Tarceva® (erlotinib) Tablets

NDA 21-743, S003

Supplemental NDA: Pancreatic Cancer

Briefing Document

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TABLE OF CONTENTS

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

The Oncologic Drugs Advisory Committee has been requested to evaluate the Supplemental New Drug Application (sNDA) for Tarceva (erlotinib) in pancreatic cancer. On 18 November 2004 the US Food and Drug Administration (FDA) granted full approval for Tarceva in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least 1 prior chemotherapy regimen. The sponsor is now seeking full approval for the use of Tarceva 100 mg administered concurrently with gemcitabine as first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer. This application was submitted to the FDA for review on 29 April 2005 and was accepted for priority review on 5 July 2005.

Unmet Medical Need

An estimated 32,180 new cases of pancreatic cancer will be diagnosed in the US in 2005 and an estimated 31,800 people will die due to pancreatic cancer, making it the 4th and 5th leading cause of cancer-related death in males and females, respectively. Patients with advanced, unresectable, or metastatic adenocarcinoma of the pancreas have an ominous prognosis with a very short survival. Pancreatic cancer has the highest mortality rate (99%) among cancer types, with 5-year survival of only 1.8% in patients diagnosed with metastatic disease. The National Cancer Institute notes "there has been little change in overall pancreatic cancer incidence or mortality rates throughout the past 3 decades."

The current standard and only approved therapy for patients with locally advanced, unresectable, or metastatic adenocarcinoma of the pancreas is gemcitabine, which, in a randomized study, offered symptom benefit and prolongation of survival over 5-fluorouracil (5-FU). With gemcitabine treatment, median time to progression is 2.1 months and the 1-year survival rate is 18%.

Since the approval of gemcitabine by the FDA in 1996, many anticancer agents have been studied in this patient population in randomized phase 3 trials. Until now, none of the agents studied, either alone or combined with gemcitabine, have demonstrated a statistically significant survival benefit over single-agent gemcitabine. Therefore, new active agents are desperately needed for these patients.

Product Rationale

Tarceva (erlotinib) is an orally-available human epidermal growth factor receptor type 1 (HER1, also known as EGFR or erbB1) tyrosine kinase inhibitor. Tarceva received full approval in the US by the FDA on 18 November 2004 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least 1 prior chemotherapy regimen.

The rationale for investigating EGFR inhibitors in pancreatic cancer is based on the high incidence (30 – 50%) of overexpression of EGFR in this tumor type, compared with normal tissue, using immunohistochemical (IHC) staining or by measuring mRNA expression. In vitro, EGF has been shown to be a potent mitogenic stimulus for pancreatic cells and it has been shown that EGF evokes a strong proliferative response in all cell types studied in the pancreas. Overall, EGFR is believed to play an important role in the development and progression of a number of human epithelial malignancies and to be a relevant target for antineoplastic therapies.

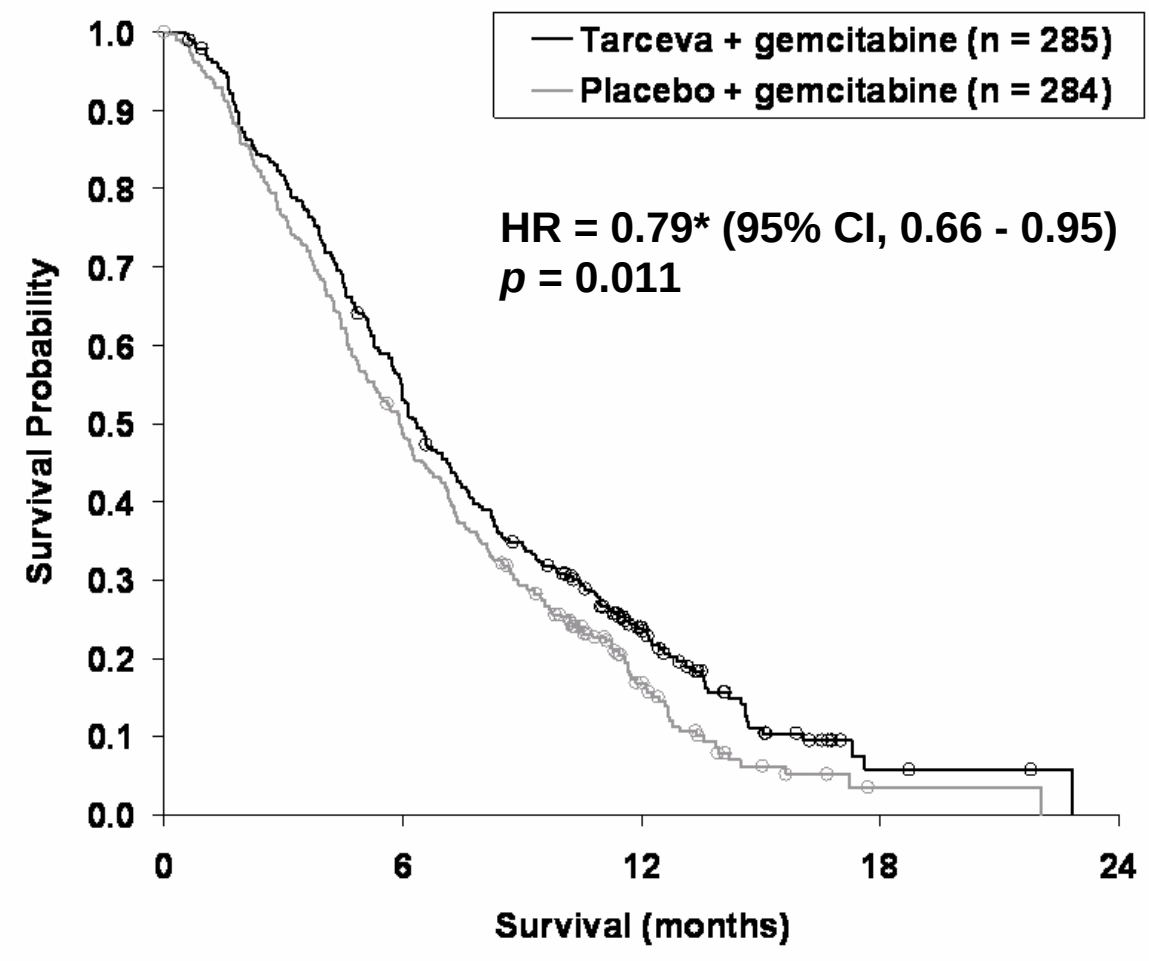
Further evidence supporting EGFR as an appropriate target for anticancer therapy was provided in a series of experiments using a pancreatic cell line (PANC-1). Co-expression of the truncated EGFR and the endogenous EGFR was demonstrated using Northern blot analysis. In these clones, marked attenuation of EGF and TGF-α mediated EGFR tyrosine phosphorylation was seen. A significant decrease in colony formation in soft agar and an increase in effect of the growth inhibition properties of cisplatin were also demonstrated.

Clinical Efficacy

The efficacy of Tarceva in the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer was demonstrated in a 569-patient, randomized, multinational, placebo-controlled phase 3 study (Study PA.3) conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and OSI Pharmaceuticals Inc. (OSI). Patients were randomized 1:1 to receive Tarceva plus gemcitabine or placebo plus gemcitabine. All patients initially received Tarceva or placebo 100 mg with concurrent gemcitabine and then, after the safety of the 100 mg dose was established, subsequent patients were enrolled at a 150 mg dose level at selected sites in Canada. Gemcitabine was dosed at 1000 mg/m^2 weekly for 7 weeks of an 8-week cycle followed by weekly for 3 weeks of a 4-week cycle.

The primary analysis was for overall survival in the intent-to-treat (ITT) population. In this ITT population (N = 569, 521 patients in the 100 mg cohort and 48 patients in the 150 mg cohort), Tarceva plus gemcitabine demonstrated a statistically significant improvement in overall survival compared with gemcitabine alone (hazard ratio [HR] = 0.79, 95% confidence interval [CI] 0.66 to 0.95, p = 0. 011), indicating Tarceva plus gemcitabine yielded a 27% increase in survival and reduced the risk of death by 21% compared with treatment with gemcitabine alone (see **Figure 1-1**). The estimated 1-year survival rate in the ITT population for patients treated with a combination of Tarceva plus gemcitabine was 24% compared with 17% for patients treated with gemcitabine alone. A subsequent FDA-requested analysis that updated survival data as of 18 months after the original cutoff date also demonstrated statistically significant improvement in overall survival: HR = 0.81, 95% CI 0.68 to 0.96, p = 0.016.

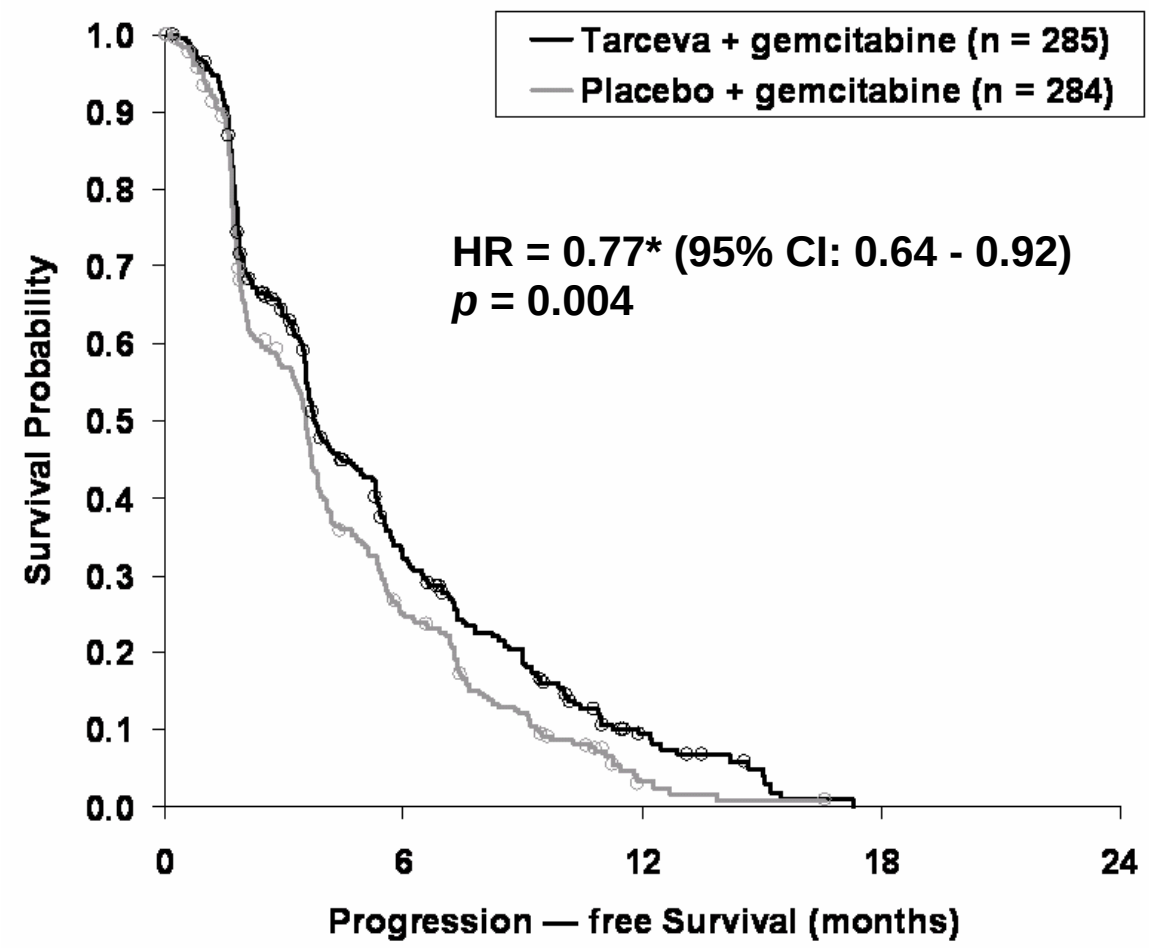
Figure 1-1: Overall Survival Primary Stratified Analysis – All Randomized Patients



* Adjusted for PS and extent of disease at randomization

Consistent with the survival benefit are the results of the secondary efficacy endpoint of progression-free survival (PFS). The HR for progression in the Tarceva arm relative to the placebo arm was 0.77 (95% CI 0.64 to 0.92, p = 0.004), representing a 6-month PFS rate of 32% for patients receiving Tarceva plus gemcitabine compared with 25% for patients receiving placebo plus gemcitabine, a 28% improvement (see **Figure 1-2**).

Figure 1-2: Progression-free Survival - All Randomized Patients



* Adjusted for PS and extent of disease at randomization

One complete response (CR) and 22 partial responses (PRs) were observed in the Tarceva arm with similar numbers (3 CRs and 18 PRs) observed in the placebo arm. Overall, stable disease (SD) was observed in 48.9% of patients in the Tarceva arm compared with 41.2% of patients in the placebo arm, for non-progression (CR + PR + SD) rates of 57.5% and 49.2% (p = 0.067).

No deterioration in global quality of life was observed in patients treated with Tarceva compared with patients in the placebo arm.

As expected, analyses performed on the large cohort of patients who were evaluated at the 100 mg Tarceva/placebo plus gemcitabine dose level (N = 521, 92% of ITT population) demonstrated nearly identical results (overall survival HR = 0.79, 95% CI 0.66 to 0.96, p = 0.017; PFS HR = 0.77, 95% CI 0.64 to 0.93, p = 0.006; non-progression rates 59% vs 49%). The number of patients in the 150 mg dose cohort was too small to draw any definitive conclusions regarding the efficacy of Tarceva at this dose level. Thus, the dose in the sought indication for the treatment of pancreatic cancer is Tarceva 100 mg once daily in combination with the approved standard regimen of gemcitabine.

Studies evaluating the pharmacokinetics of erlotinib and gemcitabine when administered in combination indicate that there were no significant effects of gemcitabine on the pharmacokinetic parameters of erlotinib and no effects of erlotinib on the pharmacokinetics of gemcitabine.

Clinical Safety

The co-administration of Tarceva and gemcitabine was well tolerated in this patient population, as dose reductions were necessary in only 13% of patients who received Tarceva 100 mg compared with 4% of patients receiving placebo.

The safety profile of the combination of Tarceva 100 mg and gemcitabine was consistent with that observed for each agent when administered as monotherapy. Rash and diarrhea, which are typically associated with EGFR inhibition, were reasonably well tolerated and only occasionally resulted in dose modification.

Since Study PA.3 included only patients with advanced pancreatic cancer, most patients died due to progression of the underlying disease. A total of 3% and 4% of patients in the 100 mg cohort who received Tarceva and placebo, respectively (and 2 patients [8%] in the placebo arm of the 150 mg cohort) died due to "other conditions or circumstances." The incidence of serious ILD-like adverse events in the Tarceva arm was higher in Study PA.3 than in previous studies with Tarceva, which might be due to a possible interaction of Tarceva with the gemcitabine dose and dosing schedule used in Study PA.3. The expected hematologic toxicity with gemcitabine was balanced between treatment groups.

Risk-Benefit Evaluation

To date, Tarceva is the first and only agent that, when added to standard gemcitabine therapy, has demonstrated in a large, randomized, placebo-controlled phase 3 trial a statistically significant survival benefit over gemcitabine alone in patients with pancreatic cancer. Because 521 out of 569 patients (92%) enrolled in this study were evaluated in the 100 mg dose cohort and the efficacy in this cohort is nearly identical to the overall population, the proposed dosing regimen for Tarceva in this indication is 100 mg once daily.

The HR for death in the Tarceva 100 mg arm relative to the placebo arm indicates Tarceva plus gemcitabine yielded a 27% improvement in survival and reduced the risk of death by 21% when compared with treatment with gemcitabine alone. One-year survival of patients receiving Tarceva 100 mg in combination with gemcitabine compared with gemcitabine treatment alone was 23% versus 17%.

This clinical benefit was achieved with only a modest change in the safety profile compared with gemcitabine alone, with generally manageable adverse events requiring few dose modifications or discontinuations and without deterioration of quality of life. Treatment with Tarceva 100 mg requires minimal additional clinical laboratory monitoring and is administered as once-a-day tablets.

Gemcitabine monotherapy, approved in 1996, remains the only available treatment option for patients with advanced or metastatic pancreatic cancer. Thus, the results from Study PA.3, which demonstrate that the addition of Tarceva to the current standard of care significantly prolongs survival and progression-free survival, represent the first advance in nearly a decade for the treatment of patients with pancreatic cancer.

2 INTRODUCTION

2.1 Background

Tarceva (erlotinib) received full approval in the US by the FDA on 18 November 2004 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least 1 prior chemotherapy regimen. The approval was based on positive data from Study BR.21, a randomized, double-blinded, placebo-controlled phase 3 study of single-agent Tarceva 150 mg oral daily versus best supportive care. The study was conducted by the NCIC CTG and OSI in 731 patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen [1]. In this study, the HR for death in the erlotinib arm relative to the placebo arm estimated from the primary analysis (adjusted for stratification factors at randomization and EGFR expression status) was 0.73 (95% CI, 0.60 – 0.87) (p = 0.001), indicating that erlotinib reduced the risk of death by 27% compared with placebo. The actuarial 12-month survival rates were 31.2% and 21.5%, respectively, in favor of Tarceva treatment. A summary of the postmarketing commitments pertaining to additional clinical studies made by the sponsor in conjunction with the approval is provided in **Section 8.1**.

The focus of this Supplemental NDA is on the use of Tarceva in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer. The pivotal phase 3 clinical study, Study PA.3, was conducted by the NCIC CTG and OSI in 17 countries across North and South America, Europe, Asia, New Zealand, and Australia in 569 patients with pancreatic cancer. Patients enrolled in the study received a daily oral dose of Tarceva or placebo concurrent with the approved regimen of gemcitabine.

2.2 Indication Sought and Treatment Regimen

Tarceva in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

The Tarceva dosing regimen for the treatment of pancreatic cancer is 100 mg once daily on a continuous schedule given in combination with gemcitabine 1000 mg/m^2 IV (Cycle 1 Days 1, 8, 15, 22, 29, 36, and 43 of an 8-week cycle and Cycle 2 and subsequent cycles Days 1, 8, and 15 of a 4-week cycle). The Tarceva 100 mg dose was selected because 521 of the 569 patients (92%) enrolled in Study PA.3 were included in the 100 mg dose

cohort and the efficacy results were nearly identical to those observed in the ITT population.

2.3 Pancreatic Cancer and Current Treatment Options

An estimated 32,180 new cases of pancreatic cancer will be diagnosed in the US in 2005, representing approximately 2% of all new cancer cases. There will be an estimated 31,800 deaths in the US due to pancreatic cancer, making it the 4th and 5th leading cause of cancer-related death in males and females, respectively. Pancreatic cancer has the highest mortality rate (99%) among cancer types, with metastatic pancreatic cancer having a 5-year survival rate of only 1.8%. The National Cancer Institute notes "there has been little change in overall pancreatic cancer incidence or mortality rates throughout the past 3 decades [2]."

Patients with locally advanced or metastatic pancreatic cancer typically present with abdominal pain (often severe), back pain, jaundice, and significant weight loss [3]. Pain and weight loss are present in 75% of patients, and weight loss of more than 10% of ideal body weight by the time of diagnosis is common. Jaundice due to biliary obstruction is present in > 80% of patients. Initial symptoms are often present for approximately 2 months prior to diagnosis.

The standard methods of diagnosis of pancreatic cancer include computerized tomography (CT) scans, magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS) [4]. A CT scan is the most often used method of diagnosis and helical CT scan is the best option. An MRI may provide slightly better tissue contrast but the spatial resolution is not as good as with a CT scan. ERCP can detect some tumors not observed by CT scan but is usually not the primary method of diagnosis. EUS can provide valuable information but is a newer technique and not typically used as an initial diagnostic method. Tissue for diagnosis is usually acquired by EUS or percutaneous CT-guided biopsy.

More than 90% of pancreatic tumors are ductal adenocarcinomas. Most (70%) pancreatic tumors occur in the head of the pancreas, with 20% in the body and 10% in the tail. By the time of their discovery, 70-80% of adenocarcinomas of the head of the pancreas have metastasized to regional lymph nodes. At diagnosis most patients have locally advanced or metastatic disease.

Historically, treatment of patients with locally advanced, unresectable pancreatic cancer with 5- fluorouracil (5-FU) in combination with radiation was shown to improve survival over radiotherapy alone [5]. The current standard and only approved therapy for patients who have advanced, metastatic or unresectable pancreatic cancer is gemcitabine, which offers improvement in survival and amelioration of symptoms. The approval of gemcitabine was based on a phase 3 randomized trial in 126 previously untreated patients with pancreatic cancer [6]. In this study, gemcitabine improved survival in comparison to 5-FU (18% 1-year survival rate versus 2%) and patients who received gemcitabine also reported a greater effect on disease-related symptoms such as pain, performance status (PS), and weight changes than those who received 5-FU. The efficacy results of this study are summarized in **Table 2–1**.

Table 2–1: Summary of Efficacy Results from Gemcitabine versus 5-FU study (Burris 1997)

	Gemcitabine	5-FU	p-value
Clinical benefit Response*	23.8%	4.8%	0.0022
Median survival (months)	5.65	4.41	0.0025
Median time to disease progression (months)	2.33	0.92	0.0002
1-year survival	18%	2%	—
Partial response	5.4%	0%	—
Stable disease	39%	19%	—

* Composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight.

Several other cytotoxic agents, including oxaliplatin [7], irinotecan [8], pemetrexed [9], exatecan [10], cisplatin [11], capecitabine [12], and combinations of agents [13, 14] have been studied in this patient population in randomized phase 3 clinical trials in combination with gemcitabine, but none of the regimens has demonstrated a statistically significant survival benefit over gemcitabine alone (see **Table 2–2**).

Table 2–2: Efficacy Results of Trials with Gemcitabine versus Gemcitabine + Chemotherapy in Pancreatic Cancer

Treatment, Patients	No. pts	OS hazard Ratio	Median survival, months	1-year survival, %	Median PFS, months	Median TTP, months
Gemcitabine	63	NR	5.65	18	–	2.33
5-FU	63		4.41	2	–	0.92
(Burris et al, 1997)			p = 0.0025			p = 0.0002
Gemcitabine	156	1.20	7.1	NR	3.7	–
Gemcitabine + oxaliplatin	157		9.0		5.8	–
(Louvet et al, 2004)			p = 0.13		p = 0.04	
Gemcitabine	169	NR	6.6	22	–	3.0
Gemcitabine + irinotecan	173		6.3	21	–	3.5
(Rocha Lima et al, 2004)			p = 0.789			p = 0.352
Gemcitabine	282	NR	6.3	20.1	3.3	3.6
Gemcitabine + pemetrexed	283		6.2	21.4	3.9	5.2
(Richards et al, 2004)			p = 0.848	p = 0.718	p = 0.11	p = 0.042
Gemcitabine	174	NR	6.2		–	3.8
Gemcitabine + exatecan	175		6.7		–	3.7
(O'Reilly et al, 2004)			p = 0.52			p = 0.22
Gemcitabine	99	NR	6.0	NR	–	2.8
Gemcitabine + cisplatin	96		8.3		–	5.4
(Heinemann et al, 2003)			p = 0.12			p < 0.01
Gemcitabine	47	NR	NR	21.3	3.3	–
Gemcitabine + cisplatin + epirubicin + 5-FU	52			38.5	5.4	–
(Reni et al, 2005)				p = 0.1119	p = 0.0033	
Gemcitabine	236	NR	6.2	22	–	–
Gemcitabine + 5-FU folinic acid	230		5.85	21	–	–
(Riess et al, 2005)			p = 0.68	p = 0.68		
Gemcitabine	319 total	NR	7.3		–	4.0
Gemcitabine + capecitabine			8.4		–	4.8
(Herrmann et al, 2005)			p = 0.314			

NR = not reported; PFS = progression-free survival; TTP = time to progression

More recently, studies have been conducted in patients with pancreatic cancer with the objective of incorporating newer agents, including farnesyl transferase inhibitors, matrix metalloproteinase inhibitors, cyclooxygenase-2 inhibitors, monoclonal antibodies, and other molecular targeted therapies (see **Table 2–3**). Phase 3 studies with these agents either as single agents or in combination with gemcitabine have also failed to show any superiority over single-agent gemcitabine [15, 16, 17, 18].

Table 2–3: Efficacy Results of Trials with Gemcitabine versus Gemcitabine + Cytostatic or Targeted Agent in Pancreatic Cancer

Treatment, Patients	No. pts	OS hazard Ratio	Median survival, months	1-year survival, %	Median PFS, months
Gemcitabine	347	1.03	6.0	24	3.6
Gemcitabine + tipifarnib	341		6.4	27	3.7
(Van Cutsem et al, 2002)			p = 0.75		p = 0.72
Gemcitabine	103	0.96	5.6	19	3.8
Gemcitabine + marimastat	102		4.2	20	1.9
(Bramhall et al, 2001)			p = 0.78	p = 0.86	p = 0.0001
Gemcitabine	119	0.99	5.5	17	3.2
Gemcitabine + marimastat	120		5.5	18	3.0
(Bramhall et al, 2002)			p = 0.95		p = 0.68
Gemcitabine	139	0.574	6.59	25	3.5
Gemcitabine + BAY 12-9566	138		3.74	10	1.68
(Moore et al, 2003)			p < 0.001		p < 0.001

NR = not reported; PFS = progression-free survival; TTP = time to progression

3 TARCEVA

3.1 Product Rationale

Tarceva is an orally-available human epidermal growth factor receptor type 1 (HER1, also known as EGFR or erbB1) tyrosine kinase inhibitor approved by the US FDA for use in patients with 2nd or 3rd line NSCLC. HER1/EGFR plays a critical role in many cell-signaling pathways that influence cell division, apoptosis, motility and adhesion [19]. The binding of a ligand to the EGFR initiates a cascade of events, with signal transduction culminating in nuclear gene activation, critical in both tumorigenesis and tumor growth. EGFR and its ligands are overexpressed or involved in autocrine growth loops in a number of tumor types [20, 21, 22].

The rationale for investigation of an anti-EGFR targeted molecule in pancreatic cancer is based on the relatively high incidence (30 – 50%) of EGFR overexpression in this tumor type, compared with normal tissue, using IHC staining or by measuring mRNA expression [23, 24].

Further evidence supporting EGFR as an appropriate target for anticancer therapy was provided by in a series of experiments using a pancreatic cell line (PANC-1) [25]. In vitro, EGF has been shown to be a potent mitogenic stimulus for pancreatic cells [26] and it has been shown that EGF evokes a strong proliferative response in all cell types studied in the pancreas [27]. Furthermore, co-expression of the receptor and both EGF and TGFα ligands is found in 20% of pancreatic tumors, and co-expression of the receptor and one of the two ligands in 18% more [28]. The concomitant overexpression of the EGFR and one or more of its ligands appears to be a marker of poor prognosis and has been correlated with enhanced ability of certain tumors to invade normal tissue, to metastasize, and to have a shorter postoperative survival period. A significant decrease in colony formation in soft agar and an increase in effect of the growth inhibition properties of cisplatin were also demonstrated.

A small molecular weight inhibitor of EGFR kinase activity (PKI166) alone or in combination with gemcitabine has been shown to inhibit the growth and metastasis of human pancreatic carcinoma cells implanted into the pancreas of nude mice [29]. In this study, the volume of the pancreatic tumors was reduced by 59% in mice treated with gemcitabine only, by 45% in those treated with PKI166 only, and by 85% in those given

both drugs. The combination therapy also significantly inhibited lymph node and liver metastasis, which led to a significant increase in overall survival.

3.2 Clinical Pharmacokinetics

Two studies have evaluated the pharmacokinetics of erlotinib and gemcitabine when administered in combination. In a phase 1 study (Study OSI-774-155), the effects of concomitant gemcitabine on erlotinib C_{max} and $AUC_{0\text{-}tau}$ were evaluated through comparison with data from a previous phase 1 single-agent study of erlotinib in patients (Study 248-004). The effect of single-agent versus combination therapy on erlotinib C_{max} and $AUC_{0\text{-}tau}$ was not statistically significant, indicating there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib. Gemcitabine pharmacokinetics were determined following the Day 1 dose (before erlotinib treatment) and the Day 8 dose (concomitant with erlotinib). There was no significant effect of erlotinib on the pharmacokinetics of gemcitabine. There were also no apparent differences between patients with pancreatic versus non-pancreatic tumors.

In a population pharmacokinetic analysis, covariate effects on pharmacokinetic parameters in patients from Study PA.3 were evaluated using the combined data from 5 single-agent studies of erlotinib and Study PA.3. There were no significant differences in the pharmacokinetic parameters between patients in Study PA.3 and the previous single-agent studies. This population pharmacokinetics analysis demonstrated that the covariates affecting erlotinib disposition in patients from Study PA.3 were very similar to those previously reported and no new covariate effects were identified. Co-administration of gemcitabine had no effect on erlotinib apparent oral clearance.

3.3 Clinical Background

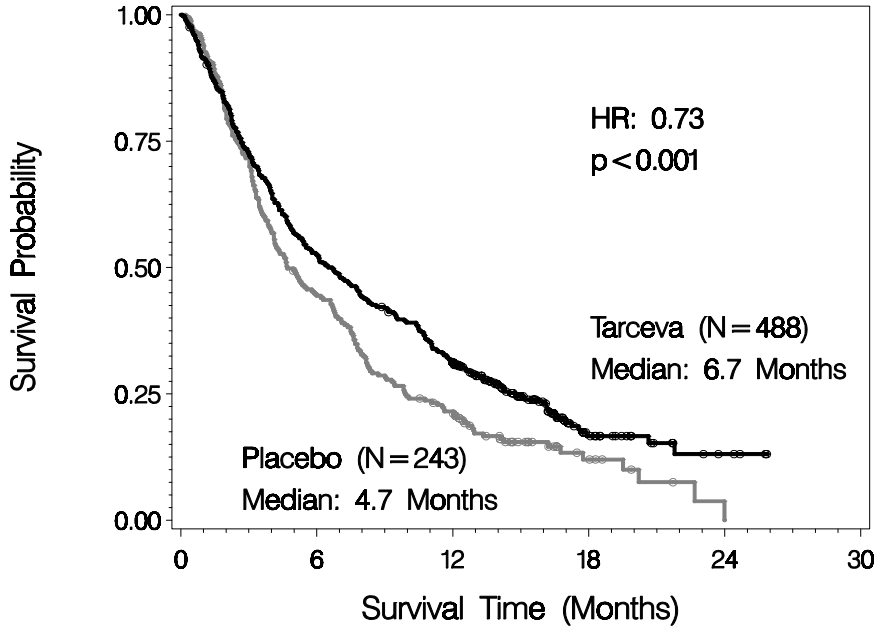
As of February 2005, Tarceva has been or is currently being studied in more than 4600 healthy subjects and cancer patients (excluding those exposed to placebo) in phase 1, 2, and 3 studies sponsored by OSI and its Tarceva development partners Genentech, Inc., and F. Hoffmann-La Roche, Ltd. In addition, more than 12,000 patients have had Tarceva prescribed since it became commercially available.

Phase 1 and phase 1b studies in approximately 600 healthy subjects and cancer patients assessed the safety and pharmacokinetics of Tarceva at various dose levels as a single agent and in combination with various chemotherapies, including gemcitabine. Phase 2

studies of single-agent Tarceva in over 1,200 patients with advanced solid tumors indicated antitumor activity in NSCLC, head and neck, and ovarian cancers. Phase 3 studies have evaluated Tarceva in over 2,600 patients: as a single agent in approximately 1,200 patients and in combination with various chemotherapy agents in approximately 1,400 patients, including approximately 300 patients exposed to Tarceva + gemcitabine and 600 patients exposed to Tarceva + gemcitabine + cisplatin. An overview of all phase 2 and phase 3 studies of Tarceva in solid tumors is provided in **Section 8.2**, **Table 8–2**. Approximately 2,200 additional patients have been enrolled in Investigator Sponsored Trials (IST).

A large, randomized, double-blind, placebo-controlled phase 3 trial (Study BR.21) evaluated the use of single-agent Tarceva for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen. In this 731-patient trial, statistically significant and clinically relevant prolongation in overall survival and progression-free survival (PFS) were observed for patients treated with Tarceva compared with patients receiving placebo, which led to the full approval of Tarceva by the FDA on 18 November 2004. In this study, the hazard ratio (HR) for death in the erlotinib arm relative to the placebo arm estimated from the primary analysis (adjusted for stratification factors at randomization and EGFR expression status) was 0.73 (95% CI, 0.60 – 0.87) ($p = 0.001$), indicating that erlotinib reduced the risk of death by 27% compared with placebo (see **Figure 3-1**). Stable disease was observed in 35.1% of erlotinib-treated patients with measurable disease, compared with 26.5% of placebo-treated patients, for a CR + PR + SD rate of 44.0% and 27.5%, respectively. This difference was statistically significant, $p = 0.004$. The responses obtained with erlotinib were durable: for patients with measurable disease, the median response duration was 34.3 weeks, ranging from 9.7 to 57.6+ weeks. An adverse event summary for Study BR.21 is provided in **Section 5.1**, **Table 5–1**.

Figure 3-1: Study BR.21 – Overall Survival in NSCLC



Two other randomized, double-blind, placebo-controlled phase 3 trials (Study BO16411 [TALENT] and Study OSI2298g [TRIBUTE]) investigated Tarceva in combination with standard chemotherapy as first-line treatment for patients with advanced NSCLC [30, 31]. Both trials failed to meet their endpoints, showing that in patients with NSCLC, the addition of Tarceva does not prolong survival over chemotherapy alone. This is similar to results shown for gefitinib, an agent in the same class of compounds [31, 32].

The open-label phase 1b, Study OSI-774-155, was conducted in patients with advanced pancreatic carcinoma or other potentially responsive malignancies. A standard dose escalation schema was used to determine the safety and tolerability of daily 100 or 150 mg doses of oral Tarceva concurrently administered with the standard approved regimen of gemcitabine, 1000 mg/m^2 IV. Based on the safety and tolerability results of this study, it was concluded that the combination of Tarceva 100 mg/day and gemcitabine 1000 mg/m^2 was tolerated in these heavily pretreated patients, and the combination of Tarceva 150 mg/day and gemcitabine 1000 mg/m^2 was tolerated in the untreated and minimally pretreated patients in this study.

Study PA.3, described in detail in the following section, had the first patient enrolled on 29 November 2001, before results from Study OSI-774-155 (which had the first patient

enrolled on 23 July 2001) were available and was conducted by NCIC CTG and OSI concurrently with Study BR.21 (first patient enrolled 1 November 2001).

4 EFFICACY OF TARCEVA IN PANCREATIC CANCER

4.1 Summary of Efficacy Claims

The results of Study PA.3 demonstrate that the addition of Tarceva daily to standard gemcitabine provides a statistically significant increase in survival to patients with locally advanced or metastatic pancreatic cancer.

Overall survival based on the ITT population was calculated after the occurrence of 484 deaths using a cutoff date of 15 January 2004. The HR for death in the Tarceva group relative to the placebo group was 0.79 (95% CI 0.66 to 0.95, p = 0.011), demonstrating that Tarceva yielded a 27% improvement in survival and reduced the risk of death by 21% compared with placebo (**Figure 4-2**). When the analysis was restricted to patients in the 100 mg cohort (n = 521), the results were virtually identical (HR = 0.79, 95% CI 0.66 to 0.96, p = 0.017), confirming that the treatment effect was maintained at this dose level (**Figure 4-3**). The HR for disease progression in the Tarceva arm relative to the placebo arm was 0.77 (95% CI 0.64 to 0.92, p = 0.004). For the 100 mg dose cohort, the HR was 0.77 (95% CI 0.64 to 0.93, p = 0.006).

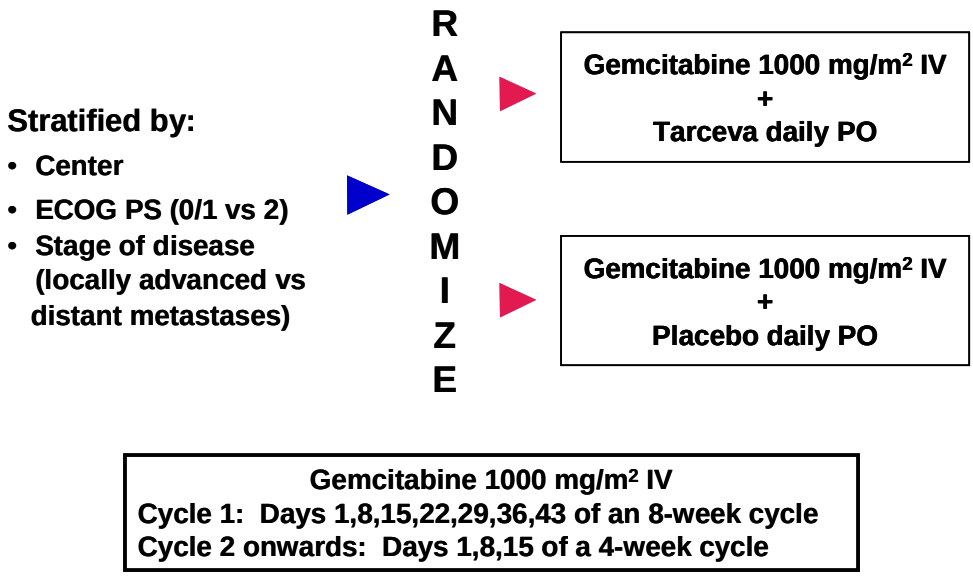
4.2 Design of Study PA.3

Study PA.3 was a multinational, randomized, double-blind, placebo-controlled study of Tarceva in patients with locally advanced, unresectable, or metastatic pancreatic cancer. NCIC CTG in collaboration with OSI conducted the trial.

Patients were stratified at enrollment by center, extent of disease (locally advanced versus metastatic disease), and ECOG performance status (PS 0/1 versus 2). Patients were randomized in a 1:1 ratio to receive Tarceva plus gemcitabine or placebo plus gemcitabine. Patients were not, however, randomized to the 100 mg or 150 mg dose cohorts. Rather, all patients initially received Tarceva or placebo 100 mg and then, after the safety of the 100 mg dose was established, patients at selected sites in Canada were enrolled at the Tarceva 150 mg dose level. Due to rapid accrual at the 100 mg dose level, relatively few patients (48 out of 569, 8%) received Tarceva/placebo 150 mg before the target enrollment was reached. The gemcitabine dosing was 1000 mg/m^2 IV, Cycle 1 Days 1, 8, 15, 22, 29, 36, and 43 of an 8-week cycle and Cycle 2 and subsequent cycles Days 1, 8, and 15 of a 4-week cycle. Tarceva or placebo dosing could continue daily until disease progression (PD) or unacceptable toxicity. Study drug could be withheld or

reduced for toxicity. Dose escalation was not permitted. The study design is shown schematically in **Figure 4-1**.

Figure 4-1: PA.3 Study Schema



Key eligibility criteria included the following:

- Histologically or cytologically-confirmed adenocarcinoma of the pancreas (measurable disease was not required)
- No prior therapy with the exception of surgery, local radiation therapy, and 5-FU or gemcitabine if they were administered as radiosensitizers
- At least 18 years of age
- Documentation of all sites of disease within 28 days prior to randomization
- No known central nervous system metastases
- ECOG performance status of 0, 1 or 2
- No history of cardiac disease within previous year and no active infection at the time of randomization
- Adequate hematological, renal and hepatic functions within 14 days prior to randomization
- No pregnant or lactating females
- Signed Informed Consent

The primary efficacy endpoint was overall survival and all randomized patients were included in the analysis of overall survival. As agreed upon with the FDA prior to unblinding of the study, the primary analysis was a stratified log-rank test in the combined treatment cohorts for overall survival using ECOG PS and extent of disease at randomization as the stratification factors [33]. Secondary efficacy analyses included PFS, tumor response, duration of response, quality of life, and an assessment of tumor EGFR status with outcomes. Tumor response and disease progression were assessed using Response Evaluation Criteria in Solid Tumors (RECIST). Patients at selected investigational sites (required in US and Canada, optional elsewhere) completed the EORTC QLQ-C30 questionnaire at each 4-week cycle evaluation to provide self-reported assessments of quality of life (QoL).

Safety was assessed every 4 weeks by evaluating hematology and biochemistry laboratory parameters and changes in physical examination and monitoring the incidence, severity, and relationship of adverse events to study drug. Adverse events were graded using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC), Version 2.0. Patients who discontinued protocol treatment were evaluated at Week 4, and survival status was assessed every 12 weeks until death.

Study PA.3 was originally designed to be conducted in conjunction with a second phase 3 study. Due to anticipated logistical difficulties in recruiting 2 large phase 3 studies in pancreatic cancer patients, the second study was never initiated and OSI and NCIC CTG agreed instead to conduct 1 larger study in approximately 800 patients with locally advanced, unresectable, or metastatic pancreatic cancer.

The protocol was subsequently amended to reduce the sample size to 450 patients with an increase in the minimum follow-up time from 2.8 months to 18 months to preserve the statistical integrity of the study by maintaining the original 80% power to detect a 33% increase in survival.

A table summarizing all changes made to the PA.3 protocol is provided in **Section 8.3**, **Table 8–3**.

4.2.1 Dose Selection/Safety Assessment

Because Study PA.3 was initiated before results of the phase 1b combination trial of Tarceva and gemcitabine (OSI-774-155) became available, a lead-in phase, initially opened in a limited number of centers in Canada, was included to assess the safety of a

100 mg dose of Tarceva in combination with gemcitabine before allowing patients to receive Tarceva at 150 mg. NCIC CTG and the sponsor collaboratively performed blinded interim assessments of safety. Three safety assessments were performed in the cohort of patients receiving 100 mg daily: after 8, 16, and 50 patients had been enrolled and completed at least 4 weeks of treatment (see **Table 4–1**). A fourth assessment was performed in the initial group of patients who received 150 mg daily. A dose was considered safe if 0/8 or ≤ 1/16 patients in the combined dose groups had a dose-limiting toxicity (DLT) deemed related to study treatment after a minimum of 4 weeks of therapy. Higher rates of DLTs would not automatically render a dose to be considered unsafe, but would mandate closer consideration and unblinding by a DSMB. Efficacy was not evaluated during these interim safety assessments.

1st Safety Assessment

In the first 8 patients, 2 equivocal DLTs were observed: 1 patient had grade 4 transaminase elevation and 1 patient experienced grade 3 febrile neutropenia. Due to confounding factors complicating the interpretation, an additional 8 patients were enrolled at the 100 mg dose level.

2nd Safety Assessment

In the combined treatment groups, 1 of 16 patients (which included the 8 in the 1st assessment) was deemed to have a DLT of transaminase elevation and 2 patients had questionable DLTs of transaminase elevation. Since the elevation was reversible in 1 of these 2 patients despite continued therapy and the other patient entered the study with grade 1 transaminases and liver metastases, it was possible that the increase in transaminases could be attributed to the underlying disease. The febrile neutropenia initially considered as an equivocal DLT was attributed to gemcitabine only. No unblinding was performed, but it was decided to evaluate at least 50 patients treated at 100 mg and open recruitment at all centers at this dose level.

3rd Safety Assessment

Following the third assessment, the 100 mg dose was declared tolerable and it was decided to start enrolling patients at the 150 mg dose level at selected Canadian sites.

4th Safety Assessment

An assessment of the first 16 patients who were enrolled at the 150 mg dose level determined the dose level was safe and enrollment could continue throughout Canada at the 150 mg dose level.

While the safety assessment of patients enrolled at the 150 mg dose level was being performed, all other institutions continued accruing patients at a Tarceva/placebo dose of 100 mg daily.

Coincidentally, the protocol was being amended at this time to reduce the sample size from an original 800 patients to 450 patients. When enrollment was stopped after a target of at least 450 patients in the 100 mg cohort had been reached, a total of 569 patients had been enrolled, with only 48 patients randomized at the 150 mg daily dose level.

A summary of key events that occurred during Study PA.3 is provided in **Table 4–1**.

Table 4–1: Summary of Key Events During Study PA.3

		Number of Patients Enrolled	
Date	**Event**	**100 mg***	**150 mg***
17 DEC 2001	Protocol amended to reflect decision to perform a single phase 3 study with a combined sample size of 800 patients	5	0
08 FEB 2002	1st blinded safety review (8 patients treated ≥4 weeks at 100 mg)	13	0
27 MAR 2002	2nd blinded safety review (16 patients treated ≥4 weeks at 100 mg) – open accrual at 100 mg in rest of world and continued in Canadian	21	0
10 SEP 2002	3rd blinded safety review (50 patients treated ≥4 weeks at 100 mg) – open accrual at 150 mg in selected Canadian sites	134	0
16 DEC 2002	Protocol amended to reduce sample size to 450 and extend follow up to maintain power	364	27
20 DEC 2002	4th blinded safety review (16 patients treated ≥4 weeks at 150 mg) – 150 mg deemed safe; continued enrollment in selected Canadian sites but did not open 150 mg in rest of world	374	32
31 JAN 2003	Last patient randomized	521	48

* Blinded, patient received either Tarceva or placebo

4.2.2 Study Endpoint

The protocol required a minimum of 381 deaths to be observed for the final analysis. On 13 January 2004, the case report form (CRF) processing center received the form documenting the 381st death in the 100 mg cohort. At that time there were also 34 documented deaths in the 150 mg cohort. As a result, 15 January 2004 was declared the data cutoff date for the final analysis and all data collected by this date were gathered

from the investigational sites. Because of the short survival time in this patient population, once all CRFs containing data obtained before the 15 January 2004 cutoff date were processed, the database contained 484 deaths.

4.3 Results from Study PA.3

4.3.1 Patient Disposition

A total of 569 patients with locally advanced, unresectable, or metastatic pancreatic cancer were enrolled in this study: 285 patients were randomized to receive gemcitabine plus 100 mg Tarceva and 284 to receive gemcitabine plus placebo. There were 521 patients in the 100 mg cohort and 48 in the 150 mg cohort.

In the 100 mg cohort, 261 patients were randomized to the Tarceva arm and 260 were randomized to the placebo arm (see **Table 4–2**). In the 150 mg cohort, 24 patients were randomized to the Tarceva arm and 24 were randomized to the placebo arm. Patient disposition is summarized in the table below.

Table 4–2: Study PA.3 Patient Disposition

	Tarceva + Gemcitabine	**Placebo + Gemcitabine**
Total randomized (ITT Population)	285	284
100 mg cohort	261	260
150 mg cohort	24	24
Never treated		
100 mg cohort	2	4
150 mg cohort	1	0
Safety evaluable		
100 mg cohort	259	256
150 mg cohort	23	24
On treatment as of January 2004	19 (7%)	11(4%)

4.3.2 Patient Characteristics

Overall, patient characteristics were typical of what is expected in this population and were well balanced except for a slight difference in the distribution of gender: male/female = 48/52% in the Tarceva arm versus 57/43% in the placebo arm. This imbalance did not affect conclusions about treatment benefit, since results from multivariate analyses that included gender were identical to those from the primary analyses that were not adjusted for gender (see **Section 4.3.3**). A similarly well-balanced

distribution of patient characteristics was observed in the 100 mg dose cohort (see **Table** 4–3).

Table 4–3: Demographics and Disease Characteristics at Randomization

	Gemcitabine + Tarceva All (N=285)		Gemcitabine + Placebo All (N=284)		Gemcitabine + Tarceva 100 mg (N=261)		Gemcitabine + Placebo 100 mg (N=260)	
Characteristics	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
ECOG Performance Status								
0 or 1	232	(81)	232	(82)	218	(84)	215	(83)
2	53	(19)	52	(18)	43	(16)	45	(17)
Disease Status								
Locally Advanced	85	(30)	82	(29)	77	(30)	75	(29)
Distant Metastasis	200	(70)	202	(71)	184	(70)	185	(71)
Gender								
Female	149	(52)	122	(43)	134	(51)	114	(44)
Male	136	(48)	162	(57)	127	(49)	146	(56)
Age (Years)								
18-39	1	(<1)	4	(1)	1	(<1)	4	(2)
40-64	153	(54)	143	(50)	135	(52)	134	(52)
≥65	131	(46)	137	(48)	125	(48)	122	(47)
Race								
White	247	(87)	253	(89)	225	(86)	231	(89)
Black	8	(3)	5	(2)	8	(3)	5	(2)
Asian	21	(7)	16	(6)	20	(8)	14	(5)
Indian Subcontinent	1	(<1)	2	(<1)	1	(<1)	2	(<1)
Unknown	1	(<1)	0	(0)	0	(0)	0	(0)
Other	7	(2)	8	(3)	7	(3)	8	(3)
Pain Intensity Score								
≤ 20	131	(46)	127	(45)	119	(46)	119	(46)
> 20	145	(51)	151	(53)	133	(51)	135	(52)
Missing	9	(3)	6	(2)	9	(3)	6	(2)

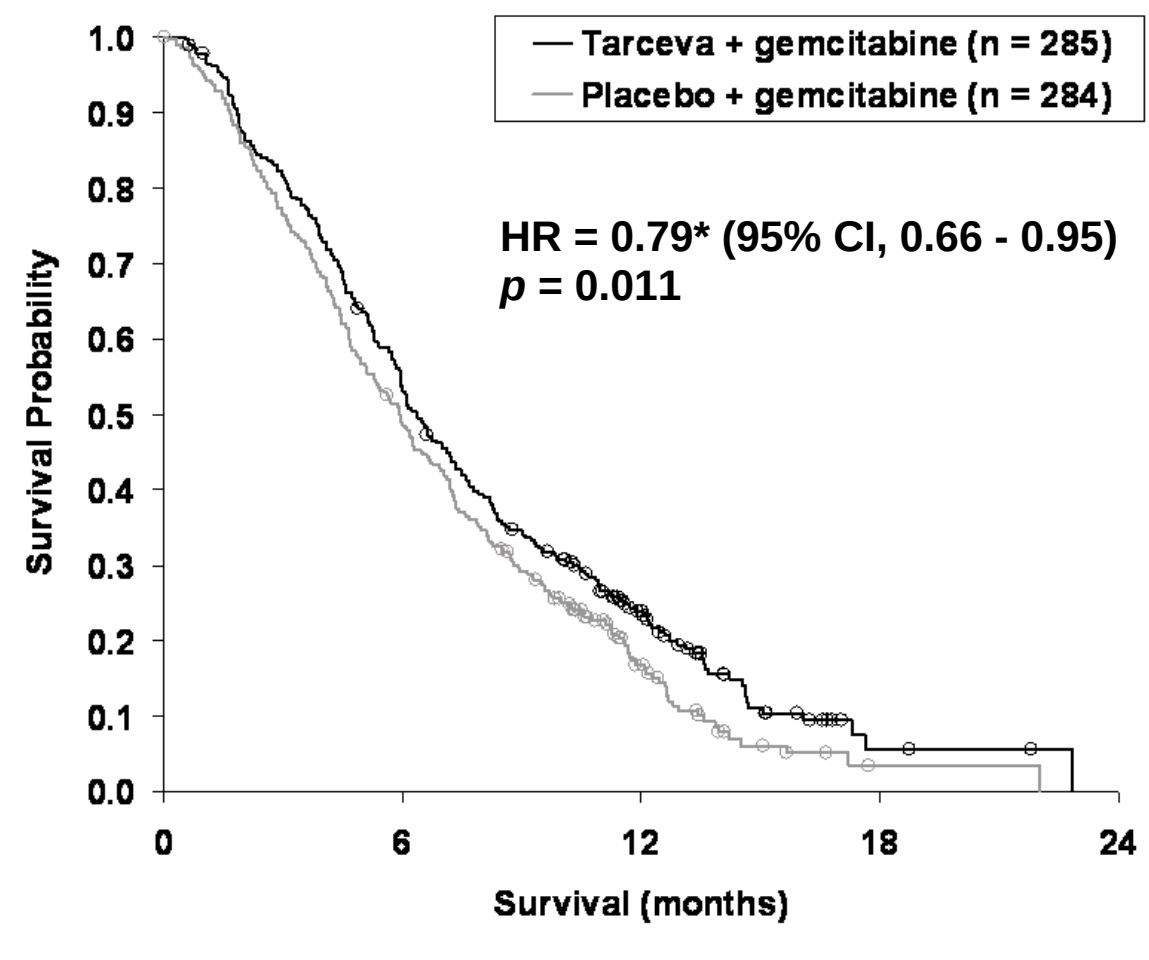
4.3.3 Overall Survival

The primary analysis was a stratified log-rank test in the combined treatment cohorts for overall survival using ECOG PS and extent of disease at randomization as the stratification factors. Overall survival based on the ITT population was calculated after the occurrence of 484 deaths using a cutoff date of 15 January 2004. The HR for death in the Tarceva group relative to the placebo group was 0.79 (95% CI 0.66 to 0.95, p = 0.011), demonstrating that Tarceva reduced the risk of death by 21% compared with

placebo (**Figure 4-2**). When the analysis was restricted to patients in the 100 mg cohort (n = 521), the results were virtually identical (HR = 0.79, 95% CI 0.66 to 0.96, p = 0.017), confirming that the treatment effect was maintained at this dose level (**Figure** 4-3). The number of patients in the 150 mg dose cohort was too small to draw any definitive conclusions regarding the efficacy of Tarceva at this dose level.

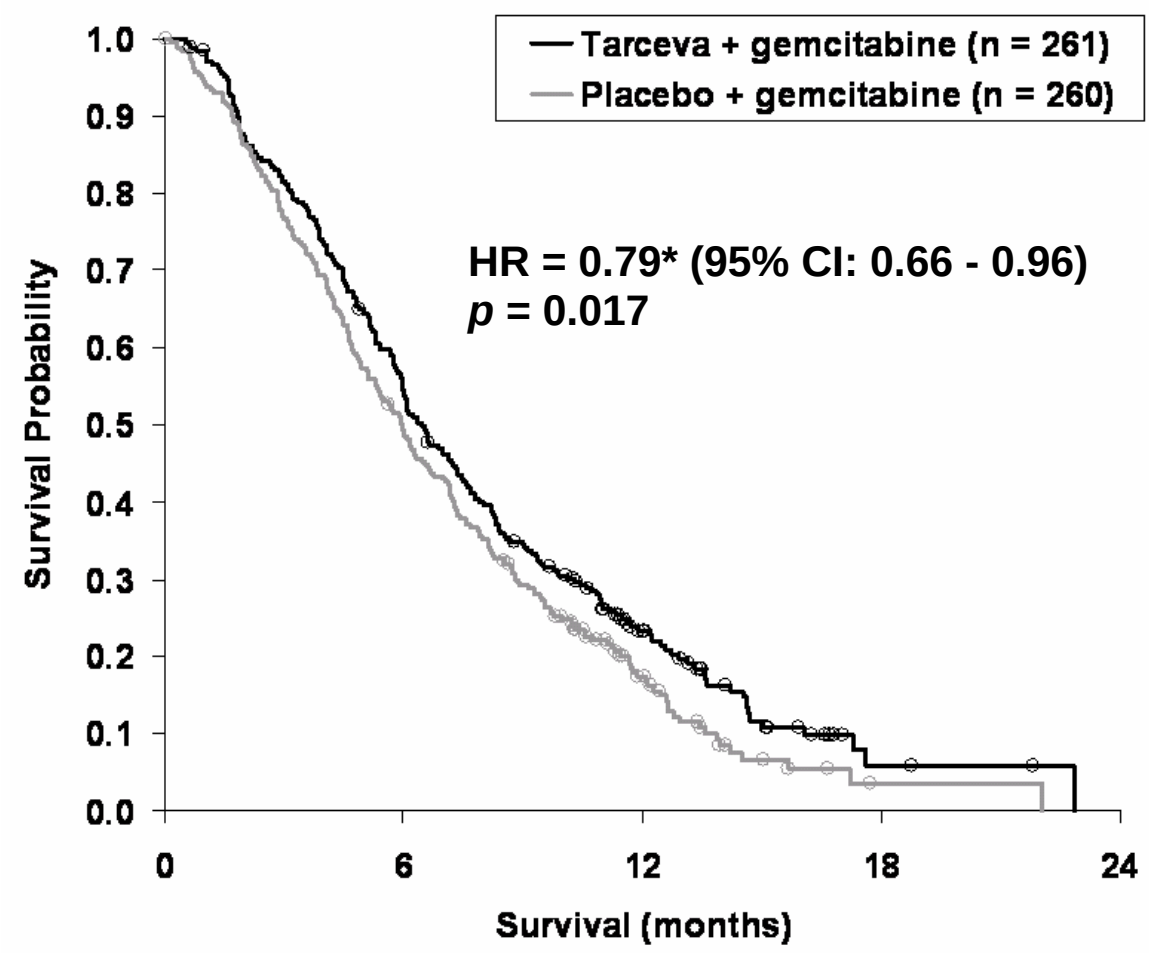
The median overall survival of the ITT population, estimated from univariate Kaplan-Meier curves, was 6.37 months in the Tarceva arm compared with 5.91 months in the placebo arm. The estimated 1-year survival rates were 24% for the Tarceva arm and 17% for the placebo arm.

Figure 4-2: Overall Survival Primary Stratified Analysis – All Randomized Patients



*Adjusted for ECOG PS and extent of disease at randomization

Figure 4-3: Overall Survival – Patients Treated with 100 mg



*Adjusted for ECOG PS and extent of disease at randomization

4.3.4 Robustness Analyses

Several robustness analyses were performed to confirm the statistically significant result obtained with the primary analysis. The results of these analyses are summarized in **Table 4–4** and discussed below.

Univariate analysis: HRs obtained from univariate survival analyses were slightly higher than those estimated from the stratified log-rank analyses, but the p-values from unstratified log-rank tests remained statistically significant.

Cox model with stratification factors at randomization: Multivariate Cox models provide a slightly different approach than stratified log-rank tests for analyzing survival data. HRs from multivariate Cox models with the stratification factors from the primary stratified analysis included as covariates were nearly identical to those from the primary analysis.

Cox model with stratification factors at baseline: For some patients, the ECOG PS and/or the extent of disease reported at the time of randomization had changed at baseline (the start of protocol therapy) after medical review. Therefore, additional multivariate Cox models were constructed using the stratification factors reported at baseline. The HRs from these analyses remained statistically significant.

Cox model with stratification factors + other prognostic factors: Additional multivariate Cox models were constructed that included the stratification factors at baseline, together with baseline pain intensity score, gender, age, race, prior chemotherapy, geographic region, and baseline albumin. Inclusion of these additional factors had very little impact on HRs or p-values. It should be noted that the slight gender imbalance noted in **Section 4.3.2** did not alter the conclusions about treatment benefit.

Univariate analysis that censored patients at the time of first anticancer therapy after completion of protocol therapy: Overall, 194 patients (34%), 102 patients in the Tarceva arm and 92 patients in the placebo arm, received subsequent anticancer therapy consisting of chemotherapy, other EGFR inhibitors, hormonal therapy, and/or radiation therapy. 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 HRs from these univariate analyses were very similar to those from the primary analyses, however, the p-values were somewhat higher. This result is to be expected since the numbers of deaths included in these analyses were greatly reduced due to the censoring, which reduced the precision of the estimates of the HRs.

Stratified log rank (381 deaths): As per protocol, a minimum of 381 deaths needed to be observed for the final analysis. At the request of the FDA, additional survival analyses were conducted restricted to the first 381 deaths in the overall population and in the 100 mg cohort. All patients who died after the date of the 381st death were censored and considered alive on that date. As for the primary analysis with 484 events at the time of data field cutoff, stratified log-rank analyses were performed with ECOG PS and extent

of disease at randomization used as stratification factors. The HRs were nearly identical to those estimated from the primary analyses, and the p-values remained statistically significant despite the reduced numbers of deaths and corresponding loss of statistical power. In conclusion, even when the survival analysis was restricted to the first 381 events, treatment with Tarceva and gemcitabine was associated with a significant improvement in survival both in the overall population and in the 100 mg dose cohort.

Table 4–4: PA.3 Robustness Analyses

	All Patients (n=569)		**100 mg Cohort (n=521)**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Stratified log rank (primary analysis)	0.79 (0.66-0.95)	0.011	0.79 (0.66-0.96)	0.017
Univariate analysis	0.82 (0.69-0.99)	0.034	0.83 (0.69-1.00)	0.046
Cox model with stratification factors at randomization	0.78 (0.65-0.93)	0.007	0.79 (0.65-0.95)	0.014
Cox model with stratification factors at baseline	0.77 (0.64-0.92)	0.004	0.79 (0.65-0.95)	0.012
Cox model with stratification factors + other prognostic factors	0.78 (0.65-0.95)	0.011	0.81 (0.66-0.98)	0.031
Univariate: censor at 1st anticancer therapy	0.81 (0.65-1.00)	0.047	0.80 (0.64-1.01)	0.054
Stratified log rank (381 deaths)	0.80 (0.65-0.98)	0.029	0.80 (0.66-0.98)	0.034

Note: Based on original analyses with cutoff date of 15 January 2004
484 deaths; 443 in the 100 mg cohort

After OSI submitted the sNDA and following a meeting with the FDA on 3 June 2005 at which the PA.3 data were presented, the FDA requested updated survival information for the 85 patients who were still alive or lost to follow up as of the sNDA cutoff date of 15 January 2004 (48 patients [16%] in the Tarceva/gemcitabine arm and 37 patients [13%] in the placebo/gemcitabine arm). In response to the FDA request, OSI and NCIC CTG updated the survival data as of 20 June 2005.

A comparison of the results of these 2 analyses is presented in **Table 4–5**, which demonstrates that the updated analysis maintained the statistical significance between the treatment groups shown in the original analysis. Because only survival information was obtained for the update, the remainder of this document discusses results from the analyses performed for the original sNDA.

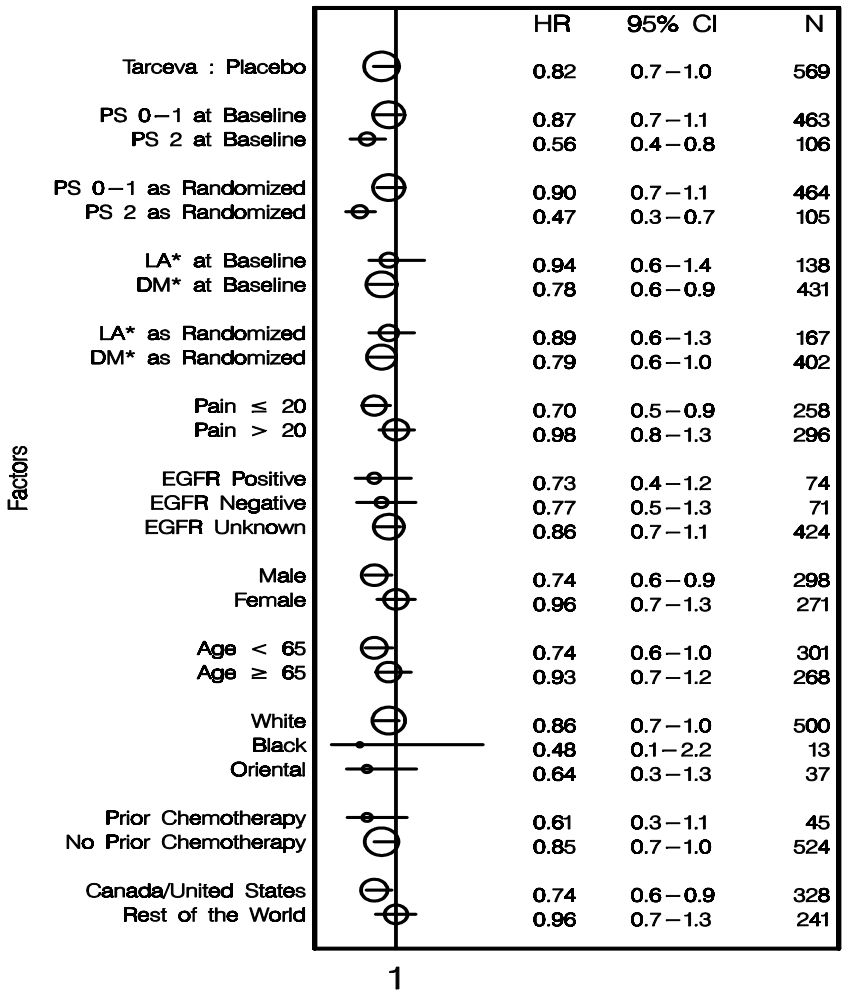
Table 4–5: Study PA.3 Stratified Log Rank Test (Primary Analysis) – Comparison of Original Analysis with Updated Analysis

	All Patients (n=569)		100 mg Cohort (n=521)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Original Analysis Cutoff Date: 15 January 2004 484 deaths: 443 in the 100 mg cohort	0.79 (0.66-0.95)	0.011	0.79 (0.66-0.96)	0.017
Updated Analysis Cutoff Date: 20 June 2005 551 deaths; 504 in the 100 mg cohort	0.81 (0.69-0.96)	0.017	0.82 (0.69-0.98)	0.028

Based on these robustness analyses, it appears the survival benefit observed in the ITT analysis does not depend on the statistical analytical approach used, remains statistically significant in a variety of multivariate analyses, cannot be explained by benefit from subsequent anticancer therapy, is not the result of over-accrual or exceeding the required number of deaths for an event-driven analysis, and does not disappear with additional follow-up.

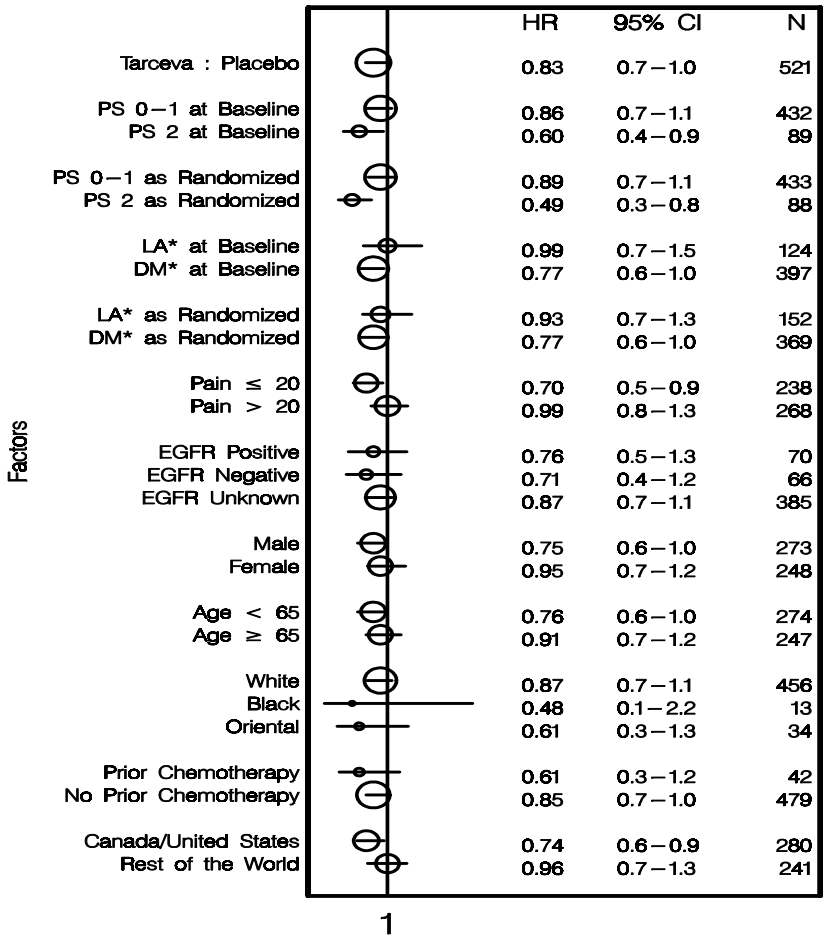
In addition, a series of unplanned, exploratory univariate analyses were performed to assess the survival benefit across subsets of patients, with the understanding that positive results do not demonstrate that a treatment benefit definitely exists and negative results do not establish lack of treatment benefit. These data are presented in **Figure 4-4** for the ITT population and in **Figure 4-5** for patients in the 100 mg dose cohort. All of the HRs for the subsets in the combined dose cohorts in the Tarceva/gemcitabine arm relative to the placebo/gemcitabine arm were less than 1.0, indicating no detrimental effect of Tarceva in any of these subsets. Formal tests of treatment-by-factor interactions indicated that the only significant interaction was for PS at baseline in the ITT population (HR = 0.87 for PS 0-1; HR = 0.56 for PS 2; p = 0.037). None of the other interactions were statistically significant.

Figure 4-4: Survival by Pretreatment Characteristics – All Randomized Patients



*LA = locally advanced, DM = distant metastases

Figure 4-5: Survival by Pretreatment Characteristics – 100 mg Cohort



*LA = locally advanced, DM = distant metastases

4.3.5 Survival by EGFR Protein Expression Status

Correlation of EGFR protein expression status as determined by IHC assays with clinical outcomes was a prespecified secondary endpoint. Availability of tissue for determination of EGFR protein expression status was not an entry requirement for this study.

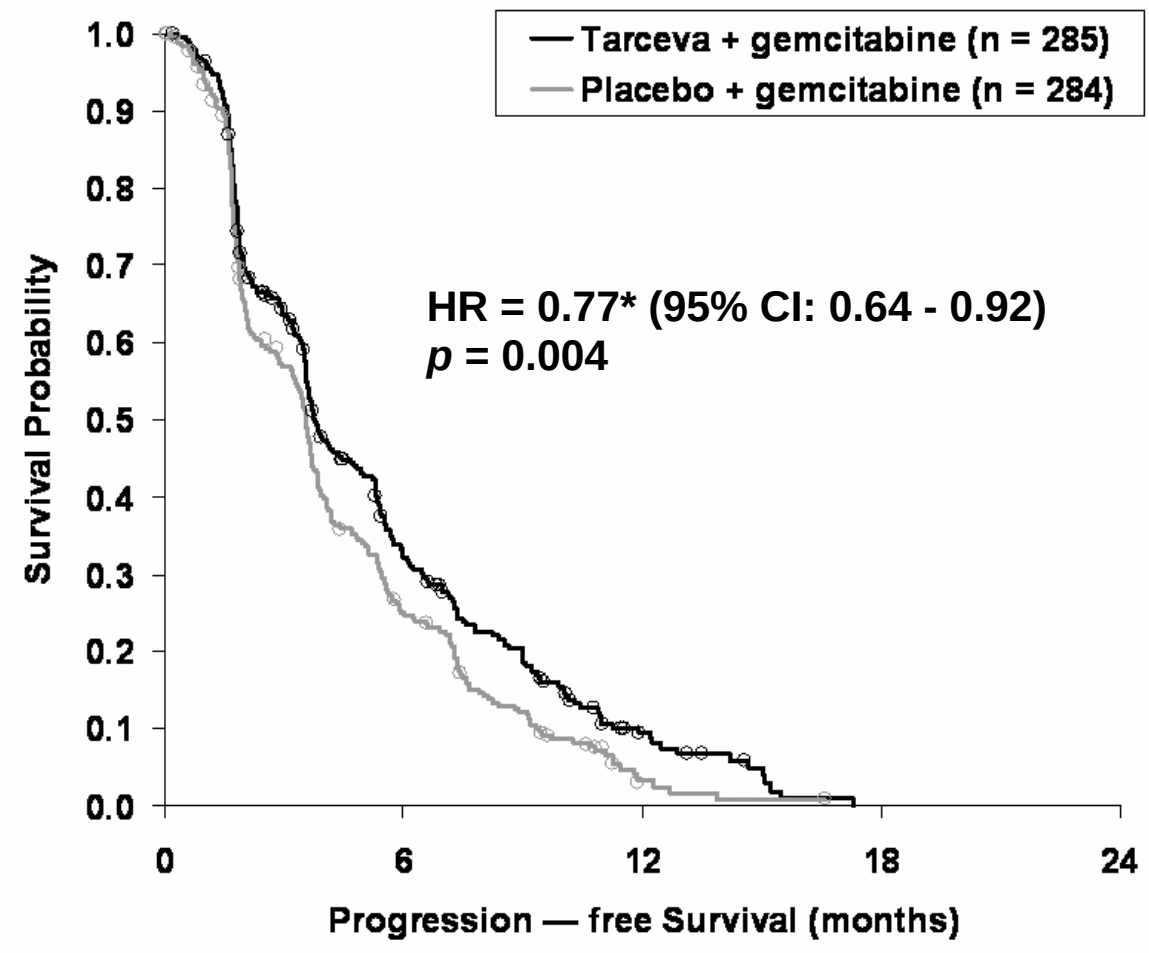
Tumor samples were available and results were interpretable for 145 patients (25%). As expected, the number of samples available was limited by the fact that patients had to separately consent to allow for their tissue to be used for this analysis and the fact that the method used for tissue collection was frequently fine needle aspiration, which is common in advanced pancreatic cancer, rather than excisional biopsy or surgery. Patients with a positive EGFR status (≥ 10% staining) in the placebo arm had a worse median survival (5.32 months) than patients with EGFR negative tumors in the same arm (6.11 months), suggesting that an EGFR positive status might be a weak negative prognostic factor for

survival in patients with pancreatic cancer. The HRs for survival in the Tarceva arms were very similar for patients with a positive EGFR status versus those with a negative EGFR status (0.73 and 0.77, respectively), suggesting the survival benefit from Tarceva plus gemcitabine relative to gemcitabine alone was not related to EGFR expression status. Caution must be taken in the interpretation of these results, however, because of the limited number of patients with known EGFR status and the fact that this was only designed as an exploratory analysis.

4.3.6 Progression-Free Survival

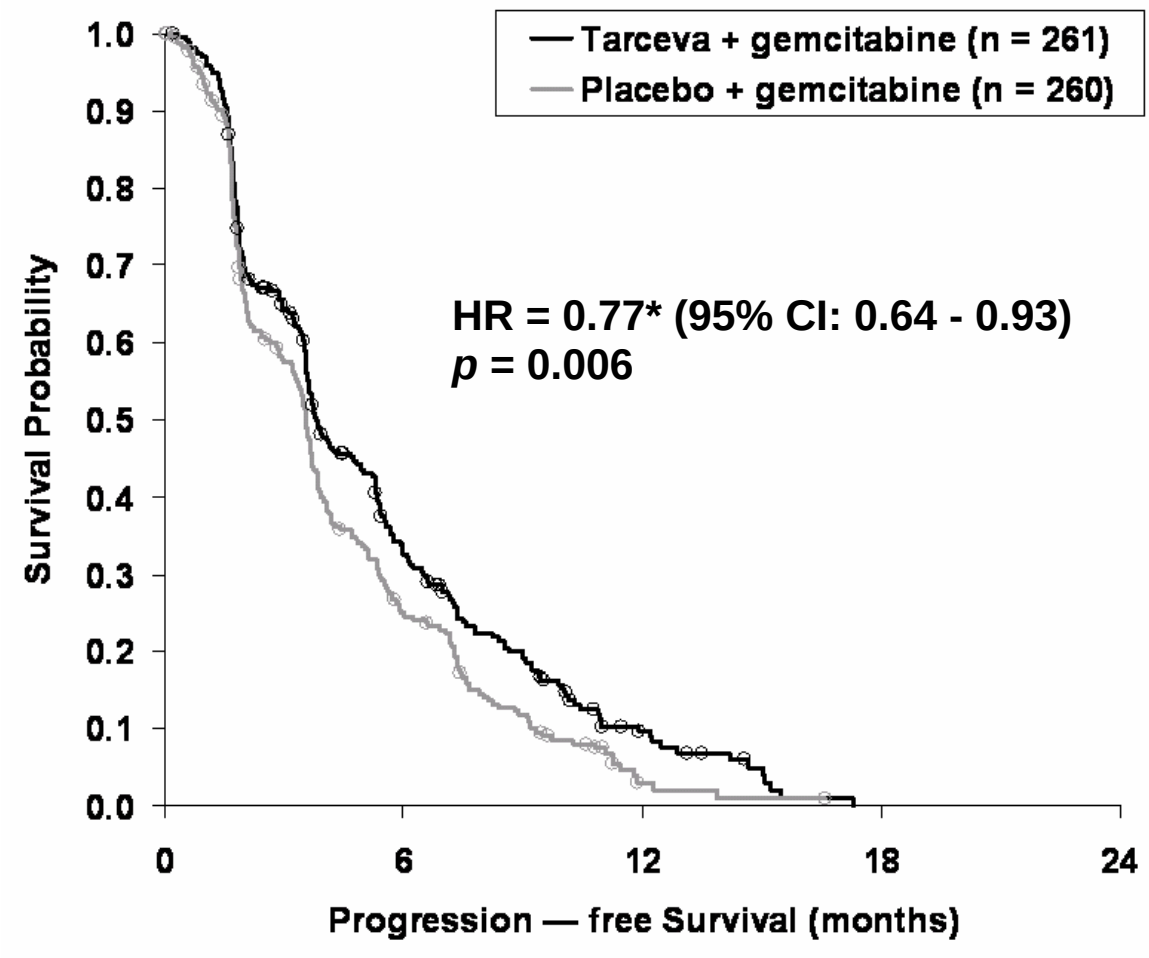
Consistent with the statistically significant survival benefit are the results of the secondary efficacy endpoint of PFS. The adjusted HR for progression in the Tarceva arm relative to the placebo arm was 0.77 (95% CI 0.64 to 0.92, p = 0.004). For the 100 mg dose cohort, the adjusted HR was 0.77 (95% CI 0.64 to 0.93, p = 0.006). The median PFS for the overall population was 3.75 months (95% CI 3.58 to 4.83) in the Tarceva arm and 3.55 months (95% CI 3.22 to 3.71) in the placebo arm (**Figure 4-6**). In the 100 mg dose cohort, the median PFS was 3.81 months (95% CI 3.58 to 4.93) and 3.55 months (95% CI 3.29 to 3.75), respectively (**Figure 4-7**).

Figure 4-6: Progression-free Survival – All Randomized Patients



*Adjusted for ECOG PS and extent of disease at randomization

Figure 4-7: Progression-free Survival – Patients Treated with 100 mg



*Adjusted for ECOG PS and extent of disease at randomization

4.3.7 Response Rate

Investigators assessed tumor response rate in patients with measurable disease: 268/285 (94%) patients in the Tarceva arm and 262/284 (92%) patients in the placebo arm. Tumor lesions were measured 28 days before randomization and 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 until disease progression.

One CR and 22 PRs were observed in the Tarceva arm and similar numbers, 3 CRs and 18 PRs, were observed in the placebo arm, for an overall objective response rate in the Tarceva arm of 8.6% (95% CI 5.5 to 12.6) and 8.0% (95% CI 5.0 to 12.0) in the placebo arm (p = 0.875). Tumor response is summarized in **Table 4–6**.

The responses for the patients with measurable disease were durable, as the median response duration was 23.3 weeks (range 3.71 to 56.00+) in the Tarceva arm and 23.3 weeks (range 6.71 to 65.29) in the placebo arm. Overall, SD was observed in 48.9% of patients in the Tarceva arm compared with 41.2% of patients in the placebo arm, yielding non-progression (CR + PR + SD) rates of 57.5% and 49.2% (p = 0.067).

Table 4–6: Best Tumor Response – All Patients with Measurable Disease

	Percentage of Patients	
	Tarceva/gemcitabine N = 268	**Placebo/gemcitabine N = 262**
CR + PR	8.6	8.0
Stable disease (SD)	48.9	41.2
Non-progression (CR + PR + SD)	57.5	49.2
Progressive disease	22.4	26.3
Not evaluable/missing	20.1	24.4
Median duration of response in weeks (range)	23.3 (range 3.71 to 56.00+)	23.3 (range 6.71 to 65.29+)

As expected, the results in the Tarceva 100 mg dose cohort were nearly identical: overall objective response 8.6% (95% CI 5.4 to 12.9) in the Tarceva arm and 7.9% (95% CI 4.8 to 12.0) in the placebo arm (p = 0.869); non-progression rates of 59.0% and 49.4% (p = 0.036).

Tumor shrinkage did not appear to be required to achieve a survival benefit, as shown in **Table 4–7**.

Table 4–7: Study PA.3 Survival after Removal of Patients with Complete or Partial Response

	Tarceva + gemcitabine		Placebo + gemcitabine			
	N	**Median**	**N**	**Median**	**HR***	**p-value***
All patients	**285**	**6.4 months**	**284**	**5.9 months**	**0.79**	**0.011**
Measurable Disease	**268**	**6.1 months**	**262**	**5.9 months**	**0.81**	**0.030**
Eliminate CR/PR	**245**	**6.0 months**	**241**	**5.3 months**	**0.82**	**0.045**

* Adjusted for PS and extent of disease at randomization

Study BR.21 in NSCLC demonstrated that response rate assessed by RECIST does not fully represent efficacy of treatment when using EGFR tyrosine kinase inhibitors. Tumor response may not correlate with more clinically relevant endpoints of improvement in survival and extension of progression-free survival. Long-term tumor stasis involving a balance in the rate of tumor cell proliferation and cell death can often benefit a patient more than short-term tumor response.

4.3.8 Quality of Life

The EORTC QLQ-C30 instrument was used in Study PA.3 to evaluate quality of life (QoL). EORTC QLQ-C30 is a well-validated, self-administered cancer-specific questionnaire with a multi-dimensional scale. It consists of 5 functional domains: Physical, Role, Emotional, Cognitive, Social; 3 symptom domains: Fatigue, Nausea and Vomiting, Pain; 6 single symptom items: Dyspnea, Sleep, Appetite, Constipation, Diarrhea, and Financial; and a global assessment domain. For each domain/item, a linear transformation was applied to standardize the raw score to the range from 0 to 100.

For each domain/item, the mean and standard deviation of the QoL scores at baseline and the mean and standard deviation of QoL change scores from baseline at each assessment time point were calculated. The Wilcoxon Rank-Sum test was used to compare change in QoL scores at each assessment time point from baseline between the 2 treatment arms. All analyses are exploratory and include all randomized patients who had at least 1 follow-up evaluation for QoL in addition to the baseline evaluation. No adjustments of p-values were made for multiple hypothesis testing. Available data at each visit were used for the analyses. No imputations were made for discontinuations or missed visits.

Although not all sites participated in the quality of life evaluation (it was required in the US and Canada but was optional elsewhere), participation across the study was very good, as summarized in **Table 4–8**.

Table 4–8: Quality of Life Participation

	Tarceva + gemcitabine	Placebo + gemcitabine
Baseline	80.4%	79.6%
Cycle 1 (8 weeks)	65.6%	62.1%
Cycle 2 (12 weeks)	76.6%	71.4%
Cycle 3 (16 weeks)	71.7%	68.3%
Cycle 4 (20 weeks)	77.2%	75.5%
Cycle 5 (24 weeks)	76.1%	69.6%
Cycle 6 (28 weeks)	70.1%	85.7%
Cycle 12 (52 weeks)	93.8%	100%

Note: QoL participation was required in US and Canada; optional elsewhere

As shown in **Table 4–9**, no significant differences were found between change scores for the global assessment domain between the Tarceva arm and the placebo arm at any of the assessment time points.

Table 4–9: Study PA.3 Cross-Sectional Analysis of Global Quality of Life Change from Baseline – All Patients

		Tarceva + Gemcitabine		Placebo + Gemcitabine		
Domain/Item	Assessment	N	Mean Change (SD)	N	Mean Change (SD)	p-value
Global QoL	Cycle 1 - End	185	2.2 (22.59)	175	0.0 (21.39)	0.262
	Cycle 2	140	6.4 (23.60)	107	3.0 (22.20)	0.378
	Cycle 3	118	5.7 (24.16)	93	1.9 (23.22)	0.141
	Cycle 4	86	7.8 (22.91)	76	1.1 (23.90)	0.036
	Cycle 5	69	5.0 (24.89)	55	7.0 (23.12)	0.859
	Cycle 6	46	4.3 (26.57)	41	6.1 (29.05)	1
	Cycle 7	37	8.8 (22.04)	36	3.0 (27.32)	0.573
	Cycle 8	29	10.6 (28.60)	22	8.7 (33.58)	0.871
	Cycle 9	24	4.2 (35.01)	19	12.3 (26.11)	0.338
	Cycle 10	20	4.6 (26.28)	14	4.8 (17.82)	0.727
	Cycle 11	16	1.6 (26.91)	8	8.3 (17.25)	0.381
	Cycle 12	14	-7.1 (26.12)	5	8.3 (18.63)	0.319
	Cycle 13	7	-1.2 (21.75)	1	0.0 (.)	1
	Cycle 14	6	-22.2 (22.77)	1	0.0 (.)	0.347
	Cycle 15	4	-8.3 (18.00)	1	0.0 (.)	0.741
	Cycle 16	4	-16.7 (18.00)	1	0.0 (.)	0.741
	Cycle 17	2	-8.3 (23.57)	1	0.0 (.)	1
	Cycle 18	1	-58.3 (.)	1	8.3 (.)	
	Progression	33	-4.8 (32.68)	19	-10.1 (28.41)	0.776
	F/U Week 4	26	-8.7 (31.66)	29	-10.1 (29.99)	0.687

Note: Positive mean change indicates improvement

QoL 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 they reported a score 10 points or better than baseline at any time point in QoL assessment. Conversely, patients were considered worsened if they reported a score minus 10 points or worse than baseline at any time point in the QoL assessment without the above-defined improvement being observed. Patients whose scores were within 10 point changes from baseline at every QoL assessment were considered stable. A chi-square test was then performed to compare the distributions of data in these 3 categories between the 2 arms. Following the chi-square test, a Mantel-Haenszel chi-square test for trend was used to test for a trend that patients in 1 treatment arm had higher proportions in the better QoL categories than those on the other arm.

As shown in **Table 4–10**, no statistically significant differences were observed for QoL response in the EORTC QLQ-C30 domains, except for significantly more diarrhea in the

Tarceva 100 mg group. No deterioration in global quality of life was observed in patients treated with Tarceva compared with patients in the placebo arm.

Table 4–10: Study PA.3 Results for QoL Response Analyses – All Patients

	Erlotinib + Gemcitabine				Placebo + Gemcitabine					
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	229	53 (23)	102 (45)	74 (32)	224	43 (19)	106 (47)	75 (33)	0.585	0.453
Role Functioning	229	92 (40)	51 (22)	86 (38)	223	78 (35)	65 (29)	80 (36)	0.225	0.664
Emotional Functioning	228	98 (43)	69 (30)	61 (27)	225	88 (39)	90 (40)	47 (21)	0.077	0.787
Cognitive Functioning	228	70 (31)	72 (32)	86 (38)	225	72 (32)	89 (40)	64 (28)	0.080	0.161
Social Functioning	228	99 (43)	48 (21)	81 (36)	225	70 (31)	68 (30)	87 (39)	0.013	0.056
Fatigue	228	100 (44)	36 (16)	92 (40)	225	87 (39)	50 (22)	88 (39)	0.196	0.640
Nausea and Vomiting	228	69 (30)	79 (35)	80 (35)	225	48 (21)	98 (44)	79 (35)	0.055	0.219
Pain	228	129 (57)	54 (24)	45 (20)	226	114 (50)	67 (30)	45 (20)	0.314	0.393
Dyspnea	228	43 (19)	94 (41)	91 (40)	224	29 (13)	111 (50)	84 (38)	0.112	0.597
Sleep	225	102 (45)	67 (30)	56 (25)	224	86 (38)	73 (33)	65 (29)	0.318	0.151
Appetite	228	95 (42)	57 (25)	76 (33)	225	88 (39)	82 (36)	55 (24)	0.017	0.414
Constipation	227	81 (36)	91 (40)	55 (24)	225	66 (29)	104 (46)	55 (24)	0.302	0.352
Diarrhea	227	31 (14)	95 (42)	101 (44)	225	48 (21)	134 (60)	43 (19)	<0.001	<0.001
Financial	226	43 (19)	111 (49)	72 (32)	222	39 (18)	137 (62)	46 (21)	0.013	0.122
Global QoL	227	98 (43)	53 (23)	76 (33)	225	97 (43)	71 (32)	57 (25)	0.069	0.307

4.4 Efficacy Conclusions

Study PA.3 demonstrated a statistically significant prolongation in survival and PFS with Tarceva in combination with gemcitabine over gemcitabine alone for patients with locally advanced, unresectable or metastatic pancreatic cancer. To date, it is the only phase 3 trial of an EGFR tyrosine kinase inhibitor or any other therapy in combination with gemcitabine that has demonstrated a statistically significant survival benefit in patients with pancreatic cancer over gemcitabine alone. No deterioration in global quality of life was observed in patients treated with Tarceva compared with patients in the placebo arm.

5 SAFETY OF TARCEVA

As of February 2005 (the cutoff date for the most recent edition of the Tarceva Investigator's Brochure), Tarceva has been or is currently being studied in more than 4,600 healthy subjects and cancer patients (excluding those exposed to placebo) in phase 1, 2, and 3 company-sponsored studies. Phase 1 studies have evaluated Tarceva as a single agent in 313 individuals (179 healthy volunteers, 134 patients). Phase 1b studies have evaluated Tarceva in combination with various chemotherapy agents in 278 patients, including 26 patients exposed to Tarceva plus gemcitabine and 25 patients exposed to Tarceva plus gemcitabine plus cisplatin. Phase 2 studies have evaluated Tarceva in 1,420 patients: as a single agent in 1,235 patients and in combination with other agents in 185 patients. Phase 3 studies have evaluated Tarceva in 2,655 patients: as a single agent in 1,244 patients and in combination with various chemotherapy agents in 1,411 patients, including 282 patients with pancreatic cancer exposed to Tarceva plus gemcitabine and 586 NSCLC patients exposed to Tarceva plus gemcitabine plus cisplatin. Approximately 2,200 additional patients have been enrolled in IST studies.

The safety of single-agent Tarceva administered at doses up to 1000 mg in healthy volunteers and up to 1600 mg in cancer patients has been evaluated. The duration of dosing in cancer patients is anticipated to be prolonged (ie, as long as the patient continues to have a beneficial effect from the treatment). Such chronic exposure is supported by the chronic toxicity studies of up to 1-year duration and the long-term use of Tarceva in cancer patients.

5.1 Summary of Safety

The recommended dose of single-agent Tarceva was 150 mg daily, based on findings of dose-limiting diarrhea in a phase 1 study of cancer patients. The adverse event profile of Tarceva 150 mg daily is dominated by rash and diarrhea. Rash occurred in approximately 75% of the Tarceva-treated patients and diarrhea was present in about half of the patients. These adverse events were usually mild and very few patients discontinued medication due to these adverse events. Grade 3 rash can generally be handled with dose reductions. Grade 3 diarrhea may be treatable with loperamide without the need for dose reduction, but dose can be reduced if treatment is not sufficient. **Table 5–1** summarizes the adverse events, regardless of causality, occurring more

frequently in the Tarceva group (≥ 3%) and in ≥ 10% of Tarceva-treated patients in the single-agent, placebo-controlled NSCLC study BR.21.

Table 5–1: Adverse Events Occurring More Frequently (≥ 3%) in the TARCEVA Group Than in the Placebo Group and in ≥ 10% of Patients in Tarceva Group - NSCLC Study BR.21

	BR.21 TARCEVA (N=485)						BR.21 Placebo (N=242)					
	Any		3		4		Any		3		4	
MedDRA Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total patients with any AE	481	(99)	195	(40)	107	(22)	233	(96)	87	(36)	54	(22)
Rash	366	(75)	40	(8)	3	(<1)	42	(17)	0	(0)	0	(0)
Diarrhoea	261	(54)	28	(6)	1	(<1)	44	(18)	2	(<1)	0	(0)
Anorexia	250	(52)	38	(8)	5	(1)	93	(38)	11	(5)	1	(<1)
Fatigue	250	(52)	67	(14)	19	(4)	108	(45)	39	(16)	10	(4)
Dyspnoea	198	(41)	82	(17)	52	(11)	84	(35)	36	(15)	27	(11)
Cough	159	(33)	18	(4)	0	(0)	70	(29)	6	(2)	0	(0)
Nausea	158	(33)	14	(3)	0	(0)	59	(24)	4	(2)	0	(0)
Infection	116	(24)	20	(4)	0	(0)	37	(15)	5	(2)	0	(0)
Vomiting	113	(23)	9	(2)	2	(<1)	47	(19)	4	(2)	0	(0)
Stomatitis	83	(17)	4	(<1)	0	(0)	8	(3)	0	(0)	0	(0)
Pruritus	61	(13)	2	(<1)	0	(0)	12	(5)	0	(0)	0	(0)
Dry skin	60	(12)	0	(0)	0	(0)	9	(4)	0	(0)	0	(0)
Conjunctivitis	57	(12)	3	(<1)	0	(0)	5	(2)	1	(<1)	0	(0)
Keratoconjunctivitis sicca	56	(12)	0	(0)	0	(0)	8	(3)	0	(0)	0	(0)
Abdominal pain	52	(11)	10	(2)	1	(<1)	17	(7)	3	(1)	1	(<1)

Class-specific but infrequent adverse events include mild eye disorders: conjunctivitis, dry eyes and, infrequently, keratitis.

Gastrointestinal bleedings have been reported infrequently in clinical trials, however, the majority of these cases were confounded by concomitant use of non-steroidal anti-inflammation drugs (NSAIDs) and/or warfarin.

Based on reports of ILD with fatal outcome from other EGFR inhibitors of a similar chemical class as Tarceva [34, 35], special attention was given to the monitoring and reporting of certain pulmonary events. Because ILD comprises a heterogeneous group of non-neoplastic disorders resulting from damage to the lung parenchyma by varying patterns of inflammation and fibrosis, it may present or be reported by using different diagnoses or radiological terms [ATS/ERS, 2002]. Reports of serious events that may constitute possible ILD, regardless of reporter causality and likely etiology, have been

thoroughly evaluated by the Sponsor by using a search strategy focusing on more than 20 relevant MedDRA preferred terms.

Serious ILD-like events from the 2nd/3rd-line NSCLC monotherapy study BR.21 were reported in 0.8% in each treatment arm. In the 1st-line placebo-controlled NSCLC study TALENT, in which Tarceva was administered with concurrent chemotherapy, the incidence of ILD-like events was balanced (1% in each treatment group for both studies). There was 1 serious ILD-like event in each treatment group.

ILD is addressed in the Warnings section of the current approved labeling for Tarceva. The sub-section pertaining to Pulmonary Toxicity advises that in the event of an acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, or fever, Tarceva therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment instituted as needed.

5.2 Safety Results from Study PA.3 in Pancreatic Cancer

5.2.1 Overall Exposure

The median duration of treatment in Study PA.3 for patients treated with Tarceva was longer than for patients treated with placebo in both dose cohorts: 100 mg cohort, 15.7 weeks versus 12.3 weeks; and 150 mg cohort, 14.0 weeks versus 10.7 weeks. The duration of exposure to gemcitabine was also slightly longer in the Tarceva arm than in the placebo arm: 100 mg cohort, 15.1 weeks versus 13.3 weeks; and 150 mg cohort, 14.1 weeks versus 12.0 weeks.

The median dose intensities of Tarceva or placebo were 99 mg/day and 100 mg/day in the 100 mg dose cohort and 129 mg/day and 150 mg/day in the 150 mg dose cohort. The percentages of patients with a relative dose intensity of > 90% were 77% versus 88% for the 100 mg dose cohort and 48% versus 92% in the 150 mg dose cohort.

The reasons for Tarceva discontinuation in the combined 100 mg and 150 mg cohorts are summarized in **Table 5–2** below.

Table 5–2: Study PA.3 Reasons for Tarceva Discontinuation - ALL

	Tarceva + Gemcitabine (N=285)		Placebo + Gemcitabine (N=284)	
	n	(%)	n	(%)
Patients Never Treated	3	(1)	4	(1)
Patients Off Tarceva	263	(92)	269	(95)
Reasons Off Tarceva				
Progressive Disease	133	(47)	162	(57)
Symptomatic Progression	42	(15)	38	(13)
Intercurrent Illness	11	(4)	10	(4)
Toxicity to Protocol Therapy	22	(8)	13	(5)
Patient Refusal	23	(8)	15	(5)
Death	26	(9)	22	(8)
Other	6	(2)	9	(3)
On Tarceva	19	(7)	11	(4)

The 7 patients who did not receive treatment were excluded from the safety analyses: 3 in the Tarceva group and 4 in the placebo group. In addition, 2 patients did not receive the correct treatment as per randomization: 1 patient was randomized to placebo but received Tarceva 100 mg during the second half of Cycle 1 and for 11 additional cycles of treatment, and 1 patient was randomized to the Tarceva arm but received placebo throughout the study. For the safety analyses, these 2 patients have been accounted for in the treatment group of what they actually received. Therefore, the population evaluable for safety included 282 patients in the Tarceva group and 280 in the placebo group.

5.2.2 Dose Modification and Discontinuation

Patients receiving 150 mg of Tarceva plus gemcitabine in Study PA.3 required more Tarceva dose reductions (48% or 10/23 patients) compared with Tarceva-treated patients in the 100 mg dose cohort (13%) and more dose interruptions for > 7 days (74% in 150 mg cohort vs 30% in 100 mg cohort). This information is consistent with the dose intensity data described above.

More patients in the Tarceva arm of the 100 mg cohort (10%) discontinued the study due to Tarceva/placebo-related adverse events compared with the patients in the placebo arm (5%). The opposite was observed in the 150 mg cohort (2 patients, 9% vs 3 patients, 13%). The Tarceva/placebo-related events most frequently resulting in discontinuation were ALT and AST elevations, fatigue, lung infiltration, rash, and decreased platelet count.

5.2.3 Adverse Events

Table 5–3 presents adverse events reported in the 100 mg cohort with a frequency ≥ 10% that occurred more frequently (≥ 3%) in Tarceva-treated patients than in the placebo group. The incidence of events was balanced between the Tarceva and placebo arms (99% vs 97%). The most commonly reported adverse events that occurred more frequently in the Tarceva arm than in the placebo arm were fatigue (73% vs 70%), rash (69% vs 30%), and diarrhea (48% vs 36%).

Table 5–3: Incidence of Patients in the 100 mg cohort with Adverse Events Occurring More Frequently in Patients in the Tarceva Arm – Limited to Adverse Events Occurring in ≥ 10% of Patients in Tarceva Arm

	Tarceva + Gemcitabine (N=259)						Placebo + Gemcitabine (N=256)					
Grade:	**Any**		**3**		**4**		**Any**		**3**		**4**	
MedDRA Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total patients with any AE	256	(99)	124	(48)	56	(22)	248	(97)	123	(48)	40	(16)
Fatigue	188	(73)	35	(14)	5	(2)	178	(70)	34	(13)	6	(2)
Rash	180	(69)	12	(5)	0	(0)	76	(30)	3	(1)	0	(0)
Diarrhoea	125	(48)	14	(5)	1	(<1)	91	(36)	5	(2)	0	(0)
Weight decreased	101	(39)	5	(2)	0	(0)	74	(29)	2	(<1)	0	(0)
Pyrexia	93	(36)	7	(3)	0	(0)	78	(30)	9	(4)	0	(0)
Infection	80	(31)	9	(3)	1	(<1)	62	(24)	15	(6)	2	(<1)
Stomatitis	56	(22)	1	(<1)	0	(0)	31	(12)	0	(0)	0	(0)
Depression	50	(19)	5	(2)	0	(0)	37	(14)	2	(<1)	0	(0)
Dyspepsia	43	(17)	2	(<1)	0	(0)	34	(13)	1	(<1)	0	(0)
Cough	42	(16)	0	(0)	0	(0)	29	(11)	0	(0)	0	(0)
Headache	39	(15)	2	(<1)	0	(0)	26	(10)	0	(0)	0	(0)
Neuropathy	34	(13)	3	(1)	1	(<1)	25	(10)	1	(<1)	0	(0)
Flatulence	33	(13)	0	(0)	0	(0)	22	(9)	2	(<1)	0	(0)
Rigors	31	(12)	0	(0)	0	(0)	22	(9)	0	(0)	0	(0)

The relatively high frequency of rash in the placebo group reflects the fact that gemcitabine treatment is also associated with rash. Additional adverse events in the 100 mg cohort for which the incidence in the Tarceva arm was higher than in the placebo arm included weight decreased (39% vs 29%), pyrexia (36% vs 30%), infection (31% vs 24%), and stomatitis (22% vs 12%). Forty-eight percent of the patients in each arm of the 100 mg cohort experienced a grade 3 adverse event while 22% and 16% of the patients in the Tarceva and placebo arms, respectively, experienced a grade 4 event. The most common grade 3 or 4 adverse event was fatigue (Tarceva: 14% grade 3 and 2%

grade 4; placebo: 13% grade 3 and 2% grade 4). The type of event with a severity of grade 3 that occurred notably more frequently in the Tarceva arm was rash (5% versus 1%), while grade 4 events were infrequent and similar between treatment arms.

More patients in the Tarceva arm experienced grade 1 epistaxis (7% versus <1%) and hemoptysis (2% versus 0). To evaluate the incidence of other clinical bleeding episodes across different system/organ classes (SOCs), an analysis was performed selecting the MedDRA Special Search Category "Hemorrhage." Eighteen percent of patients in the Tarceva arm and 7% of patients in the placebo arm of the 100 mg cohort experienced any bleeding disorder. The majority was grade 1 or 2 in severity, but 6% of the patients in the Tarceva arm and 4% in the placebo arm experienced grade 3 or 4 bleedings. These included gastrointestinal disorders in 5% and 4% of the patients in the Tarceva and placebo arms, respectively, several of which were confounded by concomitant NSAID and/or warfarin administration. One patient in each arm had concurrent thrombocytopenia.

5.2.4 Deaths Due to Adverse Events, and Other Serious Adverse Events

5.2.4.1 Deaths

Since Study PA.3 included only patients with advanced pancreatic cancer, most patients died due to progression of the underlying disease. A total of 3% and 4% of patients in the 100 mg cohort treated with Tarceva and placebo, respectively, in addition to 2 patients (8%) in the placebo arm of the 150 mg cohort, died due to "other conditions or circumstances." These causes consisted of fatal intercurrent illnesses such as cardiovascular disorders, including cardiac arrest, myocardial ischemia, thrombosis, sudden death, and other individual events.

Five patients (2%) died of toxicity attributed to protocol therapy (ie, Tarceva and/or gemcitabine) within 30 days of last dose, all in the Tarceva 100 mg dose cohort (see **Table 5–4**). These deaths included 2 patients with pneumonitis and 1 patient each with neutropenic sepsis, sepsis, and cerebral hemorrhage. None of the deaths in the placebo arm were attributed to protocol therapy. Pulmonary events have been observed in studies with single-agent Tarceva and gemcitabine, and neutropenic sepsis and sepsis are consistent with clinical experience with gemcitabine, although sepsis is a common occurrence in patients with pancreatic cancer and bile duct stents.

Table 5–4: Deaths Attributed to Protocol Treatment

Cause of Death	Investigator Causality		Days on Study
	Tarceva (100 mg)	Gemcitabine	
Pneumonitis	Possible	Possible	48
Pneumonitis and progressive disease	Possible	Unrelated	54
Non-neutropenic sepsis	Unrelated	Probable	36
Neutropenic sepsis and progressive disease	Unrelated	Probable	166
CNS bleeding and progressive disease	Possible	Possible	8

Note: No deaths attributed to protocol treatment occurred in the 150 mg cohort

5.2.4.2 Serious Adverse Events

The incidence of serious adverse events regardless of causality in the 100 mg dose cohort (see **Table 5–5**) was higher in the Tarceva arm compared with the placebo arm (51% vs 39%). This imbalance was primarily due to minor differences in the following SOCs: infections and infestations (16% vs 11%); general disorders and administration site conditions (13% vs 10%); respiratory, thoracic, and mediastinal disorders (7% vs 4%), nervous system disorders (4% vs < 1%); hepatic disorders (4% vs 2%); and renal and urinary disorders (2% vs 0%). There was no difference in the incidence of serious adverse events in the gastrointestinal SOC despite the higher incidence of diarrhea observed with Tarceva.

Table 5–5: Study PA.3 Serious Adverse Events Occurring in ≥ 2% of Patients Regardless of Causality – 100 mg Cohort

	Tarceva + Gemcitabine (N=259)						Placebo + Gemcitabine (N=256)					
	Any		1	2	3	4	Any		1	2	3	4
MedDRA System Organ Class Total Preferred Term	**n**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**n**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Total patients with any SAE	131	(51)	(2)	(5)	(28)	(17)	99	(39)	(<1)	(3)	(24)	(11)
Infections and infestations	41	(16)	(0)	(2)	(11)	(3)	29	(11)	(0)	(1)	(8)	(2)
Sepsis	11	(4)	(0)	(0)	(3)	(<1)	5	(2)	(0)	(0)	(1)	(<1)
Pneumonia	10	(4)	(0)	(0)	(3)	(1)	7	(3)	(0)	(<1)	(2)	(<1)
Cellulitis	6	(2)	(0)	(1)	(1)	(0)	0	(0)	(0)	(0)	(0)	(0)
Gastrointestinal disorders	37	(14)	(<1)	(2)	(8)	(3)	35	(14)	(0)	(2)	(9)	(2)
Vomiting	9	(3)	(0)	(2)	(2)	(0)	11	(4)	(0)	(<1)	(4)	(0)
Gastrointestinal haemorrhage	8	(3)	(0)	(0)	(3)	(<1)	7	(3)	(<1)	(0)	(2)	(<1)
General disorders and administration site conditions	33	(13)	(4)	(4)	(3)	(<1)	25	(10)	(3)	(4)	(3)	(<1)
Pyrexia	21	(8)	(4)	(3)	(<1)	(0)	18	(7)	(3)	(2)	(2)	(0)
Fatigue	8	(3)	(0)	(<1)	(2)	(<1)	7	(3)	(<1)	(<1)	(<1)	(<1)
Respiratory, thoracic and mediastinal disorders	17	(7)	(<1)	(<1)	(3)	(3)	11	(4)	(0)	(<1)	(2)	(2)
Pulmonary embolism	6	(2)	(0)	(0)	(<1)	(2)	5	(2)	(0)	(0)	(0)	(2)
Vascular disorders	16	(6)	(0)	(0)	(6)	(0)	14	(5)	(<1)	(<1)	(3)	(2)
Deep vein thrombosis	7	(3)	(0)	(0)	(3)	(0)	3	(1)	(0)	(<1)	(<1)	(0)
Thrombosis	6	(2)	(0)	(0)	(2)	(0)	5	(2)	(0)	(0)	(1)	(<1)

Pneumonitis was reported as a serious adverse event in 4 patients in the Tarceva arm of the 100 mg cohort and 1 patient in the placebo arm of the same cohort, as well as in 1 patient in the Tarceva arm of the 150 mg cohort. One case of lung infiltration also occurred in a patient in the Tarceva arm, in the 100 mg cohort. In addition, 1 patient in the Tarceva arm experienced ARDS, which was not considered serious by the investigator since it was secondary to pneumonia. This results in an incidence of ILD-like serious adverse events of 2.5% (7/282 patients) in the combined Tarceva cohorts and 0.4% (1/280 patients) in the combined placebo cohorts, although the diagnostic validity of some of the cases is questionable. Three of the 7 patients in the Tarceva group died, including the patient with ARDS secondary to pneumonia. The remaining patients recovered including 1 patient who continued Tarceva therapy.

5.2.5 Laboratory Abnormalities

No major imbalance in hematological toxicity was noted between the 2 treatment arms in the 100 mg dose cohort. Grade 3 or 4 neutropenia during study was reported in 24% and 27% of patients in the combined Tarceva and placebo groups, respectively. The worst

hematology laboratory parameter grades experienced across all cycles in the 100 mg cohort are summarized in **Table 5–6**.

Table 5–6: Summary of Worst CTC Grade in All Cycles in 100 mg Cohort for Selected Laboratory Parameters - Hematology

	Tarceva + Gemcitabine (N=259)							Placebo + Gemcitabine (N=256)						
	Any		0	1	2	3	4	Any		0	1	2	3	4
	n	(%)	(%)	(%)	(%)	(%)	(%)	n	(%)	(%)	(%)	(%)	(%)	(%)
WBC	256	(99)	(29)	(23)	(27)	(19)	(<1)	254	(99)	(33)	(20)	(29)	(15)	(2)
Neutrophils	232	(90)	(34)	(10)	(21)	(19)	(5)	226	(88)	(35)	(13)	(14)	(20)	(7)
Platelet Count	255	(98)	(24)	(49)	(14)	(11)	(0)	254	(99)	(22)	(46)	(19)	(11)	(<1)
Hemoglobin	256	(99)	(<1)	(32)	(54)	(11)	(2)	254	(99)	(3)	(38)	(46)	(9)	(3)

The worst clinical chemistry laboratory parameter grades experienced across all cycles in the 100 mg cohort are summarized in **Table 5–7**. Grade 2 ALT elevation was reported in 31% of patients in the Tarceva group and 22% of patients in the placebo group. Grade 3 ALT elevations occurred in 13% and 9% of patients, respectively. In addition, 2 patients in the Tarceva group developed grade 4 ALT toxicity.

Table 5–7: Summary of Worst CTC Grade in All Cycles in 100 mg Cohort for Selected Laboratory Parameters – Clinical Chemistry

	Tarceva + Gemcitabine (N=259)							Placebo + Gemcitabine (N=256)						
	Any		0	1	2	3	4	Any		0	1	2	3	4
	n	(%)	(%)	(%)	(%)	(%)	(%)	n	(%)	(%)	(%)	(%)	(%)	(%)
Total Bilirubin	255	(98)	(50)	(21)	(17)	(10)	(<1)	249	(97)	(61)	(13)	(11)	(10)	(3)
ALT/SGPT	250	(97)	(19)	(33)	(31)	(13)	(<1)	246	(96)	(23)	(42)	(22)	(9)	(0)
AST/SGOT	250	(97)	(16)	(45)	(24)	(10)	(<1)	243	(95)	(23)	(44)	(19)	(9)	(0)
Serum Creatinine	226	(87)	(75)	(9)	(3)	(<1)	(0)	214	(84)	(75)	(7)	(2)	(0)	(0)

5.3 Safety Conclusions

Overall, the results of Study PA.3 showed that Tarceva was well tolerated when administered in combination with gemcitabine in patients with pancreatic cancer. Tolerability of the combination is evidenced by the low percentage of patients in the 100 mg cohort who required either a dose reduction of Tarceva (13%) or who discontinued Tarceva due to toxicity (10%). The 150 mg dose in combination with gemcitabine was less tolerated as indicated by the higher rate of dose reduction as compared to the 100 mg cohort (48%), resulting in a median Tarceva dose intensity of 129 mg/day. As expected, patients treated with Tarceva had a higher incidence of rash and diarrhea than those who received placebo. The majority of the adverse events of rash and diarrhea were mild to moderate in severity. The patients treated with Tarceva had a higher incidence of infections and infestations as well as bleeding events than patients in the placebo arm. None of these events were associated with increased hematologic toxicity in the Tarceva arm compared with the placebo arm.

Although an infrequent event, the incidence of serious ILD-like adverse events in the Tarceva arm (7/282) was higher in Study PA.3 than in previous studies with Tarceva. In fact, in previous randomized studies of either single-agent Tarceva or of Tarceva in combination with chemotherapy, the rate of serious ILD-like events was similar in the Tarceva and in the control arm. In the TALENT study (a large placebo-controlled, phase 3 study investigating the concurrent administration of Tarceva and gemcitabine/cisplatin in 1st-line NSCLC [30]), 1 patient in each treatment group experienced a serious ILD-like event with an overall incidence of both serious and non-serious ILD-like events of 1% in each group. Even though the dose and schedule of gemcitabine were different, as well as the patient population, additive pulmonary toxicity of Tarceva and gemcitabine was not apparent. The weekly x 7 schedule of gemcitabine, however, as well as the dose (1000 mg/m^2) in the current PA.3 study is different than the Day 1 and Day 8 schedule every 3 weeks used in TALENT at a dose of 1250 mg/m^2, which may have made a difference in its potential to interact with Tarceva and cause a higher incidence of ILD-like events.

Overall, the toxicities observed in PA.3 were consistent with those experienced with each agent administered as monotherapy and there were no new or unexpected findings in this study.

6 RISK/BENEFIT DISCUSSION

Tarceva is the first agent administered in combination with gemcitabine to show a statistically significant survival benefit in patients with pancreatic cancer over gemcitabine alone.

The results of Study PA.3 demonstrate that the addition of Tarceva 100 mg daily to standard gemcitabine provides a statistically significant increase in survival to patients with locally advanced or metastatic pancreatic cancer. The adjusted HR for death in the Tarceva arm of the 100 mg cohort relative to the placebo arm estimated from the primary analysis was 0.79 (95% CI 0.66 to 0.96, p = 0.017), indicating that Tarceva plus gemcitabine yielded a 27% improvement in survival and reduced the risk of death by 21% compared with treatment with gemcitabine alone. In the context of advanced metastatic pancreatic cancer, which has such a poor prognosis, this represents an important incremental improvement in survival over the current standard of care. Therefore, the addition of Tarceva to gemcitabine provides a platform for development of innovative strategies to further improve survival in this patient population.

The stratified log rank test used for the primary analysis is a global test that compares the entire survival distributions throughout the period of follow-up. The HR can be considered the average ratio of the risk of dying in the Tarceva group relative to the risk of dying in the placebo group throughout the observation period. Point estimates, such as the median or 1-year survival, are more variable and less stable than the global HR, and may not accurately reflect the treatment benefit throughout the entire observation period.

The survival benefit observed with the combination of Tarceva plus gemcitabine was achieved with an orally administered formulation that, in the context of anti-cancer therapy, requires relatively few dose reductions and discontinuations and is associated with generally manageable adverse events. Treatment with Tarceva 100 mg requires minimal additional clinical laboratory monitoring and is administered as once-a-day tablets. Additionally, there are currently no treatment options available other than gemcitabine monotherapy.

These positive results with Tarceva cannot be attributed to a worse than expected outcome in the placebo arm. Both the median survival and the 1-year survival for the placebo plus gemcitabine arm in Study PA.3 are virtually identical to those published in

the randomized trial of gemcitabine versus 5-FU that led to the approval of the former. The PFS and response rate for gemcitabine are also similar in both trials. The increase in survival of 27% and the reduction in the risk of death of 21% observed in Study PA.3 represents a meaningful benefit for patients with pancreatic cancer. The study outcome was not influenced by subsequent therapy and the secondary clinical endpoint of PFS also showed a statistically significant improvement in favor of Tarceva.

Twenty-five percent (25%) of the patients had interpretable EGFR protein expression results by IHC. Analyses of EGFR expression in Study PA.3 strongly suggests EGFR testing by IHC is not a useful predictive factor for the treatment effect of Tarceva in patients with pancreatic cancer who receive the drug in combination with chemotherapy.

The safety profile of Tarceva in combination with gemcitabine was similar to its safety profile as a single agent. As expected, a higher incidence of rash and diarrhea was observed in the patients in the Tarceva arm compared with those receiving placebo. However, the majority of these cases were mild to moderate in severity. At the dose of Tarceva 100 mg/day, only 13% (compared with 4% for the placebo arm) of the patients required a dose reduction and only 10% of the patients discontinued study drug due to toxicity (compared with 5% for the placebo arm), confirming the tolerability of this treatment regimen in this patient population.

Chemotherapy-induced pulmonary toxicity has been estimated to occur in up to 10% of previously asymptomatic patients [36, 37]. However, the prevalence rises to over 50% in patients with respiratory impairment due to other drugs, radiotherapy, and metastatic lung disease [38, 39]. In an overview of a broad safety experience with gemcitabine, WHO grade 3 and 4 pulmonary toxicities were reported in 3% of the patients [40].

As previously discussed, the imbalance in ILD-like events in the current study might be due to a possible interaction of Tarceva with the different gemcitabine dose and dosing schedule used in pancreatic cancer, as opposed to that used in lung cancer with this agent, which is known to be associated with pulmonary toxicity.

The patients treated with Tarceva had a slightly higher incidence of infections and non-life threatening bleeding than those in the placebo arm. These bleeding events were not associated with thrombocytopenia. A similar observation was made in BR.21. However, when adjusted for the longer time on treatment for patients in the Tarceva arm, these differences were not apparent for most events. Importantly, no increase in the incidence

or severity of hematologic toxicity of gemcitabine was observed in the Tarceva arm compared with the placebo arm.

The results of Study PA.3 should be considered in the context of prior studies conducted in similar patient populations with pancreatic cancer. Gemcitabine received FDA approval in 1996 for the treatment of patients with this disease on the basis of a relatively small, randomized study that showed improved survival and higher clinical benefit response in patients receiving gemcitabine compared with 5-FU. During the 9-year period since the reporting of that study, numerous trials have attempted unsuccessfully to improve on the results of single-agent gemcitabine in patients with pancreatic cancer. These studies have included newer chemotherapy agents or targeted agents. None of these studies have shown a statistically significant improvement in survival with the addition of the newer agent over that achieved with gemcitabine alone.

In conclusion, Tarceva 100 mg/day in combination with gemcitabine prolongs survival and provides meaningful benefit to patients with locally advanced or metastatic pancreatic cancer.

Tarceva represents the first significant advance for the treatment of patients with locally advanced or metastatic pancreatic cancer since the approval of gemcitabine 9 years ago. The summarized data show that Tarceva in combination with gemcitabine provides a new treatment option for these patients.

7 REFERENCES

1 Shepherd FA, Rodrigues PJ, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353(2):123-32.

2 Office of Science Planning and Assessment (OSPA) [homepage]. National Cancer Institute. A Snapshot of Pancreatic Cancer [cited 2005 Jul 29]. Available from: http://prg.nci.nih.gov/snapshots/Pancreatic-Snapshot.pdf.

3 Todd KE, Gloor B, Reber HA. Pancreatic adenocarcinoma. In: Yamada T, Alpers DH, Laine L, Owyang C, Powell DW, editors. Textbook of gastroenterology. 4th ed, v 2. Philadelphia (PA): Lippincott Williams and Wilkins; 2003. p. 2178-93.

4 Levin B. Approach to the patient with a gastrointestinal neoplasm. In: Yamada T, Alpers DH, Laine L, Owyang C, Powell DW, editors. Textbook of gastroenterology. 4th ed, v 1. Philadelphia (PA): Lippincott Williams and Wilkins; 2003. p. 1050-8.

5 Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981; 48(8):1705-10.

6 Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15(6):2403-13.

7 Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, Andre T, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005; 23(15):3509-16.

8 Rocha Lima CM, Green MR, Rotche R, Miller WH, Jeffrey GM, Cisar LA, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 2004; 22(18):3776-83.

9 Richards DA, Kindler HL, Oettle H, Ramanathan R, Van Laethem JL, Peeters M, et al. A randomized phase III study comparing gemcitabine + pemetrexed versus gemcitabine in patients with locally advanced and metastatic pancreas cancer. Proc Am Soc Clin Oncol 2004; 22(14S):15 [Abstract 4007].

10 O'Reilly EM, Abou-Alfa GK, Letourneau R, Harker WG, Modiano M, Hurwitz H, et al. A randomized phase III trial of DX-8951f (exatecan mesylate; DX) and

gemcitabine (GEM) vs. gemcitabine alone in advanced pancreatic cancer (APC). Proc Am Soc Clin Oncol 2004; 22(14S):15 [Abstract 4006].

11 Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schonekas H, Rost A, et al. A phase III trial comparing gemcitabine plus cisplatin vs. gemcitabine alone in advanced pancreatic carcinoma. Proc Am Soc Clin Oncol 2003; 22:250 [Abstract 1003].

12 Herrmann R, Bodoky G, Ruhstaller B, Glimelius P, Saletti E, Bajetta J, et al. Gemcitabine (G) plus capecitabine (C) versus G alone in locally advanced or metastatic pancreatic cancer. A randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group (CECOG). Proc Am Soc Clin Oncol 2005; 23(16S) [Abstract LBA4010]

13 Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. Lancet Oncol. 2005; 6(6):369-76.

14 Riess H, Helm A, Niedergethmann M, Schmidt-Wolf I, Moik M, Hammer C, et al. A randomised, prospective, multicenter, phase III trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs. gemcitabine alone in patients with advanced pancreatic cancer. Proc Am Soc Clin Oncol 2005; 23(16S) [Abstract LBA4009]

15 Moore MJ, Hamm J, Dancey J, Eisenberg PD, Dagenais M, Fields A, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2003; 21(17):3296-302.

16 Van Cutsem E, van de Velde H, Karasek P, Oettle H, Vervenne WL, Szawlowski A, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol 2004; 22(8):1430-8.

17 Bramhall SR, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JA. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. Br J Cancer 2002; 87(2):161-7.

18 Bramhall SR, Rosemurgy A, Brown PD, Bowry C, Buckels JAC. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. J Clin Oncol 2001; 15(19):3447-55.

19 Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001; 2(2):127-37.

20 Fujino S, Enokibori T, Tezuka N, Asada Y, Inoue S, Kato H, et al. A comparison of epidermal growth factor receptor levels and other prognostic parameters in non-small cell lung cancer. Eur J Cancer 1996; 32A(12):2070-4.

21 Rusch V, Klimstra D, Venkatraman E, Pisters PW, Langenfeld J, Dmitrovsky E. Overexpression of the epidermal growth factor receptor and its ligand transforming growth factor alpha is frequent in resectable non-small cell lung cancer but does not predict tumor progression. Clin Cancer Res 1997; 3(4):515-22.

22 Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 1995; 19(3):183-232.

23 Uegaki K, Nio Y, Inoue Y, Minari Y, Sato Y, Song MM, et al. Clinicopathological significance of epidermal growth factor and its receptor in human pancreatic cancer. Anticancer Res 1997; 17(5B):3841-7.

24 Friess H, Wang L, Zhu Z, Gerber R, Schroder M, Fukuda A, et al. Growth factor receptors are differentially expressed in cancers of the papilla of vater and pancreas. Ann Surg 1999; 230(6):767-74.

25 Wagner M, Cao T, Lopez ME, Hope C, van Nostrand K, Kobrin MS, et al. Expression of a truncated EGF receptor is associated with inhibition of pancreatic cancer cell growth and enhanced sensitivity to cisplatinum. Int J Cancer 1996; 68(6):782-7.

26 Bleday R, Tzanakakis GN, Schwalke MA, Wanebo HJ, Vezeridis MP. Epidermal growth factor stimulation and metastatic rate in human pancreatic carcinoma cell lines. J Surg Res 1990; 49(3):276-9.

27 Ohlsson B, Jansen C, Ihse I, Axelson J. Epidermal growth factor induces cell proliferation in mouse pancreas and salivary glands. Pancreas 1997; 14(1):94-8.

28 Yamanaka Y, Friess H, Kobrin MS, Buchler M, Beger HG, Korc M. Coexpression of epidermal growth factor receptor and ligands in human pancreatic cancer is associated with enhanced tumor aggressiveness. Anticancer Res 1993; 13(3):565-9.

29 Bruns CJ, Solorzano CC, Harbison MT, Ozawa S, Tsan R, Fan D, et al. Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. Cancer Res 2000; 60(11):2926-35.

30 Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, Brennscheidt U, et al. Results of a phase III trial of erlotinib (OSI-774) combined with cisplatin and gemcitabine (GC) chemotherapy in advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2004; 23:617 [Abstract 7010].

31 Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005; 23(25):*Published ahead of print*.

32 Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1. J Clin Oncol 2004; 22(5):777-84.

33 Anderson GL, LeBlanc M, Liu PY, Crowley J. On use of covariates in randomization and analysis of clinical trials. In: Crowley J, Pauler, editors. The handbook of statistics in clinical oncology. 2nd ed. Boca Raton: CRC Press; In press 2005.

34 Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, et al. Severe acute interstitial pneumonia and gefitinib. Lancet 2003; 361(9352):137-139.

35 Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD, Morse D, et al. United States Food and Drug Administration Drug Approval summary: Gefitinib (ZD1839; Iressa) tablets. Clin Cancer Res 2004; 10(4):1212-8.

36 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002; 165(2):277-304.

37 Erasmus JJ, McAdams HP, Rossi SE. Drug-induced lung injury. Semin Roentgenol 2002; 37(1):72-81.

38 Limper AH, Rosenow EC. Drug-induced interstitial lung disease. Curr Opin Pulm Med 1996; 2(5):396-404.

39 Abid SH, Malhotra V, Perry MC. Radiation-induced and chemotherapy-induced pulmonary injury. Curr Opin Oncol 2001; 13(4):242-8.

40 Aapro MS, Martin C, Hatty S. Gemcitabine--a safety review. Anticancer Drugs 1998; 9(3):191-201.

8 APPENDICES

8.1 Summary of Postmarketing Clinical Study Commitments - Tarceva NSCLC

Table 8–1: Postmarketing Clinical Study Commitments

Study	Regimen	N
Non-Small Cell Lung Cancer		
BO 18192-A - A multicentre, double-blind randomised, phase III study to evaluate the efficacy of Tarceva or placebo following 4 cycles of platinum-based chemotherapy in patients with histologically documented advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) who have not experienced disease progression or unacceptable toxicity during chemotherapy. (Ongoing)	Erlotinib/placebo 150mg/day	854
BO 18602-A - A multicentre, open-label, randomized, phase III study to evaluate the efficacy of Tarceva™ or comparator Alimta® (pemetrexed) or Taxotere® (docetaxel) in patients with histologically documented, advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) non-small cell lung cancer who have experienced disease progression during platinum-based chemotherapy. (Ongoing)	Erlotinib 150mg/day. Alimta® (pemetrexed) 500mg/m^2 every 3 weeks or Taxotere® (docetaxel) 75mg/m^2 every 3 weeks	648
OSI-774-104 An Open-Label Study to Characterize the pharmacokinetic Parameters of Erlotinib (Tarceva™, OSI-774) in Cancer Patients with Advanced Solid Tumors with Adequate and Moderately Impaired Hepatic Function. (Ongoing)	150 mg dose of erlotinib	42
OSI-774-105 An Open-Label Study to Characterize the Effect of Dose Adjustment on the Pharmacokinetics of Oral Erlotinib in Healthy Male Subjects Following and During the Administration of Rifampicin. (Ongoing)	Erlotinib administered on Day 1 (150 mg) and Day 15 (450 mg). Rifampicin (600 mg) will be administered once daily on Days 8 – 18.	18

8.2 Overview of Phase 2 and Phase 3 Studies of Tarceva in Solid Tumors

Note: As reported in the Tarceva Investigator's Brochure, 9th Edition, dated 4 April 2005

Table 8–2: Overview of Phase 2 and 3 Studies of Tarceva in Solid Tumors

Study (Status)	Regimen	N
Non-Small Cell Lung Cancer		
A248-1007 - A Phase II Multicenter Open-Label Trial of OSI-774 Following Failure of Platinum Based Combination Chemotherapy in Subjects with Advanced Non-Small Cell Lung Cancer (Completed)	Erlotinib 150 mg QD	57
BR.21 - A Randomized Placebo Controlled Study of OSI-774 (Tarceva™) in Patients with Incurable Stage IIIB/IV Non-Small Cell Lung Cancer Who Have Failed Standard Therapy for Advanced or Metastatic Disease (Completed)	Erlotinib/placebo 150 mg QD	731
BO16411 - A Randomized, Double-Blind, Placebo Controlled, Multicenter, Phase III Study of Tarceva Plus Chemotherapy (Cisplatin and Gemcitabine) Versus Chemotherapy Alone in Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) Who Have Not Received Prior Chemotherapy (Completed)	Erlotinib 150 mg/day + gemcitabine 1250 mg/m^2 on Days 1, 8 q21d + cisplatin 80 mg/m^2 on Day 1 q21d	1172
OSI2298g - A Phase III Randomized Double-blind, Multicenter Trial of OSI-774 Plus Chemotherapy (Carboplatin and Paclitaxel) Versus Chemotherapy Alone in Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer Who Have Not Received Prior Chemotherapy (Completed)	Erlotinib/placebo 150 mg QD + paclitaxel 200 mg/m^2 IV and carboplatin AUC 6 IV Day 1 q21d for up to 6 cycles	1079
OSI3199g – A Multicenter, Open-label, Phase IIIb Trial of Tarceva™ (Erlotinib Hydrochloride) in Patients with Advanced Non–Small Cell Lung Cancer (Enrollment complete, study ongoing)	Erlotinib 150 mg QD	233

Table 8–2: Overview of Phase 2 and 3 Studies of Tarceva in Solid Tumors

Study (Status)	Regimen	N
MO18109/MO18424 – An Expanded Access Program of Tarceva™ (Erlotinib) in Patients with Advanced Stage IIIB/ IV Non-Small Cell Lung Cancer (NSCLC) (Enrollment ongoing)	Erlotinib 150 mg QD	523
MO17426 – A Phase II Study of TarcevaTM (Erlotinib) in Patients with Locally Advanced and/or Metastatic (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) who Have Not Received Prior Chemotherapy (Enrollment complete)	Erlotinib 150 mg QD	54
OSI2950g - A Phase II, Multicenter, Randomized Clinical Trial to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy (Docetaxel or Pemetrexed) or Tarceva™ (Erlotinib) Compared with Chemotherapy (Docetaxel or Pemetrexed) Alone for Treatment of Recurrent or Refractory Non–Small Cell Lung Cancer (Enrollment ongoing)	Erlotinib 150 mg QD Bevacizumab 15 mg/kg q 21 days	31
ML17915 – An Open, Non-randomized, Phase II Trial of the Efficacy and Safety of Tarceva (Erlotinib) in Monotherapy for Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) (Enrollment ongoing)	Erlotinib 150 mg QD	700
OSI-774-201 – A Randomized Phase II Study of Single Agent Erlotinib (Tarceva™, OSI-774) versus Standard Chemotherapy in Patients with Previously Untreated Advanced NSCLC and a Poor Performance Status (Enrollment ongoing)	Erlotinib (E) 150 mg QD *vs.* Paclitaxel (P) 200 mg/m^2 + Carboplatin (C) AUC 6 day 1 q 21 days x 4 cycles	54
OSI-774-202 - A Phase II Multicenter, Open-Label Intrapatient Dose-Escalation Study of Erlotinib in Patients with Advanced Non-Small Cell Cancer Who Have Failed Prior Chemotherapy (Enrollment ongoing)	Erlotinib 150 mg QD for 21 days followed by dose escalations every two weeks as tolerated (first escalation to 200 mg with subsequent increases in 25 mg increments)	29
JO16565 – A Phase II Study, Multicenter, Open Label Trial of Ro50-8231 (erlotinib) in Patients with Advanced Non-Small Cell Lung Cancer (Enrollment ongoing)	Erlotinib 150 mg QD	62
JO17134 – Consecutive Treatment Study of Ro50-8231 (erlotinib) in Patients with Solid Tumors (JO17134) (Extension of JO16565, enrollment complete)	Erlotinib 150 mg QD	3
Pancreatic Cancer		
PA.3 - A Randomized Placebo Controlled Study of OSI-774 (Tarceva™) Plus Gemcitabine in Patients with Locally Advanced, Unresectable or Metastatic Pancreatic Cancer (Completed)	Erlotinib/placebo 100 or 150 mg QD + gemcitabine 1000 mg/m^2 IV for 7 of 8 wks, then for 3 of 4 wks	569
Breast Cancer		
OSI2288g - A Phase II Multicenter, Open-Label Trial of OSI-774 in Patients with Advanced or Metastatic Breast Cancer and Disease Progression During or Following Chemotherapy (Completed)	Erlotinib 150 mg QD	68

Table 8–2: Overview of Phase 2 and 3 Studies of Tarceva in Solid Tumors

Study (Status)	Regimen	N
Ovarian Cancer		
A248-101 - A Phase II Multicenter, Open-Label Study of OSI-774 in Patients with Advanced Cancer of the Ovary (Completed)	Erlotinib 150 mg QD	34
Head and Neck Cancer		
A248-1003 -A Phase II Multicenter, Open-Label Study of OSI-774 Therapy in Patients with Advanced Squamous Cell Cancer of the Head & Neck (Completed) Extension study (Completed)	Erlotinib 150 mg QD	115 23
Glioma		
OSI2691g – A Phase II Multicenter, Open-Label Study of OSI-774 Therapy in patients with first relapse of Grade IV glioma (Enrollment complete, study ongoing)	Erlotinib 150 mg PO QD for patients not taking EIAEDs followed by planned dose escalation in response to CTC grade rash Erlotinib 300 mg PO QD for patients taking EIAEDs followed by planned dose escalation in response to CTC grade rash	48
BO17884 - A Phase II, Multicenter, Randomized, Open-Label Trial to Evaluate the Efficacy and Safety of Tarceva versus Temozolomide in Patients with Recurrent Glioblastoma Multiforme (Enrollment ongoing)	Erlotinib 150 mg QD for patients not taking EIAEDs, 300 mg QD for patients taking EIAEDs Temozolomide 150 mg/m^2 on Days 1-5 of 28-day cycle, to be increased to 200 mg/m^2 if no toxicity (CTCAE < 2) seen in Cycle 1	29
Other Studies		
AVF2938g – A Phase II, Multicenter, Randomized, Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of Erlotinib in Combination with Bevacizumab Versus Bevacizumab Alone for Treatment of Metastatic Renal Cell Carcinoma (Enrollment complete, study ongoing)	Erlotinib 150 mg QD Bevacizumab 15 mg/kg q 21 days	100
A248-1006 - A Phase II Single Center, Open-Label Methodology Study Evaluating ^{18}F-Fluorothymidine Positron Emission Tomography in Patients with Advanced Cancer Receiving OSI-774 (Completed)	Erlotinib 150 mg QD	9
OSI-774-DMS-D0003 - A Phase II, Open-Label, Single-Site Clinical and Pharmacologic Study of OSI-774 in Cancers of the Aerodigestive Tract (Completed)	Erlotinib 150 mg QD for 7 - 9 days	4

8.3 Summary of Changes to Study PA.3 Protocol

Table 8–3: Summary of Changes to the Protocol

Type [Date]	Changes Made	Rationale
Revision 1 [28 AUG 2001]	NCIC CTG contact information revised.	To change trial contacts. No patients had been enrolled at the time of this revision.
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.
	Changed the initial sample size for collection of drug delivery and toxicity information from 16-20 patients to 8-16 patients.	No patients had been enrolled at the time of this revision.

Table 8–3: Summary of Changes to the Protocol

Type [Date]	Changes Made	Rationale
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/m^2 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/m^2 gemcitabine 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 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.	
	NCIC CTG contacts changed.	To change trial contacts.

Table 8–3: Summary of Changes to the Protocol

Type [Date]	Changes Made	Rationale
	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.
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.