2. SYNOPSIS

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation Name of Finished Product: ABRAXANE® (ABI-007) Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: A Randomized Phase III Study of Weekly ABI-007 plus Gemcitabine versus Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas		
Principal Investigator: Investigators: Multicenter study, randomized patients at 151 sites.		
Study center(s): This multicenter study was conducted by investigators in 11 countries and randomized patients at a total of 151 sites: United States (US), 68 sites; Australia, 20 sites; Russian Federation, 19 sites; Italy, 12 sites; Canada, 7 sites; Ukraine, 7 sites; Spain, 7 sites; Germany, 4 sites; Austria, 3 sites; France, 2 sites; and Belgium, 2 sites		
Publications (reference): None.		
Studied period (years): Date first patient enrolled: 08 May 2009 Date last patient completed: Ongoing Data cut-off date: 17 Sep 2012	Phase of development: 3	

Objectives:

Primary: The primary objective of this study was to evaluate the efficacy of the combination of ABI-007 and gemcitabine versus gemcitabine alone in improving overall survival (OS) in patients with metastatic adenocarcinoma of the pancreas.

Secondary: The secondary objectives of this study were to:

- Evaluate progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, v 1.0 by independent radiological review.
- Evaluate the objective tumor response (hereafter referred to as overall response rate [ORR]) according to RECIST guidelines by independent radiological review.
- Evaluate the safety and tolerability of this combination in this patient population

Methodology: This study was an open-label, randomized, international, multicenter, Phase 3 study designed to compare ABI-007 in combination with gemcitabine administered weekly to standard treatment (gemcitabine monotherapy) with respect to OS, PFS, and ORR in patients diagnosed with metastatic adenocarcinoma of the pancreas.

Patients who met the entry criteria and who signed informed consent were enrolled into the study. Patients were assigned to one of the following treatment regimens:

- ABI-007 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 administered on Days 1, 8, 15 and 29, 36, 43 of a 56-day cycle in Cycle 1 only (ie, weekly for 3 weeks with a 1-week rest x 2) and subsequently administered on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onwards.

Or

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

- Gemcitabine 1000 mg/m^2 administered on Days 1, 8, 15, 22, 29, 36, 43 of a 56-day cycle in Cycle 1 (ie, weekly for 7 weeks and a 1-week rest period) and subsequently administered on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onwards.

Treatment was continued until the patient experienced progressive disease (PD) (based on the investigator's assessment) or unacceptable toxicity (defined as discontinued study treatment due to adverse event (AE) possibly, probably, or definitely related to study drug), required palliative radiotherapy, withdrew consent, or the patient's physician felt it was no longer in the best interest of the patient to continue on treatment. Patients who had not experienced PD (based on the investigator's assessment) were followed with regularly scheduled tumor assessments until radiographic evidence of PD was documented.

Based on the recommendations of the independent Data Monitoring Committee (DMC), the protocol was amended to implement measures to prevent or minimize the occurrence of septic events (Protocol Amendment 5, 12 Jan 2011) and to implement measures to prevent or minimize the occurrence of pneumonitis (Protocol Amendment 6, 12 Dec 2011).

Number of patients (planned and analyzed): A sample size of 421 patients randomized to each treatment arm (842 patients in total) was planned. Overall, 861 patients were randomized, with 431 patients in the ABI-007/gemcitabine arm and 430 patients in the gemcitabine arm.

Diagnosis and main criteria for inclusion:

A patient was eligible for inclusion in this study only if all the following criteria were met:

- Patient had definitive histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Initial diagnosis of metastatic disease must have occurred ≤ 6 weeks prior to randomization in the study.
- Patient had one or more metastatic tumors measurable by CT/MRI scan.
- Male or non-pregnant and non-lactating female, and ≥ 18 years of age.
- Patient must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease. Prior treatment with 5-FU or gemcitabine administered as a radiation sensitizer in the adjuvant setting was allowed, provided at least 6 months had elapsed since completion of the last dose and no lingering AEs were present. Patients who had received cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting were not eligible for this study.
- Patient had adequate biological parameters as demonstrated by the following blood counts at Baseline (obtained ≤ 14 days prior to randomization):
  - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L;
  - Platelet count ≥ 100,000/mm^3 (100 × 10^9/L);
  - Hemoglobin (Hgb) ≥ 9 g/dL.
- Patient had the following blood chemistry levels at Baseline (obtained ≤ 14 days prior to randomization):
  - Aspartate aminotranferase (AST; serum glutamic oxaloacetic transaminase [SGOT]), alanine aminotranferase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 × upper limit of

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

normal range (ULN), unless liver metastases were clearly present, then ≤ 5 × ULN was allowed;

- Total bilirubin ≤ ULN;
- Serum creatinine within normal limits or calculated clearance ≥ 60 mL/min/1.73 m^2 for patients with serum creatinine levels above or below the institutional normal value. If using creatinine clearance, actual body weight was used for calculating creatinine clearance (eg, using the Cockroft-Gault formula). For patients with a body mass index (BMI) > 30 kg/m^2, lean body weight was used instead.

- Patient had acceptable coagulation studies (obtained ≤ 14 days prior to randomization) as demonstrated by prothrombin time (PT) and partial thromboplastin time (PTT) within normal limits (±15%). (Local laboratory PT/PTT results were allowed to confirm eligibility).
- Patient had no clinically significant abnormalities in urinalysis results (obtained ≤ 14 days prior to randomization).
- Patient had a Karnofsky performance status (KPS) ≥ 70. Two observers were required to assess KPS. If discrepant, the one with the lowest assessment was considered true.
- Patient was asymptomatic for jaundice prior to Day 1. Significant or symptomatic amounts of ascites were drained prior to Day 1. Pain symptoms were stable and did not require modifications in analgesic management prior to Day 1.
- Patient had been informed about the nature of the study, and had agreed to participate in the study, and signed the ICF prior to participation in any study-related activities.

Test product, dose and mode of administration, batch number: ABI-007: ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) was obtained in the US and supplied by Celgene. Each 50-mL vial of ABI-007 contained 100 mg of paclitaxel and 900 mg of human albumin as a stabilizer. The product was a white to off-white sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP.

The lot numbers of ABI-007 used in the trial are:

The dose and schedule for ABI-007 are as indicated above (Methodology).

Duration of treatment: Tolerability to the specified dose and the need for subsequent dose modifications were determined individually based on changes (relative to baseline) in clinical laboratory values, physical examination findings, vital signs and/or clinical signs and symptoms (including AEs) and response for each patient. Doses were reduced for hematologic and other AEs.

Reference therapy, dose and mode of administration, batch number: Gemcitabine (GEMZAR®, Eli Lilly

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)	Volume:	
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)	Page:	

and Company, Indianapolis, Indiana, US) was acquired commercially in the US by Celgene. Gemcitabine was supplied in single-use vials containing 200 mg or 1 g of gemcitabine as a white-to-off-white sterile lyophilized powder for reconstitution with 0.9% sodium chloride injection. Gemcitabine was prepared and administered as specified in the GEMZAR Product Information.

The dose and schedule for gemcitabine are as indicated above (Methodology).

Criteria for evaluation:

Efficacy: The primary efficacy endpoint of this study was the OS of patients treated with ABI-007 in combination with gemcitabine compared with patients treated with gemcitabine alone. The secondary efficacy endpoints were PFS and ORR. Interpretation of radiological response for use in the PFS and ORR endpoints was completed by independent radiological reviewer assessment of CT (or MRI) scans at the centralized facility with radiologic reviewers who were blinded to treatment assignment (2 reviewers with a third reviewer for adjudication). Other efficacy endpoints included the following: Time to response and response duration (duration of response [DOR]) according to RECIST guidelines; disease control rate (ie, stable disease [SD] for ≥16 weeks or confirmed complete response [CR] or partial response [PR]); time to treatment failure (TTF); changes in serum CA19-9; tumor response based on PET scans evaluated according to EORTC criteria; determine whether a correlation exists between ORR based on CT/MRI scans (evaluated according to RECIST guidelines) and tumor response based on PET scans (evaluated according to the EORTC criteria); determination of possible correlations between ORR by CT/MRI scan and tumor response by PET scan; changes in plasma SPARC levels; determination of possible correlation between the expression of molecular markers and efficacy outcomes; determine whether correlations exist between ORR by CT or MRI scan, tumor response by PET scan, changes in serum CA19-9, and OS; determine whether correlations exist between ORR by CT or MRI scan, tumor response by PET, PFS, OS, and expression of tumor markers (eg, SPARC; nucleoside transporters).

Safety: The safety/tolerability endpoints included: Incidence of treatment-emergent AEs (TEAEs) in Medical Dictionary for Regulatory Activities (MedDRA) V15.0 terms categorized and graded according to NCI CTCAE V3.0. Central laboratory results (chemistries and blood counts) were analyzed using NCI CTCAE V3.0 grade; incidence of dose reductions and interruptions, and incidence of treatment discontinuation and reason for discontinuation.

Statistical methods: Data from all study centers were combined for analysis. There were three analysis populations as follows: Intent-to-treat (ITT) population consisted of all randomized patients. Treated population consisted of all randomized patients who received at least one dose of study drug. Per-protocol population consisted of all treated patients who met all eligibility criteria and received the same treatment as assigned by randomization.

All statistical tests of the treatment effect preserved a significance level of 0.050 for 2 sided tests. Testing of interactions was performed at the 0.100 significance level.

All mean and median values were formatted to one more decimal place than the measured value. Standard deviation values were formatted to two more decimal places than the measured value.

All listings were sorted for presentation in order of treatment arm, study center, patient, and date of procedure or event.

The day of the first dose of any study drug was defined as Day 1; baseline was defined as the last value on

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

or before the first study drug dose; and final evaluation was defined as the last on-treatment value.

SAS® Version 9.1 (or later) was the statistical software package used to produce all other data summaries, listings, graphs, and statistical analyses.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The following conclusions are based on the results of the efficacy analyses.

- A total of 861 patients were randomized at 151 centers in 11 countries to ABI-007/gemcitabine (N = 431) or gemcitabine (N = 430).
- All demographic and baseline characteristics were well balanced between the treatment arms.
- All primary and secondary efficacy analyses were based on the ITT population and were pre-specified in the SAP.

Primary efficacy endpoint: The study met the primary endpoint with highly statistically significant improvement in OS.

- The median OS in the ITT population was 8.5 months (95% confidence interval [CI] = 7.89, 9.53) in the ABI-007/gemcitabine arm compared with 6.7 months (95 % CI = 6.01, 7.23) in the gemcitabine arm, $p<0.0001$, stratified log-rank test; hazard ratio of ABI-007 followed by gemcitabine/gemcitabine alone ($HR_{A+G/G}$ = 0.72 months (95% CI = 0.617, 0.835). The 75th percentile of OS was 14.8 months in the ABI-007/gemcitabine arm versus 11.4 months in the gemcitabine arm.
- The 1-year survival rate was 35% (95% CI 29.7, 39.5) in the ABI-007/gemcitabine arm compared with 22% (95% CI = 18.1, 26.7) in the gemcitabine arm. The survival rate at 2 years was 9% (95% CI = 6.2, 13.1) in the ABI-007/gemcitabine arm compared with 4% (95% CI = 2.3, 7.2) in the gemcitabine arm.
- The treatment effect consistently favored the ABI-007/gemcitabine arm across the majority of pre-specified subgroups. The patients with the most advanced disease had the greatest reduction in the risk of death, ie, those patients with poorer KPS, presence of liver metastasis, greater than 3 metastatic lesion sites, stage IV disease at diagnosis, and CA19-9 levels ≥ 59 times ULN.
- The robustness of the positive treatment effect on survival is further confirmed by multivariate Cox models to evaluate the treatment effect adjusted for the stratification factors, and identify possible predictors for OS by including all the prognostic factors in the model. Sensitivity analyses were conducted using non-stratified factors and clinical data for the stratification factors on patient survival.
    - In a multivariate Cox model of OS adjusting for the stratification factors, the treatment effect remained significant with a similar magnitude of reduction in the risk of death compared with the primary analysis (HR = 0.71 [95% CI = 0.614, 0.828]; $p < 0.0001$).
    - In a multivariate Cox model of OS using stepwise procedure that included baseline prognostic factors, the treatment effect in the final model remained significant with a similar magnitude of reduction in the risk of death compared with the primary analysis (HR = 0.72 [95% CI= 0.605, 0.849]; $p < 0.0001$).

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

  - Two sensitivity analyses for OS, (1) using a non-stratified log rank test and (2) using the clinical database for stratification factors, show a statistically significant improvement in the ABI-007/gemcitabine arm compared with the gemcitabine arm with similar estimates of the reduction in the risk of death ($HR_{A+G}/_{G}$ = 0.74, and 0.68, respectively; both $p < 0.0001$).

- Subsequent anticancer therapy was balanced between treatment arms: 38% in the ABI-007/gemcitabine arm and 42% in the gemcitabine arm received subsequent anticancer therapy. Twenty-seven patients from the gemcitabine arm received a subsequent ABI-007 containing regimen.
  - A third sensitivity analysis censoring for OS on the initiation date of subsequent anticancer therapy shows a statistically significant improvement in the ABI-007/gemcitabine arm compared with the gemcitabine arm with similar estimates of the reduction in the risk of death ($HR_{A+G}/_{G}$ = 0.68 [95% CI = 0.559, 0.823], $p<0.0001$).
- The results for OS in the Per-protocol population were consistent with the ITT population. In the Per-protocol population, the median survival for patients in the ABI-007/gemcitabine arm was 8.6 months (95% CI = 7.89, 9.59) compared with 6.8 months (95% CI = 6.01, 7.29) in the gemcitabine arm, $p < 0.0001$; $HR_{A+G}/_{G}$ = 0.72 (95% CI =0.613, 0.844).
- The results for OS in the Treated population were consistent with the ITT and Per-protocol population. In the Treated population, the median survival for patients in the ABI-007/gemcitabine arm was 8.6 months (95% CI = 7.89, 9.66) compared with 6.8 months in the gemcitabine arm (95% CI = 6.01, 7.26), $p < 0.0001$; $HR_{A+G/G}$ = 0.70 (95% CI = 0.604, 0.823).

Key secondary endpoints: Secondary endpoints showed consistent, statistically significant improvements in the ABI-007/gemcitabine arm, supporting the results from the primary analyses of OS.

- There was significant improvement in PFS in the ABI-007/gemcitabine arm compared with the gemcitabine arm with a median PFS of 5.5 months (95% CI = 4.47, 5.95) in the ABI-007/gemcitabine arm and 3.7 months (95% CI = 3.61, 4.04) in the gemcitabine arm, $p < 0.0001$; HR = 0.69 (95% CI = 0.581, 0.821), corresponding to a 31% reduction of the risk of progression or death.
  - The absolute improvement in median PFS of 1.8 months was identical to the absolute improvement in median OS.
  - The one-year PFS rate was approximately doubled in the ABI-007/gemcitabine arm compared with the gemcitabine arm.
  - Similar to the OS analyses, the PFS analyses showed that the treatment effect consistently favored the ABI-007/gemcitabine arm across the majority of subgroups. The patients with the most advanced disease generally had the greatest reduction in the risk of progression or death, ie, those patients with poorer KPS, presence of liver metastasis, greater than 3 metastatic lesion sites, and CA19-9 $\geq$ 59 times ULN.
  - The robustness of the positive treatment effect was further confirmed by multivariate Cox models of PFS adjusting for known prognostic factors (HR = 0.69 [95% CI = 0.585, 0.825]; $p < 0.0001$) and a non-stratified analysis (HR = 0.69 [95% CI = 0.580, 0.816]; $p < 0.0001$).
- In the Per-protocol and Treated populations, similar improvements in PFS were observed (HR =

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

0.69 and 0.68, respectively; both $p < 0.0001$).

- The ORR by independent radiological review (2 reviewers with a third reviewer for adjudication) was significantly higher in the ABI-007/gemcitabine arm compared with the gemcitabine arm (23% versus 7%, $p < 0.0001$; response rate ratio [p_{A+G}/p_G] = 3.19 [95% CI = 2.178, 4.662]).
    - There was a higher rate of CR/PR and a lower rate of PD as best response in the ABI-007/gemcitabine arm.
    - The ORR by independent review was improved in all subgroups analyzed in the ABI-007/gemcitabine arm. Response rate ratios range from 1.49 to 13.54 in subgroups in favor of the ABI-007/gemcitabine arm.
    - In the Per Protocol and Treated populations as was seen in the ITT population, the ORR was 3-fold greater in the ABI-007/gemcitabine arm compared with the gemcitabine arm.
    - An exploratory analysis of best target lesion response in pancreatic lesions separate from metastatic lesions shows a similar magnitude of tumor shrinkage favoring the ABI-007/gemcitabine arm in both pancreatic and metastatic sites.

Summary of Top-Line Efficacy Results for Study CA046 (ITT Population)

	ABI-007/ Gemcitabine (N = 431)	**Gemcitabine (N = 430)**
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (months)	**8.5**	**6.7**
95% CI	7.89, 9.53	6.01, 7.23
$HR_{A+G/G}$ (95% CI) [a]	0.72 (0.617, 0.835)	
P-value[b]	<0.0001	
Progression-free Survival[c]		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	**5.5**	**3.7**
95% CI	4.47, 5.95	3.61, 4.04
$HR_{A+G/G}$ (95% CI) [a]	0.69 (0.581, 0.821)	
P-value[b]	<0.0001	
Overall Response Rate[c]		
Confirmed complete or partial overall response, n (%)	**99 (23)**	**31 (7)**
95% CI	19.1, 27.2	5.0, 10.1
p_{A+G}/p_G (95% CI)	3.19 (2.178, 4.662)	
P-value[b]	<0.0001	

CI = confidence interval, $HR_{A+G/G}$ = hazard ratio of ABI-007/gemcitabine / gemcitabine, ITT = intent-to-treat population.

[a] The associated hazard ratio and 95 % CI is estimated by using stratified Cox proportional hazard model.

[b] P-value is based on a stratified log-rank test stratified by geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).

[c] Based on Independent Radiological Reviewer Assessment.

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

Other Efficacy Endpoints:

- In the 99 patients from the ABI-007/gemcitabine arm and 31 patients from the gemcitabine arm who had either confirmed complete or partial response, the median time to response was 3.5 months for patients in both arms.
- The median DOR as measured by PFS (as determined by independent radiological reviewer assessment) in patients with a confirmed complete or partial overall response was comparable in both arms: 11.1 months (95% CI = 9.23, 13.11) in the ABI-007/gemcitabine arm compared with 11.4 months (95% CI = 9.03, NE months) in the gemcitabine arm; $HR_{A+G/G} = 1.37$ (95% CI = 0.684, 2.763). The DOR calculated from the onset date of CR/PR to date of PD was comparable in both arms, 8.5 months (95% CI = 7.43, 11.83) in the ABI-007/gemcitabine arm compared with 7.9 months (95% CI = 4.67, NE months) in the gemcitabine arm; $HR_{A+G/G} = 1.11$ (95% CI = 0.507, 2.444).
- The disease control rate (percentage of patients with confirmed CR, PR or SD ≥ 16 weeks) was 48% in the ABI-007/gemcitabine arm and 33% in the gemcitabine arm ($p_{A+G}/p_G = 1.46$ [95% CI = 1.233, 1.723]; $p < 0.0001$).
- The median TTF was 5.1 months in the ABI-007/gemcitabine arm compared with 3.6 months in the gemcitabine arm, ($HR_{A+G}/_G = 0.70$ [95% CI = 0.604, 0.803]; $p < 0.0001$).
- The investigator assessment of PFS and ORR was consistent with the independent reviewers' assessments.
    - The concordance rate of the independent radiological reviewer's assessment of overall response compared with the investigator's assessment was 67% for the ABI-007/gemcitabine arm and 64% for the gemcitabine arm.
    - The median PFS by investigator was 5.3 months (95% CI = 4.40, 5.49) in the ABI-007/gemcitabine arm compared with 3.5 months (95% CI = 3.25, 3.65) in the gemcitabine arm, $p < 0.0001$; $HR_{A+G/G} = 0.61$ (95% CI = 0.524, 0.714).
    - The ORR based on the investigator's assessment was significantly higher for the ABI-007/gemcitabine arm (29%) compared with the gemcitabine arm (8%), $p < 0.0001$; $p_{A+G}/p_G = 3.81$ (95% CI = 2.660, 5.456).
- The median maximum percentage decrease in CA19-9 from baseline was 89% for the ABI-007/gemcitabine arm and 74% for the gemcitabine arm. A ≥ 90% decrease in CA19-9 concentration from baseline was observed in 117 (42%) patients in the ABI-007/gemcitabine arm and 51 (22%) patients in the gemcitabine arm ($p < 0.0001$).
- There was no decrement in performance status in the ABI-007/gemcitabine arm compared with the gemcitabine arm during the treatment period.
- All patients were evaluated by CT or MRI scans and PET imaging until Amendment 4, at which time PET scans were no longer performed. A total of 130 patients from the ABI-007/gemcitabine arm and 127 of patients from the gemcitabine were assessed by PET imaging at baseline and follow-up. The PET response rate by independent radiological review following the EORTC PET response criteria was significantly higher in the ABI-007/gemcitabine arm (63%) compared with the

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

gemcitabine arm (38%); $p_{A+G}/p_G = 1.67$ (95% CI = 1.288, 2.162); $p < 0.0001$, chi-squared test.

- By independent radiological review, CT-based ORR correlated with PET based ORR, and response by PET scan appeared to correlate with survival and PFS outcomes.

SAFETY RESULTS:

Exposure: The longer treatment duration, greater dose intensity, and greater cumulative doses in the ABI-007/gemcitabine arm showed that this combination can be effectively administered and is generally well tolerated. The addition of ABI-007 to gemcitabine increases the cumulative delivery of gemcitabine. The suitability of the dosing regimen is confirmed by the observation that the majority of patients did not require a dose reduction.

- The median treatment duration was longer in the ABI-007/gemcitabine arm (3.9 months; 3 cycles) than in the gemcitabine arm (2.8 months; 2 cycles).
- In the ABI-007/gemcitabine arm, 41% of patients had ABI-007 dose reductions and 47% had gemcitabine dose reductions. In total, 71% of all ABI-007 doses administered in the study were at the full 125 mg/m^2 dose. The median relative dose intensity in the ABI-007/gemcitabine arm was 74% for ABI-007 and 75% for gemcitabine.
- In the gemcitabine arm, 33% of patients had gemcitabine dose reductions, resulting in a relative dose intensity of 85%.
- The median cumulative dose of gemcitabine delivered was greater in the ABI-007/gemcitabine arm, 11,400 mg/m^2, compared with 9,000 mg/m^2 in the gemcitabine arm.

SAFETY:

Exposure:

- A total of 823 patients, 421 patients in the ABI-007/gemcitabine arm and 402 patients in the gemcitabine arm, received at least 1 dose of study drug and were included in the Treated population.
- The longer treatment duration and greater cumulative dose of gemcitabine in the ABI-007/gemcitabine arm compared with the gemcitabine arm showed that this combination can be effectively administered to patients with metastatic adenocarcinoma of the pancreas.
    - The median treatment duration was longer in the ABI-007/gemcitabine arm (3.9 months; 3 cycles) than in the gemcitabine arm (2.8 months; 2 cycles).
- The suitability of the dosing regimen is confirmed by the observation that the majority of patients did not require a dose reduction. In the ABI-007/gemcitabine arm, 41% of patients had ABI-007 dose reductions and 47% had gemcitabine dose reductions. In total, 71% of all ABI-007 doses administered in the study were at the full 125 mg/m^{2}dose. The median relative dose intensity in the ABI-007/gemcitabine arm was 74% for ABI-007 and 75% for gemcitabine.
    - In the gemcitabine arm, 33% of patients had gemcitabine dose reductions, resulting in a relative dose intensity of 85%.
    - The median cumulative dose of gemcitabine delivered was greater in the ABI-007/gemcitabine arm, 11400 mg/m^2, compared with 9000 mg/m^2 in the gemcitabine arm.

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

Adverse Events and Laboratory Results:

- The most frequently reported TEAEs (reported for ≥ 40% of patients) in the ABI-007/gemcitabine arm were fatigue, nausea, peripheral neuropathy (grouped terms according to SMQ), alopecia, peripheral edema, diarrhea, anemia, neutropenia, and pyrexia. The TEAEs reported more often (≥ 10%) in the ABI-007/gemcitabine arm than in the gemcitabine arm were fatigue, peripheral neuropathy SMQ, alopecia, peripheral edema, diarrhea, neutropenia, pyrexia, decreased appetite, rash, epistaxis, and dehydration.
- Grade 3 or higher TEAEs reported more often (reported for ≥ 5% difference) in the ABI-007/gemcitabine arm than in the gemcitabine arm were neutropenia, fatigue, peripheral neuropathy (by SMQ), thrombocytopenia, leukopenia, and diarrhea.
- The proportion of patients with SAEs was similar between the 2 treatment arms (ABI-007/gemcitabine, 50%; gemcitabine arm, 43%). Fatal events were reported for 4% of patients (18 patients each) in both treatment arms.
- Treatment-emergent AEs that resulted in permanent discontinuation of study drug were reported more often in the ABI-007/gemcitabine arm (35% for ABI-007 and 30% for gemcitabine) than in the gemcitabine arm (24%). In the ABI-007/gemcitabine arm, the most commonly reported TEAEs (reported for ≥ 2% of patients) resulting in ABI-007 discontinuation were peripheral neuropathy SMQ, fatigue, and thrombocytopenia.
- Treatment-emergent AEs leading to dose reductions were more common in the ABI-007/gemcitabine arm (38% for ABI-007 and 44% for gemcitabine) than in the gemcitabine arm (31%). The most commonly reported TEAEs (reported for ≥ 5% of patients) resulting in ABI-007 dose reduction were neutropenia (10%) and peripheral neuropathy (preferred term) (6%).
- Treatment-emergent AEs leading to delayed or doses not given were more common in the ABI-007/gemcitabine arm (63% for ABI-007 and 61% for gemcitabine) than in the gemcitabine arm (48%). The most commonly reported TEAEs resulting in ABI-007 dose delay or doses not given doses were neutropenia, thrombocytopenia, fatigue, peripheral neuropathy, peripheral sensory neuropathy, anemia and diarrhea. Dose delays or doses not given due to TEAEs that occurred more often (≥ 5% difference between groups) in the ABI-007/gemcitabine arm than in the gemcitabine arm were neutropenia, thrombocytopenia, peripheral neuropathy, and peripheral sensory neuropathy. In addition, there was a greater incidence of patients with AEs in the infections and infestations SOC leading to dose delay/dose not given in the ABI-007/gemcitabine arm than in the gemcitabine arm.
- Based on central laboratory data, overall Grade 3/4 neutropenia occurred more frequently in the ABI-007/gemcitabine arm than in the gemcitabine arm (38% versus 27%, respectively); however, Grade 3/4 anemia (13% versus 12%) and Grade 3/4 thrombocytopenia (13% versus 9%) were similar in the 2 groups. The overall rates of WBC growth factors use were low and similar in the 2 treatment arms (26% versus 15%).
- The incidence of febrile neutropenia was low and similar between the treatment arms (3% versus 1%).
- The most notable difference in the safety profile between the 2 treatment arms was peripheral

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

neuropathy, which was cumulative and was rapidly reversible upon treatment interruption.

- Peripheral neuropathy (all grades) and Grade 3 events were reported more often in the ABI-007/gemcitabine arm than in the gemcitabine arm (54% versus 13%, respectively, for overall; 17% versus 1% for Grade 3). There were no reports of Grade 4 peripheral neuropathy. The incidence of peripheral neuropathy (all grades) leading to ABI-007 discontinuation was 8%.
- The median time to the first occurrence of Grade 3 peripheral neuropathy was longer in the ABI-007/gemcitabine arm (140 days) than in the gemcitabine arm (113 days). The median time to improvement by 1 grade was 21 days, and the median time to improvement to Grade ≤ 1 was 29 days.
- In the ABI-007/gemcitabine arm, the rate of Grade 3 peripheral neuropathy (by SMQ) for the average patient who received 3 or fewer cycles was 7%, and in all patients, was 17%, consistent with prior ABI-007 studies.

- Sepsis (all grades), predominantly gram negative sepsis due to abdominal biliary obstruction, were reported more often in the ABI-007/gemcitabine arm than in the gemcitabine arm (5% versus 2%, respectively). Sepsis was fatal for 5/421 patients in the ABI-007/gemcitabine arm and 2/402 patients in the gemcitabine arm.
  - The median time to onset of sepsis AEs was 76 days in the ABI-007/gemcitabine arm and 34 days in the gemcitabine arm.
  - Sepsis occurred both in neutropenic and in non-neutropenic patients.
  - The protocol was amended to provide guidance to investigators for the continuous on-study monitoring for signs and symptoms of sepsis events and, if observed, timely institution of appropriate management, as recommended by the DMC, including the use of G-CSF and broad spectrum antibiotics. After the protocol amendment, there was a reduction in the rate of septic events with most events categorized as bacteremia rather than sepsis.
- Pneumonitis was reported for 4% of patients in the ABI-007/gemcitabine arm and 1% of patients in the gemcitabine arm. Two patients (<1%) in the ABI-007/gemcitabine arm died due to pneumonitis. One additional patient in the ABI-007/gemcitabine arm with pneumonitis ongoing at the time of death was reported as having died due to tumor progression.
  - The median time to onset of pneumonitis was similar in the 2 treatment arms (86 days in the ABI-007/gemcitabine arm and 83 days in the gemcitabine arm). The median duration of pneumonitis was 15 days in the ABI-007/gemcitabine arm and 10 days in the gemcitabine arm.
  - No reliable predictor for pneumonitis was identified in this study.
  - The protocol was amended to include guidance regarding careful pre-study screening, continuous on-study monitoring for signs and symptoms of pneumonitis and, if observed, timely institution of appropriate management, as recommended by the DMC, including early discontinuation of study drug in patients diagnosed with interstitial pneumonitis and aggressive treatment with high-dose corticosteroid therapy, antibiotics, immune modulating agents, and appropriate ventilation and oxygen support, as clinically indicated.

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		

- No pneumonitis was reported among the 53 patients enrolled after Amendment 6. Although the number of patients enrolled after Amendment 6 was small, the data suggest that the guidance to investigators provided effective measures for the screening and monitoring of patients, and the management of pneumonitis.

- There were no reports of drug hypersensitivity, hypersensitivity, anaphylaxis, anaphylactic shock, anaphylactoid reaction, laryngeal edema or deaths associated with hypersensitivity.
- The percentages of patients with the known identified risks of cardiotoxicity and injection site reaction/extravasation were similar in the ABI-007/gemcitabine arm and the gemcitabine arms. There were no events of Stevens-Johnson syndrome and toxic epidermal necrolysis.
- The percentages of patients of patients with hepatic AEs or Grade 3/4 hepatic laboratory values were similar in the ABI-007/gemcitabine arm and the gemcitabine arms. There were no cases of drug-induced hepatic injury.
- There were no differences between the ABI-007/gemcitabine arm and the gemcitabine arms for known risk for gemcitabine of renal toxicity and hemolytic uremic syndrome.

In summary, treatment compliance and dose intensity was high for ABI-007 in the combination arm and for gemcitabine in both arms. Because of acceptable tolerability and greater efficacy, the treatment duration in the ABI-007/gemcitabine arm was longer by one month, allowing a greater cumulative delivery of gemcitabine. Serious life-threatening toxicity was not increased. Adverse events were acceptable and manageable. The most notable toxicity between the 2 treatment arms was peripheral neuropathy, which was cumulative and rapidly reversible upon treatment interruption. The incremental risks of sepsis and pneumonitis were managed by protocol amendments to increase the awareness and for early diagnosis and treatment to reduce the risk of fatal outcomes.

CONCLUSION:

The efficacy results of this multicenter study conducted in multiple countries showed a clinically meaningful, compelling, and statistically significant improvement in the primary endpoint of OS. The survival results were robust and consistent across subgroups. The survival benefit was supported by secondary endpoints, which showed a clinically meaningful and statistically significant improvement in PFS, ORR, disease control rate, TTF, CA19-9 response, and PET scan response. The overall safety profile for the combination of ABI-007/gemcitabine was consistent with the established profiles for the individual agents and was notable for peripheral neuropathy, neutropenia, infection/sepsis and pneumonitis. Adverse events were acceptable and manageable. Serious life-threatening toxicity was not increased. The most notable toxicity was rapidly reversible neurotoxicity observed in 7% of patients treated up to 4 months (median treatment duration) and in 17% of patients overall.

In conclusion, Study CA046 demonstrates significant benefit for the ABI-007/gemcitabine regimen in the first-line treatment of patients with adenocarcinoma of the pancreas. The benefit from the ABI-007/gemcitabine combination outweighs its risks for patients with adenocarcinoma of the pancreas.

Name of Sponsor/Company: Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ABRAXANE® (ABI-007)		
Name of Active Ingredient: Paclitaxel protein-bound particles for injectable suspension (albumin-bound)		
Date of the report: 05 Feb 2013		