PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Inlyta® / Axitinib

PROTOCOL NO.: A4061028

PROTOCOL TITLE: A Randomized, Double-Blind Phase 3 Study of Gemcitabine Plus AG-013736 Versus Gemcitabine Plus Placebo for the First-Line Treatment of Patients With Locally Advanced, Unresectable or Metastatic Pancreatic Cancer

Study Centers: A total of 159 centers took part in the study and randomized subjects; 36 in the United States, 11 in Canada, 10 each in Spain, the United Kingdom, and Japan, 9 each in France and Germany, 7 in the Russian Federation, 6 each in Belgium, Italy, and South Africa, 5 each in Austria, Hungary, and India, 4 each in Argentina and the Republic of Korea, 3 each in Australia and Taiwan, 2 each in Ireland, the Netherlands, Singapore, and Sweden, and 1 each in Hong Kong and Switzerland.

Study Initiation Date and Primary Completion Date: 23 July 2007 to 23 January 2009

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- Compare the overall survival (OS) of subjects receiving axitinib + gemcitabine versus placebo + gemcitabine

Secondary Objectives:

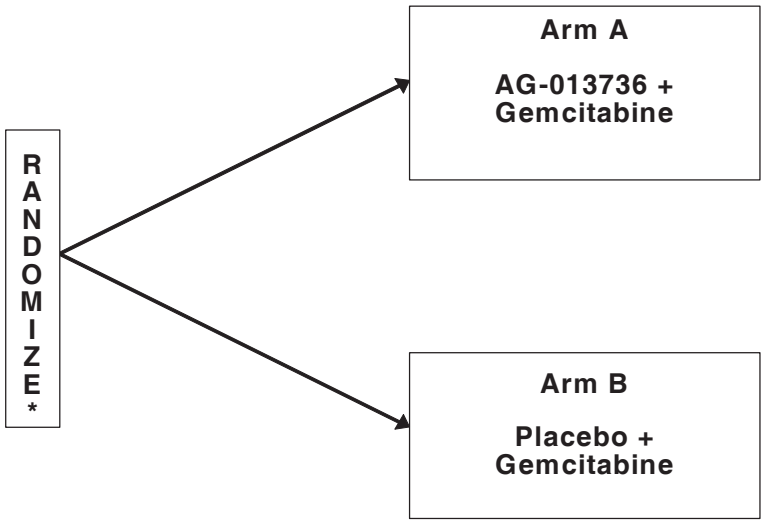
- Compare the progression-free survival (PFS) of subjects in each arm;
- Compare the objective response rate (ORR) of subjects in each arm;
- Estimate the duration of response (DR) of subjects in each arm;
- Evaluate the safety and tolerability of axitinib plus gemcitabine;
- Compare the health-related quality of life (HRQOL), pain ratings, and health status of subjects in each arm as measured by the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire-Core 30 (QLQ-C30), Pancreatic 26 (PAN26), brief pain inventory–short form (BPI-sf), and self-report questionnaire (EQ-5D).

- Conduct population pharmacokinetic (PK) analysis using axitinib plasma concentrations.

METHODS

Study Design: This was a double-blind, randomized, parallel-group (2-arm), multi-center Phase 3 study of axitinib + gemcitabine (Arm A) versus placebo + gemcitabine (Arm B) in first-line treatment of subjects with advanced pancreatic cancer. Eligible subjects were randomized and stratified by extent of disease (metastatic versus locally advanced). OS was the primary endpoint, and tumor assessments were performed approximately every 8-weeks. Crossovers of subjects from 1 arm to the other were not allowed. The study schematic is shown in Figure 1 and the schedule of activities is shown in Table 1.

Figure 1. Study Schematic



*stratification by extent of disease (locally advanced vs metastatic)

Table 1. Schedule of Activities

Observation	Screening Days –14 to Day 0	Day 1 (Predose) of Each Cycle[a]	Days 8 and 15 (Predose) of Each Cycle[a]	Day 22 (Predose) of Each Cycle[a]	Follow-up 28 Days After Last Dose
Informed consent	X				
Medical history[b]	X				
Physical exam[c]	X	X			X
Weight, temperature, BP[d], pulse	X	X[d]	X[d]	X[d]	X
Home BP monitoring[e]		Twice a day prior to each dose of axitinib/placebo			
ECOG performance status[f]	X	X			X
Electrocardiogram (ECG)[g]	X[g]	Day 15, Cycle 1 only[g]			X[g]
Hematology[h]	X	X	X	X	X
Chemistry[i]	X	X	X (Day 15) [i]		X
Urinalysis[j]	X	X			X
Thyroid function tests[k]	X	TSH every 2 weeks x 3, then every 8 weeks. T4 at Baseline[k]			X
Safety assessment (AEs)[l]	X	Monitored throughout the study			
Concomitant treatment[m]	X	Monitored throughout the study			
Tumor assessments[n]	Day –28 to 0	Every 8 weeks			X
Serum or lasma CA19-9[o]	X	Every 8 weeks			
Health-related Quality of Life (QLQ-C30 and QLQ-PAN26), pain (BPI-sf) and health status (EQ-5D)[p]	X[p]	X[p]			X
PK plasma samples[q]		See footnote q below			
Pregnancy test[r]	Day –3 to 0				
Gemcitabine treatment[s]		X	X		
Axitinib/placebo treatment[t]		Continuous twice daily dosing starting Cycle 1 Day 1			
UGT1A1 and other drug metabolizing enzyme tests[u]		X (C1 only) [u]			
Blood samples for PG (optional)[v]		X (C1 only) [v]			
Tumor specimen (archived) for PG (optional) [v]	X				
Survival[w]		Until at least 1 year after the randomization of the last subject			

AE = adverse event; BP = blood pressure; BPI-sf = brief pain inventory- short form; CA19-9 = carbohydrate antigen 19-9; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = eastern cooperative oncology group; Hgb = hemoglobin; HRQoL = health related quality of life; IEC = independent ethics committee; IRB = institutional review board; MRI = magnetic resonance imaging; OS = overall survival; PG = pharmacogenomics; PK = pharmacokinetics; PR = partial response; QLQ = quality of life questionnaire; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid stimulating hormone; UGT1A1 = uridine glucuronyl transferase; WBC = white blood cells;

a. Cycle length was 28 days. Tests and procedures were done on schedule, but occasional changes by ± 4 days were allowable for holidays, vacations, and other administrative reasons. The minimum dosing interval of gemcitabine was 7 days after Days 1 and 8, and 14 days after Day 15. Day 22 clinic visit was added after Amendment 3 of the Protocol.
b. Including history of prior treatments for pancreatic cancer and use of nicotine products.
c. Including height on initial examination. After the initial complete examination, targeted examinations based on signs and symptoms were performed.
d. BP was taken with the subject in the seated position after the subject had been sitting quietly for 5 minutes. Days 1, 8, 15 and 22 in-clinic BP measurements and safety assessments were performed in anticipation of axitinib/placebo dose titration. Measurement of weight on Day 22 was not necessary.
e. All subjects received BP monitoring devices. Subjects took BP at least twice daily prior to taking each

dose of medication and BP was recorded in a subject diary. Subject BP diary was administered and collected at each visit. Subjects were instructed to temporarily hold 1 dose and contact their doctor immediately for guidance if their systolic BP rose above 150 mm Hg, diastolic BP rose above 100 mm Hg, or if they developed symptoms perceived to be related to elevated BP (eg, headache, visual disturbance).

f. As per ECOG performance criteria.
g. 12-lead ECGs: As of March 2008, 100 subjects had been enrolled. Consequently, for subjects enrolled after March 2008 only single 12-lead ECGs were performed at screening and at the follow-up visit after last dose. Additional ECGs were performed as clinically indicated.
h. Hgb, WBC with differential, and platelets.
i. Chemistry required on Days 1 and 15 only for each cycle.
j. Protein, glucose, and blood.
k. Thyroid Stimulating Hormone (TSH) at Baseline (predose), on Day 15 of Cycle 1, on Day 1 of Cycle 2, on Day 15 of Cycle 2, every 8-weeks thereafter for all subjects. Free T_4 at Baseline, then as clinically indicated. Hypothyroidism was treated as per standard medical practice to maintain euthyroid state.
l. AEs were collected throughout the study period.
m. Collected from screening to the follow-up visit.
n. Baseline assessment of disease (CT/MRI of the chest and abdomen at the minimum) done within 28 days before randomization. Tumor assessments (CT/MRI of the chest and abdomen at the minimum) done every 2 cycles (ie, at the end of the second cycle, end of every other cycle thereafter), whenever disease progression was suspected and at follow-up. Assessment of disease was performed per RECIST. Response (CR/PR) required confirmation at least 4 weeks after the first response was noted.
o. CA19-9 was measured in all subjects at Baseline and if elevated, every 8 weeks. CA19-9 is an exploratory tumor marker and was not be used to assess response or disease progression.
p. HRQoL, pain, and health status questionnaires were self-administered by the subject in the clinic prior to dosing, and ideally before any clinical assessments. If Baseline questionnaires had been obtained within 4 days prior, questionnaires on Cycle 1 Day 1 were not necessary. For Japan: QLQ-PAN26 and BPI-sf were performed only on newly enrolled subjects after the Japanese version was available and IRB-approved.
q. Population PK samples for axitinib/placebo were obtained 15 minutes prior to the morning dose (taken in the clinic) and 1 to 2 hours after that dose. Plasma samples for axitinib/placebo were obtained on Day 1 (1 to 2 hours after the first dose), Day 29 (just before and 1 to 2 hours after the morning dose axitinib/placebo), Day 57 (just before and 1 to 2 hours after the morning dose) and then every 8 weeks thereafter (just before and 1 to 2 hours after the morning dose).
r. Subjects of childbearing potential had to have a negative serum or urine pregnancy test within 3 days prior to treatment and had to be practicing appropriate birth control. Pregnancy tests were also repeated as per request of IRB/IECs or if required by local regulations.
s. Infusion length was 30 minutes. Longer infusion could cause excessive toxicity. If axitinib/placebo was being held or discontinued for drug-related AEs, gemcitabine was continued until disease progression or intolerable toxicity.
t. If gemcitabine was being held or discontinued for drug-related AEs, axitinib/placebo was continued until disease progression or intolerable toxicity.
u. One blood sample (2 mL) was collected on Day 1 of Cycle 1 only for genotyping of UGT1A1 and other drug metabolizing enzymes.
v. A separate informed consent was required for those subjects willing to donate a blood sample and/or tumor specimen (archival) for this research. The blood sample was collected on Day 1 of Cycle 1. The collection of these samples was optional and not required for participation in this study.
w. OS was the primary endpoint of this study and obtaining accurate survival data for each subject was extremely important. All subjects were followed for survival every month for the first 6 months, then every 3 months thereafter, following discontinuation of study treatment until at least 1 year after randomization of the last subject.

Number of Subjects (Planned and Analyzed): A total of 596 subjects were planned. A total of 632 subjects were randomized (121 in the United States, 114 in Japan, 49 in France, 39 each in the United Kingdom and Canada, 35 in Spain, 27 in Italy, 25 in Netherlands, 24 in the Republic of Korea, 20 in the Russian Federation, 19 in South

Africa, 16 in Belgium, 15 in Germany, 13 in Australia, 12 each in Austria and Taiwan, 11 in India, 10 in Hungary, 8 in Sweden, 7 each in Argentina and Singapore, 6 in Ireland, 2 in Switzerland and 1 in Hongkong).

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged ≥18 years with histologically or cytologically confirmed, metastatic or locally-advanced pancreatic adenocarcinoma not amenable to curative resection, adequate renal, hepatic, and bone marrow function, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Subjects were excluded on the basis of prior treatment with any systemic chemotherapy for metastatic disease, prior treatment with gemcitabine, axitinib, or other vascular endothelial growth factor inhibitors, current or recent bleeding, thromboembolic event, and/or use of a thrombolytic agent, and inability to take oral medication.

Study Treatment: The starting dose of axitinib was 5 mg, given as film-coated tablet twice daily (BID) (at approximately 12-hour intervals) with food. Gemcitabine was administered at a dose of 1000 mg/m^2 by 30-minute intravenous infusion.

The dose of either study treatment was adjusted according to the type and grade (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE]) of adverse events (AEs) experienced, as follows:

Axitinib

The starting dose was axitinib (or placebo) 5 mg twice daily (BID) administered orally with food. Doses were taken as close to 12 hours apart as possible and at approximately the same times each day. Subjects who tolerated axitinib with no AEs related to axitinib of greater than Grade 2 CTCAE for consecutive 2-week periods had their dose increased by 1 dose level (Table 2) unless their blood pressure was >150/90 mm Hg or the subject was receiving antihypertensive medication. In cases where it was not obvious as to which drug was the major contributor to AE(s), dose titrations remained at the investigator's discretion. Once a subject had a dose reduction for study drug related toxicity, the dose was not usually re-escalated unless the toxicity was later determined to be unrelated to the study drug.

Table 2. Axitinib Dose Levels

Dose Level	Dose	Dispensed As
+2	10 mg BID	2 x 5 mg tablets BID
+1	7 mg BID	1 x 5 mg tablet + 2 x 1 mg tablets BID
0 (Starting dose)	5 mg BID	1 x 5 mg tablet BID
-1	3 mg BID	3 x 1 mg tablets BID
-2	2 mg BID	2 x 1 mg tablets BID

Gemcitabine

Commercially available gemcitabine 1000 mg/m^2 was supplied by each study center and administered by 30-minute intravenous infusion once weekly for 3-weeks followed by a week of rest from treatment. Subsequent cycles consisted of infusions once weekly for 3 consecutive weeks in 28-day cycles.

Due to radio-sensitization risk of gemcitabine, a minimum time window of 7 days (4 weeks for France only) was recommended between the administration of gemcitabine and radiotherapy. Gemcitabine could be re-started off-study after the acute effects of radiation had resolved (at least 7 days after radiation [4 weeks for France only]). This time window could have been modified per investigator discretion depending on the subject's clinical status. Preparation and administration precautions were contained in the Product Labeling (Package Insert) for gemcitabine (Gemzar®).

Once a subject had a dose reduction for study drug related toxicity, the dose was not usually re-escalated unless the toxicity was later determined to be unrelated to the study drug.

Table 3 shows available gemcitabine dose levels and dose modifications in response to drug related AEs, including specific adjustments for hematologic toxicity, febrile neutropenia, hepatic toxicity and other non-hematologic gemcitabine toxicities, were pre-specified in the protocol.

Table 3. Gemcitabine Dose Levels

Dose Level	Dose
0 (Starting dose)	1000 mg/m^2
-1	750 mg/m^2
-2	550 mg/m^2
-3	425 mg/m^2

Efficacy Endpoints:

Primary Endpoint: The primary efficacy endpoint was OS.

Secondary Endpoints: The secondary efficacy endpoints were

- PFS
- ORR

- DR
- Type, incidence, severity (graded by the National Cancer Institute [NCI], CTCAE Version 3.0), timing, seriousness, and relatedness of adverse events, and laboratory abnormalities
- PROs: EORTC QLQ-C30, QLQ-PAN26, BPI-sf, EQ-5D
- Axitinib population PK analysis

Population PK samples (2 x 7 mL blood samples) were collected from subjects receiving axitinib/placebo; samples were obtained 15 minutes prior to the morning dose (taken in the clinic) and 1 to 2 hours afterwards. Plasma samples for axitinib/placebo were obtained on Day 1 (1 to 2 hours after the first dose), Day 29 (just before and 1 to 2 hours after the morning dose of axitinib/placebo), Day 57 (just before and 1 to 2 hours after the morning dose), and every 8 weeks thereafter (just before and 1 to 2 hours after the morning dose). These data were reported separately.

A blood sample was collected from all subjects prior to dosing on Day 1 for pharmacogenomic analysis of drug metabolizing enzymes. This blood sample was planned to be used for the analysis of the uridine glucuronyl transferase (UGT) 1A1 gene involved in the metabolism of axitinib. These data are not included in this report.

Safety Evaluations: AEs, clinical laboratory measurement, electrocardiogram (ECG) and vital signs were assessed throughout the study.

Statistical Methods: The following analysis sets were defined:

- Intent-to-Treat (ITT) Population: This population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized. This was the primary population for evaluating all efficacy endpoints as well as subject characteristics.
- As–Treated (AT) Population: The AT population consisted of all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/compliance and safety. Efficacy and clinical benefit endpoints were assessed in this population as well.

OS was summarized in the ITT) population using Kaplan-Meier methods and displayed graphically where appropriate. The median event time for each treatment arm and corresponding 2-sided 95% confidence interval (CI) for the median were provided for OS. The hazard ratio and its 95% CI were estimated. A stratified (extent of disease [locally advanced versus metastatic]) log-rank test (1-sided, α=0.025) was used to compare OS between the 2 treatment arms.

An unstratified log-rank test (1-sided, α=0.025) was also calculated. Cox regression models were used to explore the potential influences of the stratification factors on the primary OS endpoint. In addition, the potential influences of baseline subject characteristics such as age, ethnic origin and sex on the primary OS endpoint were evaluated.

The survival probability at 1 year was intended to be estimated for each treatment arm using the Kaplan-Meier method and the 2-sided 95% CI for the log (-log[1-year survival probability]) was to be calculated using a normal approximation and then back transformed to give the CI for the 1 year survival rate itself. Since the study was terminated early due to futility, there was insufficient information to estimate the 1 year survival probability and corresponding CI for each arm.

Safety data were summarized for the AT population overall. Safety data were evaluated using descriptive statistics.

RESULTS

Subject Disposition and Demography: There were 632 subjects in the ITT population who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized. The AT population consisted of 617 subjects (308 in the axitinib + gemcitabine arm and 309 in the placebo + gemcitabine arm) who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. Based on the interim analysis, the independent data monitoring committee (DMC) found no evidence of improvement in the primary endpoint, OS and therefore recommended that the study be stopped. At the time of the interim analysis, data from 630 of the 632 randomized subjects were available for summarization. Two subjects did not have their randomization information entered into the clinical database at the time of the snapshot and hence were dropped from the analyses and summaries. Reasons for subject discontinuation by treatment cycle are summarized in Table 4. Most subjects discontinued axitinib/placebo or gemcitabine treatment due to disease progression or AEs. Baseline characteristics are summarized in Table 5 and demographics in Table 6.

Table 4. Reasons for Discontinuation (ITT Population)

Number of Subjects (%)	Axitinib+ Gemcitabine N=316	Placebo+ Gemcitabine N=316
Primary reason for discontinuation from gemcitabine		
Objective progression or relapse	164 (51.9%)	153 (48.4%)
Global deterioration of health status	20 (6.3%)	21 (6.6%)
Adverse events	50 (15.8%)	51 (16.1%)
Subject died	13 (4.1%)	13 (4.1%)
Protocol violation	2 (0.6%)	2 (0.6%)
Lost to follow-up	6 (1.9%)	1 (0.3%)
Subject refused continued treatment[a]	23 (7.3%)	22 (7.0%)
Withdrawn due to pregnancy	0	0
Study terminated by sponsor	14 (4.4%)	23 (7.3%)
Other	24 (7.6%)	30 (9.5%)
Primary reason for discontinuation from axitinib/placebo		
Objective progression or relapse	144 (45.6%)	128 (40.5%)
Global deterioration of health status	18 (5.7%)	20 (6.3%)
Adverse events	58 (18.4%)	53 (16.8%)
Subject died	9 (2.8%)	11 (3.5%)
Protocol violation	2 (0.6%)	2 (0.6%)
Lost to follow-up	6 (1.9%)	1 (0.3%)
Subject refused continued treatment[a]	21 (6.6%)	16 (5.1%)
Withdrawn due to pregnancy	0	0
Study terminated by sponsor	41 (13.0%)	60 (19.0%)
Other	17 (5.4%)	25 (7.9%)
Primary reason for discontinuation from study		
Objective progression or relapse	162 (51.3%)	147 (46.5%)
Global deterioration of health status	18 (5.7%)	23 (7.3%)
Adverse events	52 (16.5%)	52 (16.5%)
Subject died	15 (4.7%)	17 (5.4%)
Protocol violation	2 (0.6%)	2 (0.6%)
Lost to follow-up	6 (1.9%)	2 (0.6%)
Subject refused continued treatment[a]	24 (7.6%)	23 (7.3%)
Withdrawn due to pregnancy	0	0
Study terminated by sponsor	12 (3.8%)	26 (8.2%)
Other	25 (7.9%)	24 (7.6%)

a. Due to reason other than adverse event.
ITT = intent-to-treat; N = number of subjects.

Table 5. Baseline ECOG Performance Status and Extent of Disease at Screening (ITT Population)

	Axitinib + Gemcitabine N=314	Placebo + Gemcitabine N=316
ECOG performance status (n [%])		
0	147 (46.8%)	158 (50.0%)
1	162 (51.6%)	154 (48.7%)
Not specified	5 (1.6%)	4 (1.3%)
Extent of disease[a]		
Locally advanced	77 (24.5%)	73 (23.1%)
Metastatic	226 (72.0%)	227 (71.8%)
Not specified	11 (3.5%)	16 (5.1%)
Extent of disease[b]		
Locally advanced	76 (24.2%)	75 (23.7%)
Metastatic	238 (75.8%)	241 (76.3%)
Not specified	0	0
Stage of disease		
III	52 (16.6%)	54 (17.1%)
IV	251 (79.9%)	248 (78.5%)

a. as specified on the CRF at Screening.
b. as specified at randomization and stratification of randomization (used in the efficacy analysis).
CRF = case report form; ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat; N = number of subjects; n = number of subjects in each category.

Table 6. Subject Demographics (ITT Population)

	Axitinib + Gemcitabine N=314	Placebo + Gemcitabine N=316
Age (years)		
Mean (SD)	60.9 (9.9)	61.9 (10.6)
Median	61.0	62.0
Min, Max	(34, 84)	(35, 89)
Age (years) (n [%])		
<65	203 (64.6)	179 (56.6)
≥65	111 (35.4)	137 (43.4)
Race (n [%])		
White	211 (67.2)	220 (69.6)
Black	8 (2.5)	7 (2.2)
Asian	89 (28.3)	84 (26.6)
Other	6 (1.9)	5 (1.6)

ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; n = number of evaluable subjects; SD = standard deviation.

The efficacy analyses were performed on the ITT population that included all randomized subjects who were assigned to study treatment (314 and 316 subjects in the axitinib + gemcitabine and placebo + gemcitabine arms, respectively) and who had information in the database at the time of the interim analysis. The safety analyses were performed for the AT population (309 and 308 subjects in the placebo+ gemcitabine arm and axitinib + gemcitabine arm, respectively). Subjects were included in the treatment group to which they were initially randomized.

Table 7 shows the analysis sets for the 632 enrolled subjects.

Table 7. Subjects Analyzed

	Axitinib + Gemcitabine	Placebo + Gemcitabine
Enrolled subjects[a]	632	
Intent-to-treat population[b]	316	316
AT population[c]	308	309

AT=As-treated, ITT=Intent-to-treat.
a. All screened subjects before randomization.
b. ITT population includes all subjects who are randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects receive study drug or receive a different drug from that to which they were randomized.
c. AT population consists of all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

Efficacy Results:

Primary Endpoint: The median OS for the axitinib + gemcitabine and placebo + gemcitabine treated arms was 36.9 weeks (95% CI: 30.1, 41.1) and 35.8 weeks (95% CI: 30.0, 44.8), respectively (Table 8). Controlling for baseline stratification factor, extent of disease (locally advanced versus metastatic), the hazard ratio (axitinib + gemcitabine: placebo + gemcitabine) was 1.01 (95% CI: 0.79, 1.31; 1-sided p-value:0.54) (Table 9).

Table 8. Overall Survival (ITT Population)

	Axitinib + Gemcitabine N=314	Placebo + Gemcitabine N=316
Subject status		
Alive	196 (62.4%)	196 (62.0%)
Dead[a]	118 (37.6%)	120 (38.0%)
Median survival (weeks)	36.9	35.8
95% CI	(30.1, 41.1)	(30.0, 44.8)
Hazard ratio (AG + gem:PL + gem)[b]	1.036	
95% CI	(0.803-1.336)	
p-value[c]	0.6072	

AG = axitinib; CI = confidence interval; gem = gemcitabine; ITT = intent-to-treat; N = number of subjects; PL = placebo.
a. Subjects who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.
b. Assuming proportional hazards model, a hazard ratio less than 1 indicated a reduction in hazard rate in favor of Gem + AG: a hazard ratio greater than 1 indicated a reduction in favor of Gem + PL.
c. p-value was from a 1-sided, unstratified log-rank test.

Table 9. Overall Survival by Treatment and Stratification Factor (ITT)

	Axitinib + Gemcitabine N=314		Placebo + Gemcitabine N=316
Locally advanced	76		75
Number of subjects who died[a]	21 (27.6%)		13 (17.3%)
Median survival (weeks)	41.1		45.8
95% CI	(32.1, -)		(42.9, -)
1-year survival (%)[b]	NA		NA
95% CI	-		-
Hazard ratio (AG + gem:PL + gem)[c]		2.079	
95% CI		(1.031-4.189)	
p-value		0.9818	
Metastatic	238		241
Number of subjects who died[a]	97 (40.8)		107 (44.4)
Median survival (weeks)	30.3		29.9
95% CI	(25.1, 40.5)		(26.8, 34.6)
1-year survival (%)[b]	NA		NA
95% CI	-		-
Hazard ratio (AG + gem:PL + gem) [c]		0.904	
95% CI		(0.686-1.190)	
p-value[d]		0.2345	
Overall stratified analysis			
Hazard ratio (AG + gem:PL + gem)		1.014	
95% CI		(0.786-1.309)	
p-value[e]		0.5436	

AG = axitinib; CI = confidence interval; gem = gemcitabine; ITT = intent-to-treat; N = number of subjects; NA = not applicable; PL = placebo.

a. Subjects who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.
b. Calculated from the log (- log[1-year survival probability]) using a normal approximation and back transformation.
c. Assuming proportional hazards model, a hazard ratio less than 1 indicated a reduction in hazard rate in favor of Gem + AG: a hazard ratio greater than 1 indicated a reduction in favor of Gem + PL.
d. p-value was from a 1-sided, unstratified log-rank test.
e. p-value was from a log-rank test of treatment stratified by Locally Advanced and Metastatic cancer category.

Secondary Endpoints:

Progression Free Survival: The median PFS was 19.1 weeks (95% CI: 17.1, 24.4) and 18.9 weeks (95% CI: 16.2, 22.6) for the axitinib + gemcitabine and placebo + gemcitabine arms, respectively (Table 10). Controlling for baseline stratification factor, extent of disease (locally advanced versus metastatic), the hazard ratio (axitinib + gemcitabine: placebo + gemcitabine) was 1.01 (95% CI: 0.78, 1.30, 1-sided p-value: 0.52, Table 11). Without controlling for baseline stratification factors, the hazard ratio (axitinib + gemcitabine: placebo + gemcitabine) was 1.04 (95% CI: 0.803, 1.34, 1-sided p-value: 0.61, Table 10).

Table 10. Progression-Free Survival (ITT Population)

	Axitinib + Gemcitabine N=314	Placebo + Gemcitabine N=316
Status		
Subject progressed or died[a]	116 (36.9%)	125 (39.6%)
Subject did not progress or die	198 (63.1%)	191 (60.4%)
Median PFS (weeks)	19.1	18.9
95% CI	(17.1, 24.4)	(16.2, 22.6)
Hazard ratio (AG + gem:PL + gem)	1.036	
95% CI	0.803-1.335	
p-value[b]	0.6079	

AG = axitinib; CI = confidence interval; gem = gemcitabine; ITT =intent-to-treat; PL = placebo; PFS = progression free survival; N = number of subjects.
a. Included treatment plus 28-day follow-up period.
b. p-value was from a 1-sided, unstratified log-rank test.

Table 11. Progression-Free Survival by Treatment and Stratification Factor (ITT)

	Axitinib + Gemcitabine N=314	Placebo + Gemcitabine N=316
Locally advanced	76	75
Subject progressed or died	22 (28.9%)	17 (22.7%)
Median PFS (weeks)	25.4	39.3
95% CI	(18.1, 31.8)	(25.3, 45.8)
Hazard ratio (AG+gem:PL+gem)[a]	1.888	
95% CI	(0.978, 3.645)	
p-value[b]	0.9732	
Metastatic	238	241
Subject progressed or died	94 (39.5%)	108 (44.8%)
Median PFS (weeks)	18.0	16.4
95% CI	(16.1, 23.2)	(15.4, 19.3)
Hazard ratio (AG+gem:PL+gem) [a]	0.897	
95% CI	(0.679-1.184)	
p-value[b]	(0.2214)	
Hazard ratio (AG+gem:PL+gem) [a]	1.006	
95% CI	(0.779, 1.298)	
p-value[b]	0.5203	

AG = axitinib; CI=confidence interval; gem = gemcitabine; ITT = intent-to-treat; N = number of subjects; PFS = progression free survival; PL = placebo.
a. Assuming proportional hazards, a hazard ratio less than 1 indicated a reduction in hazard rate in favor of AG + gemcitabine: a hazard ratio greater than 1 indicated a reduction in favor of placebo + gem.
b. p-value was from a log-rank test of treatment stratified by Locally Advanced and Metastatic cancer category.

Overall Response Rate: Overall response rate was 12 subjects (4.9%) in the axitinib + gemcitabine arm and 4 subjects (1.6%) in the placebo + gemcitabine arm. One subject (0.4%) in the axitinib + gemcitabine arm who had baseline measurable disease had a CR. Eleven subjects (4.5%) had a confirmed PR in the axitinib + gemcitabine arm and 4 subjects (1.6%) had a confirmed PR in the placebo + gemcitabine arm (Table 12).

Table 12. Overall Response Rate (ITT Population with Measurable Disease)

	Axitinib + Gemcitabine	Placebo + Gemcitabine
Subjects with measurable disease at Baseline	247	255
Complete response (CR)	1 (0.4%)	0
Partial response (PR)	11 (4.5%)	4 (1.6%)
Stable disease	65 (26.3%)	69 (27.1%)
Overall response rate (ORR)	12 (4.9%)	4 (1.6%)
95% CI[a]	(2.5, 8.3)	(0.4, 4.0)
Difference in response rates (95% CI)[b]	3.3 (0.2, 6.4)	
p-value[c]	0.0180	

Percentages of subjects with measurable disease at baseline.
Response 'on study' included treatment and 28-day follow-up period.
CI = confidence interval; ITT = intent-to-treat; N = number of subjects.
a. Using exact method based on F-distribution.
b. Calculated based on a normal distribution.
c. 1-sided p-value was from a Pearson chi-square test.

Duration of Response: DR is summarized in Table 13.

Table 13. Duration of Response (Responding Subjects)

	Axitinib + Gemcitabine N=314	Placebo + Gemcitabine N=316
Subjects with response[a]	12 (3.82%)	4 (1.27%)
Subjects with a response who had not progressed or died due to any cause while on study[a]	9 (75.0%)	4 (100%)
Subjects with a response and subsequent progression or death due to any cause while on study[a]	3 (25.0%)	0 (0.0%)
Duration of response (Weeks)		
Median (95% CI)	33.1 (16.1, 33.1)	nd[b]

CI = confidence interval; N = number of subjects; nd = not done.
a. Response 'on study' included treatment and 28-day follow-up period.
b. median duration of response for placebo + gemcitabine arm not reached at the time of the data cut-off for the clinical study report (23 January 2009).

EORTC QLQ-C30 and PAN26: At Baseline, the mean QLQ-C30 and PAN26 scores did not differ greatly for the 2 arms. The QLQ-C30 and PAN26 are summarized in Table 14.

Table 14. Changes from Baseline after 1 and 3 Cycles of Treatment for Both Treatment Arms on Selected Scales from the QLQ-C30 and PAN26 Questionnaires

Scale	Axitinib + Gemcitabine (N=297)		Placebo + Gemcitabine (N=296)	
	Cycle 2 Day 1	Cycle 4 Day 1	Cycle 2 Day 1	Cycle 4 Day 1
	Mean Δ (SD)	Mean Δ (SD)	Mean Δ (SD)	Mean Δ (SD)
QLQ-C30	–	–	–	–
Functioning scales				
Emotional functioning	5.0 (21.48)	–	5.0 (18.92)	5.2 (21.12)
Physical functioning	–	-5.67 (18.86)	–	–
Symptoms				
Pain	-10.1 (29.47)	-12.2 (32.48)	-7.9 (25.28)	-7.8 (27.14)
Dyspnea	5.5 (23.58)	7.7 (26.99)	–	–
Insomnia	-13.6 (33.55)	-12.7 (38.52)	-7.3 (33.16)	-11.2 (27.41)
Constipation	–	-6.5 (35.99)	–	-10.6 (36.80)
Fatigue	–	5.6 (23.87)	–	–
Diarrhea	–	7.7 (28.00)	–	–
Loss of appetite	–		–	-6.7 (29.88)
Financial difficulties	–	-5.5 (26.33)	–	–
PAN26				
Pancreatic pain	-10.90 (24.38)	-13.20 (28.70)	-10.10 (22.93)	-11.40 (26.16)
Altered bowel habits	–	6.60 (25.52)	–	–
Body image	–	6.70 (26.20)	–	–
Cachexia	–	–	–	-6.20 (24.82)
Side effects from treatment	11.20 (23.11)	10.10 (20.64)	5.80 (22.06)	4.90 (22.48)
Fear of future health	–	–	-9.60 (28.80)	-15.90 (30.90)
Ability to plan for future	6.10 (38.19)	5.6 (36.55)	–	–

Only scales demonstrating greater than 5 points change at either occasion were reported.
QLQ = quality of life questionnaire; Δ = change; SD = standard deviation; N = number of subjects.

Brief Pain Inventory-Short-form (BPI-sf): At Baseline, the mean BPI-sf scores did not differ greatly for the 2 arms. Mean scores on all of the pain severity items were low for both groups. The mean BPI-sf score is summarized in Table 15.

Table 15. Changes from Baseline After 1 and 3 Cycles of Treatment for Both Treatment Arms on the BPI-sf Questionnaire

Scale	Axitinib + Gemcitabine (N=249)		Placebo + Gemcitabine (N=254)	
	Cycle 2 Day 1	Cycle 4 Day 1	Cycle 2 Day 1	Cycle 4 Day 1
	Mean Δ (SD)		Mean Δ (SD)	
BPI-sf				
Pain severity items				
Worst pain	-0.7 (3.04)	-1.0 (3.41)	-0.9 (2.84)	-0.9 (3.09)
Pain in last 24 hours	-0.2 (2.21)	-0.3 (2.15)	-0.3 (1.92)	-0.0 (1.96)
Average pain	-0.5 (2.02)	-0.7 (2.44)	-0.5 (2.29)	-0.6 (2.03)
Pain right now	-0.4 (2.23)	-0.6 (2.26)	-0.5 (2.37)	-0.5 (2.45)
Combined pain severity	-0.4 (1.97)	-0.6 (2.19)	-0.5 (1.97)	-0.5 (1.99)
Pain interference items				
General activity	-0.6 (2.96)	-0.4 (3.10)	-0.7 (2.55)	-0.8 (2.53)
Mood	-0.6 (2.74)	-0.3 (3.22)	-0.2 (2.46)	-0.9 (2.81)
Walking ability	0.1 (2.84)	0.3 (3.32)	-0.1 (2.61)	-0.4 (2.64)
Normal work	-0.4 (3.24)	-0.2 (3.15)	-0.1 (3.16)	-0.7 (2.90)
Relations	-0.3 (2.82)	-0.2 (3.36)	0.0 (2.18)	-0.1 (2.52)
Sleep	-1.1 (3.36)	-1.2 (3.29)	-0.9 (2.73)	-1.2 (3.02)
Enjoyment of life	-0.6 (2.99)	-0.6 (3.58)	-0.5 (2.89)	-0.9 (2.70)
Combined pain interference	-0.5 (2.44)	-0.4 (2.62)	-0.4 (1.97)	-0.7 (2.12)

BPI-sf = brief pain inventory-short form; N = number of subjects who completed as least one item on the measure; SD = standard deviation; Δ = change.

EQ-5D: Table 16 provides a summary of the proportion of individuals scoring at different levels of problems with the 5 questions on the EQ-5D at the baseline assessment. Although there was some variability, the differences in proportions of reported problems between the 2 arms were not significant.

Table 16. Baseline Values for Both Treatment Arms on the EQ-5D Questionnaire

Scale	Axitinib + Gemcitabine (N=289)	Placebo + Gemcitabine (N=290)
	n (%)	n (%)
EQ-5D		
Mobility		
No problem	215 (74.4)	202 (69.7)
Some problem	74 (25.6)	87 (30.0)
Extreme problem	0 (0.0)	1 (0.3)
Self-care		
No problem	270 (93.4)	272 (93.8)
Some problem	18 (6.2)	16 (5.5)
Extreme problem	1 (0.3)	2 (0.7)
Usual activities		
No problem	143 (49.5)	153 (52.8)
Some problem	124 (42.9)	118 (40.7)
Extreme problem	22 (7.6)	19 (6.6)
Pain/discomfort		
No problem	74 (25.6)	86 (29.7)
Some problem	182 (63.0)	182 (62.8)
Extreme problem	33 (11.4)	22 (7.6)
Anxiety/depression		
No problem	137 (47.4)	133 (45.9)
Some problem	139 (48.1)	149 (51.4)
Extreme problem	13 (4.5)	8 (2.8)

EQ-5D = self report questionnaire; N = number of subjects who completed as least 1 item on the measure; n = number of subjects who responded to that item.

Safety Results: Table 17 summarizes treatment-emergent AEs in ≥5% subjects with System Organ Class/Preferred Terms. The most frequently occurring AEs in the axitinib + gemcitabine arm were nausea, fatigue, anorexia, diarrhea and vomiting.

Table 17. Treatment-Emergent Non-Serious Adverse Events in ≥5% of Subjects, by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Axitinib + Gemcitabine n (%)	Gem + PL n (%)
No. (%) of Subjects:		
Evaluable for Adverse Events	**304**	**309**
With Adverse Events	**276 (90.8)**	**276 (89.3)**
Blood and lymphatic system disorders	112 (36.8)	103 (33.3)
Anaemia	25 (8.2)	51 (16.5)
Leukopenia	23 (7.6)	13
Neutropenia	73 (24.0)	53 (17.2)
Thrombocytopenia	48 (15.8)	34 (11.0)
Gastrointestinal disorders	230 (75.7)	222 (71.8)
Abdominal pain	54 (17.8)	52 (16.8)
Abdominal pain upper	24 (7.9)	24 (7.8)
Constipation	88 (28.9)	91 (29.4)
Diarrhoea	96 (31.6)	64 (20.7)
Dry mouth	14	14
Dyspepsia	14	22 (7.1)
Nausea	138 (45.4)	112 (36.2)
Stomatitis	52 (17.1)	12
Vomiting	91 (29.9)	95 (30.7)
General disorders and administration site conditions	194 (63.8)	193 (62.5)
Asthenia	38 (12.5)	38 (12.3)
Fatigue	125 (41.1)	113 (36.6)
Mucosal inflammation	34 (11.2)	13
Oedema peripheral	22 (7.2)	46 (14.9)
Pain	16 (5.3)	7
Pyrexia	38 (12.5)	44 (14.2)
Investigations	126 (41.4)	121 (39.2)
Alanine aminotransferase increased	29 (9.5)	24 (7.8)
Aspartate aminotransferase increased	24 (7.9)	21 (6.8)
Blood thyroid stimulating hormone increased	16 (5.3)	0
Haemoglobin decreased	18 (5.9)	26 (8.4)
Neutrophil count decreased	31 (10.2)	38 (12.3)
Platelet count decreased	43 (14.1)	40 (12.9)
Weight decreased	44 (14.5)	29 (9.4)
White blood cell count decreased	20 (6.6)	16 (5.2)
Metabolism and nutrition disorders	131 (43.1)	110 (35.6)
Decreased appetite	115 (37.8)	87 (28.2)
Musculoskeletal and connective tissue disorders	70 (23.0)	79 (25.6)
Back pain	34 (11.2)	30 (9.7)
Nervous system disorders	86 (28.3)	72 (23.3)
Dizziness	10	17 (5.5)
Dysgeusia	25 (8.2)	14
Headache	45 (14.8)	26 (8.4)
Psychiatric disorders	58 (19.1)	49 (15.9)
Anxiety	16 (5.3)	19 (6.1)
Insomnia	25 (8.2)	18 (5.8)
Renal and urinary disorders	31 (10.2)	24 (7.8)
Proteinuria	17 (5.6)	12

Table 17. Treatment-Emergent Non-Serious Adverse Events in ≥5% of Subjects, by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Axitinib + Gemcitabine n (%)	Gem + PL n (%)
Respiratory, thoracic and mediastinal disorders	111 (36.5)	67 (21.7)
Cough	24 (7.9)	19 (6.1)
Dysphonia	68 (22.4)	12
Dyspnoea	24 (7.9)	20 (6.5)
Skin and subcutaneous tissue disorders	110 (36.2)	96 (31.1)
Alopecia	31 (10.2)	20 (6.5)
Palmar-plantar erythrodysaesthesia syndrome	18 (5.9)	2
Pruritus	14	17 (5.5)
Rash	43 (14.1)	41 (13.3)
Vascular disorders	103 (33.9)	60 (19.4)
Hypertension	84 (27.6)	26 (8.4)

Subjects are only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
Gem = gemcitabine; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; PL = placebo; v = version.

Table 18 summarizes treatment-related AEs experienced by ≥5% subjects in the axitinib + gemcitabine arm. The most frequently occurring treatment-related AEs in the axitinib + gemcitabine arm were nausea (in the placebo + gemcitabine arm) and fatigue.

SAEs: All causality SAEs were experienced by 108 subjects (35.5%) in the axitinib + gemcitabine arm and 102 subjects (33.0%) subjects in the placebo + gemcitabine arm. The most frequently occurring SAEs in the axitinib + gemcitabine arm were abdominal pain, pyrexia and vomiting. The most frequently occurring SAEs in the placebo + gemcitabine arm were vomiting and abdominal pain. Table 19 and Table 20 summarizes all causality and treatment-related SAEs, respectively.

Table 18. Treatment Related Adverse Events in ≥5% of Subjects, by System Organ Class and Preferred Term

System Organ Class Preferred Term	Axitinib + Gemcitabine n (%)	Gem + PL n (%)
Any Adverse Event	294 (95.5)	277 (89.6)
Blood and lymphatic system disorders	131 (42.5)	120 (38.8)
Neutropenia	88 (28.6)	66 (21.4)
Thrombocytopenia	65 (21.1)	60 (19.4)
Anaemia	43 (14.0)	45 (14.6)
Leukopenia	28 (9.1)	18 (5.8)
Endocrine disorders	25 (8.1)	5 (1.6)
Hypothyroidism	23 (7.5)	5 (1.6)
Gastrointestinal disorders	222 (72.1)	177 (57.3)
Nausea	140 (45.5)	118 (38.2)
Diarrhoea	98 (31.8)	58 (18.4)
Vomiting	83 (26.9)	82 (26.5)
Stomatitis	55 (17.9)	11 (3.6)
Constipation	50 (16.2)	34 (11.0)
Dry mouth	11 (3.6)	17 (5.5)
General disorders and administration site conditions	192 (62.3)	177 (57.3)
Fatigue	129 (41.9)	112 (36.2)
Asthenia	40 (13.0)	31 (10.0)
Mucosal inflammation	37 (12.0)	16 (5.2)
Pyrexia	37 (12.0)	32 (10.4)
Oedema peripheral	16 (5.2)	19 (6.1)
Investigations	109 (35.4)	109 (35.3)
Platelet count decreased	47 (15.3)	45 (14.6)
Neutrophil count decreased	35 (11.4)	42 (13.6)
Blood thyroid stimulating hormone increased	22 (7.1)	0
White blood cell count decreased	22 (7.1)	16 (5.2)
Weight decreased	21 (6.8)	13 (4.2)
Haemoglobin decreased	20 (6.5)	28 (9.1)
Alanine aminotransferase increased	19 (6.2)	19 (6.1)
Metabolism and nutrition disorders	107 (34.7)	90 (29.1)
Decreased appetite	99 (32.1)	80 (25.9)
Nervous system disorders	77 (25.0)	66 (21.4)
Headache	37 (12.0)	19 (6.1)
Dysgeusia	25 (8.1)	20 (6.5)
Renal and urinary disorders	28 (9.1)	20 (6.5)
Proteinuria	23 (7.5)	13 (4.2)
Respiratory, thoracic and mediastinal disorders	96 (31.2)	50 (16.2)
Dysphonia	67 (21.8)	13 (4.2)
Epistaxis	17 (5.5)	5 (1.6)
Dyspnoea	24 (7.9)	15 (4.9)
Skin and subcutaneous tissue disorders	114 (37.0)	88 (28.5)
Rash	44 (14.3)	34 (11.0)
Alopecia	40 (13.0)	25 (8.1)
Palmar-plantar erythrodysaesthesia syndrome	31 (10.4)	3 (1.0)
Vascular disorders	113 (36.7)	46 (14.9)
Hypertension	105 (34.1)	29 (9.4)

% = (number of subjects/N)*100
Gem = gemcitabine; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with evaluable adverse events; PL = placebo; v = version.

Table 19. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) - For Events having a Frequency Rate ≥ 0

System Organ Class Preferred Term	Axitinib + Gemcitabine n (%)	Gem + PL n (%)
Number (%) of Subjects:		
Evaluable for adverse events	**304**	**309**
With adverse events	**108 (35.5)**	**102 (33.0)**
Blood and lymphatic system disorders	4	6
Anaemia	1	4
Febrile neutropenia	1	1
Neutropenia	0	1
Splenic vein thrombosis	0	1
Thrombocytopenia	2	1
Cardiac disorders	3	5
Acute myocardial infarction	1	0
Angina pectoris	1	0
Atrial fibrillation	0	1
Cardiac arrest	0	1
Cardiac failure	0	1
Cardiac failure congestive	0	2
Tachycardia	1	0
Congenital, familial and genetic disorders	1	0
Pyloric stenosis	1	0
Ear and labyrinth disorders	1	0
Deafness	1	0
Endocrine disorders	1	0
Adrenal insufficiency	1	0
Hypothyroidism	1	0
Gastrointestinal disorders	36 (11.8)	36 (11.7)
Abdominal discomfort	0	1
Abdominal distension	0	1
Abdominal pain	14	10
Abdominal pain lower	0	1
Abdominal pain upper	0	2
Anal fistula	1	0
Ascites	0	1
Colonic obstruction	1	0
Constipation	1	5
Diarrhoea	2	4
Duodenal obstruction	0	1
Duodenal ulcer	1	0
Dysphagia	1	0
Enterocutaneous fistula	1	0
Gastrointestinal haemorrhage	2	1
Gastrointestinal perforation	1	0
Haematemesis	1	1
Ileus	0	3
Intestinal fistula	1	0
Intestinal obstruction	2	1
Intestinal perforation	1	1
Large intestinal obstruction	1	1
Large intestine perforation	0	1
Melaena	1	0
Nausea	7	3
Obstruction gastric	0	1
Pancreatitis acute	1	0
Peritonitis	2	1
Rectal haemorrhage	0	1
Small intestinal haemorrhage	0	1

Table 19. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) - For Events having a Frequency Rate ≥ 0

System Organ Class Preferred Term	Axitinib + Gemcitabine n (%)	Gem + PL n (%)
Small intestinal perforation	1	0
Subileus	2	0
Vomiting	9	11
General disorders and administration site conditions	39 (12.8)	31 (10.0)
Asthenia	8	2
Chest pain	1	0
Complication of device insertion	1	0
Death	3	1
Device dislocation	0	1
Device occlusion	2	2
Disease progression	9	15
Drug interaction	0	1
Fatigue	4	0
General physical health deterioration	2	3
Generalised oedema	0	1
Impaired healing	1	0
Mucosal inflammation	0	1
Obstruction	1	1
Oedema peripheral	0	2
Pain	0	1
Performance status decreased	1	0
Pyrexia	13	5
Hepatobiliary disorders	21 (6.9)	14
Acholia	0	1
Bile duct obstruction	2	2
Cholangitis	7	3
Cholecystitis acute	1	0
Cholestasis	3	0
Cytolytic hepatitis	1	0
Gallbladder necrosis	1	0
Hepatic function abnormal	1	1
Hyperbilirubinaemia	1	3
Jaundice	6	4
Jaundice cholestatic	3	2
Immune system disorders	0	1
Contrast media allergy	0	1
Infections and infestations	12	17 (5.5)
Abdominal abscess	1	0
Biliary tract infection	2	0
Cellulitis	0	2
Cytomegalovirus infection	0	1
Device related infection	0	1
Diverticulitis	1	0
Ear infection	0	1
Escherichia urinary tract infection	1	0
Gastroenteritis	1	0
Infection	1	2
Peritoneal infection	0	1
Pneumonia	2	4
Respiratory tract infection	0	1
Sepsis	1	5
Septic shock	1	0
Urinary tract infection	1	1
Urinary tract infection fungal	1	0
Urosepsis	1	1

Table 19. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) - For Events having a Frequency Rate ≥ 0

System Organ Class Preferred Term	Axitinib + Gemcitabine n (%)	Gem + PL n (%)
Injury, poisoning and procedural complications	0	4
Drug dispensing error	0	1
Fall	0	1
Hand fracture	0	1
Wrist fracture	0	1
Investigations	6	6
Alanine aminotransferase increased	1	0
Aspartate aminotransferase increased	1	0
Blood alkaline phosphatase increased	1	0
Blood bilirubin increased	0	1
Blood creatinine increased	0	1
Haemoglobin decreased	1	3
Liver function test abnormal	1	1
Neutrophil count decreased	1	1
Platelet count decreased	2	1
White blood cell count decreased	1	0
Metabolism and nutrition disorders	16 (5.3)	12
Decreased appetite	7	4
Dehydration	4	4
Diabetes mellitus	0	1
Hypercalcaemia	1	0
Hyperglycaemia	1	1
Hypoalbuminaemia	0	1
Hypoglycaemia	2	0
Hypokalaemia	4	1
Hyponatraemia	0	1
Hypophagia	1	0
Malnutrition	2	0
Tumour lysis syndrome	0	1
Musculoskeletal and connective tissue disorders	3	2
Arthralgia	1	0
Back pain	2	2
Neoplasms benign, malignant and unspecified(incl cysts and polyps)	4	4
Duodenal neoplasm	0	1
Metastatic neoplasm	1	0
Neoplasm progression	1	0
Pancreatic carcinoma	1	1
Tumour associated fever	0	1
Tumour pain	1	1
Nervous system disorders	9	4
Cerebral ischaemia	1	0
Cerebrovascular accident	1	1
Cognitive disorder	1	0
Diabetic coma	0	1
Dysgeusia	1	0
Grand mal convulsion	1	0
Psychomotor skills impaired	1	0
Reversible posterior leukoencephalopathy syndrome	1	0
Sensory disturbance	2	0
Somnolence	1	0
Syncope	0	1
Thrombotic stroke	0	1
Transient ischaemic attack	1	1

Table 19. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) - For Events having a Frequency Rate ≥ 0

System Organ Class Preferred Term	Axitinib + Gemcitabine n (%)	Gem + PL n (%)
Psychiatric disorders	6	5
Agitation	0	1
Anxiety	1	0
Confusional state	4	3
Depression	1	0
Mental status changes	1	1
Renal and urinary disorders	8	6
Chromaturia	0	1
Renal failure	3	1
Renal failure acute	3	3
Ureteric perforation	1	0
Urethral obstruction	0	1
Urinary incontinence	1	0
Respiratory, thoracic and mediastinal disorders	7	16 (5.2)
Dyspnoea	2	3
Hiccups	0	1
Hypoxia	1	1
Interstitial lung disease	0	2
Pleural effusion	0	2
Pneumonitis	1	2
Pulmonary embolism	2	6
Respiratory failure	1	0
Skin and subcutaneous tissue disorders	1	3
Erythema	0	1
Rash	0	2
Skin ulcer	1	0
Vascular disorders	3	10
Bleeding varicose vein	0	1
Deep vein thrombosis	1	3
Hypertension	1	1
Hypotension	1	2
Phlebitis	0	1
Shock	0	1
Venous thrombosis	0	1
Venous thrombosis limb	0	1

Subjects are only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
Gem = Gemcitabine; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; PL = placebo v = version.

Table 20. Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (As-Treated Population)

	Gem + PL N=309	Axitinib + Gemcitabine N=308
System Organ Class **Preferred Term**	**n (%)**	**n (%)**
Any Treatment-Related SAEs	47 (15.2)	48 (15.6)
Blood and lymphatic system disorders	9 (2.9)	3 (1.0)
Anaemia	6 (1.9)	0 (0.0)
Neutropenia	2 (0.6)	0 (0.0)
Febrile neutropenia	1 (0.3)	1 (0.3)
Haemolytic uraemic syndrome	1 (0.3)	0 (0.0)
Thrombocytopenia	1 (0.3)	2 (0.6)
Cardiac disorders	3 (1.0)	1 (0.3)
Cardiac failure	1 (0.3)	0 (0.0)
Atrial fibrillation	1 (0.3)	0 (0.0)
Cardiac failure congestive	1 (0.3)	0 (0.0)
Tachycardia	0 (0.0)	1 (0.3)
Ear and labyrinth disorders	0 (0.0)	1 (0.3)
Deafness	0 (0.0)	1 (0.3)
Endocrine disorders	0 (0.0)	1 (0.3)
Adrenal insufficiency	0 (0.0)	1 (0.3)
Endocrine disorders		
Hypothyroidism	0 (0.0)	1 (0.3)
Gastrointestinal disorders	12 (3.9)	14 (4.5)
Diarrhoea	4 (1.3)	1 (0.3)
Gastrointestinal haemorrhage	2 (0.6)	2 (0.6)
Vomiting	2 (0.6)	3 (1.0)
Abdominal pain	1 (0.3)	1 (0.3)
Constipation	1 (0.3)	0 (0.0)
Gastrointestinal fistula	1 (0.3)	0 (0.0)
Haematemesis	1 (0.3)	0 (0.0)
Ileus	1 (0.3)	0 (0.0)
Rectal haemorrhage	1 (0.3)	0 (0.0)
Anal fistula	0 (0.0)	1 (0.3)
Gastric haemorrhage	0 (0.0)	1 (0.3)
Gastrointestinal perforation	0 (0.0)	2 (0.6)
Intestinal perforation	0 (0.0)	1 (0.3)
Nausea	0 (0.0)	1 (0.3)
Pancreatitis acute	0 (0.0)	1 (0.3)
Peritonitis	0 (0.0)	1 (0.3)
Gastrointestinal disorders		
Small intestinal perforation	0 (0.0)	1 (0.3)
General disorders and administration site conditions	3 (1.0)	13 (4.2)
Pyrexia	2 (0.6)	3 (1.0)
Drug interaction	1 (0.3)	0 (0.0)
Oedema peripheral	1 (0.3)	0 (0.0)
Asthenia	0 (0.0)	4 (1.3)
Death	0 (0.0)	1 (0.3)
Disease progression	0 (0.0)	1 (0.3)
Fatigue	0 (0.0)	2 (0.6)
General physical health deterioration	0 (0.0)	1 (0.3)
Impaired healing	0 (0.0)	1 (0.3)
Oedema	0 (0.0)	1 (0.3)

Table 20. Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (As-Treated Population)

	Gem + PL N=309	Axitinib + Gemcitabine N=308
System Organ Class **Preferred Term**	**n (%)**	**n (%)**
Hepatobiliary disorders	1 (0.3)	2 (0.6)
Cholangitis	1 (0.3)	1 (0.3)
Gallbladder necrosis	0 (0.0)	1 (0.3)
Infections and infestations	7 (2.3)	8 (2.6)
Pneumonia	3 (1.0)	3 (1.0)
Cellulitis	1 (0.3)	0 (0.0)
Cytomegalovirus infection	1 (0.3)	0 (0.0)
Device related infection	1 (0.3)	0 (0.0)
Lower respiratory tract infection	1 (0.3)	1 (0.3)
Sepsis	1 (0.3)	0 (0.0)
Upper respiratory tract infection	1 (0.3)	0 (0.0)
Urinary tract infection	1 (0.3)	1 (0.3)
Urosepsis	1 (0.3)	0 (0.0)
Abdominal abscess	0 (0.0)	1 (0.3)
Gastroenteritis	0 (0.0)	1 (0.3)
Liver abscess	0 (0.0)	1 (0.3)
Investigations	3 (1.0)	4 (1.3)
Haemoglobin decreased	1 (0.3)	1 (0.3)
Neutrophil count decreased	1 (0.3)	1 (0.3)
Platelet count decreased	1 (0.3)	2 (0.6)
White blood cell count decreased	0 (0.0)	1 (0.3)
Metabolism and nutrition disorders	3 (1.0)	8 (2.6)
Decreased appetite	1 (0.3)	4 (1.3)
Hyponatraemia	1 (0.3)	0 (0.0)
Tumour lysis syndrome	1 (0.3)	0 (0.0)
Dehydration	0 (0.0)	4 (1.3)
Hypercalcaemia	0 (0.0)	1 (0.3)
Hyperglycaemia	0 (0.0)	1 (0.3)
Hypoglycaemia	0 (0.0)	1 (0.3)
Hypophagia	0 (0.0)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts	1 (0.3)	0 (0.0)
Pancreatic carcinoma	1 (0.3)	0 (0.0)
Nervous system disorders	1 (0.3)	4 (1.3)
Thrombotic stroke	1 (0.3)	0 (0.0)
Cerebral ischaemia	0 (0.0)	1 (0.3)
Cerebrovascular accident	0 (0.0)	1 (0.3)
Grand mal convulsion	0 (0.0)	1 (0.3)
Posterior reversible encephalopathy syndrome	0 (0.0)	1 (0.3)
Transient ischaemic attack	0 (0.0)	1 (0.3)
Psychiatric disorders	2 (0.6)	1 (0.3)
Confusional state	2 (0.6)	1 (0.3)
Renal and urinary disorders	3 (1.0)	1 (0.3)
Renal failure acute	3 (1.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	9 (2.9)	2 (0.6)
Pneumonitis	3 (1.0)	0 (0.0)
Pulmonary embolism	3 (1.0)	2 (0.6)
Interstitial lung disease	2 (0.6)	0 (0.0)

Table 20. Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (As-Treated Population)

	Gem + PL N=309	Axitinib + Gemcitabine N=308
System Organ Class **Preferred Term**	**n (%)**	**n (%)**
Pleural effusion	1 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.6)	0 (0.0)
Erythema	1 (0.3)	0 (0.0)
Rash	1 (0.3)	0 (0.0)
Vascular disorders	6 (1.9)	3 (1.0)
Deep vein thrombosis	2 (0.6)	1 (0.3)
Arterial thrombosis limb	1 (0.3)	0 (0.0)
Hypertension	1 (0.3)	1 (0.3)
Vascular disorders		
Phlebitis	1 (0.3)	0 (0.0)
Venous thrombosis limb	1 (0.3)	0 (0.0)
Venous occlusion	0 (0.0)	1 (0.3)

% = (number of subjects/N)*100
Gem = gemcitabine; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with evaluable adverse events; PL = placebo; v = version.

Permanent Discontinuations Due to AEs: Forty-two subjects (13.8%) in the axitinib + gemcitabine arm and 45 subjects (14.6%) in the placebo + gemcitabine arm discontinued axitinib or placebo due to AEs. Forty-three subjects (14.1%) in the axitinib + gemcitabine arm and 42 subjects (13.6%) in the placebo + gemcitabine arm discontinued gemcitabine due to AEs. Table 21 summarizes AEs that led to discontinuation for >1 subject in either group.

Table 21. Discontinuations from Treatment due to Adverse Events (>1 Subject in Either Arm) (AT Population)

	Axitinib + Gemcitabine N=305	Placebo + Gemcitabine N=308
Discontinuation of axitinib or placebo		
Ileus	2 (0.7%)	1 (0.3%)
Fatigue	2 (0.7%)	3 (1.0%)
General physical health deterioration	2 (0.7%)	2 (0.6%)
Asthenia	3 (1.0%)	0
Back pain	2 (0.7%)	0
Confusional state	3 (1.0%)	0
Renal failure acute	1 (0.3%)	3 (1.0%)
Interstitial lung disease	0	2 (0.6%)
Pneumonitis	0	2 (0.6%)
Discontinuation of gemcitabine		
Ileus	2 (0.7%)	1 (0.3%)
Fatigue	2 (0.7%)	3 (1.0%)
General physical health deterioration	2 (0.7%)	1 (0.3%)
Asthenia	3 (1.0%)	0
Cholestasis	2 (0.7%)	0
Back pain	2 (0.7%)	0
Confusional state	3 (1.0%)	0
Renal failure acute	1 (0.3%)	3 (1.0%)
Interstitial lung disease	0	2 (0.6%)
Pneumonitis	0	2 (0.6%)

Disease progression led to discontinuation of gemcitabine for 4 subjects (1.3%) in the axitinib + gemcitabine group and 9 subjects (2.9%) in the placebo + gemcitabine group and to discontinuation of axitinib or placebo for 3 subjects (1.0%) in the axitinib + gemcitabine group and 9 subjects (2.9%) in the placebo + gemcitabine group. Disease progression was not considered an adverse event.
AT = As-Treated; N = number of subjects.

Dose Reductions or Temporary Discontinuations Due to Adverse Events: One hundred and twenty-five subjects (41.0%) and 100 subjects (32.5%) in the axitinib + gemcitabine and placebo + gemcitabine arms, respectively, had a dosing reduction of gemcitabine at some point during the study.

Deaths: Thirty-seven subjects (12.1%) in the axitinib + gemcitabine arm and 45 subjects (14.6%) in the placebo + gemcitabine arm, died Table 22 during study treatment or within 28 days of last dose of treatment.

Table 22. Deaths (AT Population)

	Axitinib + Gemcitabine N=305	Placebo + Gemcitabine N=308
Subjects who died	113 (37.0%)	117 (38.0%)
Subjects who died on-study[a]	37 (12.1%)	45 (14.6%)
Disease under study	32 (10.5%)	36 (11.7%)
Study treatment toxicity	0	1 (0.3%)
Unknown	2 (0.7%)	1 (0.3%)
Other	3 (1.0%)	7 (2.3%)
Subjects who died during follow-up[b]	76 (24.9%)	72 (23.4%)
Disease under study	66 (21.6%)	63 (20.5%)
Study treatment toxicity	1 (0.3%)	1 (0.3%)
Unknown	5 (1.6%)	6 (1.9%)
Other	4 (1.3%)	2 (0.6%)

AT = As-Treated; N = number of subjects,

a. On-study deaths were those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.

b. Follow-up deaths were those that occurred more than 28 days after the last dose of study drug.

Laboratory Evaluations: Table 23 summarizes the maximum grade for laboratory test results for each treatment arm.

Table 23. Maximum CTCAE Grade on Treatment for Hematology and Biochemistry Test Results (AT Population)

Subjects (%)	Maximum CTCAE Grade					
Parameter	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All Grades**
Axitinib + Gemcitabine N=305						
Hematology						
Hemoglobin	47 (15.4%)	175 (57.4%)	69 (22.6%)	7 (2.3%)	1 (0.3%)	299 (98.0%)
Lymphocytes (abs)	62 (20.3%)	51 (16.7%)	38 (12.5%)	12 (3.9%)	1 (0.3%)	164 (53.8%)
Neutrophils (abs)	62 (20.3%)	27 (8.9%)	44 (14.4%)	40 (13.1%)	8 (2.6%)	181 (59.3%)
Platelets	67 (22.0%)	146 (47.9%)	56 (18.4%)	24 (7.9%)	4 (1.3%)	297 (97.4%)
White Blood Cells	77 (25.2%)	74 (24.3%)	96 (31.5%)	31 (10.2%)	2 (0.7%)	280 (91.8%)
Biochemistry						
ALT	96 (31.5%)	109 (35.7%)	49 (16.1%)	33 (10.8%)	0	287 (94.1%)
Albumin	135 (44.3%)	94 (30.8%)	48 (15.7%)	4 (1.3%)	0	281 (92.1%)
ALP	95 (31.1%)	110 (36.1%)	54 (17.7%)	31 (10.2%)	0	290 (95.1%)
AST	116 (38.0%)	116 (38.0%)	34 (11.1%)	24 (7.9%)	0	290 (95.1%)
Bicarbonate	151 (49.5%)	31 (10.2%)	3 (1.0%)	2 (0.7%)	0	187 (61.3%)
Bilirubin (total)	226 (74.1%)	24 (7.9%)	14 (4.6%)	23 (7.5%)	5 (1.6%)	292 (95.7%)
Creatinine	269 (88.2%)	13 (4.3%)	7 (2.3%)	3 (1.0%)	0	292 (95.7%)
Glucose	44 (14.4%)	106 (34.8%)	90 (29.5%)	37 (12.1%)	7 (2.3%)	284 (93.1%)
Potassium	180 (59.0%)	92 (30.2%)	6 (2.0%)	12 (3.9%)	1 (0.3%)	291 (95.4%)
Sodium	162 (53.1%)	107 (35.1%)	0	22 (7.2%)	0	291 (95.4%)
Placebo + Gemcitabine N=308						
Hematology						
Hemoglobin	16 (5.2%)	148 (48.1%)	117 (38.0%)	19 (6.2%)	2 (0.6%)	302 (98.1%)
Lymphocytes (abs)	64 (20.8%)	45 (14.6%)	27 (8.8%)	19 (6.2%)	6 (1.9%)	161 (52.3%)
Neutrophils (abs)	76 (24.7%)	20 (6.5%)	32 (10.4%)	31 (10.1%)	8 (2.6%)	167 (54.2%)
Platelets	96 (31.2%)	137 (44.5%)	41 (13.3%)	16 (5.2%)	7 (2.3%)	297 (96.4%)
White Blood Cells	87 (28.2%)	73 (23.7%)	81 (26.3%)	36 (11.7%)	2 (0.6%)	279 (90.6%)
Biochemistry						
ALT	85 (27.6%)	124 (40.3%)	61 (19.8%)	15 (4.9%)	1 (0.3%)	286 (92.9%)
Albumin	130 (42.2%)	93 (30.2%)	54 (17.5%)	5 (1.6%)	0	282 (91.6%)
ALP	98 (31.8%)	121 (39.3%)	44 (14.3%)	25 (8.1%)	0	288 (93.5%)
AST	113 (36.7%)	125 (40.6%)	39 (12.7%)	10 (3.2%)	0	287 (93.2%)
Bicarbonate	159 (51.6%)	30 (9.7%)	0	0	0	189 (61.4%)
Bilirubin (total)	232 (75.3%)	23 (7.5%)	15 (4.9%)	14 (4.5%)	4 (1.3%)	288 (93.5%)
Creatinine	257 (83.4%)	23 (7.5%)	6 (1.9%)	2 (0.6%)	2 (0.6%)	290 (94.2%)
Glucose	58 (18.8%)	107 (34.7%)	67 (21.8%)	42 (13.6%)	9 (2.9%)	283 (91.9%)
Potassium	194 (63.0%)	73 (23.7%)	9 (2.9%)	11 (3.6%)	0	287 (93.2%)
Sodium	175 (56.8%)	91 (29.5%)	1 (0.3%)	21 (6.8%)	0	288 (93.5%)

abs = absolute; AST = aspartate aminotransferase; ALT = alanine aminotransferase, ALP = alkaline phosphatase, AT = As-Treated, CTC = common toxicity criteria, N = number of subjects.

Of the 298 axitinib + gemcitabine subjects who had a systolic blood pressure (SBP) of <160 Hg mm at Baseline and had at least 1 post-Baseline measurement, 85 (28.5%) had a maximum SBP of ≥160 Hg mm post-baseline. Of the 296 placebo + gemcitabine subjects who had a SBP of <160 Hg mm at baseline and had at least one post-baseline measurement, 41 (13.9%) had a maximum SBP of ≥160 Hg mm post baseline. Of the 299 axitinib + gemcitabine subjects who had a diastolic blood pressure (DBP) of <105 Hg mm at baseline and had at least one post-Baseline measurement, 32 (10.7%) had a

maximum DBP of ≥105 Hg mm post-baseline. Of the 299 placebo + gemcitabine subjects who had a DBP of <105 Hg mm at Baseline and had at least 1 post-Baseline measurement, 9 (3.0%) had a maximum DBP of ≥105 Hg mm post-baseline.

Mean corrected QT (QTc) results (QTcF and QTcB) and changes from Baseline were similar for both treatment arms.

CONCLUSIONS:

- There was no statistically significant difference in OS between the axitinib + gemcitabine and placebo + gemcitabine arms. The median OS for the axitinib + gemcitabine and placebo + gemcitabine treated arms was 36.9 weeks (95% CI: 30.1, 41.1) and 35.8 weeks (95% CI: 30.0, 44.8), respectively. Controlling for Baseline stratification factor, extent of disease (locally advanced versus metastatic), the hazard ratio (axitinib + gemcitabine: placebo + gemcitabine) was 1.01 (95% CI: 0.79, 1.31; 1-sided p-value: 0.54).

- The median PFS was 19.1 weeks (95% CI: 17.1, 24.4) and 18.9 weeks (95% CI: 16.2, 22.6) for the axitinib + gemcitabine and placebo + gemcitabine arms, respectively. Controlling for baseline stratification factor, extent of disease (locally advanced versus metastatic), the hazard ratio (axitinib + gemcitabine: placebo + gemcitabine) was 1.01 (95% CI: 0.78, 1.30, 1-sided p-value: 0.52).

- In subjects with measurable disease at Baseline, the overall ORR (CR + PR) was 12/247 (4.9%) and 4/255 (1.6%) in the axitinib + gemcitabine and placebo + gemcitabine arms, which showed a statistically significant difference of 3.3% between the arms (95% CI: 0.2, 6.4, 1-sided p-value=0.018).

- In comparison to the placebo + gemcitabine arm, the axitinib + gemcitabine arm had a higher incidence of ≥5% ≥Grade 3 all causality AEs for neutropenia and hypertension.

- Clinically meaningful changes were observed in several aspects of HRQOL as measured by the EORTC QLQ-C30 and PAN26, and pain as measured by the BPI-sf. These changes were observed for individuals in both the axitinib + gemcitabine and the placebo + gemcitabine arms.

- The population PK analysis is reported separately.