG	Pneumonia ARDS[b]	48	Died
USYH0457	PG	Pneumonitis	51	Recovered

Source: (adapted from applicant's table 12.47)

Skin:

Rash:

A well recognized adverse event with erlotinib is rash. In this study, 12 cases of severe rash were observed in the EG group (4.6 %). In contrast, only 3 patients had severe rash in the PG group (1.2%). The median time to onset of rash for all rash grades was 10 days (see Table 30). However, median time to Onset of for ≥ grade 2 was 8 days.

Table 30. Time to Onset of Rash (Days)

		Gemcitabine+Erlotinib (N=259)	Gemcitabine+Placebo (N=256)
Rash	n	171.0	72.0
	Median time to onset (days)	10.0	10.0
	Range (days)	1.0 - 421.0	1.0 - 298.0

Source: applicant's table 14.3.1.**11**

Selected Gastrointestinal events:

Diarrhea:

A very significant and consistent severe toxicity in the EG group was diarrhea refractory to supportive care. Significant diarrhea (almost 3 fold difference) was observed in 15 patients in the EG group (incidence 5.8 %), in comparison to 5 patients in the G group (2%). The time to onset of diarrhea is shown in table 31. The median to onset of diarrhea is 15 days in the EG group compared with 25.5 days in the PG group.

Table 31 Time to Onset of Diarrhea (Days)

		Gemcitabine+Erlotinib (N=259)	Gemcitabine+Placebo (N=256)
Diarrhea	n	111.0	78.0
	Median time to onset (days)	15.0	25.5
	Range	1.0 - 317.0	1.0 - 294.0

Source: applicant's Table 14.3.1.11

GI bleeding:

Severe bleeding included gastrointestinal disorders in 15 (5.8%) and 8 (3.1%) of the patients in the EG and PG arm, respectively. Three cases were fatal, all in the EG group. No patient died due to GI bleeding in the placebo group.

A significant number of patients received concurrent NSAID administration (including COX-2 inhibitors) in 6 patients in the EG arm and in 5 patients in the PG arm in both cohorts. Similarly, 3 patients in the combined erlotinib arms and 2 patients in the placebo arms were receiving warfarin. Grade 3 thrombocytopenia was observed concurrently with a bleeding episode in only 1 patient in the erlotinib arm and in 1 patient in the placebo arm

Liver function test elevation:

Based on the theoretical possibility of increase in liver toxicity in the PG group, the applicant paid attention during the dose evaluation phase of this PA.3 to possible hepatic toxicity above that expected for gemcitabine. Three of the initial 16 patients developed transaminase elevation. Following unblinding, it was determined all 3 patients were receiving erlotinib. One of the 16 patients in the 100 mg cohort developed a DLT of Grade 3 transaminase elevation. Following unblinded, it was determined this patient was receiving placebo.

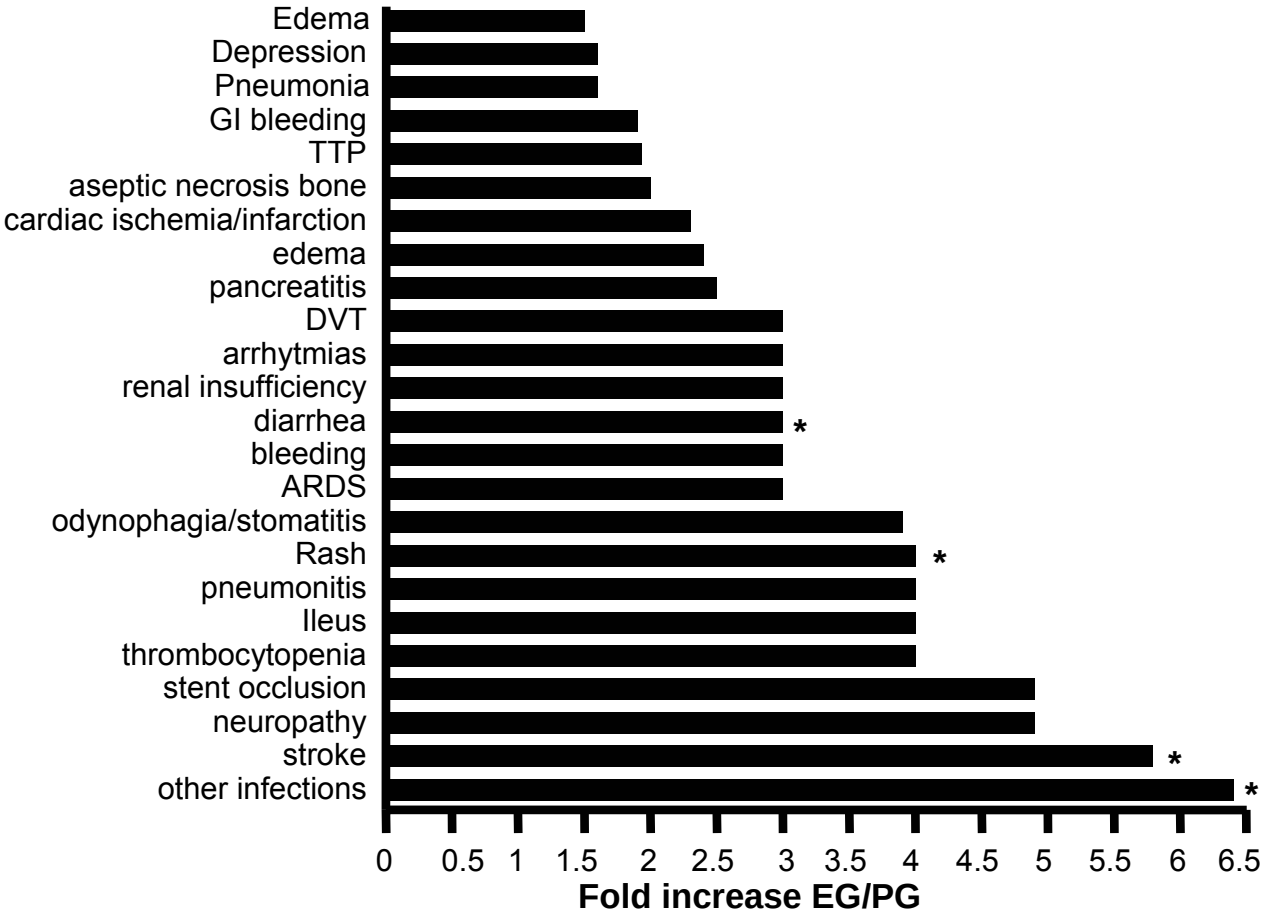
A total of nineteen patients in the EG group developed severe LFTs (7.3 %) versus 15 patients in the placebo group (5.9 %). Moreover, a higher incidence of cholangitis was observed in the combination group.

Summary:

The difference in severe AE in the GI category is statistically significant (PG/EG, p= 0.026)

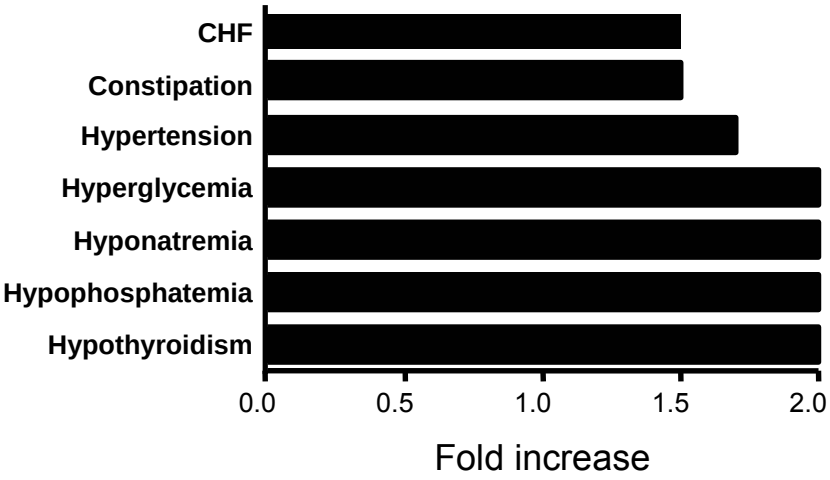
Figure 21 represents the fold increase (≥ 1.5) in severe AEs for the EG vs PG arms. Moreover, figure 22 represents the fold increase (≥ 1.5) in severe AEs for PG over EG.

Figure 21 Severe AEs in the 100 mg EG arm: fold increase over PG arm



Note: severe: ≥ grade 3. Only AEs ≥ 1.5 fold. * p <0.05 by two-sided, Fisher Exact Test. Also, GI AEs as a group are statistically significant. For some groups, fold increase values is an underestimation as for some groups such as TTP as the PG group did not have any event. For exact percentage, please refer to Table 28.

Figure 22 Severe AEs in 100 mg PG/Gem group, Fold increase over EG arm.



Note: severe: ≥ grade 3. Only AEs ≥ 1.5 fold. For some groups, fold increase values is an underestimation as for some groups such as TTP as the PG group did not have any event. For exact percentage, please refer to Table 28.

Summary:

In summary, the EG appears significantly more toxic that PG. Increase incidence of severe AEs were observed in these categories (see Table 28 and Figure 21): stroke, cardiac ischemia/ infarction, stent occlusion, ARDS, pneumonitis, DVT, edema, arrhythmias, other infections, rash, diarrhea, ileus, pancreatitis, odynophagia/stomatitis, thrombocytopenia, neuropathy and renal insufficiency. The severe AEs that were statistically significantly different were stroke (p=0.03), gastrointestinal system as a whole (p=0.02), ischemic events (p=0.006), other infections (p=0.006), rash (p=0.03), diarrhea (p=0.03).

In contrast, few severe AEs were overrepresented in the PG arms (see Table 28 and figure 22) such as hypothyroidism, hypophosphatemia, hyperglycemia, hypertension and congestive heart failure.

Notwithstanding the limitation of cross-study comparisons, EG combination appears significantly more toxic than erlotinib monotherapy. Several recognized toxicities such as ILD-like event (2.3 %) or liver function test elevation (7.3%) were higher in the combination, compared with erlotinib monotherapy (NSCLC study BR.21). Moreover, new and previously unrecognized toxicities were overrepresented in the combination such as stroke, peripheral neuropathy, arrhythmias, ileus, edema, pancreatitis, renal failure, TTP and stent occlusion.

Although there is an increase in death due to erlotinib/gemcitabine toxicity and there is an increase in death in patients receiving drug within the last 30 days, we believe that this is an underestimation of the incidence of drug induced death as the cause of death was unclear in several cases when there is disease progression along with drug toxicity.

Another important caveat for this study is the lack of information in relation to hospitalization. Of note, the definition of Serious Adverse Event (SAE) includes" death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/ birth defect". The applicant did not capture the hospitalizations in this trial. Thus, the number of SAEs in this trial is a clear under representation of the true SAE incidence.

5.3.3 Dropouts and Other Significant Adverse Events

5.3.3.1 Overall profile of dropouts

Table 32 Summary of reasons for erlotinib/placebo discontinuations

	Gemcitabine+Erlotinib N=259		Gemcitabine+Placebo N=256	
	n	(%)	n	(%)
Progressive Disease	121	(46)	149	(57)
Symptomatic Progression	41	(16)	36	(14)
Adverse events	62	(24)	37	(14)
Intercurrent Illness	10	(4)	10	(4)
Patient Refusal	22	(8)	15	(6)
Death	25	(10)	21	(8)
Other	6	(2)	8	(3)

Note: Patient CAVC0149 in the 100 mg cohort of the erlotinib arm was never treated with study drug but had an off-study reason of 'Patient refusal'. Source adapted from applicant's table 10.4 and analysis of patient.XPT SAS file. Adverse events were obtained from ADR.xpt SAS file: analysis of aewdraw subgroup "Withdrawn from Study due to AE.

The great majority of patients that discontinued treatment were due to progression of disease. However, patients in the EG group have higher evidence of AEs that lead to discontinuation of therapy (24% vs 14%, respectively). Please note that patients may appear in the same or different categories for discontinuation of EG and PG. Patients could discontinue treatment due to more than 1 event or reason.

5.3.3.2 Adverse events associated with dropouts

Table 33 Incidence of AEs based on Withdrawn from Study due to AE

	Fold increase EG/PG	Erlotinib + gemcitatine N=259		Placebo + gemcitatine N=256	
		N	%	N	%
LFT	4.0	4	1.5	1	0.4
diarrhea	4.0	4	1.5	1	0.4
thrombocytopenia	3.9	4	1.5	0	0.0
rash	2.0	4	1.5	2	0.8
pneumonitis	3.0	3	1.2	1	0.4
neutropenia	1.9	2	0.8	0	0.0

	Fold increase EG/PG	Erlotinib + gemcitatine N=259		Placebo + gemcitatine N=256	
		N	%	N	%
fatigue	0.4*	2	0.8	5	2.0
CHF	0.5*	0	0.0	2	0.8
Hemolytic anemia	1.9	2	0.8	0	0.0
Nausea/vomiting	0.4*	2	0.8	5	2.0
edema	1.0	2	0.8	2	0.8
renal	1.9	2	0.8	0	0.0
anorexia	~1	1	0.4	0	0.0
stroke	~1	1	0.4	0	0.0
dehydration	~1	1	0.4	0	0.0
dyspnea	0.5*	1	0.4	2	0.8
Abd pain	~1	0	0.0	1	0.4
GI bleeding	~1	1	0.4	0	0.0
myalgia	~1	0	0.0	1	0.4
anemia	1.0	1	0.4	1	0.4
hyponatremia	~1	1	0.4	0	0.0
infection	1.0	1	0.4	1	0.4
Myocardial infarction/ischemia	~1	1	0.4	0	0.0
neuropathic pain	~1	1	0.4	0	0.0
urticaria	~1	0	0.0	1	0.4
Palmar-plantar syndrome	~1	1	0.4	0	0.0
peripheral ischemia	~1	1	0.4	0	0.0
Pleural effusion	~1	1	0.4	0	0.0
proteinuria	~1	1	0.4	0	0.0
pruritus	~1	1	0.4	0	0.0
pyrexia	1.0	1	0.4	1	0.4
Thrombocythaemia	~1	1	0.4	0	0.0
TTP	~1	1	0.4	0	0.0
vaginitis	~1	1	0.4	0	0.0
vertigo	~1	1	0.4	0	0.0
Weight decreased	~1	1	0.4	0	0.0

Note: For some groups, fold increase values is an underestimation as for some groups such as TTP as the PG group did not have any event. For exact percentage, please refer to Table 36. Source: Adverse events were obtained from ADR.xpt SAS file. "~1": only 1 event in 1 group with no event in the other group. * represents that the PG group incidence has higher number of events compared with EG group

Table 33 depicts the incidence and causes associated with discontinuation of treatment due to AEs in the 100 mg group. A total of 62 (24 %) patients discontinued therapy due to AE events in the EG group. In contrast, only 37 (14 %) patients discontinued therapy due to AE in the PG group. Of note, this table does not include patients that refused therapy due to adverse events (see section 5.3.4).

Reviewer's comment: A higher number of patients discontinued therapy due to AE in the erlotinib group 62 vs 37, respectively (24 % vs 14%, respectively).

5.3.4 Refusal of further therapy:

Of a total of 521 patients in the 100 mg dose (261 drug and 260 placebo), a total of 37 patients refused further therapy. 22 patients refused further therapy in the erlotinib group (8.5%) and 15 patients refused further therapy in the placebo groups (5.8%).

The factors associated with refusal of further therapy are presented in table 34. Approx. 55 % of patients (N=12) who withdrew consent in the EG group were associated with severe toxicities (see table 35). In contrast, only 20 % (N=3) withdrew consent in the PG group due to severe AEs.

Table 34 Causes for dropouts in patients that refused further therapy

Causes	Erlotinib/gemcitabine (N=259)	Placebo/Gemicitabine (N= 256)
Total (%)	22	15
Severe (≥ Grade 3) toxicity	12	3
Other causes	10	12

Source: ADR.XPT database analyzed in jmp 5.1.1. Also, analysis of corresponding CRFs

Table 35 Adverse events associated with refusal of further therapy.

Causes	**Erlotinib/gemcitabine (N=12)**	**Placebo/gemcitabine (N= 3)**
Liver enzymatic elevations	6	0
Deep venous thrombosis	3	0
sepsis	3	0
Pneumonia	2	0
GI bleed	2	0
Congestive heart failure	1	0
Ileus/dehydration	1	0
Dysphagia	1	0
Aseptic necrosis of bone	0	1
Arrhythmia	0	1
Arthralgias/muscle weakness	0	1

Source: ADR.XPT database analyzed in jmp 5.1.1. Also, analysis of corresponding CRFs

The main cause associated with refusal of therapy in the EG group was hepatic enzymes elevation (total of 6 patients) followed by deep vein thrombosis and sepsis. In contrast, in the placebo group was 1 case of arrhythmia, 1 case of arthralgia/muscle pain and 1 case of aseptic bone necrosis (see table 35).

Reviewer's comment: A higher number of patients refused therapy in the EG group. Moreover, the majority of patients that refused therapy in the EG group was due severe AEs.

5.3.5 Common adverse event profile in PA.3

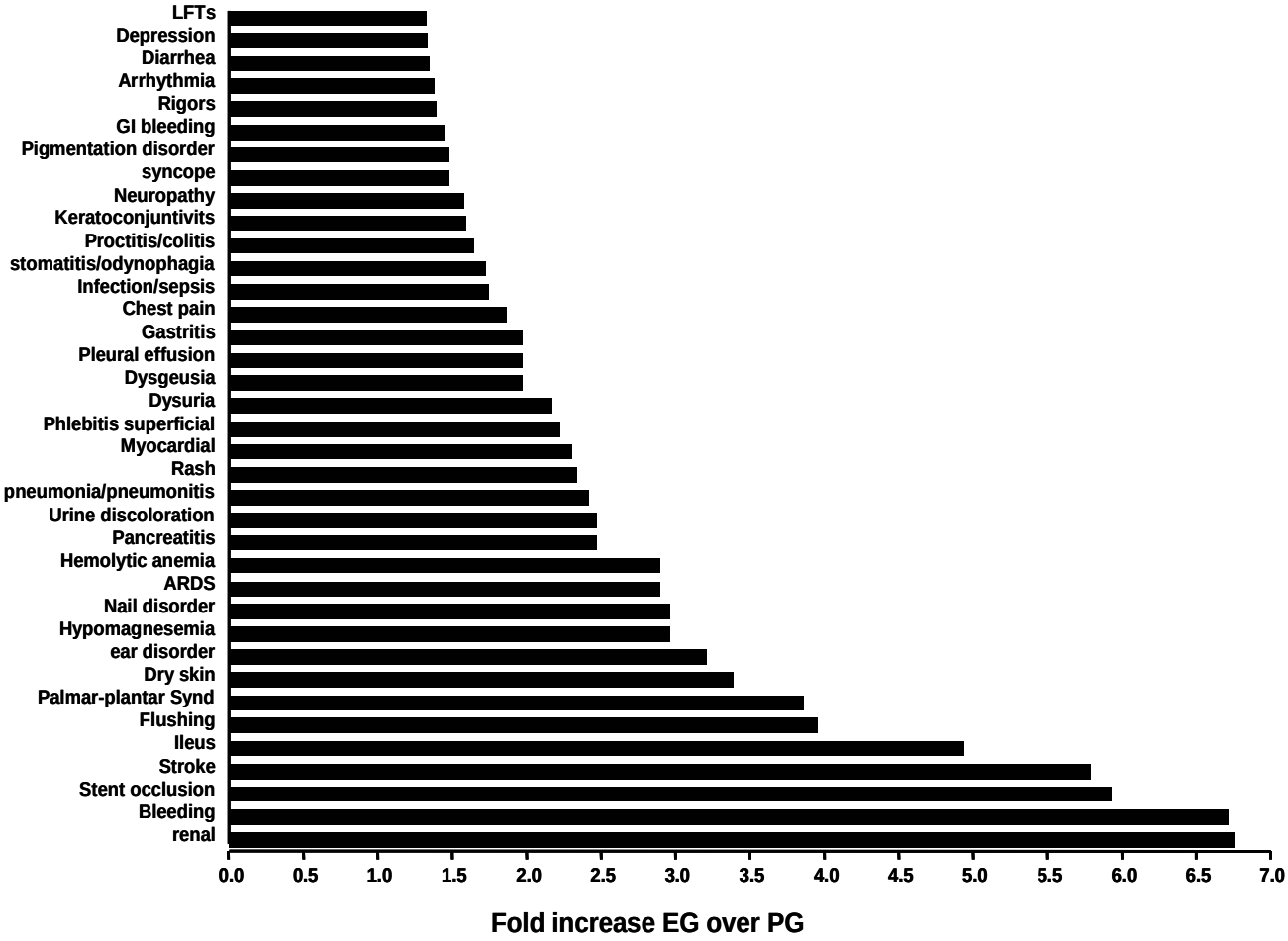
Table 36: Adverse Events in ≥ 1% of Patients

AEPREF	Fold increase EG/PG	Erlotinib + gemcitabine N=261		Placebo + gemcitabine N=260	
		Total patients	% total	Total patients	% total
Nausea/vomiting	1.0	261	100.0	252	98.4
Fatigue	1.0	188	72.6	178	69.5
Rash	2.3	180	69.5	76	29.7
Infection/sepsis	1.7	138	53.3	78	30.5
Anorexia	1.0	134	51.7	132	51.6
Diarrhea	1.3	124	47.9	91	35.5
Abdominal pain	1.0	117	45.2	115	44.9
Weight decreased	1.3	101	39.0	74	28.9
Edema	1.0	100	38.6	96	37.5
Pyrexia	1.2	93	35.9	78	30.5
Constipation	0.9*	80	30.9	86	33.6
Stomatitis/odynophagia	1.7	70	27.0	40	15.6
Bone pain	1.1	65	25.1	60	23.4
Dyspnea	1.0	62	23.9	63	24.6
Myalgia	1.1	54	20.8	50	19.5
Depression	1.3	50	19.3	37	14.5
Dyspepsia	1.3	43	16.6	34	13.3
Cough	1.4	42	16.2	29	11.3
Neuropathy	1.6	40	15.4	25	9.8
Dizziness	1.1	39	15.1	34	13.3
LFTs	1.3	39	15.1	29	11.3
Headache	1.5	39	15.1	26	10.2
Insomnia	0.9*	38	14.7	41	16.0
Alopecia	1.3	37	14.3	29	11.3
Anxiety	1.2	34	13.1	29	11.3
Bleeding	6.7	34	13.1	5	2.0
Flatulence	1.5	33	12.7	22	8.6
Rigors	1.4	31	12.0	22	8.6
Keratoconjuntivitis	1.6	29	11.2	18	7.0
DVT/thrombosis	1.1	27	10.4	24	9.4
Pruritus	1.1	24	9.3	22	8.6
Dry skin	3.4	24	9.3	7	2.7
Gastrointestinal bleeding	1.4	22	8.5	15	5.9
Pneumonia/pneumonitis	2.4	22	8.5	9	3.5
Arthralgia	1.3	21	8.1	16	6.3
Rhinitis allergic	0.8*	20	7.7	24	9.4
Dehydration	0.9*	20	7.7	22	8.6
Dry mouth	0.7*	17	6.6	24	9.4
Chest pain	1.9	17	6.6	9	3.5
Dysgeusia	2.0	16	6.2	8	3.1
Proctitis/colitis	1.6	15	5.8	9	3.5
Arrhythmia	1.4	14	5.4	10	3.9
Ear disorder	3.2	13	5.0	4	1.6
Injection site reaction	0.8*	13	5.0	16	6.3
Hiccups	1.2	12	4.6	10	3.9
Hypokalaemia	0.8	11	4.2	13	5.1

AEPREF	Fold increase EG/PG	Erlotinib + gemcitabine N=261		Placebo + gemcitabine N=260	
		Total patients	% total	Total patients	% total
Confusional state	0.9*	11	4.2	12	4.7
Dysuria	2.2	11	4.2	5	2.0
Hyperhidrosis	0.5	10	3.9	18	7.0
Hypertension	1.0	10	3.9	10	3.9
Hypotension	0.9*	9	3.5	10	3.9
Phlebitis superficial	2.2	9	3.5	4	1.6
Hyperglycaemia	0.8*	8	3.1	10	3.9
Pollakiuria	0.8*	8	3.1	10	3.9
Proctitis	1.3	8	3.1	6	2.3
Pleural effusion	2.0	8	3.1	4	1.6
Influenza like illness	0.9*	7	2.7	8	3.1
Contusion	1.0	7	2.7	7	2.7
Myocardial ischamia/infarction	2.3	7	2.7	3	1.2
Renal	6.76	7	2.7	0	0.0
Pulmonary embolism	1.2	6	2.3	5	2.0
Depressed level of consciousness	1.2	6	2.3	5	2.0
syncope	1.5	6	2.3	4	1.6
Stent occlusion	5.9	6	2.3	1	0.4
Tremor	0.8*	5	1.9	6	2.3
Hoarseness	1.0	5	1.9	5	2.0
Back pain	1.0	5	1.9	5	2.0
Pancreatitis	2.5	5	1.9	2	0.8
Urine discoloration	2.5	5	1.9	2	0.8
Ileus	4.9	5	1.9	1	0.4
Stroke	5.8	6	2.3	0	0.0
Vision blurred	0.5*	4	1.5	8	3.1
Gastritis	2.0	4	1.5	2	0.8
Flushing	4.0	4	1.5	1	0.4
Palmar-plantar erythrodysesthesia syndrome	3.9	4	1.5	0	0.0
Muscular weakness	0.4*	3	1.2	8	3.1
Hallucination	0.5*	3	1.2	6	2.3
Hyponatremia	0.6*	3	1.2	5	2.0
Hypoglycemia	0.6*	3	1.2	5	2.0
Hemoglobin abnormal	0.7*	3	1.2	4	1.6
Catheter site pain	1.5	3	1.2	2	0.8
Pigmentation disorder	1.5	3	1.2	2	0.8
Hypomagnesemia	3.0	3	1.2	1	0.4
Nail disorder	3.0	3	1.2	1	0.4
Acute respiratory distress syndrome	2.9	3	1.2	0	0.0
Hemolytic anemia	2.9	3	1.2	0	0.0

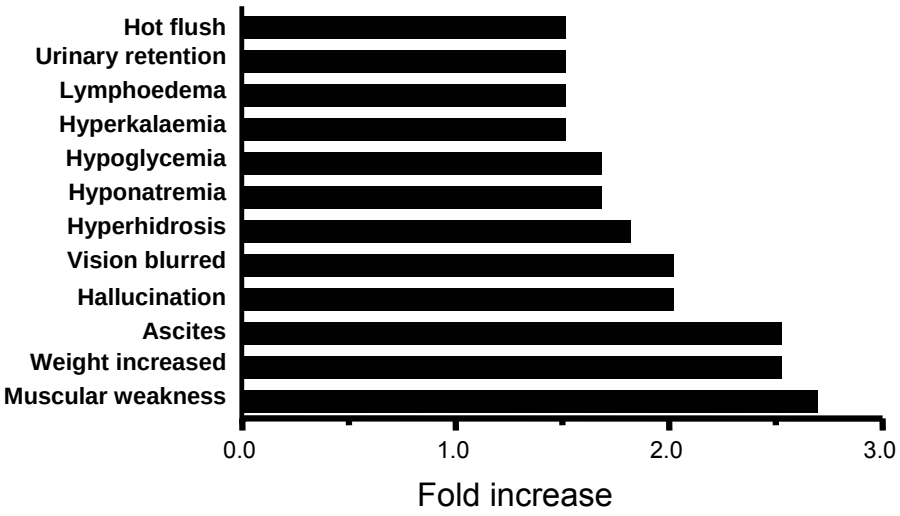
Note: for some groups, fold increase values is an underestimation as for some groups did not have any event
* represents that the PG group incidence has higher number of events compared with EG group.

Figure 23 Adverse events for all grades overrepresented in EG arm vs PG arm



Note: for some groups, fold increase values is an underestimation as for some groups did not have any event

Figure 24 Adverse events for all grades overrepresented in PG arm vs EG arm



Note: for some groups, fold increase values is an underestimation as for some groups did not have any event

Reviewer's comment: Most toxicities were more frequent on the EG arm. Moreover, there are several AEs that are overrepresented. Few examples include: Renal, bleeding, stent occlusion, stroke, ileus, palmar-plantar syndrome, ear disorder, pancreatitis, pneumonitis, ARDS, hemolytic anemia, myocardial ischemia/infarction. However, few AEs were overrepresented in the PG arm including muscle weakness, ascites, hyponatremia and hyperkalemia.

6 SUMMARY AND CONCLUSIONS

6.1 Statistical Issues and Collective Evidence:

The study PA.3 was a double-blinded randomized multicenter study. It was designed to demonstrate a survival improvement for the use of erlotinib in combination with gemcitabine in patients with locally advanced or metastatic pancreatic carcinoma. A phase 3 study, of 569 (521 patients at the dose of 100 mg and 48 patients at the dose of 150 mg) patients with locally advanced or metastatic pancreatic carcinoma was conducted. The primary endpoint of the trial was overall survival. The trial was powered to demonstrate a 33% improvement in survival from 6.8 months with gemcitabine alone to 8.8 months for the combination treatment, (80% power, hazard ratio of ~ 0.75). The target accrual of 450 patients was necessary in order to achieve the required number of events (N = 381) for the final analysis. Thus, the primary analysis for this study was overall survival when 381 events occurred. Progression-free survival, antitumor response rate and quality of life were secondary endpoints.

The final analysis was initially performed when 484 deaths occurred, an excess of 100 deaths over the original planned for this analysis (381 deaths). An updated survival database was provided with 504 patient deaths. The median overall survival, estimated from 504 death univariate Kaplan-Meier curves, was 6.37 months (95% CI: 5.84 to 7.33) in the EG arm and 5.95 months (95% CI 5.09 to 6.70), in the PG, a difference of ~ 12 days in favor of the EG group (p= 0.0596, unadjusted log-rank test). When the overall survival was analyzed at 381 events, as planned in the protocol, similar results were obtained. Moreover, the hazard ratio (HR) for overall survival (504 deaths) in the EG arm relative to the PG arm, estimated from a univariate Cox model, was 0.84 (95% CI 0.70 to 1.007, p = 0.06). Similar results were obtained in the censored analysis (381 deaths). However, when multivariate Cox model was constructed that included treatment and both of the specified covariates, namely ECOG PS and extension of disease, the adjusted HR (504 death) for overall survival in the 100 mg erlotinib arm relative to the PG arm was 0.81 (95% CI: 0.68 to 0.97, p = 0.02). In the 100 mg cohort (381 events), the adjusted HR was 0.79 (95 % CI: 0.65 to 0.97, p = 0.026). The adjusted analysis was the protocol specified primary analysis.

With respect to the secondary objectives, the median PFS for 100 mg cohort, estimated from univariate Kaplan-Meier curves, was 3.81 months (95 % CI: 3.58 to 4.92) and 3.55 months (95 % CI: 3.22 to 3.75, p= 0.01, unadjusted log-rank test and adjusted HR: 0.76 (95% CI: 0.63 to 0.921372, p =0.004), respectively. Although the median PFS represents a difference in ~10 days, this difference was statistically significant. In contrast, there was not statistically significant difference in tumor response (8.6% and 8.0%, respectively, p=0.869). Finally, with respect to quality of life, a statistically significant worsening in diarrhea ($p<0.001$) was accompanied by other decrements that approached statistical significance including cognitive functioning, social functioning, dyspnea, nausea/vomiting and loss of appetite. Of note, gemcitabine was approved for this disease due to a significant improvement of clinical symptoms with increase in overall survival.

The combination arm was associated with a significant increased toxicity and discontinuations due to adverse events (AEs): The frequency of grade ≥ 4 AEs, serious AEs leading to discontinuation all were higher on the EG arm. Moreover, a greater number of patients in the EG group died due to toxicity of protocol treatment. Also, a greater number of patients died on treatment or within 30 days of therapy.

There are several relevant issues regarding this sNDA application. The first issue is, although some analyses showed statistically significant differences between combination and gemcitabine alone, no clinically meaningful differences in response rate, duration of response, PFS or overall survival were observed. Second, some patients were considered ineligible by the FDA due to lack of pathological confirmation of the diagnosis. Reanalysis excluding these patients might lead to a different result. An analysis excluding these patients will be presented at the ODAC meeting. Third, is the lack of a second supportive well-controlled clinical trial for this combination in patients with adenocarcinoma of pancreas. This is quite relevant as the difference in survival observed between the combination EG and PG is of marginal clinical importance while

the combination has a significant increase in SAEs, death due to toxicity, discontinuation due to AEs and increase in withdrawing consent due to AEs.

6.2 Conclusions:

In summary, a single randomized double-blind study presented in this application (PA.3) demonstrated a statistically significant increase in overall survival for the combination of 100 mg erlotinib/gemcitabine, only when cox proportional hazards ratio were adjusted for PS and extent of disease. However, the very small increase in median overall survival (12.8 days) and median PFS (11 days) raises the question whether the difference is clinically important. In addition, there is lack of differential response rate , along with a significant increase in toxicity associated with toxic death and SAEs (e.g. > 6 fold increase in strokes) leading to drug discontinuation and worse quality of life, suggesting that the benefit with erlotinib/gemcitabine combination in the treatment of advanced or metastatic pancreatic carcinoma may not outweigh the risks associated with this therapy. Although diarrhea and skin rash are the most frequent EG toxicities in relation to placebo/gemcitabine, there are several serious toxicities that, while low in frequency, are more frequent in the EG arm. These include stroke, cardiac ischemia/infarction, stent occlusion, infections, ILD-like events and GI bleeding. A confirmatory second well-controlled and well-conducted trial may help to discern whether erlotinib adds a clinically significant improvement to gemcitabine with an acceptable toxicity profile in the therapy of locally advanced or metastatic pancreatic adenocarcinoma.

7 Recommendations: deferred pending advice of the ODAC.

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