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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-743/SE1-003
Drug Name:	Erlotinib (OSI-774, Tarceva)
Indication(s):	Treatment of Patients with Advanced, Unresectable or Metastatic Pancreatic Cancer
Applicant:	OSI Pharmaceuticals, Inc.
Date(s):	Date of receipt: May 2, 2005
Action Goal Date:	November 2, 2005
Review Priority:	Priority
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Keywords: Log rank test, Cox regression, subgroup analysis, survival analysis.

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Erlotinib, together with gemcitabine, significantly reduced the risk of all-cause mortality when compared with placebo plus gemcitabine in patients with locally advanced, unresectable or metastatic pancreatic cancer. The adjusted estimated hazard ratio of death for erlotinib plus gemcitabine relative to placebo plus gemcitabine was 0.79 (95% CI (0.65, 0.95)) with p-value = 0.017 for the 100 mg cohort. It seemed that it also prolonged the disease progression free survival in this patient population. Whether the observed magnitude of effect is adequate is a clinical decision. This application will be discussed at the Oncology Drugs Advisory Committee (ODAC) on September 13, 2005.

1.2 Brief Overview of Clinical Studies

The Sponsor submitted this application based on the results of their PA.3 study. This study was a randomized, double-blind, Phase 3 study of erlotinib or placebo plus gemcitabine in patients with locally advanced, unresectable or metastatic pancreatic cancer. A total of 569 patients were randomized in a 1:1 ratio into erlotinib group (n = 285, 261 at 100 mg dose and 24 at 150 mg dose) or placebo group (n = 284, 260 at 100 mg dose and 24 at 150 mg dose). Among the 140 sites used for patient enrollment, 59 sites were in the US, 25 sites were in Canada and the rest were in other countries. For each patient, treatment could continue daily until progressive disease (PD) or unacceptable toxicity. Erlotinib/placebo and/or gemcitabine could be withheld or reduced for toxicity. Intra-patient dose escalation was not permitted for erlotinib/placebo but was permitted for gemcitabine. The study was conducted from November 2001 to September 2004.

1.3 Statistical Issues and Findings

The protocol required 381 deaths for the final analysis based on the sample size calculation. According to the Sponsor, prior to unblinding, a field cut-off date was to be made of when this number of events would be reached. However, a total of 485 (444 in the 100 mg cohort) deaths actually occurred when the field cut-off date was reached. The main results were based on the data when 485 deaths occurred. As sensitivity analyses, the overall survival was also analyzed after 381 deaths and based on the data updated until July 8, 2005 (551 deaths). The estimates for the hazard ratios were very similar in these analyses, with the adjusted hazard ratio (HR) = 0.81 (adjusted nominal p-value = 0.055) for the data after 381 deaths occurred and the adjusted hazard ratio = 0.81 (adjusted nominal p-value = 0.028) for the data updated until July 8, 2005.

Log-rank test was originally specified for the main analysis of the overall survival stratified by Eastern Cooperative Oncology Group (ECOG) performance status, extent of disease and pain score. Per discussion with the Agency, agreement was reached that the pain score would be

omitted from the analysis since it was not a randomized stratification factor. A sensitivity analysis was conducted with pain score included, and the results were similar with nominal p-value = 0.050 (HR= 0.81) for the 100 mg dose group.

The Kaplan-Meier curve for the survival of the erlotinib group was better than the placebo group. However, the estimated median overall survival was 6.47 months compared with 5.95 months in the placebo group in the 100 mg dose cohort. This was only 8.7% increase in the median survival time with about 2-week prolongation. Based on the Kaplan-Meier survival curves, the two curves narrowed at the median time.

In summary, statistical significance was achieved for overall survival. It seemed that erlotinib significantly prolonged the progression free survival as well, with estimated hazard ratio = 0.76 (95% CI (0.64, 0.92)) and nominal p-value = 0.006.

At this time, the clinical reviewer and the sponsor disagree on the diagnosis of pancreatic cancer at study entry for some patients. After reaching further discussions and consensus, updated analysis may be presented at the ODAC meeting.

2 INTRODUCTION

2.1 Overview

After conducting the current PA.3 study, the Sponsor submitted this efficacy supplement application based on the results from this trial. In this submission, the Sponsor is seeking the indication that erlotinib in combination with gemcitabine significantly increase the survival and delay disease progression relative to gemcitabine alone in patients with locally advanced, unresectable or metastatic pancreatic cancer who did not receive prior cytotoxic therapy for this disease.

2.1.1 HISTORY OF DRUG DEVELOPMENT

Erlotinib was approved in the US on November 18, 2004 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. Two other randomized, double-blind, placebo-controlled Phase 3 trials (TRIBUTE and TALENT) have investigated erlotinib in combination with standard chemotherapy as first-line treatment for patients with advanced NSCLC. Both trials failed to meet their endpoints, showing that erlotinib does not prolong survival when given concurrently with chemotherapy in this patient population.

2.1.2 SPECIFIC STUDIES REVIEWED

The PA.3 study is fully reviewed. The Sponsor is seeking the indications based on the results of this study.

2.1.3 MAJOR STATISTICAL ISSUES

It was specified in the protocol that the final analysis would be conducted after 381 deaths occurred. The Sponsor stated that prior to unblinding, a projection for the field cut-off date was made when 381 deaths would be observed. However, the death rate was underestimated and a total of 485 (444 in the 100 mg cohort) deaths were observed when the field cut-off date was reached. As a result, a sensitivity analysis would be conducted based on the data after 381 deaths occurred. In addition, when the database was locked, 85 of the 569 patients were thought to be alive or lost to follow-up. The Agency asked the Sponsor to update the database after the sNDA submission. The database was updated until July 8, 2005. A total of 551 patients were known to be dead, and 18 patients were thought to be alive at last follow-up. Sensitivity analyses were also conducted based on the updated data.

The main analysis for the primary endpoint (overall survival) was specified to be conducted by the log-rank test stratified by ECOG performance status, extent of disease and pain score at randomization. Per discussion with the Agency, agreement was reached that the pain score would be omitted from the analysis since it was not a randomized stratification factor. Another sensitivity analysis was conducted with the pain score as a stratification factor.

2.2 Data Sources

The materials submitted electronically are located at \\cdsesub1\n21743\S_003. The study report was fully reviewed. The main analyses were independently performed and verified by this reviewer. SAS data sets are located at \\cdsesub1\n21743\S_003\2005-04-29\crt\datasets\PA3.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY DESIGN AND ENDPOINT

This was a randomized, double-blind, placebo-controlled Phase 3 study of erlotinib or placebo plus gemcitabine in patients with locally advanced, unresectable or metastatic pancreatic cancer. A total of 569 pateints were randomized in a 1:1 ratio into erlotinib group (n = 285, 261 at 100 mg dose and 24 at 150 mg dose) or placebo group (n = 284, 260 at 100 mg dose and 24 at 150 mg dose). Among the 140 sites used for patient enrollment, 59 sites were in the US, 25 sites

were in Canada and the rest were in other countries. For each patient, treatment could continue daily until progressive disease (PD) or unacceptable toxicity. Erlotinib/placebo and/or gemcitabine could be withheld or reduced for toxicity. Intra-patient dose escalation was not permitted for erlotinib/placebo but was permitted for gemcitabine. The study was to continue until 381 patients reached the primary endpoint. The first patient was randomized on November 29, 2001 and the last patient was randomized on January 31, 2003. The field cut-off sate was January 15, 2004 and the database was locked on September 17, 2004. The database was updated for the overall survival until July 8, 2005 per the Agency's request. When the database was updated, 551 deaths occurred and 18 patients were thought to be alive at the last follow-up.

The primary endpoint was time from randomization to death due to any cause. Secondary endpoints were

1. Progression free survival (time from randomization to the first observation of disease progression or death due to any cause)
2. Tumor response (determined by using RECIST (Response Evaluation Criteria in Solid Tumors) criteria)
3. Response rate (calculated as the number of responders (complete responders (CR) + partial responders (PR)) divided by all patients who are evaluable for RECIST response)
4. Duration of response (measured as the time that criteria for CR/PR are first met until the first date that recurrent or progressive disease or death was objectively documented)
5. Quality of life (QoL, assessed by the EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30)

3.1.2 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Three patients were declared lost to follow-up: 2 patients in the erlotinib group and 1 patient in the placebo group. Table 1 is the summary of the reasons for treatment discontinuation. Patients who discontinued treatment were followed 4 weeks post-treatment and every 12 weeks thereafter until death. It seems that there was no significant difference between the treatment groups in the number of patients who discontinued. The majority of treatment discontinuations were due to PD or symptomatic progression. Ten percent of the patients discontinued due to toxicity related to protocol therapy in the erlotinib group compared with 6% in the placebo group.

Table 1. Summary of Reasons for Discontinuation

		Erlotinib+Gemcitabine			Placebo+Gemitabine		
	Dose	N	n	(%)	N	n	(%)
Patients Never Treated	All	285	3	(1)	284	4	(1)
	100mg	261	2	(<1)	260	4	(2)
	150mg	24	1	(4)	24	0	(0)
Patients off erlotinib	All	285	272	(95)	284	276	(97)
	100mg	261	251	(96)	260	252	(97)

	150mg	24	21	(88)	24	24	(100)
Reasons off erlotinib							
Progressive disease	All	285	133	(47)	284	163	(57)
	100mg	261	121	(46)	260	149	(57)
	150mg	24	12	(50)	24	14	(58)
Symptomatic progression	All	285	42	(15)	284	38	(13)
	100mg	261	41	(16)	260	36	(14)
	150mg	24	1	(4)	24	2	(8)
Intercurrent illness	All	285	12	(4)	284	10	(4)
	100mg	261	10	(4)	260	10	(4)
	150mg	24	2	(8)	24	0	(0)
Toxicity to protocol therapy	All	285	29	(10)	284	16	(6)
	100mg	261	27	(10)	260	13	(5)
	150mg	24	2	(8)	24	3	(13)
Patient refusal	All	285	24	(8)	284	17	(6)
	100mg	261	21	(8)	260	15	(6)
	150mg	24	3	(13)	24	2	(8)
Death	All	285	26	(9)	284	23	(8)
	100mg	261	25	(10)	260	21	(8)
	150mg	24	1	(4)	24	2	(8)
Other	All	285	6	(2)	284	9	(3)
	100mg	261	6	(2)	260	8	(3)
	150mg	24	0	(0)	24	1	(4)
Not off erlotinib	All	285	10	(4)	284	4	(1)
	100mg	261	8	(3)	260	4	(2)
	150mg	24	2	(8)	24	0	(0)

Source: Table 10-4 of the Sponsor's final clinical study report PA.3.

Table 2 summarizes baseline characteristics by treatment group in all patients and the 100 mg dose cohort. It appears that it was comparable between the two groups for the listed variables.

Table 2. Summary of Baseline Characteristics

	All patients		100 mg dose group	
	Erlotinib N = 285	Placebo N = 284	Erlotinib N = 261	Placebo N = 260
Characteristics	n (%)	n (%)	n (%)	n (%)
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 (1)
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)
Oriental	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)
ECOG performance status				
0	85 (30)	85 (30)	82 (31)	83 (32)
1	145 (51)	147 (52)	134 (51)	132 (51)
2	54 (19)	52 (18)	44 (17)	45 (17)
Unknown	1 (<1)	0 (0)	1 (<1)	0 (0)
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)
Age (Years)				
Median	63	64	64	63
Range	37 - 84	36 - 92	37 - 84	36 - 92
Pain intensity score				
n	276	278	252	254
Median	21	23	22	22
Range	0 - 100	0 - 100	0 - 100	0 - 100

Source: Tables 11-1, 11-2, 11-3 and 11-4 of the Sponsor's final clinical study report PA.3.

Table 3 summarizes baseline disease characteristics by treatment groups for all patients and for the 100 mg cohort. It appears that it was balanced between the two treatment groups for the disease status at baseline.

Table 3. Summary of Baseline Disease Characteristics

	All patients		100 mg dose group	
	Erlotinib N = 285	Placebo N = 284	Erlotinib N = 261	Placebo N = 260
	n (%)	n (%)	n (%)	n (%)
Specimen type				
Histological	187 (66)	175 (62)	173 (66)	160 (62)
Cytological	96 (34)	107 (38)	86 (33)	98 (62)
Missing	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Extent of disease at first diagnosis				
Resectable	21 (7)	29 (10)	19 (7)	21 (8)
Locally advanced/unresectable	84 (29)	87 (31)	75 (29)	81 (31)
Metastatic	180 (63)	168 (59)	167 (64)	158 (61)
Disease status at baseline				

Locally advanced	67 (24)	71 (25)	61 (23)	63 (24)
Distant metastasis	218 (76)	213 (75)	200 (77)	197 (76)
Time from initial diagnosis to randomization in months				
<6	264 (93)	253 (89)	242 (93)	237 (91)
6 - 12	12 (4)	19 (7)	12 (5)	14 (5)
>12	9 (3)	12 (4)	7 (3)	9 (3)
Median	1.1	1.0	1.0	1.0
Range	0.1 – 33.2	0.1 – 42.7	0.1 – 31.4	0.1 – 42.7

Source: Tables 11-11, 11-12, 11-13 and 11-14 of the Sponsor's final clinical study report PA.3.

3.1.3 STATISTICAL METHODOLOGIES

The primary endpoint, overall survival, was analyzed using the stratified log-rank test. Locally advanced versus distant metastases and performance status (ECOG 0, 1 versus 2) at randomization were included as strata. Kaplan-Meier curves of survival in each treatment arm were constructed, and 95% confidence intervals for the median survivals were computed. The primary analysis was conducted in the intent-to-treat population, which included all randomized patients. Patients who were alive at the final analysis were censored at their last contact date. The hazard ratio and its 95% CI were obtained from a Cox proportional hazards model, with the same stratification factors that were included in the stratified log rank test. Other time-to-event variables were analyzed in the way similar to the primary endpoint. Tumor responses (CR+PR vs. other) were summarized in frequency tables. The comparison of response rate was done using a Cochran-Mentel-Haenszel (CMH) test stratified for ECOG performance status, extent of the disease. The analyses of the QoL variables were exploratory. The QoL data were collected by EORTC QLQ-C30. The scores were normalized to 0 – 100 range. The mean and standard deviation of QoL scores at baseline and mean and standard deviation of QoL change scores from baseline at each assessment time were calculated. Then the Wilcoxon rank-sum test was used to compare two treatment groups at each assessment time. QoL response was calculated for a function domain as follows: a change score of 10 points from baseline was defined as clinically relevant. Patients were considered improved if reported a score 10-point or better than baseline at any time of QoL assessment. Conversely, patients were considered worsened if reported a minus score 10-points or worse than baseline at any time of QoL assessment without previously specified improvement. Otherwise, patients were considered as stable. Chi-square test was used to compare the distributions of these 3 categories between the two groups.

3.1.4 RESULTS AND CONCLUSION

Overall Survival:

Table 4 presents the results for the analysis of the primary endpoint in all patients and the 100 mg dose cohort. For all patients, the hazard ratio for death was 0.78 for erlotinib relative to

placebo (95% CI (0.65 – 0.93)) with p-value = 0.011. The hazard ratio for death was 0.79 in the 100 mg dose cohort for erlotinib relative to placebo (95% CI (0.65 – 0.95)) with p-value = 0.017. Other supportive analyses seemed to confirm the main analysis results. It should be noted that when the analyses were conducted without stratification, the p-values were 0.034 and 0.046 for all patients and 100 mg dose cohort, respectively.

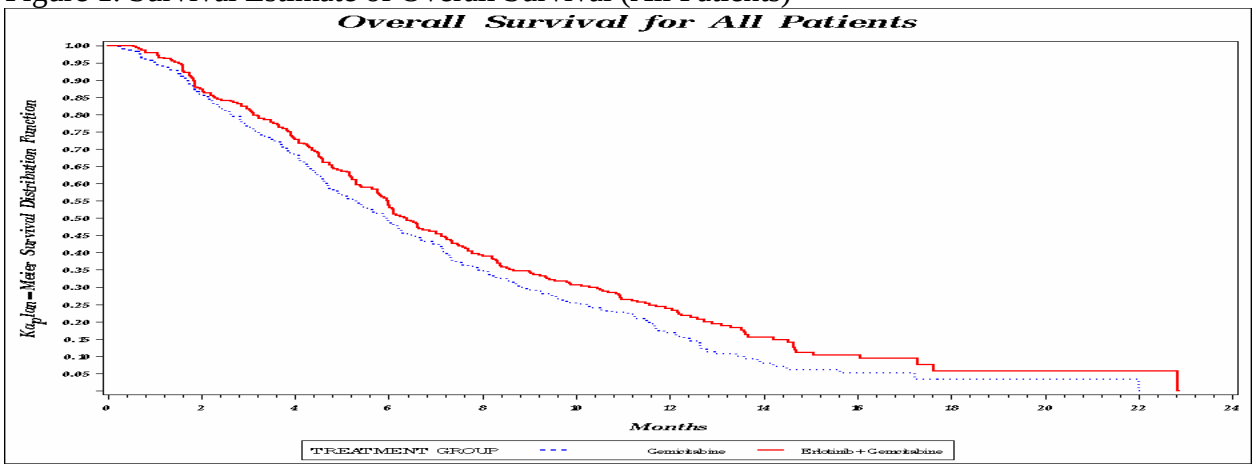
Table 4. Analyses of the Primary Endpoint

		Univariate Analysis				Multivariate Analysis[1]		
Treatment/Stratification Factors	N	Median Survival (Month)	Hazard Ratio	95% CI	Log_ Rank P-value	Hazard Ratio	95% CI	Cox P-value
All patients								
Treatment								**0.011***
Placebo	284	5.91	0.82	(0.69,0.99)	0.034	0.78	(0.65-0.93)	0.007
Erlotinib	285	6.37						
ECOG performance Status								
0-1	464	6.60	1.77	(1.42-2.21)	<0.001	1.83	(1.47-2.29)	<0.001
2	105	4.21						
Disease Status								
Locally advanced	167	8.21	1.62	(1.32-1.98)	<0.001	1.62	(1.32-1.98)	<0.001
Distant Metastasis	402	5.62						
100 mg dose cohort								
Treatment								**0.017***
Placebo	260	5.95	0.83	(0.69-1.00)	0.046	0.79	(0.65-0.95)	0.014
Erlotinib	261	6.47						
ECOG performance Status								
0-1	433	6.60	1.75	(1.38-2.22)	<0.001	1.79	(1.41-2.28)	<0.001
2	88	4.21						
Disease Status								
Locally advanced	152	7.79	1.47	(1.19-1.82)	<0.001	1.47	(1.19-1.82)	<0.001
Distant Metastasis	369	5.72						

Source: Tables 11-21 and 11-22 of the Sponsor's final clinical study report PA.3. Hazard ratios, 95% CIs and p-values were from Cox regression models. Univariate analysis used only treatment as the independent variable, while multivariate analysis used ECOG performance status and disease status as independent variables. *p-value was from stratified log-rank test with ECOG performance status and disease status as stratification variables. Results were independently confirmed by this reviewer. [1]: Protocol specified analysis

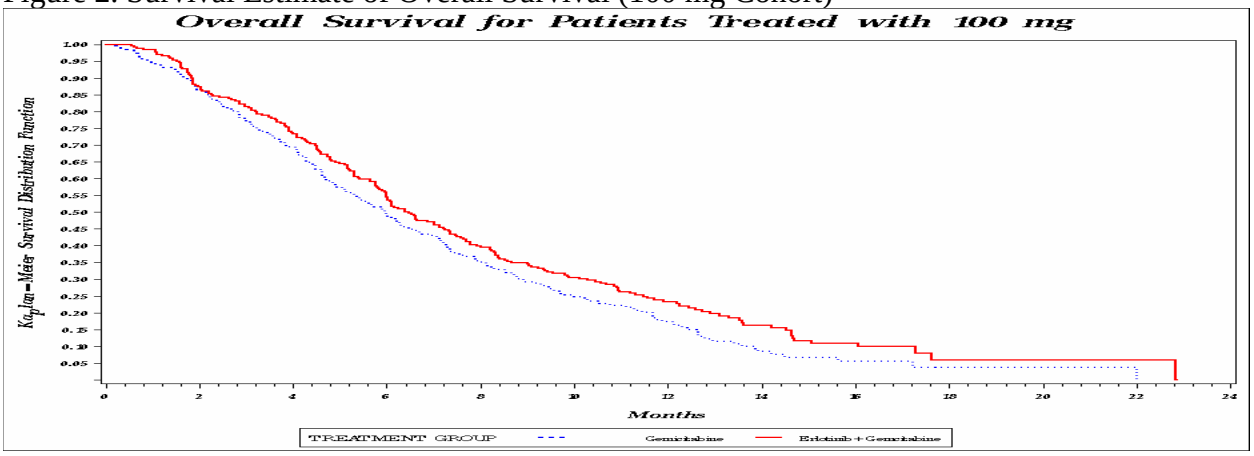
Figures 1 and 2 are the Kaplan-Meier estimates for the overall survival for all patients and the 100 mg dose cohort, respectively. For the 100 mg cohort, the estimated median overall survival was 6.47 months in the erlotinib group compared with 5.95 months in the placebo group. At the 75th percentile time, the estimated overall survival was 11.47 months and 9.99 months for erlotinib group and placebo group, respectively.

Figure 1. Survival Estimate of Overall Survival (All Patients)



Source: Reviewer's analysis.

Figure 2. Survival Estimate of Overall Survival (100 mg Cohort)



Source: Reviewer's analysis.

Table 5 summarizes the analysis for overall survival including the pain score as one of the stratification variables. There were 15 patients (all in the 100 mg dose cohort) with pain score missing and these patients were excluded from the analysis. It can be seen that the estimates of hazard ratios were similar as in the analyses without pain score. The nominal p-values were larger but still less or equal to 0.05.

Table 5. Analyses of the Primary Endpoint Including Pain Score

	All patients					**100 mg dose cohort**				
Treatment	N	HR	95% CI	Cox P-value	Log Rank P-value	N	HR	95% CI	Cox P-value	Log Rank P-value
Erlotinib	276	0.80	(0.67,0.96)	0.017	0.035	252	0.81	(0.67, 0.98)	0.031	0.050
Placebo	278					254				

Source: Reviewer's analysis. HR: hazard ratio of erlotinib over placebo. Log rank p-value was from stratified log-rank test with ECOG performance status, disease status and pain score (>20 or <=20) as stratification variables.

Patients with pain score missing were excluded from the analyses. HR, 95% CI, Cox p-value were from a Cox regression model with treatment, ECOG performance status, disease status and pain score (>20 or <=20) as independent variables.

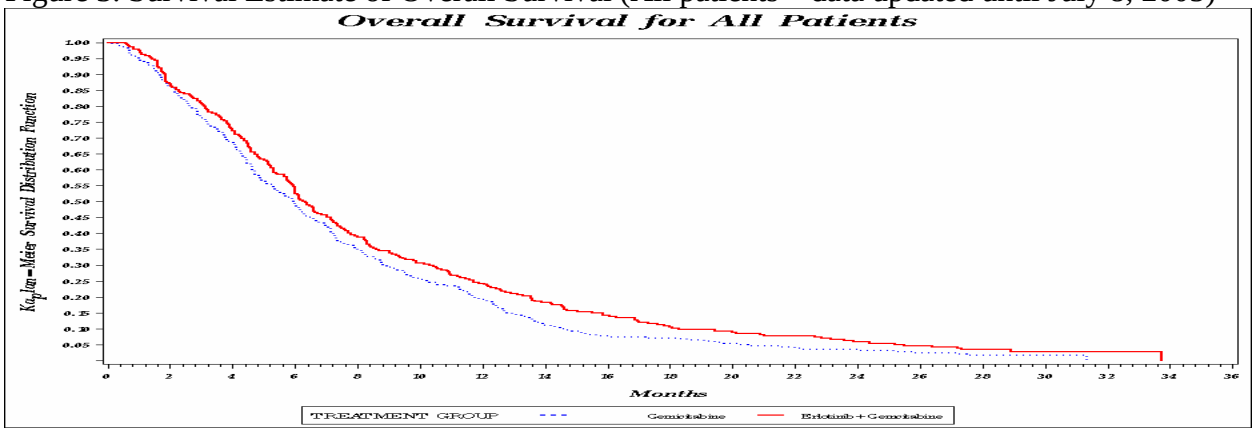
The original database of this sNDA was locked on September 17, 2004. On that date, 85 patients were thought to be alive or lost to follow-up. The Agency requested that the database be updated for the 85 patients. The Sponsor updated the database until July 8, 2005. Table 6 summarizes the results for the analysis of the primary endpoint based on the updated data. Figures 3 and 4 are the Kaplan-Meier estimates for the overall survival for all patients and the 100 mg dose cohort for the updated data, respectively. The results were similar to those in Table 4.

Table 6. Analyses of the Primary Endpoint (Based on the Data Updated Until July 8, 2005)

		Univariate Analysis				Multivariate Analysis[1]		
Treatment/Stratification Factors	N	Median Survival (Month)	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
All patients					0.039*			0.016*
Placebo	284	5.93	0.84	(0.71,0.99)	0.040**	0.80	(0.67-0.94)	0.008**
Erlotinib	285	6.34						
100 mg dose cohort					0.06*			0.028*
Placebo	260	5.96	0.85	(0.71-1.01)	0.06**	0.81	(0.68-0.97)	0.020**
Erlotinib	261	6.37						

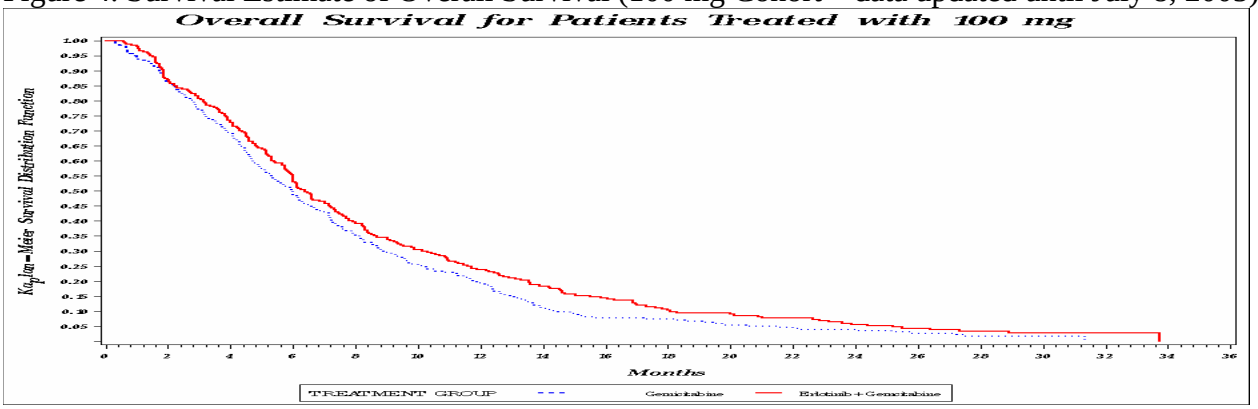
Source: Reviewer's analysis based on the addendum to response to FDA question received June 6, 2005. The analyses were similar to those provided by the Sponsor. *p-value was from log rank test, **p-value was from Cox regression models. [1]: Protocol specified analysis

Figure 3. Survival Estimate of Overall Survival (All patients – data updated until July 8, 2005)



Source: Reviewer's analysis.

Figure 4. Survival Estimate of Overall Survival (100 mg Cohort – data updated until July 8, 2005)



Source: Reviewer's analysis.

Table 7 summarizes the results of the analysis of the primary endpoint after 381 deaths occurred per the original sample size calculation. This was another sensitivity analysis of the primary endpoint. The hazard ratios were very similar to those in Tables 4 and 6. The nominal P-values were larger since the number of deaths was smaller.

Table 7. Analyses of the Primary Endpoint (After 381 Deaths Occurred)

		Univariate Analysis				Multivariate Analysis[1]		
Treatment/Stratification Factors	N	Median Survival (Month)	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
All patients					0.069*			0.033*
Placebo	284	5.93	0.83	(0.68,1.02)	0.070**	0.80	(0.65-0.98)	0.028**
Erlotinib	285	6.37						
100 mg dose cohort					0.086*			0.055*
Placebo	260	5.96	0.84	(0.69-1.03)	0.087**	0.81	(0.66-0.99)	0.043**
Erlotinib	261	6.37						

Source: Reviewer's analysis based on the data submitted by the Sponsor dated July 14, 2005. The results were similar to those by the Sponsor. The hazard ratios and 95 CIs were from Cox regression models. *p-value was from log rank test, **p-value was from Cox regression models. [1]: Protocol specified analysis

Progression-Free Survival:

Table 8 presents the results of the analysis of progression free survival. The results were in favor of erlotinib with small nominal p-values.

Table 8. Analyses of Progression Free Survival

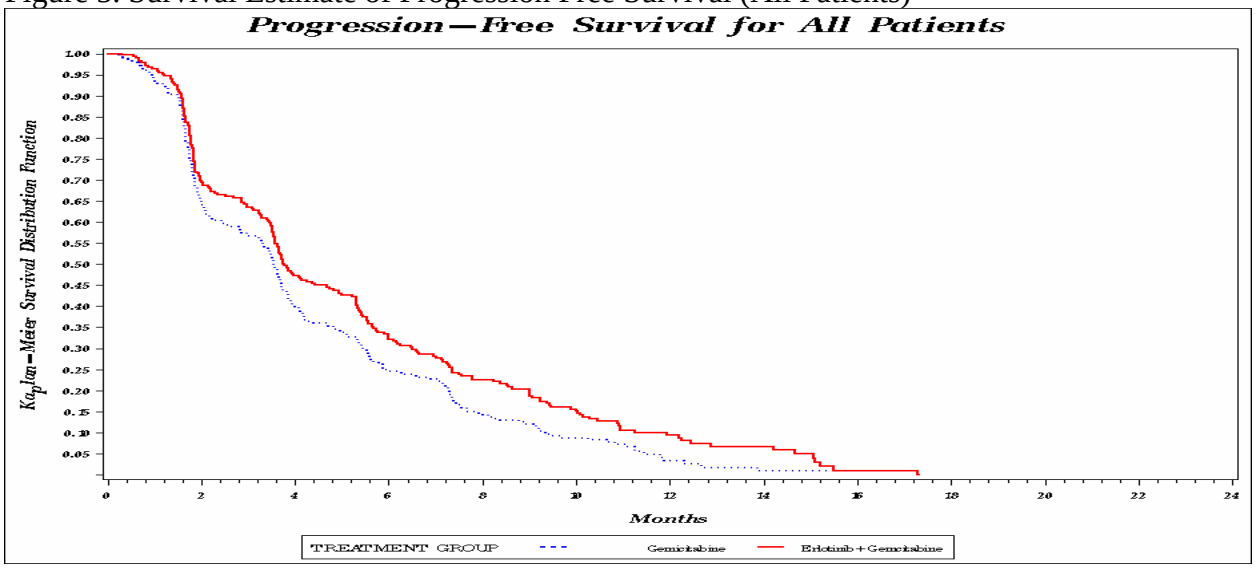
		Univariate Analysis				Multivariate Analysis		
Treatment	N	Median Survival (Month)	Hazard Ratio	95% CI	Log-Rank P-value	Hazard Ratio	95% CI	Cox P-value
All patients								**0.004***
Placebo	284	3.55	0.79	(0.66,0.95)	0.009	0.76	(0.64-0.91)	0.003

Erlotinib	285	3.75						
100 mg dose cohort								**0.006***
Placebo	260	3.55	0.79	(0.66,0.95)	0.012	0.76	(0.64-0.92)	0.005
Erlotinib	261	3.81						

Source: Tables 11-35, 11-36 of the Sponsor's final clinical study report PA.3. The methods used for the analyses were similar to those of the primary endpoint. Results were independently confirmed by this reviewer. *p-value was from stratified log rank test with ECOG performance status and disease status as stratification variables.

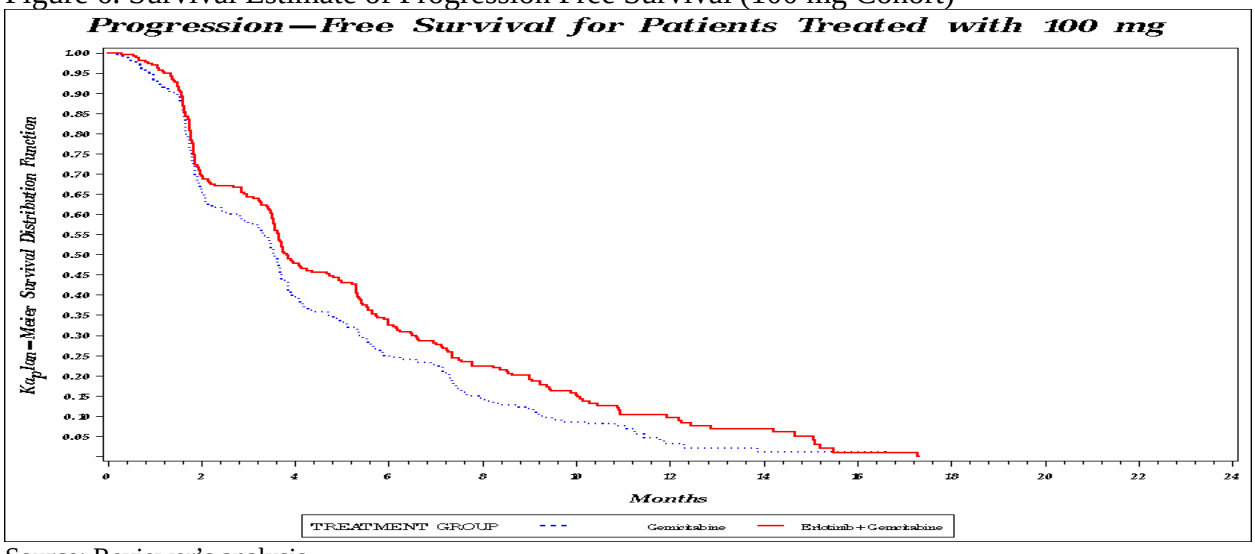
Figures 5 and 6 are the Kaplan-Meier estimates for the progression free survival for all patients and the 100 mg dose cohort, respectively.

Figure 5. Survival Estimate of Progression Free Survival (All Patients)



Source: Reviewer's analysis.

Figure 6. Survival Estimate of Progression Free Survival (100 mg Cohort)



Source: Reviewer's analysis.

Objective Response:

The summary of best response and results of the analysis of response rate are presented in Table 9. Table 10 summarizes the analysis of duration of response. These analyses are restricted to the subset of patients with measurable disease. No statistical significant results were found.

Table 9. Summary of Best Response for Patients with Measurable Disease

Response	All Patients			100 mg dose cohort		
	Erlotinib N = 268 n (%)	Placebo N = 262 n (%)	P-Value	Erlotinib N = 244 n (%)	Placebo N = 241 n (%)	P-value
Complete Response (CR)	1 (0.4)	3 (1.1)		1 (0.4)	2 (0.8)	
Partial Response (PR)	22 (8.2)	18 (6.9)		20 (8.2)	17 (7.1)	
Stable Disease (SD)	131 (48.9)	108 (41.2)		123 (50.4)	100 (41.5)	
Progressive Disease (PD)	60 (22.4)	69 (26.3)		55 (22.5)	63 (26.1)	
Missing	3 (1.1)	4 (1.5)		1 (0.4)	4 (1.7)	
Inevaluable for Response or Not Assessed	51 (19.0)	60 (22.9)		44 (18.0)	55 (22.8)	
Overall response						
CR+PR	23 (8.6)	21 (8.0)	0.875	21 (8.6)	19 (7.9)	0.869
CR+PR+SD	154 (57.5)	129 (49.2)	0.067	144 (59.0)	119 (49.4)	0.036

Source: Tables 11-45, 11-46 of the Sponsor's final clinical study report PA.3.

Table 10. Analyses of Duration of Response

Response	All Patients			100 mg dose cohort		
Duration	Erlotinib N = 268 n (Median)	Placebo N = 262 n (Median)	P-Value	Erlotinib N = 244 n (Median)	Placebo N = 241 n (Median)	P-value
Complete Response (CR)	1 (23.3)	1 (33.7)	0.317	1 (23.3)	1 (33.7)	0.317
Overall response (CR+PR)	23 (23.3)	18 (23.3)	0.813	21 (23.9)	17 (23.3)	0.719
Stable Disease (SD)	131 (24.6)	108 (23.3)	0.122	123 (24.1)	100 (23.1)	0.138

Source: Tables 14.2.51, 14.2.52 of the Sponsor's final clinical study report PA.3. P-value was from log-rank test.

The patient compliance rates with completion of QoL questionnaires were similar between the two treatment groups for both the overall population and the 100 mg dose cohort according to the Sponsor. It was mandatory only for North American patients to submit QoL data. Only the results for the 100 mg dose cohort are presented here. Table 13 (See Appendix) summarizes the baseline QoL assessment by treatment groups. It seems that there was no difference between the two groups at baseline for QoL assessment. Table 14 (See Appendix) presents the results in change in QoL scores at each assessment time point from baseline between the two groups. In addition to the pre-specified analysis by Wilcoxon rank-sum tests, the reviewer also performed analysis using t-test as a sensitivity analysis. Diarrhea was significantly worse in the erlotinib group, other QoL scores seemed comparable between the two treatment groups. Table 15 (See Appendix) summarizes the results of response analysis for QoL assessment. It seemed to confirm that diarrhea was worse in the erlotinib, and other QoL scores were comparable.

The EORTC QoL instruments are developed and validated to be used in totality. There is no development and validation of the instruments to support conclusions about individual concepts based on the use of single items from the instruments. The validity of the instrument subscales to measure these specific concepts is questionable. Furthermore, the symptom questions ask patients to average their experience over the past week. This approach may not give the true picture.

3.2 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, and Ethnic group

Subgroup analysis of the primary endpoint by age, gender and race was performed. Since the Sponsor only seeks indications for the 100 mg dose, the results of the subgroup analysis are presented for this cohort. The results for all patients are similar and not presented here. The estimates for the hazard ratios were less than 1 (in favor of erlotinib) in all the subgroup.

Table 11. Subgroup Analysis of the Primary Endpoint (100 mg cohort)

	Erlotinib		Placebo			
Subgroup	N	Median Survival (Month)	N	Median Survival (Month)	Hazard Ratio 95% CI	Log-Rank P-value*
Age (years)						
< 65	136	6.6	138	6.18	0.76 (0.58, 0.99)	0.038
>= 65	125	6.47	122	5.88	0.91 (0.70, 1.19)	0.490
Gender						
Male	127	6.11	146	5.29	0.75 (0.58, 0.97)	0.028
Female	134	6.60	114	6.70	0.95 (0.72, 1.25)	0.691
Race						
White	225	6.37	231	5.93	0.87 (0.71, 1.06)	0.179
Black	8	10.17	5	9.46	0.48 (0.11, 2.20)	0.336
Oriental	20	5.16	14	4.47	0.61 (0.29, 1.29)	0.187
Other	8	10.27	10	7.33	0.40 (0.12, 1.31)	0.115

Source: Table 11-24 of the Sponsor's final clinical study report PA.3. The hazard ratios were erlotinib over placebo.
*: Not adjusted for multiplicity

4.2 Other Subgroup Populations

The results of subgroup analysis of the primary endpoint by other pre-specified subgroups are presented in Table 12. The results seemed to be consistent among the subgroups.

Table 12. Additional Subgroup Analysis of the Primary Endpoint (100 mg cohort)

	Erlotinib		Placebo			
Subgroup	N	Median Survival (Month)	N	Median Survival (Month)	Hazard Ratio 95% CI	Log-Rank P-value
ECOG performance status at baseline						
0-1	217	6.64	215	6.47	0.86 (0.70, 1.06)	0.167
2	44	4.73	45	3.22	0.60 (0.38, 0.94)	0.023
ECOG performance status as randomized						
0-1	218	6.60	215	6.54	0.89 (0.73, 1.10)	0.285
2	43	5.16	45	3.22	0.49 (0.31, 0.77)	0.002
Disease status at baseline						
Locally advanced	61	8.51	63	8.18	0.99 (0.66, 1.48)	0.945
Distance metastasis	200	5.98	197	5.06	0.77 (0.62, 0.95)	0.016
Disease status as randomized						
Locally advanced	77	8.21	75	7.33	0.93 (0.65, 1.34)	0.706
Distance metastasis	184	5.98	185	5.29	0.77 (0.62, 0.96)	0.021
Pain intensity score						
EGFR Status						
Positive	41	7:00	29	5.32	0.76 (0.45, 1.27)	0.285
Negative	34	6.47	32	5.93	0.71 (0.42, 1.19)	0.191
Unknown	186	6.24	199	6.01	0.87 (0.70, 1.08)	0.202
<= 20	119	7.62	119	6.21	0.70 (0.52, 0.93)	0.013
> 20	133	5.75	135	5.11	0.99 (0.77, 1.28)	0.937
Unknown	9	9.03	6	5.68	0.49 (0.15, 1.66)	0.243
Any prior chemotherapy						
Yes	19	8.38	23	4.47	0.61 (0.32, 1.17)	0.133
No	242	6.24	237	5.98	0.85 (0.70, 1.03)	0.100
Region						
Canada/USA	142	6.60	138	5.68	0.74 (0.57, 0.95)	0.017
Rest of the world	119	6.24	122	6.11	0.96 (0.72, 1.27)	0.764

Source: Table 11-24 of the Sponsor's final clinical study report PA.3. The hazard ratios were erlotinib over placebo.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The study was conducted with both doses, with n = 521 in the 100 mg dose group and n = 48 in the 150 mg dose group. Since there were not enough patients in the 150 mg dose group, the Sponsor is seeking indications only for the 100 mg dose. Because the results for the all population (both doses) were statistically more significant than the results for the 100 mg dose group, and the 100 mg dose cohort was the majority of the patient population (92%), it is acceptable to consider the indications for the 100 mg dose in this reviewer's opinion.

The protocol specified that the final analysis would be conducted after 381 deaths occurred. The Sponsor stated that prior to unblinding, the field cut-off date was made too late since the death

rate was underestimated. When the field cut-off date was reached, a total of 485 (444 in the 100 mg cohort) deaths were observed. The main analysis for the primary endpoint was based on the database locked when the projected cut-off date was reached. However, sensitivity analyses were conducted. One sensitivity analysis was based on the data after 381 deaths occurred. Another sensitivity analysis was performed based on the data updated until July 8, 2005 after the sNDA submission. The Agency asked the Sponsor to update the database after the sNDA submission. The reason is that when the database was locked, 85 of the 569 patients were thought to be alive or lost to follow-up. In the updated database, a total of 551 patients were known to be dead, and 18 patients were thought to be alive at last follow-up. The results from these analyses were consistent, with the estimated hazard ratios being similar from all the models. The nominal p-values were less than 0.05 in general for the overall survival in these analyses.

The main analysis for the primary endpoint (overall survival) was specified to be analyzed by the log-rank test stratified by ECOG performance status, extent of disease and pain score at baseline. The Sponsor stated that per discussion with the Agency, agreement was reached that the pain score would be omitted from the analysis since it was not a randomized stratification factor. A sensitivity analysis was conducted with pain score as a stratification variable as well. The results were similar, but the p-value was larger when the pain score was included in the model.

The Kaplan-Meier curves for the two groups were separated in favor of the erlotinib group. However, the estimated median overall survival was 6.47 months in the erlotinib group compared with 5.95 months in the placebo group. This was only 8.7% increase in the median survival time (2 weeks). The two curves narrowed at the median time based on the Kaplan-Meier survival curves. At the 75^{th} percentile time, the estimated overall survival was 11.47 months and 9.99 months for erlotinib group and placebo group (6 weeks prolongation), respectively.

5.2 Conclusions and Recommendations

Erlotinib, together with gemcitabine, significantly reduced the risk of all-cause mortality when compared with placebo plus gemcitabine in patients with locally advanced, unresectable or metastatic pancreatic cancer. The adjusted estimated hazard ratio for death for erlotinib plus gemcitabine relative to placebo plus gemcitabine was 0.79 (95% CI (0.65, 0.95)) with p-value = 0.017 for the 100 mg cohort.

It seemed that it also prolonged the disease progression free survival in this patient population. The estimated hazard ratio of erlotinib plus gemcitabine relative to placebo plus gemcitabine was 0.76 (95% CI (0.64, 0.92)) for progression free survival, with nominal p-value = 0.006 in the 100 mg dose group. Whether the observed magnitude of effect is adequate is a clinical decision.

Appendix (Tables for QoL analyses)

Table 13. Baseline QoL Assessment for Each Domain/Item (100 mg cohort)

	Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)		
Domain/Item	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***
Physical Functioning	206	76.7 (21.78)	201	74.1 (22.28)	0.182
Role Functioning	206	61.7 (32.40)	200	61.8 (32.99)	0.940
Emotional Functioning	206	65.1 (25.49)	202	67.9 (22.23)	0.335
Cognitive Functioning	206	82.4 (22.37)	202	79.6 (20.86)	0.050
Social Functioning	206	65.6 (30.93)	202	68.3 (28.89)	0.456
Fatigue	206	43.2 (27.44)	202	45.2 (24.83)	0.329
Nausea and Vomiting	206	15.8 (22.04)	202	13.6 (20.03)	0.398
Pain	206	39.8 (30.02)	203	41.2 (29.82)	0.592
Dyspnea	205	15.9 (24.60)	201	16.1 (22.63)	0.631
Sleep	204	35.1 (32.79)	201	33.5 (30.64)	0.736
Appetite	206	44.3 (34.96)	202	45.4 (35.24)	0.774
Constipation	205	28.9 (35.04)	202	30.2 (33.68)	0.546
Diarrhea	206	11.5 (22.39)	202	14.4 (23.69)	0.109
Financial	204	22.2 (31.50)	199	21.8 (29.12)	0.710
Global QoL	206	53.0 (24.08)	202	54.8 (22.77)	0.404

Source: Table 11-42 of the Sponsor's final clinical study report PA.3. The results were confirmed by this reviewer.
*: Not adjusted for multiplicity

Table 14. Analysis of Change from Baseline for QoL Assessment (100 mg cohort)

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
Physical Functioning	Cycle 1 - End	169	-6.5 (17.60)	158	-4.0 (17.79)	0.248	0.202
	Cycle 2	128	-3.5 (19.85)	95	-3.0 (18.21)	0.965	0.862
	Cycle 3	111	-3.2 (21.63)	83	-2.2 (21.15)	0.644	0.765
	Cycle 4	81	-3.2 (20.74)	70	-4.0 (21.99)	0.427	0.812
	Cycle 5	63	-1.0 (19.74)	50	2.4 (18.91)	0.393	0.355
	Cycle 6	42	-2.5 (21.84)	38	2.8 (24.21)	0.629	0.308
	Cycle 7	33	-0.9 (21.49)	32	-1.3 (24.56)	0.737	0.952
	Cycle 8	25	6.1 (19.33)	21	0.6 (30.69)	0.627	0.482
	Cycle 9	22	0.4 (23.16)	18	7.4 (22.62)	0.155	0.339
	Cycle 10	17	-0.9 (30.38)	13	2.1 (12.88)	0.675	0.723
	Cycle 11	14	-3.3 (16.69)	8	0.8 (14.45)	0.972	0.547
	Cycle 12	13	-8.2 (17.46)	5	-6.7 (20.00)	0.694	0.884
	Cycle 13	8	-3.3 (8.73)	1	0.0 ()	0.846	
	Cycle 14	6	-8.9 (10.89)	1	0.0 ()	0.465	
	Cycle 15	4	-16.7 (20.73)	1	-6.7 ()	0.741	
	Cycle 16	4	-13.3 (18.05)	1	-6.7 ()	0.735	
	Cycle 17	2	-6.7 (9.43)	1	-6.7 ()	1	
	Cycle 18	1	-26.7 ()	1	-6.7 ()		
	Progression	31	-10.1 (19.92)	18	-10.4 (23.34)	0.835	0.968
	F/U Week 4	25	-17.5 (31.33)	25	-21.5 (28.90)	0.530	0.646
Role Functioning	Cycle 1 - End	169	-1.0 (33.47)	156	-2.6 (31.91)	0.651	0.663
	Cycle 2	128	2.0 (36.14)	95	-0.9 (31.64)	0.360	0.534
	Cycle 3	111	2.0 (32.55)	83	0.2 (33.08)	0.561	0.713
	Cycle 4	81	2.9 (31.27)	70	1.0 (33.92)	0.746	0.718
	Cycle 5	63	3.4 (31.56)	50	7.3 (31.25)	0.579	0.513
	Cycle 6	42	4.8 (35.55)	38	7.9 (39.28)	0.649	0.710
	Cycle 7	33	10.1 (37.95)	32	5.2 (36.52)	0.756	0.598

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 8	25	13.3 (32.63)	21	4.0 (48.28)	0.603	0.455
	Cycle 9	22	5.3 (40.30)	18	11.1 (37.92)	0.923	0.642
	Cycle 10	17	2.9 (43.40)	13	2.6 (34.59)	0.801	0.979
	Cycle 11	14	-2.4 (26.84)	8	16.7 (17.82)	0.094	0.060
	Cycle 12	13	-5.1 (24.89)	5	3.3 (21.73)	0.526	0.497
	Cycle 13	8	0.0 (23.57)	1	16.7 ()	0.569	
	Cycle 14	6	-11.1 (41.72)	1	0.0 ()	1	
	Cycle 15	4	-8.3 (16.67)	1	0.0 ()	1	
	Cycle 16	4	-25.0 (16.67)	1	16.7 ()	0.337	
	Cycle 17	2	-50.0 (23.57)	1	0.0 ()	0.602	
	Cycle 18	1	-66.7 ()	1	16.7 ()		
	Progression	31	-11.3 (30.55)	18	-3.7 (39.42)	0.313	0.487
	F/U Week 4	25	-17.3 (37.11)	25	-12.7 (47.21)	0.619	0.699
Emotional Functioning	Cycle 1 - End	168	5.5 (20.23)	158	4.7 (20.27)	0.811	0.740
	Cycle 2	128	7.7 (22.55)	95	5.8 (23.26)	0.660	0.528
	Cycle 3	111	7.0 (24.03)	83	9.1 (20.27)	0.429	0.516
	Cycle 4	81	6.8 (23.84)	70	8.8 (23.26)	0.572	0.593
	Cycle 5	63	9.2 (21.43)	50	10.5 (23.56)	0.825	0.765
	Cycle 6	41	4.3 (25.28)	38	10.5 (29.49)	0.637	0.321
	Cycle 7	33	11.5 (24.59)	32	5.7 (24.99)	0.161	0.349
	Cycle 8	24	15.0 (24.50)	21	11.9 (25.49)	0.707	0.676
	Cycle 9	22	8.2 (20.99)	18	14.8 (13.87)	0.229	0.240
	Cycle 10	17	10.6 (13.65)	13	10.3 (11.36)	0.882	0.937
	Cycle 11	14	5.0 (12.19)	8	9.4 (13.68)	0.304	0.462
	Cycle 12	13	7.3 (16.18)	5	11.7 (12.64)	0.557	0.556

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 13	8	3.1 (13.32)	1	0.0 ()	1	
	Cycle 14	6	-2.8 (6.80)	1	8.3 ()	0.170	
	Cycle 15	4	-8.3 (26.35)	1	8.3 ()	0.741	
	Cycle 16	4	-12.5 (28.46)	1	8.3 ()	0.741	
	Cycle 17	2	4.2 (5.89)	1	0.0 ()	1	
	Cycle 18	1	0.0 ()	1	8.3 ()		
	Progression	31	-1.2 (24.45)	18	3.7 (33.97)	0.556	0.598
	F/U Week 4	25	-7.6 (18.68)	26	-8.3 (25.60)	0.895	0.901
Cognitive Functioning	Cycle 1 - End	169	-1.3 (21.82)	158	-1.6 (21.76)	0.707	0.900
	Cycle 2	128	1.3 (21.19)	95	0.0 (18.83)	0.995	0.628
	Cycle 3	111	1.4 (21.69)	83	-0.4 (18.40)	0.804	0.544
	Cycle 4	81	-2.1 (20.65)	70	0.5 (16.29)	0.430	0.401
	Cycle 5	63	-1.3 (21.02)	50	1.7 (17.58)	0.347	0.412
	Cycle 6	42	-1.6 (21.40)	38	3.1 (17.27)	0.230	0.285
	Cycle 7	33	1.5 (20.57)	32	-0.5 (21.37)	0.642	0.696
	Cycle 8	25	4.7 (21.79)	21	4.0 (24.67)	0.826	0.920
	Cycle 9	22	-1.5 (22.95)	18	3.7 (17.67)	0.439	0.421
	Cycle 10	17	0.0 (17.68)	13	1.3 (8.23)	0.673	0.794
	Cycle 11	14	-1.2 (13.81)	8	4.2 (17.25)	0.472	0.466
	Cycle 12	13	-7.7 (18.78)	5	0.0 (11.79)	0.370	0.319
	Cycle 13	8	-6.3 (23.46)	1	16.7 ()	0.455	
	Cycle 14	6	-11.1 (13.61)	1	16.7 ()	0.242	
	Cycle 15	4	-12.5 (15.96)	1	16.7 ()	0.337	
	Cycle 16	4	-16.7 (23.57)	1	16.7 ()	0.337	
	Cycle 17	2	-8.3 (11.79)	1	16.7 ()	0.602	

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 18	1	-50.0 ()	1	16.7 ()		
	Progression	31	-3.8 (24.99)	18	-1.9 (18.86)	0.400	0.763
	F/U Week 4	25	-3.3 (20.41)	26	-16.0 (22.35)	0.059	0.039
Social Functioning	Cycle 1 - End	169	-0.7 (27.60)	158	-6.1 (27.92)	0.052	0.078
	Cycle 2	127	-0.3 (29.25)	95	-1.6 (28.25)	0.511	0.735
	Cycle 3	111	2.6 (28.00)	83	-0.8 (31.01)	0.265	0.438
	Cycle 4	81	4.1 (28.32)	70	1.0 (29.34)	0.203	0.503
	Cycle 5	63	5.8 (27.13)	50	3.7 (31.28)	0.729	0.700
	Cycle 6	42	2.0 (34.57)	38	6.1 (34.10)	0.917	0.590
	Cycle 7	33	6.6 (30.03)	32	2.6 (36.93)	0.454	0.637
	Cycle 8	25	11.3 (39.30)	21	9.5 (42.35)	0.973	0.882
	Cycle 9	22	4.5 (42.16)	18	13.9 (43.25)	0.688	0.496
	Cycle 10	17	1.0 (41.86)	13	0.0 (37.27)	0.880	0.946
	Cycle 11	14	-1.2 (27.32)	8	-4.2 (24.80)	0.805	0.797
	Cycle 12	13	-7.7 (26.01)	5	-6.7 (19.00)	0.692	0.928
	Cycle 13	8	-4.2 (23.15)	1	0.0 ()	1	
	Cycle 14	6	-16.7 (10.54)	1	0.0 ()	0.347	
	Cycle 15	4	0.0 (13.61)	1	0.0 ()	1	
	Cycle 16	4	-8.3 (21.52)	1	0.0 ()	1	
	Cycle 17	2	-8.3 (11.79)	1	0.0 ()	1	
	Cycle 18	1	-33.3 ()	1	0.0 ()		
	Progression	31	-3.2 (36.37)	17	-5.9 (33.82)	0.973	0.801
	F/U Week 4	24	-14.6 (33.45)	26	-9.6 (33.39)	0.684	0.601
Fatigue	Cycle 1 - End	167	6.1 (27.26)	158	2.6 (22.79)	0.443	0.206
	Cycle 2	128	0.4 (27.61)	95	-0.2 (22.22)	0.826	0.851

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 3	110	-0.7 (29.70)	82	-0.3 (24.73)	0.581	0.925
	Cycle 4	81	-0.5 (25.87)	70	-2.8 (26.98)	0.723	0.606
	Cycle 5	63	-1.9 (27.04)	50	-6.4 (27.04)	0.163	0.381
	Cycle 6	41	-1.9 (33.69)	38	-7.0 (32.31)	0.507	0.492
	Cycle 7	32	-10.4 (32.17)	32	-2.3 (31.67)	0.550	0.310
	Cycle 8	25	-12.0 (31.21)	21	-11.6 (38.89)	0.692	0.972
	Cycle 9	22	-6.8 (33.24)	18	-14.2 (27.43)	0.325	0.446
	Cycle 10	16	-5.6 (37.84)	13	-5.1 (22.51)	0.759	0.970
	Cycle 11	13	-5.1 (22.04)	8	-5.6 (17.82)	0.715	0.961
	Cycle 12	13	4.3 (32.56)	5	15.6 (28.97)	0.365	0.494
	Cycle 13	8	-6.9 (22.17)	1	0.0 ()	1	
	Cycle 14	6	0.0 (22.22)	1	0.0 ()	1	
	Cycle 15	4	-11.1 (20.29)	1	0.0 ()	1	
	Cycle 16	4	0.0 (24.00)	1	0.0 ()	1	
	Cycle 17	2	0.0 (47.14)	1	0.0 ()	1	
	Cycle 18	1	44.4 ()	1	0.0 ()		
	Progression	31	17.9 (27.32)	18	1.9 (27.81)	0.059	0.057
	F/U Week 4	25	14.4 (30.43)	26	17.5 (23.76)	0.707	0.689
Nausea and Vomiting	Cycle 1 - End	168	2.1 (20.97)	158	4.5 (21.25)	0.456	0.295
	Cycle 2	128	0.7 (20.21)	95	0.4 (15.56)	0.874	0.900
	Cycle 3	110	-1.5 (23.63)	82	0.2 (19.15)	0.503	0.578
	Cycle 4	81	0.6 (19.44)	70	-1.2 (21.29)	0.542	0.589
	Cycle 5	63	-1.3 (19.00)	50	-1.3 (21.25)	1	0.997
	Cycle 6	41	2.8 (26.33)	38	-1.3 (23.69)	0.979	0.461
	Cycle 7	33	-8.6 (17.24)	32	2.6 (21.63)	0.037	0.024

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 8	25	-8.0 (25.06)	21	-2.4 (15.17)	0.313	0.355
	Cycle 9	22	-2.3 (29.23)	18	-1.9 (9.72)	0.917	0.949
	Cycle 10	17	1.0 (19.96)	13	-3.8 (15.45)	0.586	0.461
	Cycle 11	14	1.2 (12.17)	8	10.4 (21.71)	0.448	0.295
	Cycle 12	13	2.6 (21.35)	5	0.0 (11.79)	1	0.751
	Cycle 13	8	2.1 (22.60)	1	16.7 ()	0.559	
	Cycle 14	6	0.0 (10.54)	1	0.0 ()	1	
	Cycle 15	4	12.5 (15.96)	1	0.0 ()	0.712	
	Cycle 16	4	0.0 (13.61)	1	16.7 ()	0.497	
	Cycle 17	2	8.3 (35.36)	1	0.0 ()	1	
	Cycle 18	1	0.0 ()	1	0.0 ()		
	Progression	30	3.9 (21.30)	18	-5.6 (9.90)	0.058	0.043
	F/U Week 4	25	1.3 (19.20)	26	7.7 (18.99)	0.087	0.240
Pain	Cycle 1 - End	168	-13.9 (29.33)	158	-8.3 (26.85)	0.150	0.075
	Cycle 2	128	-16.8 (29.47)	95	-12.1 (24.00)	0.271	0.191
	Cycle 3	110	-13.3 (34.00)	82	-9.1 (26.21)	0.467	0.336
	Cycle 4	81	-12.1 (31.84)	70	-12.6 (26.38)	0.684	0.919
	Cycle 5	63	-13.5 (34.89)	50	-15.0 (25.48)	0.765	0.791
	Cycle 6	42	-17.1 (35.59)	38	-13.6 (27.90)	0.555	0.627
	Cycle 7	33	-24.2 (24.68)	32	-6.8 (31.07)	0.020	0.014
	Cycle 8	25	-23.3 (29.27)	21	-15.9 (34.75)	0.408	0.440
	Cycle 9	22	-16.7 (34.88)	18	-14.8 (30.19)	0.723	0.858
	Cycle 10	17	-19.6 (22.23)	13	-10.3 (23.11)	0.193	0.274
	Cycle 11	14	-6.0 (34.35)	8	-22.9 (33.26)	0.193	0.273
	Cycle 12	13	-6.4 (26.82)	5	-20.0 (21.73)	0.306	0.295

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 13	8	-10.4 (40.76)	1	-16.7 ()	1	
	Cycle 14	6	5.6 (32.77)	1	-16.7 ()	0.809	
	Cycle 15	4	-8.3 (16.67)	1	-16.7 ()	0.712	
	Cycle 16	4	8.3 (39.67)	1	-16.7 ()	1	
	Cycle 17	2	16.7 (70.71)	1	-16.7 ()	1	
	Cycle 18	1	33.3 ()	1	-16.7 ()		
	Progression	31	3.8 (34.62)	18	9.3 (27.55)	0.832	0.544
	F/U Week 4	25	-2.0 (36.43)	26	-7.1 (30.61)	0.761	0.595
Dyspnea	Cycle 1 - End	168	3.2 (22.56)	158	4.9 (24.33)	0.496	0.519
	Cycle 2	127	3.4 (26.51)	95	6.3 (27.20)	0.266	0.427
	Cycle 3	109	2.8 (24.06)	83	7.2 (25.53)	0.180	0.218
	Cycle 4	79	5.5 (25.28)	70	4.8 (23.59)	0.847	0.856
	Cycle 5	62	3.8 (24.22)	50	3.3 (25.42)	0.981	0.927
	Cycle 6	40	9.2 (29.22)	38	0.9 (27.39)	0.260	0.199
	Cycle 7	32	6.3 (32.17)	32	4.2 (29.02)	0.671	0.786
	Cycle 8	25	-4.0 (26.03)	21	-6.3 (37.44)	0.846	0.809
	Cycle 9	22	3.0 (28.93)	18	-1.9 (26.75)	0.582	0.583
	Cycle 10	15	-2.2 (26.63)	13	7.7 (30.89)	0.493	0.375
	Cycle 11	13	5.1 (18.49)	8	8.3 (23.57)	1	0.748
	Cycle 12	13	5.1 (22.96)	5	20.0 (44.72)	0.823	0.511
	Cycle 13	8	0.0 (17.82)	1	0.0 ()	1	
	Cycle 14	6	0.0 (21.08)	1	0.0 ()	1	
	Cycle 15	4	0.0 (0.00)	1	0.0 ()	1	
	Cycle 16	4	16.7 (19.25)	1	0.0 ()	0.704	
	Cycle 17	2	0.0 (0.00)	1	0.0 ()	1	

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 18	1	0.0 ()	1	0.0 ()		
	Progression	31	6.5 (21.81)	18	7.4 (21.56)	0.980	0.882
	F/U Week 4	25	20.0 (33.33)	25	18.7 (39.77)	0.763	0.898
Sleep	Cycle 1 - End	166	-9.8 (30.76)	156	-3.8 (34.07)	0.131	0.099
	Cycle 2	126	-13.0 (31.54)	92	-3.6 (36.80)	0.062	0.051
	Cycle 3	110	-13.9 (32.68)	81	-9.9 (33.93)	0.429	0.407
	Cycle 4	80	-13.8 (32.99)	68	-5.4 (34.37)	0.174	0.135
	Cycle 5	63	-13.8 (30.31)	49	-15.0 (31.96)	0.764	0.839
	Cycle 6	42	-14.3 (32.21)	37	-14.4 (35.61)	0.833	0.986
	Cycle 7	33	-19.2 (33.36)	31	-15.1 (38.33)	0.576	0.647
	Cycle 8	24	-20.8 (29.18)	20	-21.7 (40.86)	0.979	0.939
	Cycle 9	22	-18.2 (35.23)	17	-11.8 (33.21)	0.614	0.563
	Cycle 10	17	-17.6 (37.49)	12	-11.1 (35.77)	0.591	0.638
	Cycle 11	14	-16.7 (40.82)	6	-5.6 (38.97)	0.768	0.577
	Cycle 12	13	-20.5 (46.23)	5	-13.3 (44.72)	0.880	0.770
	Cycle 13	7	-19.0 (37.80)	1	-33.3 ()	0.474	
	Cycle 14	6	-5.6 (38.97)	1	-33.3 ()	0.343	
	Cycle 15	4	-25.0 (16.67)	1	-33.3 ()	0.497	
	Cycle 16	4	-16.7 (43.03)	1	-33.3 ()	0.741	
	Cycle 17	2	-33.3 (47.14)	1	-33.3 ()	1	
	Cycle 18	1	33.3 ()	1	-33.3 ()		
	Progression	31	2.2 (34.36)	18	-1.9 (33.28)	0.909	0.690
	F/U Week 4	25	0.0 (37.27)	25	1.3 (36.62)	0.960	0.898
Appetite	Cycle 1 - End	167	-0.8 (33.12)	157	-1.1 (34.47)	0.878	0.944
	Cycle 2	127	-5.2 (32.10)	94	-13.1 (40.37)	0.078	0.120

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 3	110	-9.1 (36.66)	82	-17.5 (37.12)	0.134	0.121
	Cycle 4	81	-13.6 (38.65)	70	-16.7 (40.43)	0.444	0.633
	Cycle 5	63	-12.7 (39.45)	50	-24.0 (36.91)	0.082	0.119
	Cycle 6	42	-18.3 (41.12)	38	-25.4 (31.42)	0.408	0.380
	Cycle 7	33	-27.3 (38.60)	32	-17.7 (37.85)	0.340	0.317
	Cycle 8	25	-34.7 (41.37)	21	-28.6 (41.21)	0.771	0.620
	Cycle 9	22	-18.2 (56.09)	18	-33.3 (37.92)	0.403	0.316
	Cycle 10	17	-17.6 (47.31)	13	-30.8 (37.17)	0.186	0.402
	Cycle 11	14	-16.7 (40.82)	8	-20.8 (50.20)	0.972	0.844
	Cycle 12	13	-12.8 (50.07)	5	-33.3 (52.70)	0.555	0.477
	Cycle 13	8	-16.7 (39.84)	1	-33.3 ()	0.553	
	Cycle 14	6	0.0 (21.08)	1	-33.3 ()	0.307	
	Cycle 15	4	0.0 (27.22)	1	-33.3 ()	0.497	
	Cycle 16	4	0.0 (0.00)	1	-33.3 ()	0.208	
	Cycle 17	2	0.0 (47.14)	1	-33.3 ()	1	
	Cycle 18	1	-33.3 ()	1	-33.3 ()		
	Progression	31	4.3 (31.90)	18	-3.7 (44.12)	0.644	0.505
	F/U Week 4	25	9.3 (37.91)	26	-2.6 (37.62)	0.275	0.266
Constipation	Cycle 1 - End	166	-5.2 (34.42)	156	-4.5 (34.31)	0.833	0.848
	Cycle 2	128	-11.2 (36.29)	95	-9.5 (31.76)	0.969	0.706
	Cycle 3	110	-13.3 (38.37)	82	-11.0 (33.97)	0.853	0.653
	Cycle 4	81	-15.2 (36.91)	70	-12.9 (32.74)	0.998	0.676
	Cycle 5	63	-11.6 (33.42)	50	-12.7 (30.78)	0.456	0.865
	Cycle 6	42	-11.9 (40.87)	38	-17.5 (30.74)	0.209	0.485
	Cycle 7	33	-17.2 (37.38)	32	-15.6 (25.38)	0.724	0.845

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 8	25	-25.3 (41.14)	21	-23.8 (33.57)	0.897	0.890
	Cycle 9	21	-20.6 (42.79)	18	-18.5 (28.52)	0.810	0.855
	Cycle 10	17	-11.8 (37.16)	13	-17.9 (29.24)	0.411	0.613
	Cycle 11	14	-11.9 (40.52)	8	-25.0 (38.83)	0.399	0.465
	Cycle 12	13	-15.4 (32.25)	5	-20.0 (29.81)	0.581	0.781
	Cycle 13	8	-8.3 (42.72)	1	-66.7 ()	0.173	
	Cycle 14	6	5.6 (13.61)	1	-66.7 ()	0.170	
	Cycle 15	4	8.3 (16.67)	1	-66.7 ()	0.301	
	Cycle 16	4	8.3 (16.67)	1	-66.7 ()	0.301	
	Cycle 17	2	16.7 (23.57)	1	-66.7 ()	0.602	
	Cycle 18	1	0.0 ()	1	-66.7 ()		
	Progression	31	-10.8 (39.80)	18	-1.9 (26.75)	0.413	0.355
	F/U Week 4	25	-12.0 (31.74)	26	1.3 (38.27)	0.263	0.183
Diarrhea	Cycle 1 - End	167	11.8 (27.64)	156	-1.9 (26.30)	<0.001	<0.001
	Cycle 2	127	5.8 (25.23)	94	-5.7 (27.50)	<0.001	0.001
	Cycle 3	109	8.0 (32.99)	82	-2.8 (27.32)	0.007	0.014
	Cycle 4	81	9.9 (24.97)	70	-5.2 (25.15)	<0.001	<0.001
	Cycle 5	63	6.3 (22.29)	50	-4.7 (25.21)	0.011	0.017
	Cycle 6	41	13.0 (29.70)	37	-0.9 (31.90)	0.041	0.050
	Cycle 7	33	11.1 (19.84)	32	-9.4 (24.30)	<0.001	<0.001
	Cycle 8	23	5.8 (21.68)	21	-14.3 (27.02)	0.016	0.010
	Cycle 9	22	7.6 (22.84)	18	-13.0 (25.92)	0.016	0.012
	Cycle 10	17	3.9 (20.01)	13	-12.8 (34.80)	0.194	0.138
	Cycle 11	14	7.1 (32.50)	8	4.2 (11.79)	0.931	0.760
	Cycle 12	13	2.6 (34.59)	5	-6.7 (14.91)	0.771	0.441

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 13	8	-4.2 (11.79)	1	0.0 ()	1	
	Cycle 14	6	-5.6 (13.61)	1	0.0 ()	1	
	Cycle 15	4	-16.7 (19.25)	1	-33.3 ()	0.704	
	Cycle 16	4	-16.7 (19.25)	1	-33.3 ()	0.704	
	Cycle 17	2	-33.3 (47.14)	1	-33.3 ()	1	
	Cycle 18	1	33.3 ()	1	-33.3 ()		
	Progression	31	12.9 (22.24)	18	9.3 (22.30)	0.295	0.584
	F/U Week 4	25	1.3 (15.15)	26	1.3 (29.03)	0.655	0.993
Financial	Cycle 1 - End	166	4.2 (29.17)	154	-1.1 (23.31)	0.135	0.072
	Cycle 2	125	3.5 (28.02)	94	0.7 (23.43)	0.242	0.429
	Cycle 3	109	3.4 (30.41)	82	-0.4 (23.71)	0.389	0.336
	Cycle 4	78	3.8 (26.31)	70	1.4 (23.70)	0.463	0.557
	Cycle 5	60	4.4 (20.78)	50	2.0 (21.73)	0.477	0.550
	Cycle 6	40	3.3 (23.63)	38	1.8 (23.18)	0.734	0.766
	Cycle 7	30	1.1 (26.96)	32	0.0 (22.40)	0.935	0.861
	Cycle 8	23	4.3 (25.23)	21	-1.6 (19.65)	0.323	0.387
	Cycle 9	20	6.7 (17.44)	18	-9.3 (19.15)	0.017	0.011
	Cycle 10	15	2.2 (15.26)	13	-5.1 (18.49)	0.284	0.267
	Cycle 11	13	0.0 (13.61)	8	-8.3 (15.43)	0.237	0.230
	Cycle 12	12	2.8 (22.29)	5	0.0 (0.00)	1	0.674
	Cycle 13	8	8.3 (15.43)	1	0.0 ()	0.796	
	Cycle 14	6	0.0 (21.08)	1	0.0 ()	1	
	Cycle 15	4	0.0 (0.00)	1	0.0 ()	1	
	Cycle 16	4	-8.3 (16.67)	1	0.0 ()	1	
	Cycle 17	2	16.7 (23.57)	1	0.0 ()	1	

		Gemcitabine+Erlotinib 100 mg (N=261)		Gemcitabine+Placebo 100 mg (N=260)			
Domain/Item	**Assessment**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**p-value***	**p-value****
	Cycle 18	1	0.0 ()	1	0.0 ()		
	Progression	30	4.4 (34.72)	17	5.9 (24.25)	0.282	0.868
	F/U Week 4	24	12.5 (23.70)	25	10.7 (28.41)	0.626	0.807
Global QoL	Cycle 1 - End	169	1.4 (22.14)	157	-0.7 (21.52)	0.253	0.392
	Cycle 2	127	6.0 (24.09)	95	3.6 (22.50)	0.683	0.438
	Cycle 3	111	5.7 (23.84)	83	2.8 (22.63)	0.226	0.390
	Cycle 4	80	7.6 (23.47)	69	1.1 (24.54)	0.058	0.101
	Cycle 5	63	4.5 (25.52)	50	7.3 (23.67)	0.699	0.542
	Cycle 6	42	4.6 (27.44)	37	6.1 (29.89)	0.960	0.815
	Cycle 7	33	9.1 (23.05)	32	4.9 (26.76)	0.797	0.506
	Cycle 8	25	11.3 (30.51)	21	10.3 (33.53)	1	0.915
	Cycle 9	21	3.2 (37.22)	18	13.4 (26.37)	0.243	0.322
	Cycle 10	17	5.4 (27.94)	13	5.8 (18.13)	0.755	0.964
	Cycle 11	14	0.0 (28.12)	8	8.3 (17.25)	0.299	0.399
	Cycle 12	13	-7.7 (27.10)	5	8.3 (18.63)	0.336	0.181
	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	30	-6.1 (33.11)	17	-10.3 (26.27)	0.929	0.636
	F/U Week 4	24	-10.4 (31.78)	26	-13.5 (28.87)	0.556	0.725

Source: Table 14.2.45 of the Sponsor's final clinical study report PA.3 and reviewer's analysis. Results were confirmed by this reviewer. *p-value was from Wilcoxon rank-sum test, **p-value was from t-test, not adjusted for multiplicity.

Table 15. Response Analysis of QoL (100 mg cohort)

	Gemcitabine+Erlotinib 100 mg				Gemcitabine+Placebo 100 mg					
Domain/Item	**N**	**Improved n (%)**	**Stable n (%)**	**Worsened n (%)**	**N**	**Improved n (%)**	**Stable n (%)**	**Worsened n (%)**	**Chi-Square p-value**	**Mantel-Haenszel p-value**
Physical Functioning	205	48 (23)	97 (47)	60 (29)	200	38 (19)	94 (47)	68 (34)	0.438	0.201
Role Functioning	205	82 (40)	44 (21)	79 (39)	199	73 (37)	57 (29)	69 (35)	0.248	0.949
Emotional Functioning	205	85 (41)	60 (29)	60 (29)	201	76 (38)	78 (39)	47 (23)	0.111	0.779
Cognitive Functioning	205	63 (31)	60 (29)	82 (40)	201	63 (31)	77 (38)	61 (30)	0.075	0.203
Social Functioning	205	88 (43)	42 (20)	75 (37)	201	60 (30)	60 (30)	81 (40)	0.013	0.050
Fatigue	205	90 (44)	28 (14)	87 (42)	201	79 (39)	45 (22)	77 (38)	0.072	0.958
Nausea and Vomiting	205	62 (30)	69 (34)	74 (36)	201	41 (20)	90 (45)	70 (35)	0.028	0.264
Pain	205	117 (57)	45 (22)	43 (21)	202	102 (50)	58 (29)	42 (21)	0.264	0.420
Dyspnea	204	37 (18)	80 (39)	87 (43)	200	24 (12)	99 (50)	77 (39)	0.068	0.775
Sleep	203	91 (45)	61 (30)	51 (25)	200	72 (36)	64 (32)	64 (32)	0.154	0.055
Appetite	205	88 (43)	48 (23)	69 (34)	201	78 (39)	73 (36)	50 (25)	0.012	0.571
Constipation	204	74 (36)	77 (38)	53 (26)	201	61 (30)	89 (44)	51 (25)	0.343	0.484
Diarrhea	205	27 (13)	84 (41)	94 (46)	201	44 (22)	119 (59)	38 (19)	<0.001	<0.001
Financial	203	40 (20)	95 (47)	68 (33)	198	35 (18)	120 (61)	43 (22)	0.012	0.148
Global QoL	205	91 (44)	48 (23)	66 (32)	201	88 (44)	63 (31)	50 (25)	0.119	0.420

Source: Table 11-44 of the Sponsor's final clinical study report PA.3. Results were confirmed by this reviewer.