Summary ID#2938

Clinical Study Summary: Study H3E-MC-JMDB

A Randomized Phase 3 Trial of ALIMTA® and Cisplatin versus GEMZAR® and Cisplatin in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Date summary approved by Lilly: 23 January 2008

Brief Summary of Results

The primary objective of this randomized, open-label, Phase 3 trial was to compare pemetrexed plus cisplatin with gemcitabine plus cisplatin in terms of overall survival (OS) of chemonaive patients with Stage IIIB (not amenable to curative treatment) and Stage IV non-small cell lung cancer (NSCLC). The results of the study are as follows:

- A total of 1725 patients were randomized to either the pemetrexed plus cisplatin arm (AC arm) or gemcitabine plus cisplatin arm (GC arm).
- The baseline patient disease characteristics and prognostic factors were well balanced between the treatment arms.
- The median OS was 10.28 months for both treatment arms. The primary endpoint of this study was met, such that AC was statistically significantly noninferior to GC. The Cox adjusted hazard ratio (HR) was estimated to be 0.94 (95% CI: 0.84 to 1.05; noninferiority $p<0.001$), with the entire confidence interval well below the 1.17647 noninferiority margin.

- A prespecified analysis of OS by NSCLC histology was performed. In patients with adenocarcinoma and large cell carcinoma, OS was statistically significantly superior for AC compared to GC (p=0.033 for adenocarcinoma; p=0.027 for large cell carcinoma). In squamous cell patients, OS was marginally superior for GC compared to AC (p=0.050). Neither AC nor GC was statistically superior in patients classified as "other" histology (those that did not qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma).
- The median progression-free survival (PFS) was 4.83 months in the AC arm and 5.06 months in the GC arm, with a Cox adjusted HR of 1.04 (95% CI: 0.94 to 1.15). For time-to-progressive disease (TtPD), the median was 5.19 months in the AC arm and 5.39 months in the GC arm, with a Cox adjusted HR of 1.03 (95% CI: 0.93 to 1.14). Both PFS and TtPD were statistically significant for noninferiority (PFS, p=0.008; TtPD, p=0.007).
- There was no statistically significant difference in objective tumor response rate between the AC arm compared to the GC arm (30.6% versus 28.2%) (p=0.312).
- Duration of response (AC, 4.50 months; GC, 5.09 months) and median time-to-treatment failure (AC, 4.44 months; GC, 4.53 months) were similar between treatment arms.
- A total of 3648 cycles of AC were administered to 839 patients, and 3626 cycles of GC were administered to 830 patients. A median of 5 cycles of therapy was administered to patients on both study arms.
- The number of deaths reported by investigators to be possibly related to study drug toxicity was 9 deaths (1.1%) in the AC arm and 6 deaths (0.7%) in the GC arm.
- The number of patients experiencing any possibly study drug-related treatment-emergent adverse event (TEAE) or serious adverse event (SAE) was similar between treatment arms. There were no significant differences in the numbers of patients who discontinued study treatment due to possibly study drug-related SAEs between treatment arms.
- Among the possibly study drug-related SAEs, patients on the AC arm experienced statistically significantly lower incidences of febrile neutropenia (p=0.005) and pyrexia (p=0.006) than patients on the GC arm but statistically higher incidences of renal failure (p=0.031) and anorexia (p=0.006).
- Patients in the GC arm experienced statistically significantly more possibly study drug-related Grade 3/4 laboratory toxicities than patients in the AC arm (p<0.001). Statistically significantly more patients on the GC arm experienced Grade 3/4 hematologic toxicities – anemia, leukopenia, neutropenia, and thrombocytopenia (p<0.001).

- Overall, there was no significant difference in the total number of patients experiencing any possibly study drug-related nonlaboratory toxicity between treatment arms (p=0.320). Patients in the GC arm experienced significantly more possibly study-drug related Grade 3/4 febrile neutropenia (p=0.002), Grade 3/4 sensory neuropathy (p=0.030), Grade 3/4 syncope (p=0.030), and any grade of alopecia (p<0.001). Patients in the AC arm experienced significantly more possibly study-drug related Grade 3/4 anorexia (p=0.009) and Grade 3/4 nausea (p=0.004) than patients on the GC arm.
- There were significantly fewer transfusions (p<0.001), red blood cell transfusions (p<0.001), and platelet transfusions (p=0.002) administered to patients on the AC arm as compared to the GC arm.
- Supportive care was received by statistically significantly more patients on GC arm as compared to patients on AC arm: Erythropoietin/darbepoetin (p<0.001), iron preparations (p=0.021), and G-CSF/GM-CSF (p=0.004).
- The risk/benefit ratio for the AC arm was 0.84 (<1) and 1.23 for the GC arm (>1). For the AC arm, the 1-year survival benefit (43.8%) was greater than the risk of Grade 3/4 possibly study drug-related toxicity (36.6%).
- There was a statistically significantly longer survival without study-drug related Grade 3/4 toxicity for AC compared with GC (p <0.001).

Title of Study: A Randomized Phase 3 Trial of ALIMTA® and Cisplatin versus GEMZAR and Cisplatin in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Investigator(s): This multicenter study included 177 principal investigators.

Study Center(s): This study was conducted at 177 study centers in 26 countries.

Length of Study: 2 years and 6 months
Date of first patient enrolled: 06 July 2004
Date of last patient visit: 25 January 2007

Phase of Development: 3

Objectives:

Primary:

- To compare pemetrexed (Alimta) plus cisplatin with gemcitabine plus cisplatin in terms of overall survival (OS) of previously untreated patients with Stage IIIB (not amenable to curative treatment) and Stage IV non-small cell lung cancer (NSCLC).

Secondary:

- to compare the following between treatment arms:
  - progression-free survival time (PFS)
  - time-to-progressive disease (TtPD)
  - duration of tumor response (DoR)
  - time-to-treatment failure (TtTF)
  - objective tumor response
  - toxicities and risk/benefit (relative to survival).

In addition, a prespecified analysis of OS by NSCLC histology was performed to assess for evidence of a differential treatment effect with respect to histology groups (adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and other/unknown histology).

Study Design: This was a multicenter, randomized, open-label, Phase 3 study for first-line treatment of chemonaive patients with Stage IIIB (not amenable to curative treatment) or Stage IV NSCLC. Patients were to be randomly assigned to receive pemetrexed plus cisplatin (AC) or gemcitabine plus cisplatin (GC). The study design is schematically represented in Figure JMDB.1. Investigational sites involved in Study JMDB were also invited to participate in an optional companion biomarker research protocol. The primary objective of the companion biomarker research protocol was to explore any relationship that may exist between levels of multiple biomarkers and clinical outcome (including overall survival, tumor response, and toxicity) following treatment with either AC or GC. Participation in the companion biomarker protocol was optional for investigational sites and for patients.

Number of Patients:
Planned: 1700 patients (850 per treatment arm)
Entered: 1833 patients
Randomized (enrolled): 1725 patients (AC arm = 862 patients; GC arm = 863 patients)
Treated: 1669 patients (AC arm = 839 patients; GC arm = 830 patients)

Diagnosis and Main Criteria for Inclusion: Patients enrolled in this study were men or women at least 18 years of age with a histologic or cytologic diagnosis of Stage IIIB (not amenable to curative treatment) or Stage IV NSCLC. Patients had to have adequate bone marrow reserve and hepatic and renal function, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Therasse et al. 2000). Patients could not have received prior systemic chemotherapy for lung cancer. Prior radiation therapy was allowed to <25% of the bone marrow if it was completed at least 4 weeks before study enrollment and all toxicities had resolved.

Test Product, Dose, and Mode of Administration:

Treatment for AC Arm (every 21 days):

- pemetrexed 500 mg/m^2, 10-minute intravenous (iv) infusion, Day 1
- cisplatin 75 mg/m^2 intravenously (iv), Day 1 (approximately 30 minutes after pemetrexed infusion)

Patients also received folic acid and vitamin B_{12} supplementation plus dexamethasone as a premedication.

Reference Therapy, Dose, and Mode of Administration:

Treatment for GC Arm (every 21 days):

- gemcitabine 1250 mg/m^2, 30 to 60-minute iv infusion, Day 1 and Day 8
- cisplatin 75 mg/m^2 iv, Day 1 (approximately 30 minutes after gemcitabine infusion).

Patients also received folic acid and vitamin B_{12} supplementation plus dexamethasone as a premedication (dexamethasone was not required for Day 8 gemcitabine).

Duration of Treatment: Patients could receive up to 6 cycles of treatment and a cycle was defined as 21 days.

Variables:

Efficacy:

- Primary: OS was the primary efficacy variable in this study. Overall survival duration was measured on the randomized [intent-to-treat (ITT)] population from the date of randomization to the date of death from any cause.
- Secondary: Investigators assessed patients' tumor responses for each cycle using RECIST criteria. Objective progression was defined as progression based on RECIST criteria using tumor measurements. Clinical progression was defined as other evidence of progression that was not based on RECIST criteria and hence not based on tumor measurements (eg, investigator assessment of patient symptoms).

Safety:

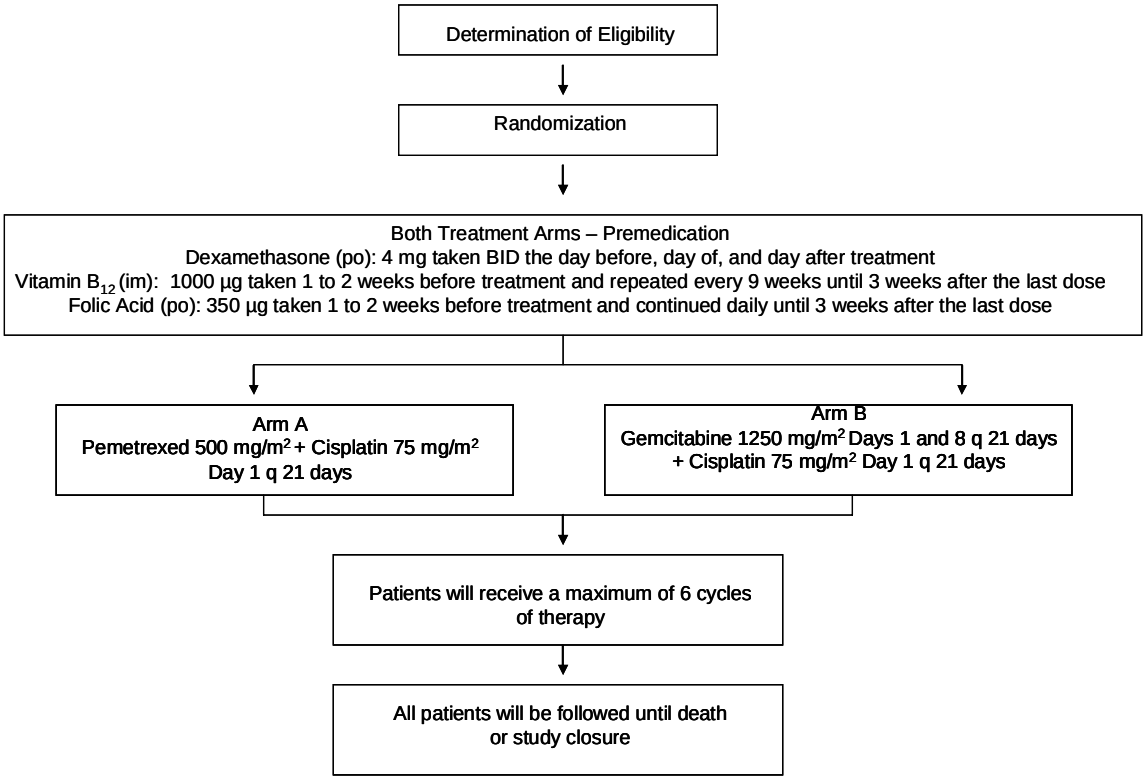
- Adverse events were reported using the Medical Dictionary for Regulatory Activities (MedDRA), Version: 10.0. Investigators assessed the causality of any adverse event experienced by a patient and graded it using the Common Toxicity Criteria (CTC) rating scale (v2.0, NCI 1998).

Evaluation Methods:

Statistical: The hazard ratio (HR) was defined by comparing AC to GC, so that a HR < 1 demonstrates a survival (or PFS, TTPD, TtTF, or DoR) benefit for AC, and a HR > 1 demonstrates a benefit for GC. A Cox (Cox 1972) proportional hazard model (adjusted for prognostic factors) was used to assess noninferiority of AC to GC for all time-to-event variables (OS, PFS, TtPD, TtTF, and DoR). The protocol-defined noninferiority margin, determined by the fixed margin method, was set at 1.17647. The Kaplan-Meier (Kaplan and Meier 1958) method was used to estimate parameters (medians, quartiles, and point estimates) for time-to-event endpoints. Tumor response rates were compared between treatment arms based on an unadjusted, normal-distribution approximation for the difference in rates. Log-rank statistics were calculated to compare unadjusted estimates for time-to-event endpoints, and the Fisher's exact test was used to compare treatments for categorical variables. Tests were conducted as follows: noninferiority tests at one-sided alpha (α) = 0.025 level, superiority tests at α=0.05 level, and two-sided confidence intervals (CI) at 95%. The sample size and determination of the fixed margin was based on a one-sided test, assuming a true value of HR = 1.0, with 80% probability of rejecting H_0: HR $\geq$ 1.7645; this corresponds to GC having a 15% lower hazard (risk of death) than AC (ie, AC has 15% higher risk of death than GC). These assumptions required at least 1190 deaths of patients randomized for treatment for the final analyses. After 1190 death events were known and confirmed by Lilly, the database was locked. After the time of validation and final datalock, the total number of deaths was 1270.

Study Design

The study design is presented in Figure JMDB.1.



Abbreviations: BID = twice daily, im = intramuscular, po = per oral, q = every day.

Figure JMDB.1. Study design.

Results:

Patient Demographics

Table JMDB.1 summarizes demographics and other baseline characteristics of the intent-to-treat (ITT) population. The ITT population consisted of all patients who were randomized (regardless of whether they were treated or not), and analyzed according to the therapy as randomized (regardless of what they received). A total of 1725 patients were randomized to either pemetrexed plus cisplatin (AC arm) or gemcitabine plus cisplatin (GC arm). The baseline patient disease characteristics and prognostic factors were balanced between the 2 treatment arms. Among all patients randomized, the median age was 61 years, and the majority were Caucasian, male, reported ever using tobacco, had Eastern Cooperative Oncology Group performance status (ECOG PS) of 1, Stage IV disease, and histopathologic diagnosis as the basis for initial diagnosis. In both treatment arms, adenocarcinoma was the predominant histological subtype.

Table JMDB.1. Patient Disease Characteristics and Prognostic Factors by Treatment Group All Randomized Patients

Variable	AC (N = 862)	GC (N = 863)	All (N = 1725)
Sex, n (%)			
Number of Patients	862	863	1725
Male	605 (70.2)	605 (70.1)	1210 (70.1)
Female	257 (29.8)	258 (29.9)	515 (29.9)
Origin, n (%)			
Number of Patients	862	863	1725
African Descent	18 (2.1)	18 (2.1)	36 (2.1)
Caucasian	669 (77.6)	680 (78.8)	1349 (78.2)
East/Southeast Asian	116 (13.5)	104 (12.1)	220 (12.8)
Hispanic	27 (3.1)	23 (2.7)	50 (2.9)
Other	2 (0.2)	1 (0.1)	3 (0.2)
Western Asian	30 (3.5)	37 (4.3)	67 (3.9)
Age Group, n (%)			
Number of Patients	862	863	1725
Age <65 Years	541 (62.8)	577 (66.9)	1118 (64.8)
Age ≥65 Years	321 (37.2)	286 (33.1)	607 (35.2)
Age (years)			
Number of Patients	862	863	1725
Mean (SD)	60.52 (9.22)	60.20 (9.34)	60.36 (9.28)
Median	61.05	60.95	61.00
Smoking History, n (%)			
Number of Patients	862	863	1725
Yes	629 (73.0)	637 (73.8)	1266 (73.4)
Performance Status, n (%)			
ECOG PS 0	305 (35.4)	307 (35.6)	612 (35.5)
ECOG PS 1	556 (64.5)	554 (64.2)	1110 (64.3)
ECOG PS Unknown[a]	1 (0.1)	2 (0.2)	3 (0.2)
Basis for Diagnosis, n (%)			
Cytological	289 (33.5)	288 (33.4)	577 (33.4)
Histopathological	573 (66.5)	575 (66.6)	1148 (66.6)

(continued)

Table JMDB.1. Patient Demographics and Other Baseline Characteristics by Treatment Group All Randomized Patients (Concluded)

Variable	AC (N = 862)	GC (N = 863)	All (N = 1725)
Stage of Disease, n (%)			
Stage IIIB	205 (23.8)	210 (24.3)	415 (24.1)
Stage IV	657 (76.2)	653 (75.7)	1310 (75.9)
Diagnosis/Histology, n (%)			
Adenocarcinoma	436 (50.6)	411 (47.6)	847 (49.1)
Large Cell Carcinoma	76 (8.8)	77 (8.9)	153 (8.8)
Squamous Cell Carcinoma	244 (28.3)	229 (26.5)	473 (27.4)
Other[b]	106 (12.3)	146 (16.9)	252 (14.6)

Abbreviations: AC = pemetrexed plus cisplatin, cm = centimeter, GC = gemcitabine plus cisplatin, ECOG PS = Eastern Cooperative Oncology Group performance status, kg = kilograms, N = number of randomized patients, n = number of patients in category, SD = standard deviation.

*Frequencies were analyzed using Fisher's exact test.

**Means were analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.

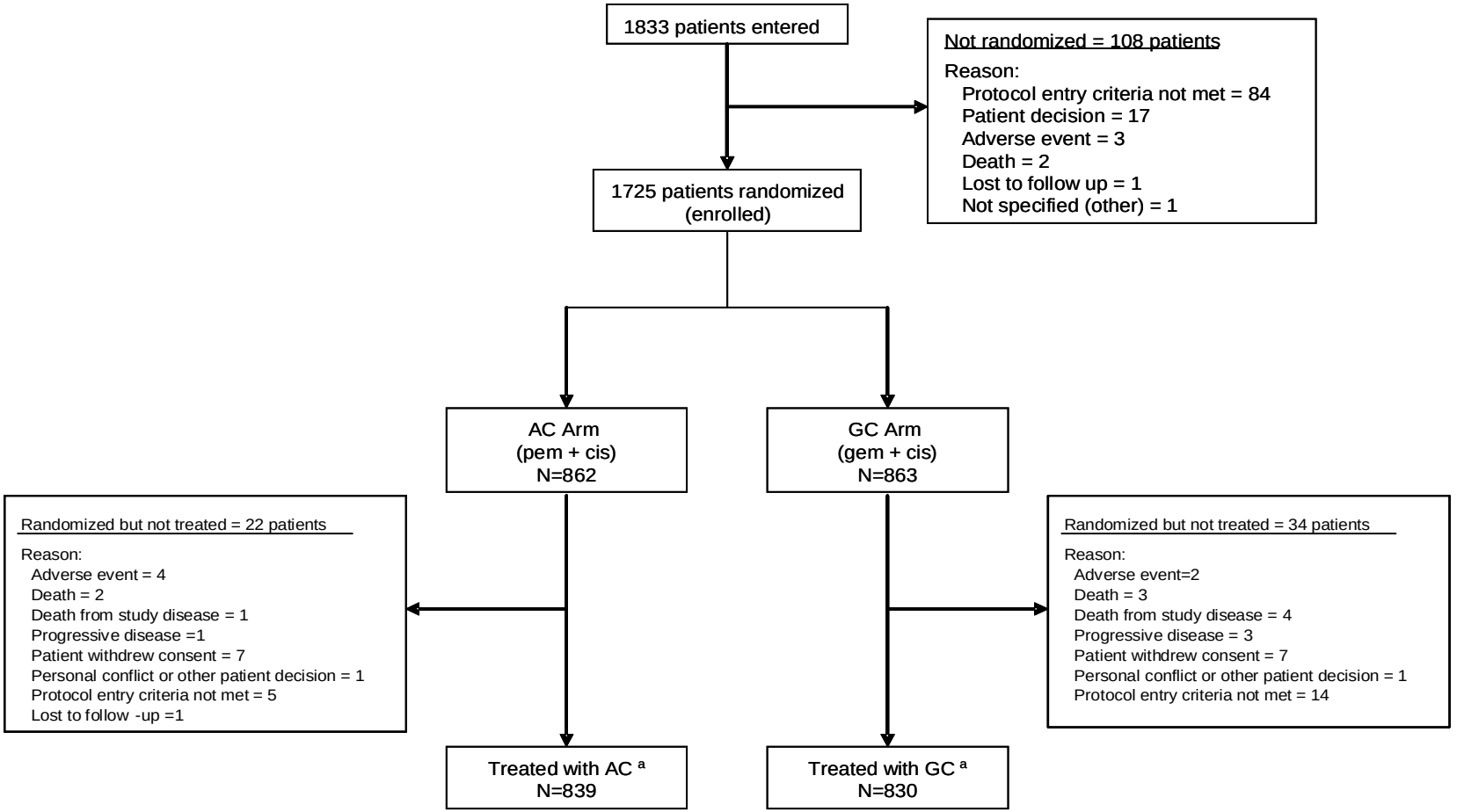
***Frequencies were analyzed using a chi-square test.

[a] Unknown indicates that data was not reported for these patients.

[b] The category of "other" histology represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

Patient Disposition

Figure JMDB.2 presents disposition for patients who entered in the study. Of the 1833 patients entered, a total of 1725 patients were enrolled into the study. Of the enrolled patients, 862 patients were randomized to the AC arm, and 863 patients were randomized to the GC arm. A total of 1669 received study treatment consisting of at least 1 dose of pemetrexed, cisplatin, or gemcitabine (AC, n = 839; GC, n = 830).



Abbreviations: AC = pemetrexed plus cisplatin; cis = cisplatin; GC = gemcitabine plus cisplatin; gem = gemcitabine; N = number; pem = pemetrexed.
[a] One patient was assigned to the AC arm but received GC therapy. This patient was included in the GC arm of the randomized and treated population for the safety analysis.

Figure JMDB.2. Patient disposition.

Table JMDB.2 summarizes reasons for discontinuation for all patients who entered the study. Reasons for discontinuation were balanced between treatment arms. Of the 108 patients who entered the study but were not randomized, the most common reason for study discontinuation was protocol criteria not met. Among all enrolled patients (ie, those randomized to treatment) in both treatment arms, the most common reasons for study discontinuation were protocol completion, lack of efficacy due to progressive disease, and adverse events.

Table JMDB.2. Reasons for Discontinuation

Reason for Discontinuation	A/C (N=862) n(%)	G/C (N=863) n(%)	Not Randomized (N=108) n(%)	ALL (N=1833) n(%)
Adverse event	99 (11.5)	117 (13.6)	3 (2.8)	219 (11.9)
Death	33 (3.8)	33 (3.8)	2 (1.9)	68 (3.7)
Death from Study Drug Toxicity	9 (1.0)	6 (0.7)	0 (0.0)	15 (0.8)
Death from study disease	24 (2.8)	21 (2.4)	0 (0.0)	45 (2.5)
Lack of efficacy, patient and physician perception	18 (2.1)	17 (2.0)	0 (0.0)	35 (1.9)
Lack of efficacy, progressive disease	280 (32.5)	253 (29.3)	0 (0.0)	533 (29.1)
Other	3 (0.3)	1 (0.1)	1 (0.9)	5 (0.3)
Patient decision	0 (0.0)	0 (0.0)	17 (15.7)	17 (0.9)
Patient withdrew consent	19 (2.2)	17 (2.0)	0 (0.0)	36 (2.0)
Personal conflict or other patient decision	19 (2.2)	20 (2.3)	0 (0.0)	39 (2.1)
Protocol Violation	2 (0.2)	6 (0.7)	0 (0.0)	8 (0.4)
Protocol completed	305 (35.4)	305 (35.3)	0 (0.0)	610 (33.3)
Protocol entry criteria not met	8 (0.9)	18 (2.1)	84 (77.8)	110 (6.0)
Satisfactory response, patient and physician perception	37 (4.3)	44 (5.1)	0 (0.0)	81 (4.4)
Unable to contact patient (lost to follow-up)	6 (0.7)	5 (0.6)	1 (0.9)	12 (0.7)

Abbreviations: A/C = pemetrexed/cisplatin, G/C = gemcitabine/cisplatin, N = number of patients, n = number of patients with events.
Noninferiority p-values were calculated for Cox adjusted analyses at a one-sided, 0.025 significance level.

Primary Efficacy Measures

Overall survival (OS) was the primary efficacy variable in this study. Overall survival duration was measured from the date of randomization to the date of death from any cause; patients who had not died were censored at the date of last prior contact. A total of 862 patients on the AC arm and 863 patients on the GC arm (ITT population) were included in the OS analysis.

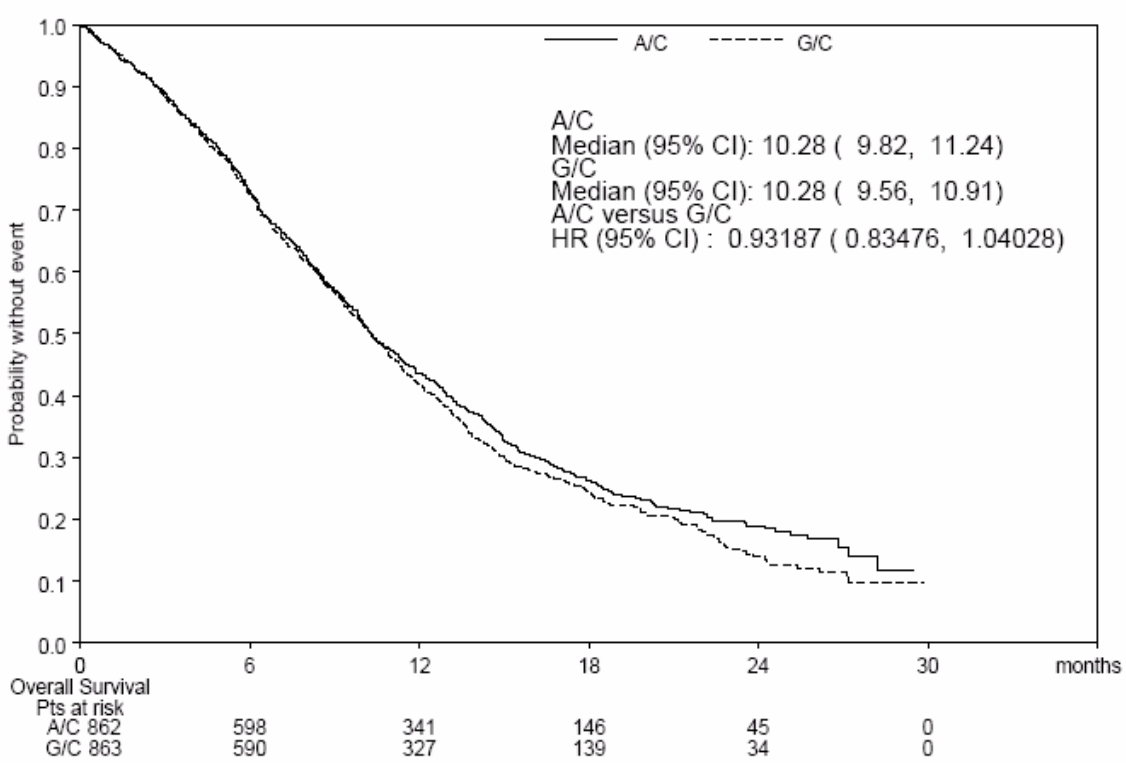
The median OS time was 10.28 months for both treatment arms. The 1- and 2-year survival rates were 43.48% and 18.94%, respectively, for the AC arm and 41.94% and 13.98%, respectively, for the GC arm. Using the Cox regression adjusted model for the primary analysis, the primary noninferiority test was statistically significant (one-sided $p<0.001$), with the primary cofactor-adjusted survival hazard ratio (HR) estimated to be 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval for HR well below the 1.17647 noninferiority margin. The confidence interval for the survival HR implies that the risk of death on the AC arm was 16% lower than that on the GC arm in the best-case scenario and 5% higher in the worst-case scenario. (The noninferiority study used a fixed margin of 1.17647, which corresponded to GC having a 15% lower hazard than that of AC, and was tested at a one-sided 0.025 alpha level.) Table JMDB.3 summarizes results of the primary Cox regression adjusted analysis. Figure JMDB.3 displays the Kaplan-Meier survival graph for randomized patients. The superiority comparisons for OS between the AC and GC arms in the total population were not statistically significant.

Table JMDB.3. Primary Cox Regression Adjusted Analysis of Overall Survival All Randomized Patients

Covariate	HR(95%CI)	Superiority p-value	Non-inferiority p-value
Assigned Study Treatment Arm (A/C versus G/C)	0.93852 (0.84066-1.04778)	0.259	<.001
Disease Stage (IIIB versus IV)	0.81574 (0.71481-0.93092)	0.003	.
ECOG performance status (0 versus 1+)	0.64847 (0.57634-0.72963)	<.001	.
Sex (Females versus males)	0.76004 (0.67212-0.85946)	<.001	.
Basis for initial pathological diagnosis (histopathological versus cytological)	1.02404 (0.91025-1.15206)	0.693	.

Abbreviations: A/C = pemetrexed/cisplatin, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, G/C = gemcitabine/cisplatin, HR = hazard ratio.

Noninferiority p-values were calculated for Cox adjusted analyses at a one-sided, 0.025 significance level.



Abbreviations: A/C = pemetrexed plus cisplatin; CI = confidence interval; G/C = gemcitabine plus cisplatin; HR = hazard ratio; Pts = patients.

Figure JMDB.3. Kaplan-Meier graph of survival time by treatment group for all randomized patients.

Secondary Efficacy Measures

The analyses of secondary time-to-event endpoints (PFS, TTPD, TtTF, DoR) were analyzed using the same methods as described for the primary analysis for overall survival (that is, the Cox regression adjusted model and Kaplan-Meier estimation). A statistical noninferiority test (using the same 1.17647 HR margin) was repeated for each of these secondary time-to-event variables.

Tumor response was assessed according to the RECIST criteria (Therasse et al. 2000). Response rate was calculated as the proportion of tumor-response qualified (TRQ) patients having a confirmed best response of partial response (PR) or complete response (CR) (762 patients in the AC arm and 755 patients in the GC arm). The TRQ population consisted of patients who had eligible study disease, did not receive prohibited anticancer therapy prior to study treatment discontinuation, had a baseline scan and at least one follow-up scan, and received at least one dose of study treatment.

Duration of response (DoR) was analyzed for the subgroup of patients in the TRQ population with a confirmed PR or CR. Duration of response (DoR) was measured from the date of the first objective status assessment of a complete or partial response to the first date of progression of disease (clinical or objective), or death from any cause. For each patient who was not known to have died or to have had progression of disease as of the data inclusion cut-off date for a particular analysis, DoR was censored at the date of last prior contact. A total of 446 patients were considered confirmed responders and were included in the DoR analysis: 233 patients in the AC arm and 213 patients in the GC arm.

Table JMDB.4 summarizes the results of the secondary efficacy analyses.

Table JMDB.4. Secondary Efficacy Endpoints
All Randomized Patients

Efficacy Endpoints	AC (N=862)	GC (N=863)	Adjusted HR (95% CI)	NI p-Value
PFS				
Median, months	4.83	5.06	1.04	0.008
(95% CI)	(4.57-5.32)	(4.63-5.52)	(0.95-1.15)	
TtPD				
Median, months	5.19	5.39	1.03	0.007
(95% CI)	(4.73-5.45)	(4.96-5.59)	(0.93-1.14)	
TtTF				
Median, months	4.44	4.53	1.05	0.041
(95% CI)	(4.24-4.63)	(4.27-4.76)	(0.92-1.19)	
Response*				
Response rate, %	30.6	28.2	—	—
(95% CI)	(27.3-33.9)	(25.0-31.4)		
DoR*				
Median, months	4.50	5.09	1.14	0.362
(95% CI)	(4.27-5.32)	(4.57-5.52)	(0.94-1.38)	

Abbreviations: AC = pemetrexed plus cisplatin; CI = confidence interval; DoR = duration of response; GC = gemcitabine plus cisplatin; HR = hazard ratio; ITT = intent to treat; n = number; N = total population size; NI = noninferiority; OS = overall survival; PFS = progression-free survival; TtPD = time-to-progressive disease; TtTF = time-to-treatment failure.

*Tumor response-qualified patient population.

Histology Results

Table JMDB.5 provides results of the Cox and Kaplan-Meier prespecified analyses of OS by treatment arm for each of 4 histologic groups.

Table JMDB.5. Analysis of Overall Survival in Histologic Subgroups All Randomized Patients

	Median OS (mo)	Adjusted HR[a] (95% CI)	NI p-value[a]	Sup. p-Value[a]
Adenocarcinoma (N=847)				
AC (n=436)	12.55	0.84 (0.71–0.99)	<0.001	0.033
GC (n=411)	10.94			
Large Cell (N=153)				
AC (n=76)	10.38	0.67 (0.48–0.96)	<0.001	0.027
GC (n=77)	6.67			
Squamous Cell (N=473)				
AC (n=244)	9.36	1.23 (1.00–1.51)	0.663	0.050
GC (n=229)	10.84			
Unknown or "Other" Histology (N=252)[b]				
AC (n=106)	8.57	1.08 (0.81–1.45)	0.291	0.586
GC (n=146)	9.17			

Abbreviations: AC = pemetrexed plus cisplatin; GC = gemcitabine plus cisplatin; HR = hazard ratio; mo = months; N= number of patients per histologic subgroup; n = number of patients per treatment arm; NI = noninferiority; NSCLC = non-small cell lung cancer; OS = overall survival; Sup = superiority.

[a] Adjusted HR and superiority and NI p-values from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

[b] The subcategory of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

Safety

Extent of Exposure

All patients who received at least 1 dose of pemetrexed, gemcitabine, or cisplatin (AC, 839; GC, 830) were included in the safety population. Patients in the safety population were analyzed according to the therapy they received in the first treatment cycle. A total of 3648 cycles of AC were administered to 839 patients on the AC arm, and 3626 cycles of GC were administered to 830 patients on the GC arm. Table JMDB.6 provides a summary of the number of cycles given for all patients who received any dose of study drug. The percent planned dose (ratio of actual mean dose delivered divided by planned mean dose times 100) intensity for pemetrexed and cisplatin was 94.8% and 95.0%, compared with 85.8% and 93.5% for gemcitabine and cisplatin.

Table JMDB.6. Summary of Cycles Given by Treatment Arm
All Patients Who Received Study Drug

	A/C (N=839)		G/C (N=830)	
	A	C	G	C
No. Patients	839	839	830	829
Mean	4.3	4.3	4.4	4.3
Median	5.0	5.0	5.0	5.0
Standard Dev.	1.82	1.82	1.84	1.84
Minimum	1.0	1.0	1.0	1.0
Maximum	7.0	7.0	8.0	8.0
Patients completed at least:				
1 cycle	85 (10.1)	86 (10.3)	87 (10.5)	87 (10.5)
2 cycles	122 (14.5)	121 (14.4)	110 (13.3)	110 (13.3)
3 cycles	42 (5.0)	42 (5.0)	52 (6.3)	54 (6.5)
4 cycles	149 (17.8)	149 (17.8)	147 (17.7)	145 (17.5)
5 cycles	61 (7.3)	63 (7.5)	45 (5.4)	46 (5.5)
6 cycles	379 (45.2)	377 (44.9)	385 (46.4)	383 (46.2)
7 cycles	1 (0.1)	1 (0.1)	3 (0.4)	3 (0.4)
8 cycles	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

Abbreviations: A/C = pemetrexed/cisplatin, dev = deviation, G/C = gemcitabine/cisplatin, N = number of patients who received study drug, no = number of patients.

Dose Delays

A total of 815 dose delays were reported on the AC arm, and 929 dose delays were reported on the GC arm. In both treatment arms, scheduling conflict was the most commonly reported reason for dose delays (486 in the AC arm and 514 in the GC arm) and the most common clinical reasons for dose delays were neutropenia (138 in the AC arm and 188 in the GC arm) and anemia (25 in the AC arm and 43 in the GC arm).

Dose Reductions

In the AC arm, 54 dose reductions were reported for pemetrexed, and 64 dose reductions were reported for cisplatin. For both study therapies of the AC arm, the most common reasons for dose reductions were neutropenia (17 for pemetrexed and 17 for cisplatin), fatigue (6 for pemetrexed and 8 for cisplatin), nausea (5 for pemetrexed and 8 for cisplatin), and febrile neutropenia (5 for pemetrexed and 5 for cisplatin). On the GC arm, 362 dose reductions were reported for gemcitabine, and 154 dose reductions were reported for cisplatin. For both study therapies of the GC arm, the most common reasons for dose reductions were neutropenia (184 for gemcitabine and 59 for cisplatin), thrombocytopenia (82 for gemcitabine and 37 for cisplatin), and febrile neutropenia (15 for gemcitabine and 12 for cisplatin).

Dose Omissions

According to the protocol, dose omissions were permitted only for Day 8 gemcitabine.

On the GC arm, 341 dose omissions occurred in patients receiving gemcitabine and were attributed to neutropenia (69), thrombocytopenia (26), and fatigue (20). Of these, only 2 omissions occurred for Day 1 and the remaining were for Day 8.

In addition, there were 3 dose omissions for pemetrexed and 4 for cisplatin on the AC arm, and 11 dose omissions for cisplatin on the GC arm.

Overview of Adverse Events

Table JMDB.7 presents an overview of adverse events reported during the study.

Table JMDB.7. Overview of Adverse Events By Treatment Group All Patients Who Received Study Drug

	Number of Patients with an Event			
	Regardless of Drug Causality		Possibly Drug Related	
Adverse Events	AC (N=839)	GC (N=830)	AC (N=839)	GC (N=830)
Patients with ≥1 SAE	294 (35.0%)	315 (38.0%)	139 (16.6%)	136 (16.4%)
Serious, unexpected, reportable event[a]	NA	NA	11 (1.3%)	4 (0.5%)
Discontinuations due to SAE	30 (3.6%)	46 (5.5%)	15 (1.8%)	23 (2.8%)
Deaths (on-study)	63 (7.5%)	53 (6.4%)	9 (1.1%)[b]	6 (0.7%)[b]
Deaths (within 30 days of last dose)	13 (1.5%)	14 (1.7%)	0	0
Patients with ≥1 TEAE	812 (96.8%)	807 (97.2%)	751 (89.5%)	755 (91.0 %)

Abbreviations: AC = pemetrexed plus cisplatin, AE = adverse event, GC = gemcitabine plus cisplatin, N = total population size, NA = not applicable, SAE = serious adverse event, SUR = serious, unexpected, reportable, TEAE = treatment-emergent adverse event.

[a] All SURs are considered to be possibly drug related. Of note, on the AC arm, 1 of the 11 cases reported as serious, unexpected, and reportable was identified as an SUR based on neutropenia, which was erroneously identified as unlisted in the investigator's brochure and other labeling documents of both pemetrexed and cisplatin. Neutropenia is a well-known side effect of both drugs.

[b] These numbers represent the deaths possibly due to study drug toxicity as reported on the case report form by investigators. A Lilly review of patient summaries found possibly study drug-related causes for death in 1 additional patient on the AC arm and 4 additional patients on the GC arm, for a total of 10 deaths possibly due to study drug toxicity on each study arm.

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as events that emerged after administration of at least 1 dose of study drug, or events present at the time of enrollment that worsened after administration of at least 1 dose of study drug. Seven-hundred fifty one patients (89.5%) in the AC arm and 755 patients (91.0%) in the GC arm experienced at least 1 TEAE. On both treatment arms, the most commonly reported possibly study drug-related TEAEs were anemia, neutropenia, nausea, vomiting, and fatigue. The TEAEs experienced by statistically significantly more patients on the GC arm than in the AC arm were as follows: anemia (42.9% vs 30.5%, $p<0.001$), neutropenia (36.0% vs 27.5%, $p<0.001$), thrombocytopenia (25.2% vs 9.4%, $p<0.001$), fatigue (34.0% vs 28.7%, $p=0.023$), pyrexia (4.6% vs 2.4%, $p=0.016$), febrile neutropenia (4.1% vs 1.7%, $p=0.003$), alopecia (21.4% vs 11.7%, $p<0.001$), hypokalemia (2.5% vs 1.2%, $p=0.047$), neuropathy (1.2% vs 0.1%, $p=0.006$), peripheral sensory neuropathy (6.0% vs 3.2%, $p=0.007$), tinnitus (4.3% vs 2.1%, $p=0.013$), and epistaxis (3.9% vs 1.8%, $p=0.012$). The TEAEs experienced by statistically significantly more patients on the AC arm than in the GC arm were as follows: Eye disorders (8.8% vs 2.8%, $p<0.001$) as a whole (mostly conjunctivitis and increased lacrimation), acute renal failure (0.7% vs 0.0%, $p=0.031$), dry skin (1.3% vs 0.2%, $p=0.022$), and pigmentation disorder (2.0% vs 0.2%, $p<0.001$).

Deaths

Table JMDB.8 summarizes the deaths reported on therapy or within 30 days of the last study drug dose for all patients who received study drug. A total of 116 on-therapy deaths and 27 deaths within 30 days of last study drug dose were reported; of these, 15 were reported by the investigator to be possibly related to study drug toxicity (9 on AC, 6 on GC). The sponsor reviewed all deaths on-study and within 30 days, and identified 5 additional deaths (1 on AC and 4 on GC) that could possibly be related to study treatment, although these were not reported as such by the investigator. In the patient narratives describing these 5 deaths, the investigator either determined that the events leading up to death were possibly due to study-drug toxicity or could not rule out the possibility of relatedness, though these cases were not reported as deaths due to study-drug toxicity on the case report forms.

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Table JMDB.8. Summary of Deaths (On-Therapy or Within 30 Days of Last Study Drug Dose)
Patients Who Received Study Drug

	AC (N=839) n (%)		GC (N=830) n (%)		Total (N=1669) n (%)		p-value[a]
On-therapy deaths	**63**	**(7.5)**	**53**	**(6.4)**	**116**	**(7.0)**	**0.387**
Study Disease	**23**	**(2.7)**	**17**	**(2.0)**	**40**	**(2.4)**	**0.424**
Drug Toxicity	**9**	**(1.1)**	**6**	**(0.7)**	**15**	**(0.9)**	**0.606**
Other Causes:	**31**	**(3.7)**	**30**	**(3.6)**	**61**	**(3.7)**	**1.000**
Cardiac (total):	**8**		**7**				
Myocardial infarction	4		4				
Cardiac/cardiorespiratory arrest	2		1				
Cardiac/cardiopulmonary failure	1		2				
Cardiogenic shock	1		0				
Pulmonary (total):	**14**		**9**				
Pulmonary/respiratory failure	3		2				
Pulmonary embolism	1		5				
Respiratory distress/dyspnea/apnea	3		1				
Pulmonary edema	2		0				
COPD	1		0				
Pneumonia/aspiration	4		1				
Bleeding event (total):	**3**		**3**				
Hemoptysis	1		1				
Upper GI hemorrhage	1		0				
Pulmonary/pleural hemorrhage	0		2				
Intracranial hemorrhage	1		0				
Death, no cause reported	**3**		**5**				
Miscellaneous causes	**3**		**6**				
Deaths within 30 days of last dose	**13**	**(1.5)**	**14**	**(1.7)**	**27**	**(1.6)**	**0.849**
Study Disease	**11**	**(1.3)**	**11**	**(1.3)**	**22**	**(1.3)**	**1.000**
Drug Toxicity	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	
Other Causes:	**2**	**(0.2)**	**3**	**(0.4)**	**5**	**(0.3)**	**0.685**
Cardiogenic shock	0		1				
Respiratory failure	1		0				
Miscellaneous causes	1		2				

Abbreviations: AC = pemetrexed plus cisplatin, COPD = chronic obstructive pulmonary disease, GC = pemetrexed plus cisplatin, GI = gastrointestinal, N = number of randomized and treated patients, n = number of patients who died.

[a] p-value is from Fisher's exact test.

Serious Adverse Events

Table JMDB.9 summarizes the possibly study drug-related serious adverse events (SAEs) that were experienced by ≥2% of patients or were statistically significantly different between study arms or were otherwise clinically relevant. Patients on the AC arm

experienced statistically significantly lower incidences of febrile neutropenia and pyrexia than patients on the GC arm but statistically higher incidences of acute renal failure and anorexia.

Table JMDB.9. Summary of Selected Serious Adverse Events Possibly Related to Study Drug Patients Who Received Study Drug

System Organ Class Preferred Term[a]	Number (%) of Patients Study JMDB AC (N=839)	GC (N=830)	p-value[b]
Patients with at least 1 event	**139 (16.6)**	**136 (16.4)**	**0.947**
Vomiting	34 (4.1)	23 (2.8)	0.178
Anemia	22 (2.6)	28 (3.4)	0.392
Nausea	30 (3.6)	19 (2.3)	0.147
Thrombocytopenia	16 (1.9)	28 (3.4)	0.067
Febrile neutropenia	9 (1.1)	25 (3.0)	**0.005**
Anorexia	11 (1.3)	1 (0.1)	**0.006**
Pyrexia	1 (0.1)	10 (1.2)	**0.006**
Renal failure acute	6 (0.7)	0	**0.031**
Renal failure	5 (0.6)	6 (0.7)	0.773
Acute prerenal failure	1 (0.1)	0	1.000

Abbreviations: AC = pemetrexed plus cisplatin, GC = gemcitabine plus cisplatin, N = total number of patients.

[a] Possibly related events were chosen if they occurred in at least 2% of all patients who received study drug, were clinically significant, or occurred in significantly different numbers of patients between study arms.

[b] Fisher's exact test.

Discontinuations

A total of 76 patients discontinued study drug due to SAEs, regardless of causality, in both treatment arms – 30 patients in the AC arm and 46 patients in the GC arm. Of these patients, 15 patients (1.8%) in the AC arm and 23 patients (2.8%) in the GC arm discontinued due to SAEs that were considered to be possibly related to study drug. Other than cerebrovascular accident (AC: 0.1%, GC: 0.8%; p=0.038), there were no other significant differences in the numbers of patients who discontinued study drug, regardless of causality, between treatment arms.

Clinical Laboratory Evaluation

Laboratory Toxicities

Table JMDB.10 summarizes the Common Toxicity Criteria (CTC) Grade 3 and Grade 4 laboratory events reported during the study that were considered to be possibly related to study drug. On the GC arm, patients experienced statistically significantly more Grade 3 and 4 laboratory toxicities than patients on the AC arm. The individual toxicities experienced by statistically significantly more patients on the GC arm than in the AC arm were hematologic and included anemia, leukopenia, neutropenia, and thrombocytopenia. No Grade 3/4 laboratory toxicities occurred significantly more often on the AC arm.

Table JMDB.10. Summary of CTC Grade 3 and 4 Laboratory Toxicities per Treatment Arm Possibly Related to Study Therapy Patients Who Received Study Drug

	Number (%) of patients						
	AC (N=839)			GC (N=830)			p-Value[a]
Laboratory CTC Toxicity	**Grade 3**	**Grade 4**	**Grade 3/4**	**Grade 3**	**Grade 4**	**Grade 3/4**	
Any G3/G4 laboratory toxicity	**143 (17.0)**	**47 (5.6)**	**190 (22.6)**	**224 (27.0)**	**107 (12.9)**	**331 (39.9)**	**<0.001**
Hematologic toxicity							
Hemoglobin	41 (4.9)	6 (0.7)	47 (5.6)	72 (8.7)	10 (1.2)	82 (9.9)	**0.001**
Leukocytes	32 (3.8)	8 (1.0)	40 (4.8)	55 (6.6)	8 (1.0)	63 (7.6)	**0.019**
Lymphopenia	1 (0.1)	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1.000
Neutrophils/granulocytes	89 (10.6)	38 (4.5)	127 (15.1)	141 (17.0)	81 (9.8)	222 (26.7)	**<0.001**
Platelets	27 (3.2)	7 (0.8)	34 (4.1)	89 (10.7)	16 (1.9)	105 (12.7)	**<0.001**
Nonhematologic toxicity							
Bilirubin	1 (0.1)	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1.000
Cardiac troponin T	0	0	0	1 (0.1)	0	1 (0.1)	0.497
Creatinine	7 (0.8)	0	7 (0.8)	3 (0.4)	1 (0.1)	4 (0.5)	0.548
Hypercalcemia	1 (0.1)	0	1 (0.1)	0	1 (0.1)	1 (0.1)	1.000
Hyperglycemia	1 (0.1)	0	1 (0.1)	0	0	0	1.000
Hyperkalemia	1 (0.1)	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1.000
Hypocalcemia	1 (0.1)	0	1 (0.1)	0	0	0	1.000
Hypokalemia	5 (0.6)	0	5 (0.6)	5 (0.6)	0	5 (0.6)	1.000
Hypomagnesemia	1 (0.1)	0	1 (0.1)	3 (0.4)	0	3 (0.4)	0.372
Hyponatremia	1 (0.1)	0	1 (0.1)	4 (0.5)	0	4 (0.5)	0.216
SGOT (AST)	1 (0.1)	1 (0.1)	2 (0.2)	0	0	0	0.500
SGPT (ALT)	2 (0.2)	1 (0.1)	3 (0.4)	1 (0.1)	0	1 (0.1)	0.625

Abbreviations: AC = pemetrexed plus cisplatin, ALT = alanine transaminase, AST = aspartate transaminase, CTC = Common Toxicity Criteria, G = grade, GC = gemcitabine plus cisplatin, N = number of patients.

[a] Fisher's exact test, p-value is Grade 3/4 AC versus Grade 3/4 GC.

Nonlaboratory Toxicities

On the GC arm, patients experienced similar Grade 3 and 4 nonlaboratory toxicities as patients on the AC arm (23.5% versus 21.5%, p=0.320). Patients on the AC arm experienced statistically significantly more study drug-related Grade 3/4 anorexia (2.4% versus 0.7%, p=0.009) and nausea (7.2% versus 3.9%, p=0.004). Although Grade 3/4 nausea occurred in significantly more patients on the AC arm, the incidences of Grade 3/4 vomiting (6.1% versus 6.1%, p=1.000), Grade 3/4 weight loss (0% versus 0.1%, p=0.497), and Grade 3/4 dehydration (1.2% versus 0.7%, p=0.452) were similar between arms. Possibly study drug-related Grade 3/4 febrile neutropenia occurred in statistically significantly more patients on the GC arm than on the AC arm (3.7% versus 1.3%, p=0.002), as did Grade 3/4 sensory neuropathy (0.6% versus 0, p=0.030), Grade 3/4 syncope (0.6% versus 0, p=0.030), and any grade of alopecia (21.4% versus 11.9%, p<0.001). Other Grade 3 and 4 toxicities occurred with similar frequency on both study arms.

Transfusions and Supportive Care

There were significantly fewer transfusions (16.4% versus 28.9%, p<0.001), red blood cell transfusions (16.1% versus 27.3%, p<0.001), and platelet transfusions (1.8% versus 4.5%, p=0.002) in patients on the AC arm as compared to the GC arm. Patients on the GC arm received significantly more erythropoietin/darbepoetin than patients on the AC arm (18.1% versus 10.4%; p<0.001) and more iron preparations than patients on the AC arm (7.0% versus 4.3%; p=0.021). Patients on the GC arm also received significantly more G-CSF/GMCSF than patients on the AC arm (6.1% versus 3.1%; p=0.004).

Risk/Benefit Analyses

Risk/Benefit Ratio

A risk/benefit ratio was calculated per treatment arm as the ratio of the percentage of patients experiencing a toxicity (CTC Grade 3 or higher) to the Kaplan-Meier estimated percentage of patients surviving 1 year. Table JMDB.11 shows the risk/benefit ratio for patients who received study drug. The risk/benefit ratio for the AC arm was 0.84 and for the GC arm was 1.23. For the AC arm, the 1-year survival proportion (43.8%) was more than Grade 3/4 possibly study drug-related toxicity (36.6%).

Table JMDB.11. Risk/Benefit Ratio[a] Patients Who Received Study Drug

	AC (N=839)	GC (N=830)
Grade 3/4 CTCs, possibly study drug related	36.6%	52.7%
1-year survival proportion	43.8%	42.7%
Risk-benefit ratio	0.84	1.23

Abbreviations: AC = pemetrexed plus cisplatin, CTC = Common Toxicity Criteria, GC = gemcitabine plus cisplatin, N = number of patients.

[a] The risk/benefit ratio for each treatment arm was calculated as ratio of the percentage of patients experiencing Grade 3/4 drug-related toxicity divided by the 1-year survival rate.

Survival without Grade 3/4 Toxicity

A survival without Grade 3/4 toxicity analysis was performed to measure benefit relative to risk by comparing overall survival time relative to the first occurrence of study-drug related CTC Grade 3/4 toxicity between treatment arms. Survival without Grade 3/4 toxicity was defined as the time from randomization to a study-drug related Grade 3/4 toxicity or death. All randomized patients who received at least 1 dose of study therapy were included in these analyses. Table JMDB.12 summarizes unadjusted statistics and the results of the Cox regression adjusted analysis for survival without study-drug related Grade 3/4 toxicity. The median time for this endpoint was 5.59 months for the AC arm and 2.82 months for the GC arm. There was a statistically significantly longer survival without study-drug related Grade 3/4 toxicity for AC compared with GC (HR = 0.70; 95% CI: 0.63 to 0.78, p <0.001).

Table JMDB.12. Survival without Study-Drug-Related Grade 3/4 Toxicity All Patients Who Received Study Drug

Parameter	AC (N=839)	GC (N=830)
No. Events (%)	675 (80.45%)	743 (89.52%)
No. Censored (%)	164 (19.55%)	87 (10.48%)
Median (95% CI)	5.59 (4.73 – 6.37)	2.83 (2.53 – 3.12)
6 mo. Prob (95% CI)	48.05 (44.63 – 51.47)	33.34 (30.09 – 36.58)
12 mo. Prob (95%CI)	28.64 (25.50 – 31.78)	17.94 (15.26 – 20.61)
18 m. Prob (95% CI)	17.67 (14.87 – 20.47)	9.25 (7.11 – 11.38)
24 mo. Prob (95%CI)	13.12 (10.34 – 15.91)	4.65 (2.71 – 6.59)
Unadjusted Hazard Ratio* (95% CI)	0.69685 (0.62758 – 0.77376)	
Unadjusted Non-inferiority p-value*	<0.0001	
Unadjusted log-rank superiority p-value	<0.0001	
Adjusted HR** (95%CI):	0.70349 (0.63351 – 0.78119)	
Adjusted Noninferiority p-value**	<0.001	
Adjusted Superiority p-value**	<0.001	

Abbreviations: AC = pemetrexed plus cisplatin, CI = confidence interval, GC = gemcitabine plus cisplatin, HR = hazard ratio, mo. = month, N = number of patients, Prob = probability.

*Unadjusted HR and p-value from Cox model with treatment as the only cofactor.

**Adjusted HR and p-value from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

Companion Biomarker Research Results

Of the 366 randomized patients (174 on AC arm and 192 on GC arm) entered, 232 patients provided samples (113 on AC arm and 119 on GC arm), where 16 patients (10 on AC arm and 6 on GC arm) provided insufficient tumor tissue for analysis. The patient demographics and baseline disease characteristics for patients included in biomarker analysis were balanced between treatment arms. Patients with immunohistochemistry data included 90 patients in AC arm and 91 patients in Arm GC. Patients with gene expression data within reference range included 26 patients in AC arm and 43 patients in GC arm. Patients with at least 1 result for both gene and protein analyses included 13 patients in AC arm and 21 patients in GC arm. In this study, because of the small sample size, results were considered useful for exploratory purposes only. For each assay, patients were dichotomized into high- and low-expression subgroups.

Higher epidermal growth factor receptor (EGFR) was associated with improved progression-free survival time (PFS) and time-to-progressive disease (TtPD) regardless of treatment (PFS HR = 0.344, 95% CI: 0.187 to 0.633, p=0.009; TtPD HR = 0.404, 95% CI: 0.216 to 0.756, p=0.049). For patients treated with AC, lower thymidylate synthase (TS) expression was associated with increased TtPD (HR = 1.249, 95% CI: 0.830 to 1.880) and TtTF (HR = 1.514, 95% CI: 0.881 to 2.600) and lower excision repair cross-complementing 1 (ERCC1) expression was associated with increased TtTF (HR = 2.739, 95% CI: 0.925 to 8.105). For patients treated with GC, higher TS expression was

associated with increased TtPD (HR = 0.623 95% CI: 0.435 to 0.892) and TtTF (HR = 0.601 95% CI: 0.343 to 1.052) and lower ERCC1 was associated with decreased TtTF (HR = 0.551, 95% CI: 0.303 to 1.003). A higher folylpoly-glutamate synthetase (FPGS) gene expression was associated with improved TtPD, regardless of treatment (HR = 0.400, 95% CI: 0.226 to 0.708, p=0.021).

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