European Medicines Agency

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Product name**: Alimta**
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SCIENTIFIC DISCUSSION

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SCIENTIFIC DISCUSSION

Introduction

The active substance of Alimta is pemetrexed, an antifolate that exerts its antineoplastic activity by disrupting the folate-dependent metabolic processes essential for cell replication.
In vitro studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are crucial for the *de novo* biosynthesis of thymidine and purine nucleotides. Polyglutamated metabolites of pemetrexed and their prolonged intracellular half-life are resulting in prolonged drug action in malignant cells.

Alimta was granted a Marketing Authorisation (MA) in the European Union (EU) on 20 September 2004. Alimta is indicated in combination with cisplatin for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma. Alimta is also indicated in combination with cisplatin for the first line treatment, and as monotherapy for the second line treatment, of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

Lung cancer

Over one million new cases of lung cancer are diagnosed each year worldwide, resulting in close to one million deaths. It is the second most common cancer in men as well as women, accounting for about 13% of cancer diagnoses, but it is the leading cause of cancer-related deaths in industrialized countries. It is one of the few that continues to show an increasing incidence. Prognosis is poor with relative 1-year survival rates of approximately 30% and 5-year survival rates around 10%. 134.171 men and 29.948 women died of lung cancer in the European Union in 1985. Although the standardised mortality ratio is declining slightly in men it is still rising in women in the vast majority of European Countries.

Lung cancer is subdivided in two groups: small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC). SCLC is recognized by its chemo- and radiosensitivity. NSCLC is a heterogenous group of tumours with common treatment and prognosis.
NSCLC represents about 80% of all lung cancer cases. The most common histologies are epidermoid or squamous cell carcinoma (~40% of cases), adenocarcinoma (~35% of cases), and large cell carcinoma (~25% of cases). The frequency of these different histological subsets varies across countries and over time, with a decrease in squamous cell histology in industrialised countries.

Surgery is the preferred treatment of patients with early disease. However, more than 60-65% of patients present with a locally advanced (stage IIIB) or metastatic disease (stage IV) and are not suitable for surgery. Current standard of care of patients presenting with locally advanced or metastasising NSCLC is systemic chemotherapy with platinum based doublets. Typically, these platinum based doublets are administered for 4 to 6 cycles (provided that progression of disease does not occur). For patients with a disease staged as IIIB or IV the primary goal of therapy is palliative treatment. Only moderate gains in survival and other outcomes like time to disease progression and quality of life have been shown with platinum-based chemotherapy.

Bevacizumab was approved as first-line therapy for advanced NSCLC based on improvement in overall survival (OS) when combined with carboplatin and paclitaxel, and improved progression-free survival (PFS) when combined with cisplatin and gemcitabine, as compared to the platinum doublet alone. Bevacizumab was administered in combination with paclitaxel and carboplatin for up to 6 cycles, followed by single-agent bevacizumab until disease progression.
A second 3-arm study evaluated 2 doses of bevacizumab in combination with gemcitabine and cisplatin for up to 6 cycles, followed by single-agent bevacizumab until disease progression. Bevacizumab therapy is limited to patients with non-squamous NSCLC histology.

Alimta in combination with cisplatin has also recently been approved for the first-line treatment of patients with advanced NSCLC other than predominantly squamous cell histology. This approval was based on results from Study JMDB, a phase 3 study of pemetrexed plus cisplatin (AC) compared to gemcitabine plus cisplatin (GC). The primary objective of Study JMDB was the comparison of OS time between patients treated with AC versus GC as first-line treatment for locally advanced or metastatic NSCLC. Patients were treated for a maximum of 6 cycles of therapy.

Once first line treatment with platinum doublets has been completed, there are currently only second line treatment options available in patients progressing. Licensed second line treatments include docetaxel monotherapy, and Alimta monotherapy (limited to non-squamous NSCLC histologies).

The concept of maintenance treatment in NSCLC has been investigated in the past without convincing results. However, maintenance therapy studies of single-agent docetaxel, paclitaxel, and gemcitabine have suggested benefit of single-agent treatment with improved OS, time to disease progression (TtP), PFS, or response rate (RR) following first-line (induction) therapy.

Scope of the variation

This type II variation concerns an extension of indication to include monotherapy maintenance treatment of locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC). Sections 4.1, 4.8 and 5.1 of the SPC have been updated and the Package Leaflet has been updated accordingly. Further, the MAH has updated annex IIB to include the version number of the latest Risk Management Plan (version 2.1) agreed with the CHMP.

For this new indication, the proposed posology is the one already authorised for Alimta as monotherapy in the 2nd line treatment of NSCLC. In patients treated for NSCLC after prior chemotherapy, the recommended dose of Alimta is 500 mg/m2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

The new NSCLC maintenance treatment indication is supported by one pivotal, multicentre, randomised, placebo-controlled, Phase 3 study (JMEN), which evaluated the efficacy and safety of maintenance treatment with Alimta plus best supportive care (BSC) (n=441) with that of placebo plus BSC (n=222) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC who did not progress after 4 cycles of first line doublet therapy containing Cisplatin or Carboplatin in combination with Gemcitabine, Paclitaxel, or Docetaxel. First line doublet therapy containing ALIMTA was not included because the results of the first-line study with Alimta-cisplatin were not yet available.

Clinical aspects

GCP compliance

All clinical studies included in the dossier have been conducted in compliance with the principles of Good Clinical Practice (GCP).

Clinical pharmacology

No new data concerning clinical pharmacology have been submitted in support of the present application, which is acceptable.

The clinical pharmacology of pemetrexed has been well characterized as part of the initial marketing authorisation application for MPM and for previously treated NSCLC. Given the extensive information available regarding the clinical pharmacology of pemetrexed, both administered as a single agent and in combination with cisplatin, no further pharmacokinetic information was collected in the Phase III Study JMEN. Clinical pharmacology for the maintenance indication is not expected to be different from other approved indications for pemetrexed (e.g., second-line treatment with single-agent pemetrexed).

Clinical Efficacy

As mentioned above, the new requested indication is mainly supported by one pivotal, multicentre, randomised, double-blind, placebo controlled Phase 3 study (JMEN).

Pivotal clinical Phase III study - JMEN

Methods

The primary objective of study JMEN was to compare maintenance therapy with pemetrexed plus best standard care (BSC) *versus* placebo plus BSC, in terms of objective PFS in patients with Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or Stage IV NSCLC who had not progressed during 4 cycles of platinum-based induction chemotherapy.

Secondary objectives of the study were to compare (i) overall survival (OS) time, (ii) additional time-to-event efficacy endpoints (time to objective progressive disease (TtP), time to worsening of symptoms (TWS), (iii) objective tumor response rate, (iv) adverse events and finally (v) changes in individual symptom scores and quality of life using the Lung Cancer Symptom Scale (LCSS) between the randomized study arms.
An additional secondary objective was the consideration of efficacy with respect to histologic types, including an assessment of treatment-by-histology interaction.

Study Design

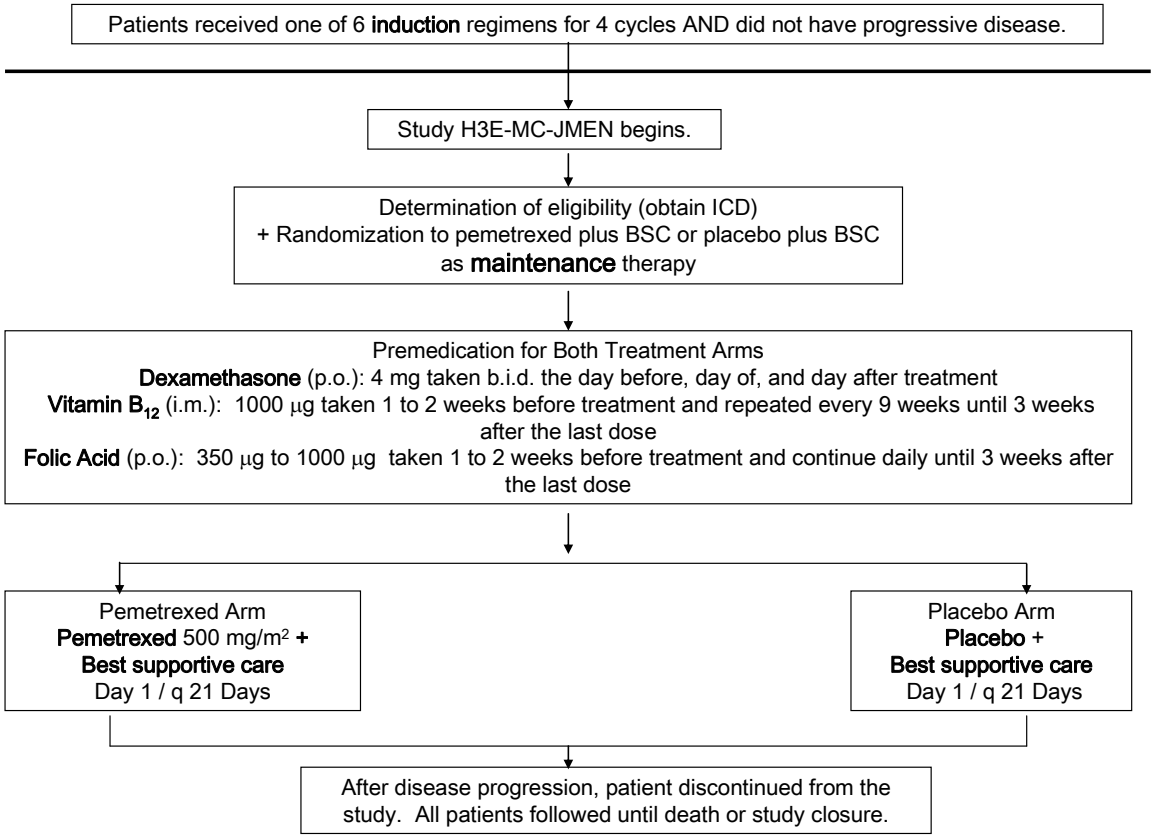
Study JMEN was a global, multicenter, randomized, double-blind, placebo-controlled study. Approximately 660 patients were planned to be enrolled. Subjects were randomized (in a 2:1 ratio) to the experimental study arm (pemetrexed plus BSC) or the control arm (placebo plus BSC) following induction therapy. Patients were required to be chemo naive prior to induction chemotherapy. According to the protocol, patients in both study arms were required to receive folic acid and vitamin B_{12} supplementation and dexamethasone.

A minimization principle was adopted to balance patient assignment between study arms, using a probability factor of 0.75, based on the following factors:

- disease stage prior to administration of induction therapy (IIIB versus IV)
- ECOG performance status just prior to randomization (0 versus 1)
- best tumor response to induction chemotherapy (CR/PR versus SD)
- gender (male versus female)
- previously treated brain metastases (yes versus no)
- non-platinum component of induction chemotherapy (gemcitabine versus paclitaxel versus docetaxel).

Each patient underwent a treatment period and a follow-up period. The treatment period consisted of treatment cycles, each 21 days long. Patients received treatment (experimental or control) until objective disease progression. The follow-up period began when the patient discontinued study treatment; follow-up included periodic tumor response evaluation until objective disease progression. Investigators followed all patients until death or study closure. Maintenance treatment had to begin ≥ 21 and ≤ 42 days from the last dose of induction therapy.

Figure 1: JMEN study design



Abbreviations: b.i.d. = twice daily; BSC = best supportive care; ICD = informed consent document; i.m. = intramuscular; p.o. = oral; q = every.

Study Participants

Inclusion criteria	Exclusion criteria
-Histologic or cytologic diagnosis of NSCLC Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or Stage IV prior to induction therapy; -One of the following induction therapies for treatment of Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or Stage IV NSCLC: gemcitabine plus carboplatin, paclitaxel plus carboplatin, docetaxel plus carboplatin, gemcitabine plus cisplatin, paclitaxel plus cisplatin, or docetaxel plus cisplatin; -Patients must have received only 1 chemotherapeutic doublet lasting precisely 4 cycles; -Documented evidence of a tumor response of CR, PR, or SD; -PET scans and ultrasounds could not be used for lesion measurements for response determination; -ECOG performance status of 0 or 1; -At least 18 years of age.	-Prior systemic anticancer therapy (including adjuvant early-stage treatment for NSCLC) or any systemic treatment for any other cancer. -Received treatment within the last 30 days with a drug that had not received regulatory approval for any indication at the time of study entry. -Inability to comply with protocol or study procedures. -Serious cardiac condition, such as myocardial infarction within 6 months, angina, or heart disease, as defined by the New York Heart Association Class III or IV (see Appendix 16.1.1). -Central nervous system (CNS) metastases (unless the patient had completed successful local therapy for CNS metastases and had been off of corticosteroids for at least 4 weeks before starting study therapy). A screening computed tomography (CT) or magnetic resonance imaging (MRI) before enrollment in the absence of a clinical suspicion of brain metastases was not required. -Presence of clinically detectable) third-space fluid collections; for example, ascites or pleural effusions that could not be controlled by drainage or other procedures prior to study entry. -Concurrent administration of any other antitumor therapy. -Received an induction chemotherapy regimen that

	was not based on a 21-day cycle. Pregnant or breast feeding. -A prior malignancy other than NSCLC, carcinoma in situ of the cervix, or nonmelanoma skin cancer, unless that prior malignancy was diagnosed and definitively treated at least 5 years previously with no subsequent evidence of recurrence.

Treatment regimen

Patients were randomly assigned (within 42 days of Cycle 4 [Day 1] induction therapy) to 1 of 2 study therapies.

Experimental (Pemetrexed) Arm: pemetrexed 500 mg/m^2 on Day 1 every 21 days, plus BSC.
Control (Placebo) Arm: normal saline (0.9% sodium chloride) on Day 1 every 21 days, plus BSC.

Patients were allowed to receive full supportive-care therapies concomitantly during the study. No other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications was permitted while patients were participating in Study JMEN, including patients who the study had randomized to receive placebo plus BSC. Any disease progression requiring other forms of systemic ant tumor therapy were cause for early discontinuation of study therapy.

CSFs: The protocol did not permit the routine use of colony-stimulating factors (CSFs) during treatment. Physicians used G-CSF only for patients who had ANC < 0.5 ´ 10^9/L, neutropenic fever, or documented infections while neutropenic.

NSAIDs: Patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) or salicylates were not allowed the NSAID or salicylate 2 days before, the day of, and 2 days after receiving study therapy. If a patient was taking an NSAID or salicylate with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone), it was not permitted 5 days before, the day of, or 2 days after receiving study therapy.

Leucovorin Rescue: Leucovorin was allowed in order to treat Grade 4 myelosuppression lasting more than 3 days, including CTCAE Grade 4 leukopenia and CTCAE Grade 4 neutropenia. In addition, leucovorin could be used immediately for CTCAE Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis.

Diarrhea: the following supportive measures were allowed: hydration, octreotide, and antidiarrheals. If diarrhea was severe (requiring intravenous rehydration) and/or associated with fever or severe (CTCAE Grade 3 or 4) neutropenia, broad-spectrum antibiotics were prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting were hospitalized for intravenous hydration and correction of electrolyte imbalances.

Febrile Neutropenia: Physicians managed patients who had febrile neutropenia, especially when accompanied by diarrhea, in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

Efficacy and Safety variables

Objective Progression-free survival (PFS) was the primary efficacy variable in this study.

Objective PFS was measured from the date of randomization (after completion of induction chemotherapy) to the first date of objective progression of disease or of death from any cause. For each patient who was not known to have died or to have had objective progression of disease as of the data-inclusion cut-off date for the analysis, PFS was censored at the date of the patient's last tumour assessment prior to that cut-off date.

Overall survival time (OS) is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date for the analysis, OS was to be censored at the date of last prior contact.

Time to objective progressive disease (TPD) is measured from the date of randomization to the first date of objective progression of disease. For each patient who is not known to have had an objective progression of disease as of the data-inclusion cut-off date for the analysis, or who has died without objective progressive disease, TPD will be censored for that analysis at the date of the patient's last tumour assessment prior to that cut-off date. Please note that TPD, else than PFS, does not include death as an event.

Time to worsening of symptoms (TWS) was measured from the date of randomization to the first date of a worsening in any one of the 6 Lung Cancer Symptom Scale (LCSS) symptoms (as defined by a 15-mm increase from baseline in the patient-reported score for any symptom).

Tumour response was assessed using RECIST criteria.

Adverse events were rated using the NCI CTCAE scale.

Statistical Methods

The study was designed to randomize approximately 660 patients at a 2:1 ratio between 2 maintenance study arms: (a) pemetrexed 500 mg/m^2 plus BSC administered until disease progression (approximately 440 patients), or (b) a treatment option utilizing placebo plus BSC until disease progression (approximately 220 patients).
The Sponsor originally selected this sample size to provide a final analysis of OS with 80% power using a one-sided alpha level of 0.025, assuming 475 events and an OS HR of 0.767. The implemented protocol amendment (a) changed the primary endpoint of this trial to PFS while maintaining nearly identical statistical assumptions and error control of the originally planned final analysis of OS.

All study outcomes were analyzed at the time of PFS analysis (after a minimum of 462 PFS events).

According to the protocol, in order to maintain an overall one-sided alpha error probability of 0.025 (for the PFS and OS analyses), the study applied the following statistical gate keeping and alpha-spending scheme:
(i) the primary statistical test of PFS was performed using a nominal one-sided alpha level of 0.025.
(ii) a one-sided alpha level of 0.025 was split between the preliminary and final analyses of OS: a nominal one-sided level of 0.00001 was spent for the preliminary analysis of OS, leaving a nominal level of 0.02499 to be spent for the final analysis of OS.

The primary analysis assumed the PFS HR as approximately constant during the period of follow-up after randomization and estimated the PFS HR from the study data using a Cox proportional hazards model with assigned treatment as the only covariate. From this Cox model, a two-tailed 95% confidence interval was used to assess the following statistical hypotheses:

- H0: PFS HR $\geq$ 1.00 (null hypothesis)
- HA: PFS HR < 1.00 (alternative, research hypothesis)

If the 95% confidence interval for the PFS HR was found to fall entirely below the margin of 1.00, the null hypothesis H0 would be rejected at a nominal one-sided 0.025 significance level.
Assuming the primary analysis included at least 462 PFS events, and assuming the true value of the PFS HR would be 0.75, there was an 85% probability of rejecting the null hypothesis H0.

The final analysis of OS would include a minimum of 475 OS events (projected to occur approximately 1 year after the primary analysis). A one-sided test of hypotheses was planned to be performed at a nominal 0.02499 level (using hypotheses analogous to those described above for PFS). Assuming the true value of the OS HR is 0.767, there is approximately an 80% probability of a

statistically significant test. Therefore, this amended analysis plan was supposed to preserve the original protocol-designed statistical power for assessing OS.

Covariate-adjusted analyses of time-to-event variables were performed using the Cox proportional hazards model stratified by the non-platinum component of the induction chemotherapy (gemcitabine versus taxanes). The following covariates were considered for inclusion in the adjusted models:

-Assigned study treatment (pemetrexed plus BSC over placebo plus BSC)
-ECOG performance status just prior to randomization (0 over 1)
-Platinum component of induction therapy (cisplatin over carboplatin)
-Best tumor response to induction chemotherapy (CR/PR over SD)
-Ethnic origin (Southeast Asian over other)
-Smoking status (never smoker over ever smoker)
-Gender (female over male)
-Age group prior to randomization (< 65 over ≥ 65)
-Disease stage prior to administration of induction therapy (IIIB over IV)
-Previously treated brain metastases (no over yes)
-Squamous histology (no over yes)

Results

Demographic and other baseline characteristics

Seven hundred and forty one patients from 20 countries were included into the study. Of these patients, 663 (89.5%) were randomly assigned (enrolled) to receive either pemetrexed plus BSC or placebo plus BSC.

Table 1: Patient demographic characteristics at baseline by study arm

	Variable	Pemetrexed N = 441	Placebo N = 222	Total N = 663
Gender n (%)	Male	322 (73.0)	161 (72.5)	483 (72.9)
	Female	119 (27.0)	61 (27.5)	180 (27.1)
Age at randomization (years)	Median age (25th-75th percentile)	60.6 (54.3-67.5)	60.4 (53.8-67.0)	60.6 (54.1-67.4)
Age group n (%)	Age < 65 years	294 (66.7)	149 (67.1)	443 (66.8)
	Age ≥ 65 years	147 (33.3)	73 (32.9)	220 (33.2)
Origin n (%)	Aboriginal	0 (0.0)	1 (0.5)	1 (0.2)
	African	6 (1.4)	0 (0.0)	6 (0.9)
	Caucasian	279 (63.3)	149 (67.1)	428 (64.6)
	East Asian	104 (23.6)	50 (22.5)	154 (23.2)
	Hispanic	13 (2.9)	6 (2.7)	19 (2.9)
	West Asian[a]	39 (8.8)	16 (7.2)	55 (8.3)
Smoking status n (%)	Ever smoker	324 (73.5)	158 (71.2)	482 (72.7)
	Never smoker	113 (25.6)	63 (28.4)	176 (26.5)

Abbreviations: N = number of randomized patients; n = number of patients in category.
[a]West Asian refers to patients originating from the Indian subcontinent.

Randomization factors

This study enrolled patients who were initially treated with 4 cycles of 1 of 6 prespecified induction therapy regimens, but only if patients had not progressed following induction treatment. Randomization factors included the non-platinum component of induction chemotherapy (gemcitabine *versus* paclitaxel versus docetaxel), as well as best response to induction therapy (CR/PR *versus* SD), disease stage prior to induction therapy, ECOG performance status at the time of randomization, gender, and previously treated brain metastases.

Table 2: Baseline Characteristics and Randomization Factors by Study Arm

	Variable	Pemetrexed N = 441	Placebo N = 222	Total N = 663
Gender n (%)	Male	322 (73.0)	161 (72.5)	483 (72.9)
	Female	119 (27.0)	61 (27.5)	180 (27.1)
Disease stage prior to	Stage IIIB	79 (17.9)	47 (21.2)	126 (19.0)
induction therapy n (%)	Stage IV	361 (81.9)	175 (78.8)	536 (80.8)
ECOG PSa at randomization	0	176 (39.9)	85 (38.3)	261 (39.4)
n (%)	1	263 (59.6)	136 (61.3)	399 (60.2)
Best tumor response to	Complete Response	6 (1.4)	1 (0.5)	7 (1.1)
induction therapy n (%)	Partial Response	202 (45.8)	116 (52.3)	318 (48.0)
	Stable Disease	229 (51.9)	105 (47.3)	334 (50.4)
	Progressive Diseaseb	3 (0.7)	0 (0.0)	3 (0.5)
Previously treated	Yes	33 (7.5)	18 (8.1)	51 (7.7)
Brain metastases n (%)	No	408 (92.5)	204 (91.9)	612 (92.3)
Nonplatinum component of	Docetaxel	28 (6.3)	11 (5.0)	39 (5.9)
induction therapy n (%)	Gemcitabine	253 (57.4)	132 (59.5)	385 (58.1)
	Paclitaxel	159 (36.1)	79 (35.6)	238 (35.9)
Platinum component of	Carboplatin	260 (59.0)	114 (51.4)	374 (56.4)
induction therapyc n (%)	Cisplatin	180 (40.8)	108 (48.6)	288 (43.4)
Specific induction regimenc	Docetaxel + Carboplatin	21 (4.8)	7 (3.2)	28 (4.2)
n (%)	Docetaxel + Cisplatin	7 (1.6)	4 (1.8)	11 (1.7)
	Gemcitabine + Carboplatin	107 (24.3)	48 (21.6)	155 (23.4)
	Gemcitabine + Cisplatin	146 (33.1)	84 (37.8)	230 (34.7)
	Paclitaxel + Carboplatin	132 (29.9)	59 (26.6)	191 (28.8)
	Paclitaxel + Cisplatin	27 (6.1)	20 (9.0)	47 (7.1)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; N = number of randomized patients; n = number of patients in category.

a Three patients were missing ECOG PS and 1 patient was missing disease stage status.

b Protocol violations: patients randomized but not treated due to progressive disease at the time of study entry.

c Not a specific randomization factor, provided for informational purposes.

Histology

Table 3: Histologic Classifications by Study Arm

Histologic Classifications[a]	Lilly Assigned System Codes	Pemetrexed N = 441	Placebo N = 222	Total N = 663
Nonsquamous Histology[b]		326 (73.9)	156 (70.3)	482 (72.7)
Adenocarcinoma		223 (50.6)	106 (47.7)	329 (49.6)
Bronchioalveolar carcinoma	2140	7 (1.6)	3 (1.4)	10 (1.5)
Adenocarcinoma	1882	216 (49.0)	103 (46.4)	319 (48.1)
Large Cell Carcinoma	920	11 (2.5)	9 (4.1)	20 (3.0)
Other[c] or Indeterminate		92 (20.9)	41 (18.5)	133 (20.1)
NSCLC	1897	65 (14.7)	30 (13.5)	95 (14.3)
Poorly differentiated NSCLC	1432	25 (5.7)	11 (5.0)	36 (5.4)
Mixed cell carcinoma, lung	1883	1 (0.2)	0	1 (0.2)
Other	99	1 (0.2)	0	1 (0.2)
Squamous Cell Carcinoma	1884	115 (26.1)	66 (29.7)	181 (27.3)

Abbreviations: N = number of randomized patients; NSCLC = non-small cell lung cancer.

a Grouped by WHO classification of lung tumors (Travis et al. 1999).

b Nonsquamous histology includes adenocarcinoma, large cell, and other histologies.

c 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. Patient 100-1003 had squamous cell carcinoma of the trachea.

Concomitant medications

As regards the baseline (and on treatment) factor concomitant medications there was a higher rate of erythropoietic growth factors received by patients in the pemetrexed compared to the placebo arm. No differences were observed in other classes of medications used in this patient population.

Table 4: Summary of Select Concomitant Medications on Study or within 30 Days of Discontinuation All Randomized Patients, Study JMEN

	Pemetrexed (N = 441) n	(%)	Placebo (N = 222) n	(%)	p-Value
Patients receiving no concomitant medication	2	(0.5)	0	(0.0)	0.554
Patients receiving any concomitant medication	439	(99.5)	222	(100.0)	0.554
Antiemetics and antinauseants					
any	136	(30.8)	68	(30.6)	>.999
serotonin (5HT3) antagonists	132	(29.9)	68	(30.6)	0.858
other, including NK1 antagonists	10	(2.3)	2	(0.9)	0.355
Analgesics					
any	187	(42.4)	92	(41.4)	0.868
non-steroidal anti-inflammatory agents	57	(12.9)	28	(12.6)	>.999
opioids	123	(27.9)	60	(27.0)	0.854
Anti-infectives (systemic)					
any	115	(26.1)	43	(19.4)	0.066
antibiotics	109	(24.7)	43	(19.4)	0.142
antivirals	3	(0.7)	1	(0.5)	>.999
antifungals	5	(1.1)	6	(2.7)	0.195
Erythropoietic agents	26	(5.9)	4	(1.8)	0.017
G-CSF or GM-CSF	13	(2.9)	8	(3.6)	0.644

Discontinuation

The study design allowed to receive treatment (experimental or control) until objective disease progression; accordingly, PD was the most common reason for study discontinuation in both study arms. A higher percentage of patients in the placebo arm discontinued due to PD or death compared to the pemetrexed arm, while a higher percentage of patients in the pemetrexed arm discontinued due to subject decision, AE, or physician decision

Protocol violation

A total of 217 randomized patients (32.7%) were reported to have at least 1 protocol violation. The most commonly identified protocol violations for the randomized patient population were for prolonged intervals between lesion assessments (13.1%); each of the remaining violations occurred at a rate less than 10%. In general, protocol violations in this study were balanced between study arms such that they were not likely to have affected the analyses or conclusions presented in this report.

Primary efficacy analysis

Objective Progression-Free Survival (PFS) following induction chemotherapy

The PFS analysis of the study was measured from the date of randomisation, which occurred after completion of induction therapy, to the date of progression or death from any cause. A total of 504 PFS events had occurred at the time of database lock; 123 patients (27.9%) in the pemetrexed arm and 36 patients (16.2%) in the placebo arm were censored for the PFS analysis. Median PFS was 4.27 months in the pemetrexed arm and 2.60 months in the placebo arm, and the primary statistical comparison between arms was statistically significant (HR = 0.50; 95% confidence interval [CI]: 0.42 to 0.61; $p < 0.00001$).

Table 5: Summary of Objective Progression-Free Survival All Randomized Patients

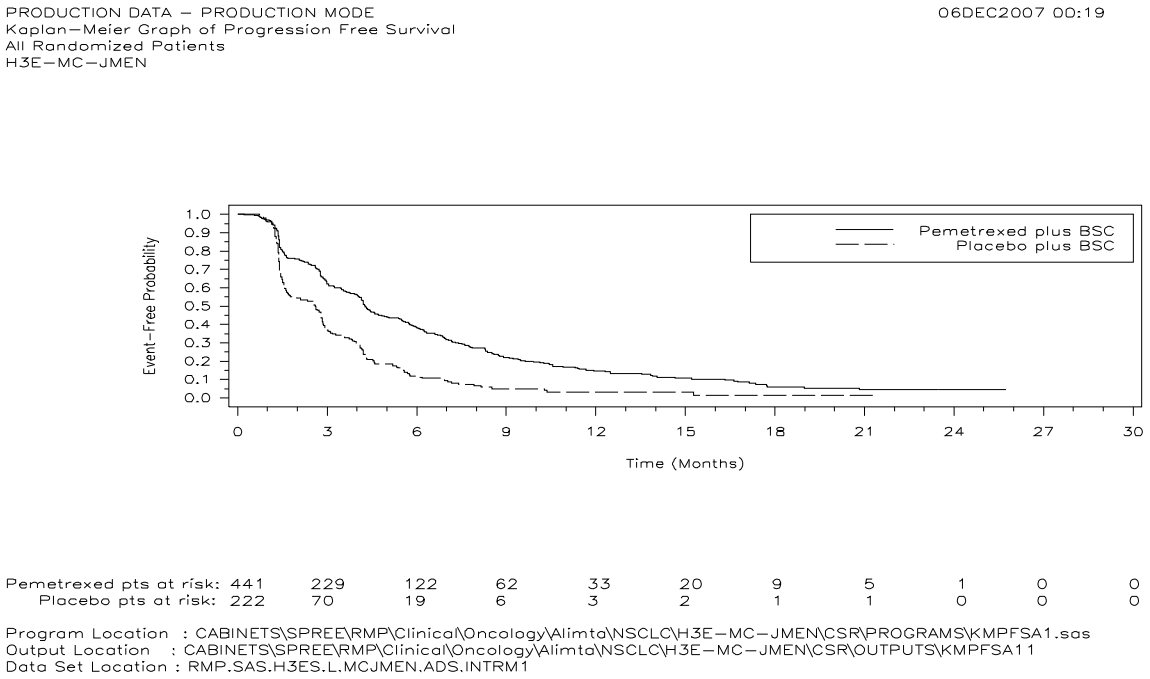
	PFS[a] (N = 663)	
	Pemetrexed N = 441	**Placebo N = 222**
Number (%) of events	318 (72.1)	186 (83.8)
Number (%) censored	123 (27.9)	36 (16.2)
25th percentile	2.10	1.38
(95% CI)	(1.54 - 2.66)	(1.35 - 1.41)
Median PFS – months	4.27	2.60
(95% CI)	(4.07 - 4.73)	(1.68 - 2.83)
75th percentile	8.38	4.21
(95% CI)	(7.39 - 9.46)	(3.84 - 4.57)
Rate of patient with PFS of at least:		
3 months	0.62	0.37
(95% CI)	(0.57 - 0.67)	(0.30 - 0.44)
6 months	0.38	0.12
(95% CI)	(0.33 - 0.43)	(0.07 - 0.17)
9 months	0.22	0.05
(95% CI)	(0.17 - 0.26)	(0.02 - 0.09)
12 months	0.15	0.03
(95% CI)	(0.11 - 0.19)	(0 - 0.06)
Hazard ratio[b]	0.50	
95% CI for hazard ratio	0.42 - 0.61	
Log rank p-value	< 0.00001	

Abbreviations: CI = confidence interval; HR = hazard ratio; N = number of patients; PFS = progression-free survival.

a Investigator-assessed data.

b Unadjusted HR and p-values from Cox model with treatment as the only cofactor. HR < 1.0 favors pemetrexed study arm, HR > 1.0 favors comparator.

Figure 2: Kaplan-Meier graph of objective progression-free survival time by study arm



Covariate-Adjusted Analyses of Progression-Free Survival (PFS)

A covariate-adjusted analysis of PFS was performed using the Cox proportional hazards model. The treatment effect (HR = 0.52; 95% CI: 0.43 to 0.62; p < 0.0001) was similar to that observed in the primary unadjusted analysis. None of the cofactors had a statistically significant effect on PFS (all cofactor p-values > 0.10)

Table 6: Cofactor-adjusted summary statistics for PFS

Variable (N = 654[a,b], 498 events)	HR (95% CI)	p-Value[c]
Study Treatment Arm (Pemetrexed vs Placebo)	0.52 (0.43-0.62)	< 0.0001
ECOG PS (1 vs 0)	1.00 (0.83-1.21)	0.988
Cisplatin[d] (yes vs no)	1.04 (0.85-1.28)	0.703
Induction response (PR/CR vs SD)	1.06 (0.88-1.27)	0.556
East Asian (yes vs no)	1.13 (0.91-1.39)	0.274
Nonsmoker (yes vs no)	0.99 (0.79-1.26)	0.957
Gender (Female vs Male)	0.83 (0.66-1.04)	0.106
Age (< 65 vs ≥ 65)	1.05 (0.86-1.27)	0.663
Stage (IIIB vs IV)	1.16 (0.92-1.45)	0.217

Abbreviations: CI = confidence interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; N = number of patients; PFS = progression-free survival; PR = partial response; SD = stable disease; vs = versus.

a Stratified by nonplatinum component of induction therapy (gemcitabine versus paclitaxel/docetaxel).

b Nine patients were excluded due to missing values for 1 or more cofactors.

c p-value is from the Mantel-Haenszel chi-square test.

d Description of platinum agent in induction regimen: all patients were treated with a platinum-based regimen, either with cisplatin (yes) or carboplatin (no).

Progression-Free Survival Measured from Start of Induction Treatment: The primary PFS analysis of the study was measured from the date of randomization, which occurred after completion of induction therapy. An additional analysis of PFS was calculated from the date of the first dose of induction chemotherapy to the first date of objective progression of disease or of death from any cause. It was expected that this analysis would add approximately 3 months to the median times observed in the primary analysis. Evaluating from the start of induction therapy did not change the HR or the p-value compared to the primary analysis. Median PFS measured from the start of induction treatment was 7.72 months in the pemetrexed arm and 5.91 months in the placebo arm.

Independently Reviewed Progression-Free Survival: To further evaluate the robustness of PFS, the Sponsor established an independent review of PFS to assess the potential for investigator bias in the determination of progressive disease between study arms. Of the 663 randomized patients with investigator assessments of PFS, reviewable scans were available for independent review for 581 patients (87.6%). Independently assessed median PFS following induction therapy was 4.04 months in the pemetrexed arm and 1.97 months in the placebo arm, with the unadjusted HR estimated to be 0.60 (95% CI: 0.49 to 0.73). This analysis demonstrated that results of investigator-assessed PFS were consistent with those of the independently reviewed assessments in terms of the relative efficacy of the 2 arms.

Sensitivity Analyses

Sensitivity analyses of PFS were performed to evaluate the robustness of the primary analysis with respect to the definition of censoring and the timing of radiologic assessments. The first sensitivity analysis (SA1) defined PFS as in the primary analysis, but with additional censoring at the date a patient initiated postdiscontinuation anticancer therapy. A total of 13 additional patients were censored compared to the primary analysis. The results of SA1 are nearly identical to results from the primary PFS analysis.

The other 2 sensitivity analyses (SA2 and SA3) adjusted the definition of PFS dependent on the timing of the first radiologic assessment with PD. According to the Study Schedule, radiologic assessments were conducted after every 2 cycles of therapy (approximately every 42 days). Compared to the

placebo arm, a greater number of patients in the pemetrexed arm experienced dose delays which may have led to delayed radiologic assessments. Thus, SA2 and SA3 were conducted to assess whether there was any bias affecting the analysis caused by delayed assessments in the pemetrexed arm.

For patients who had PD occurring more than 49 days after the previous radiologic assessment, SA2 moved the date of the PD back to the date when the radiologic assessment would have occurred if there had been no delay (that is, 42 days after the previous assessment). While median PFS times under this definition were slightly shorter on both arms compared to those under the primary analysis, the estimated hazard ratio was very similar to the primary analysis.

For those patients who had PD occurring more than 49 days after the previous radiologic assessment, SA3 censored the PFS times of these patients back to the date of the earlier assessment. The results are very similar to the findings in the primary analysis.
These sensitivity analyses support the robustness of the primary analysis; they strongly indicate that postdiscontinuation therapy and delayed radiologic assessments did not bias the primary analysis in favor of pemetrexed.

Table 7: Progression-Free Survival, Sensitivity Analyses

	Median PFS (95% CI)		HR[a] (95% CI)
	Pemetrexed N = 441	**Placebo N = 222**	
Primary PFS Analysis	4.27 (4.07 - 4.73)	2.60 (1.68 - 2.83)	0.50 (0.42 - 0.61)
PFS Sensitivity Analyses			
SA1: Objective PD censored at date of postdiscontinuation anticancer therapy.	4.27 (4.11 - 4.83)	2.60 (1.68 - 2.83)	0.50 (0.42 - 0.61)
SA2: Objective PD for delayed assessments censored (back-dated) at date when assessment would have occurred without delay.	4.14 (3.75 - 4.27)	2.33 (1.54 - 2.73)	0.53 (0.44 - 0.63)
SA3: Objective PD for delayed assessments censored at date of previous assessment.	4.37 (4.21 - 5.78)	2.60 (1.61 - 2.79)	0.48 (0.39 - 0.59)

Abbreviations: CI = confidence interval; HR = hazard ratio; N = number of patients; PD = progressive disease; PFS = progression-free survival; SA = sensitivity analysis.

a Unadjusted HR and p-values from Cox model with treatment as the only cofactor. HR < 1.0 favors pemetrexed study arm, HR > 1.0 favors comparator.

Progression-Free Survival within Key Subgroups

Subgroup analyses were performed to assess whether the PFS results within certain key subgroups were consistent with survival results for the overall study, or whether there is evidence of differential treatment benefit in certain subgroups. Subgroups were analyzed separately as defined by the following factors: NSCLC histology, age, gender, origin, smoking status, ECOG performance status, induction platinum, and induction response. Several of these factors are commonly found to be prognostic of OS in advanced NSCLC.

Additional rationale for certain subgroup analyses are described further below:
- The choice of ever-smoker versus never-smoker is based on erlotinib data showing that erlotinib was more effective in patients who had never been smokers than in current or former smokers. In addition, smoking status may be associated with histologic cell type and other patient comorbidities, which may impact patient prognosis. In Study JMDB, smoking status was identified as a significant prognostic factor for first-line NSCLC patients.
- Safety and efficacy analyses by age and origin (as well as gender, included as a randomization factor) are regulatory requirements; the categories for origin were divided into 3 groups based on a blinded review of Study JMEN baseline data, permitting adequately sized categories for meaningful comparisons.

- Histologic categories of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the most common NSCLC cell types. The prospective decision to perform histologic subgroup analyses in Study JMEN was based on results of the pivotal Phase 3 Study JMDB, and on a retrospective analysis of the Phase 3 study of pemetrexed in previously treated NSCLC (Study JMEI), which suggested a possible correlation between histology and efficacy.

The subgroup analyses showed that PFS was significantly superior in the pemetrexed arm for the subcategories of age (< 65, ≥ 65) and gender. The majority of patients were either Caucasian or East Asian (87.8% of patients); the PFS for these patients was similar to the overall population, with a significant increase in PFS in the pemetrexed arm.

Table 8: Summary of Progression-Free Survival by Age, Gender, and Origin

	Median PFS (months)		
	Pemetrexed	**Placebo**	**HR (95% CI)**
Subgroups	**N = 441**	**N = 222**	**p-Value**
Age			
< 65	**4.21**	**1.68**	0.49 (0.39-0.61)
	N=294	n=149	< 0.00001
≥ 65	**4.99**	**2.83**	0.52 (0.37-0.73)
	N=147	n=73	0.00014
Gender			
Female	**4.44**	**2.79**	0.51 (0.36-0.73)
	N=119	n=61	0.00017
Male	**4.21**	**2.60**	0.49 (0.39-0.61)
	N=322	n=161	< 0.00001
Origin			
Caucasian	**4.30**	**2.63**	0.52 (0.41-0.65)
	N=279	n=149	< 0.00001
East Asian	**4.21**	**1.71**	0.48 (0.33-0.69)
	N=104	n=50	0.00011
Hispanic	**2.37**	**4.60**	1.08 (0.28-4.20)
	N=13	n=6	0.91258
West Asian[a]	**4.44**	**2.10**	0.35 0.17-0.70)
	N=39	n=16	0.00311

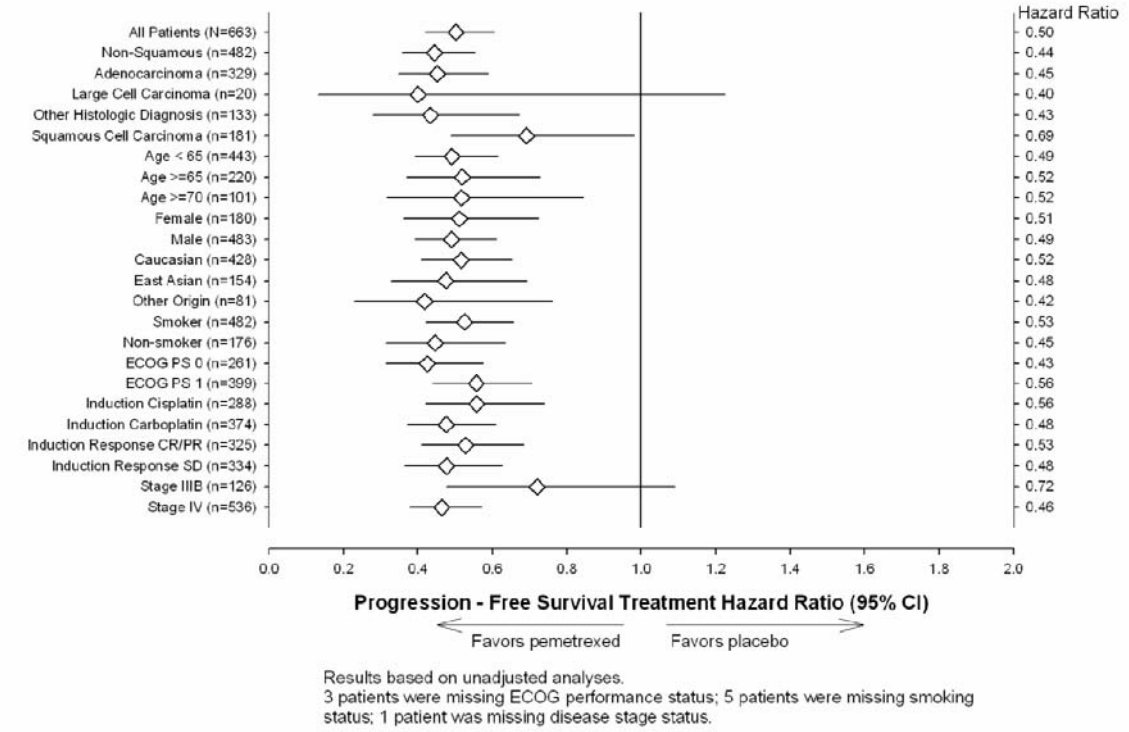
Abbreviations: CI = confidence interval; HR = hazard radio; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival.

[a] Indian subcontinent.

Note: Bold text indicates a statistically significant difference between study arms.

The following figure shows a plot of the treatment hazard ratios for PFS (with 95% confidence intervals) for each of several subgroups. Treatment hazard ratios are fairly consistent across the subgroups considered. Results for non-squamous histologies show a larger advantage for pemetrexed compared to results for patients with squamous histology.

Figure 3: hazard ratios (pemetrexed over placebo) in subgroups according to baseline characteristics



Secondary efficacy parameters

Final Overall Survival (OS) results – Overall Population

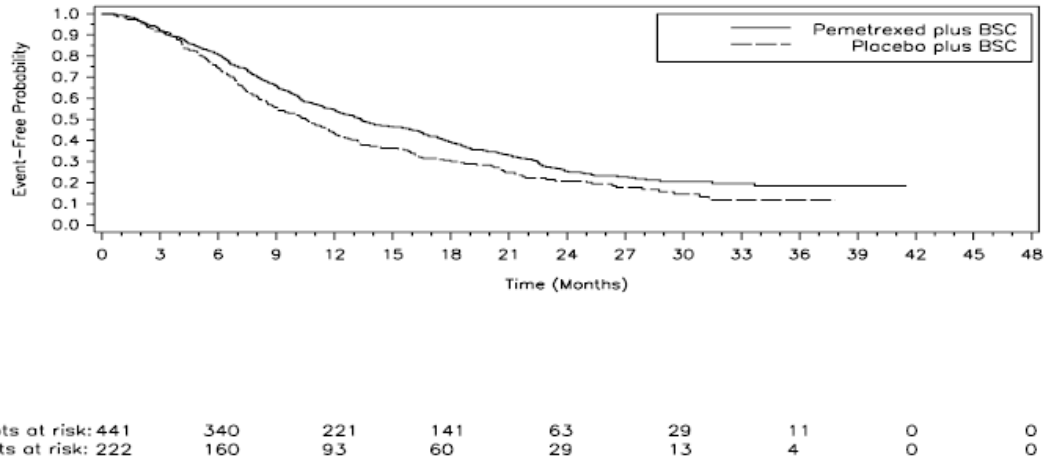
The OS analysis of the study was measured from the date of randomisation, which occurred after completion of induction therapy, to the date of death from any cause. Table 3.1 presents summary statistics of OS for all randomised patients. The OS results indicated a statistically significant improvement of OS for the pemetrexed arm in the overall study population, with a hazard ratio of 0.79 (95% CI: 0.65 to 0.95; p = 0.01192), representing a 21% reduction in the risk of death for patients receiving pemetrexed. Median OS was 13.4 months for patients receiving pemetrexed and 10.6 months for patients receiving placebo. The 1-year survival rate in the randomised population was estimated at 55% for the pemetrexed arm and 43% for the placebo arm.

Table 9: Summary of Final Overall Survival. All Randomised Patients. Study JMEN

	Pemetrexed N = 441	**Placebo N = 222**
Number (%) of events	303 (68.7)	174 (78.4)
Number (%) censored	138 (31.3)	48 (21.6)
Median OS – months (95% CI)	13.37 (11.93-15.87)	10.58 (8.74-12.02)
One-year survival (95% CI)	55% (50% - 59%)	43% (37% - 50%)
Hazard ratioa	0.787	
95% CI for hazard ratio	0.65-0.95	
Cox unadjusted p-value	0.01192	

Abbreviations: CI = confidence interval; HR = hazard ratio; N = number of randomised patients; OS = overall survival. a Unadjusted HR and p-values from Cox model with treatment as the only cofactor. HR < 1.0 favors pemetrexed study arm, HR > 1.0 favors comparator.

Figure 4: Kaplan-Meier graph of final overall survival time for all randomised patients, Study JMEN.



Objective Tumor Response Rate (ORR) – Overall Population

The tumor response rate (CR+PR) measured from randomisation to maintenance therapy was 6.8% in the pemetrexed arm and 1.8 % in the placebo arm (p = 0.005), and the disease control rate (CR+PR+SD) was 51.7% for patients receiving pemetrexed and 33.3% for patients receiving placebo (p < 0.001).

Table 10: Summary of Tumor Response Rate - All Randomized Patients

	Number (%) of Patients (95% CI)		
Best Tumor Response[a]	**Pemetrexed (N = 441)**	**Placebo (N = 222)**	**p-Value[b]**
CR n (%)	3 (0.7)	0 (0.0)	0.555
95% CI[c]	(0.00-0.02)	(0.98-1.00)	
PR n (%)	27 (6.1)	4 (1.8)	0.011
95% CI[c]	(0.04-0.09)	(0.00-0.05)	
SD n (%)	198 (44.9)	70 (31.5)	0.001
95% CI[c]	(0.40-0.50)	(0.25-0.38)	
PD n (%)	139 (31.5)	122 (55.0)	< 0.001
95% CI[c]	(0.27-0.36)	(0.48-0.62)	
Other/Not determined n (%)[d]	74 (16.8)	26 (11.7)	0.107
95% CI[c]	(0.13-0.21)	(0.08-0.17)	
Rate for CR/PR n (%)	30 (6.8)	4 (1.8)	0.005
95% CI[c]	(0.05-0.10)	(0.00-0.05)	
Rate for CR/PR/SD n (%)	228 (51.7)	74 (33.3)	< 0.001
95% CI[c]	(0.47-0.56)	(0.27-0.40)	

Abbreviations: CI = confidence interval; CR = complete response; N = number of randomized patients; n = number of patients in category; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

a RECIST response criteria.

b p-value is from the Fisher exact test.

c Confidence intervals based on exact binomial.

d Progression was not documented or 1 or more target or nontarget sites were not assessed.

Independently Reviewed Objective Tumor Response Rate – Overall Population

A total of 387 patients (87.8%) in the pemetrexed arm and 194 patients (87.4%) in the placebo arm had sufficient assessment data from which to determine a best response of CR, PR, SD, or PD. The independently reviewed tumor response rate (CR+PR) was 3.4% in the pemetrexed arm and 0.5 % in the placebo arm (p = 0.042), and the disease control rate (CR+PR+SD) was 49.1% for patients receiving pemetrexed and 28.9% for patients receiving placebo (p < 0.001). This analysis

demonstrated that results of investigator-assessed RR and disease control rate were consistent with those of the independently reviewed assessments in terms of the relative efficacy of the 2 arms.

Table 11: Summary of Tumor Response Rate All Patients with Independent Assessments

Best Tumor Response[a]	Number (%) of Patients (95% CI) Pemetrexed (N = 387)	Placebo (N = 194)	p-Value[b]
CR n (%)	0	0	-
95% CI[c]	(0.99-1.00)	(0.98-1.00)	
PR n (%)	13 (3.4)	1 (0.5)	0.042
95% CI[c]	(0.02-0.06)	(0.00-0.03)	
SD n (%)	177 (45.7)	55 (28.4)	< 0.001
95% CI[c]	(0.41-0.51)	(0.22-0.35)	
PD n (%)	151 (39.0)	113 (58.2)	< 0.001
95% CI[c]	(0.34-0.44)	(0.51-0.65)	
Other/Not determined n (%)	46 (11.9)	25 (12.9)	0.788
95% CI[c]	(0.09-0.16)	(0.09-0.18)	
Rate for CR/PR n (%)	13 (3.4)	1 (0.5)	0.042
95% CI[c]	(0.02-0.06)	(0.00-0.03)	
Rate for CR/PR/SD n (%)	190 (49.1)	56 (28.9)	< 0.001
95% CI[c]	(0.44-0.54)	(0.23-0.36)	

Abbreviations: CI = confidence interval; CR = complete response; N = number of patients with independent assessments; n = number of patients in category; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

a RECIST response criteria.

b p-value is from the Fisher exact test.

c Confidence intervals based on exact binomial.

Efficacy Analyses Considering Histology

Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated strong evidence of histology-by-treatment interactions for pemetrexed. These interactions indicated that for patients treated with pemetrexed, those with non-squamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better survival and PFS compared to patients with squamous histology.

Prespecified tests for histology-by-treatment interaction were performed using Cox models that included cofactors potentially prognostic for PFS and OS. Based on the results of cofactor-adjusted analyses, most cofactors did not appear to be prognostic for either PFS or OS. Tests for interaction were stratified by the non-platinum component of induction therapy (gemcitabine versus paclitaxel/docetaxel) and included terms for treatment (pemetrexed versus placebo), squamous histology (no *versus* yes), treatment-by-squamous interaction (nonsquamous pemetrexed versus all other patients), ECOG performances status (0 *versus* 1), induction response (CR/PR *versus* SD), East Asian ethnicity (yes *versus* no), smoking status (never *versus* ever), gender (female versus male), and age (< 65 *versus* ≥ 65). The platinum component of induction therapy and the stage of disease were the only factors omitted because they showed no tendency toward any prognostic effect.

The results showed statistically significant interactions for PFS (interaction HR = 0.65; p = 0.036) and for OS (interaction HR = 0.66; p = 0.041). These tests confirmed the results seen in previous Phase 3 studies (Study JMEI and Study JMDB), showing that patients with non-squamous histology in the pemetrexed arm tended to have better PFS and OS compared to patients with squamous cell histology.

Table 12: Baseline Characteristics of Squamous and Non-squamous Patients by Study Arm

		Nonsquamous Histology		Squamous Histology	
	Variable	**Pemetrexed N = 326**	**Placebo N = 156**	**Pemetrexed N = 115**	**Placebo N = 66**
Gender n (%)	Male	223 (68.4)	108	99 (86.1)	53 (80.3)
	Female	103 (31.6)	(69.2)	16 (13.9)	13 (19.7)
			48		
			(30.8)		
Age at randomization (yrs)	Median Age	60.5	60.2	60.8	60.9
	(25th-75th percentile)	(53.7-67.4)	(52.1-	(55.5-67.7)	(56.2-66.8)
			68.0)		
Age group n (%)	Age < 65 years	221 (67.8)	102	73 (63.5)	47 (71.2)
	Age ≥ 65 years	105 (32.2)	(65.4)	42 (36.5)	19 (28.8)
			54		
			(34.6)		
Origin n (%)	Aboriginal	0	0	0	1 (1.5)
	African	6 (1.8)	0	0	0
	Caucasian	196 (60.1)	98	83 (72.2)	51 (77.3)
	East Asian	88 (27.0)	(62.8)	16 (13.9)	9 (13.6)
	Hispanic	8 (2.5)	41	5 (4.3)	3 (4.5)
	West Asian	28 (8.6)	(26.3)	11 (9.6)	2 (3.0)
			3 (1.9)		
			14 (9.0)		
Disease stage prior to Induction n (%)	Stage IIIB	55 (16.9)	30	24 (20.9)	17 (25.8)
	Stage IV	270 (82.8)	(19.2)	91 (79.1)	49 (74.2)
			126		
			(80.8)		
ECOG PS n (%)	0	134 (41.1)	60	42 (36.5)	25 (37.9)
	1	190 (58.3)	(38.5)	73 (63.5)	41 (62.1)
			95		
			(60.9)		
Smoking status n (%)	Ever Smoker	225 (69.0)	107	99 (86.1)	51 (77.3)
	Never Smoker	98 (30.1)	(68.6)	15 (13.0)	15 (22.7)
			48		
			(30.8)		
Previously treated brain metastases n (%)	Yes	30 (9.2)	13 (8.3)	3 (2.6)	5 (7.6)
	No	296 (90.8)	143	112 (97.4)	61 (92.4)
			(91.7)		
Best tumor response to Induction therapy n (%)	CR	5 (1.5)	0	1 (0.9)	1 (1.5)
	PR	145 (45.5)	79	57 (49.6)	37 (56.1)
	SD	2 (0.6)	(50.6)	1 (0.9)	0
	PD	173 (53.1)	0	56 (48.7)	28 (42.4)
			77		
			(49.4)		
Platinum component of Induction therapy n (%)	Carboplatin	193 (59.2)	79	67 (58.3)	35 (53.0)
	Cisplatin	132 (40.5)	(50.6)	48 (41.7)	31 (47.0)
			77		
			(49.4)		
Nonplatinum component of induction therapy n (%)	Gemcitabine	198 (60.7)	98	55 (47.8)	34 (51.5)
	Paclitaxel	108 (33.1)	(62.8)	51 (44.3)	30 (45.5)
	Docetaxel	19 (5.8)	49	9 (7.8)	2 (3.0)
			(31.4)		
			9 (5.8)		
Specific induction regimen n (%)	Gemcitabine + Carbo	90 (27.6)	37	17 (14.8)	11 (16.7)
	Gemcitabine + Cis	108 (33.1)	(23.7)	38 (33.0)	23 (34.8)
	Paclitaxel + Carbo	89 (27.3)	61	43 (37.4)	23 (34.8)
	Paclitaxel + Cis	19 (5.8)	(39.1)	8 (7.0)	7 (10.6)
	Docetaxel + Carbo	14 (4.3)	36	7 (6.1)	1 (1.5)
	Docetaxel + Cis	5 (1.5)	(23.1)	2 (1.7)	1 (1.5)
			13 (8.3)		
			6 (3.8)		
			3 (1.9)		

Abbreviations: Carbo = carboplatin; Cis = cisplatin; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; N = number of randomized patients; n = number of patients in category; PD = progressive disease; PR = partial response; SD = stable disease; yrs = years.

Results for Specific Histologic Subgroups

For the combined non-squamous population, there was a statistically significant PFS advantage for the pemetrexed arm compared to placebo (HR = 0.44; p-value < 0.00001). Median PFS within the squamous group was similar between arms (2.8 months for the pemetrexed arm *versus* 2.6 months for the placebo arm; HR = 0.69; p = 0.039), but the arms separated more clearly in favour of pemetrexed among patients who performed better than the medians.

Table 13: Progression-Free Survival and Overall Survival by Histologic Subgroups

	Final PFS		**Preliminary OS**	
	Pemetrexed (N = 441) median mos	**Placebo (N = 222) median mos**	**Pemetrexed (N = 441) median mos**	**Placebo (N = 222) median mos**
Histologic Subgroup	**HR (95% CI) p-Value**		**HR (95% CI) p-Value**	
Nonsquamous (n = 482)	4.50	2.60	14.36	9.43
	0.44 (0.36-0.55)		0.66 (0.49-0.88)	
	< 0.00001		0.005	
Adenocarcinoma (n = 329)	4.73	2.60	16.39	11.73
	0.45 (0.35-0.59)		0.73 (0.50-1.05)	
	< 0.00001		0.091	
Large Cell (n = 20)	3.48	2.09	9.13	5.45
	0.40 (0.13-1.22)		0.42 (0.13-1.38)	
	0.109		0.154	
Other/Indeterminate (n = 133)	4.21	2.79	11.27	7.03
	0.43 (0.28-0.670)		0.47 (0.28-0.80)	
	0.0002		0.005	
Squamous (n = 181)	2.79	2.60	9.63	11.86
	0.69 (0.49-0.98)		1.28 (0.85-1.93)	
	0.039		0.231	

Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months; N = number of randomized patients; n = number of patients in category; OS = overall survival; PFS = progression-free survival.

For patients with non-squamous histology, results for preliminary median OS suggest a strong trend favoring the pemetrexed arm with a 5-month advantage for pemetrexed compared to placebo (14.4 months *versus* 9.4 months; HR = 0.66; p = 0.005). Although not statistically significant, the preliminary OS results in patients with squamous histology suggest a disadvantage for pemetrexed (9.6 months) compared to placebo (11.9 months; HR = 1.28; p = 0.231).

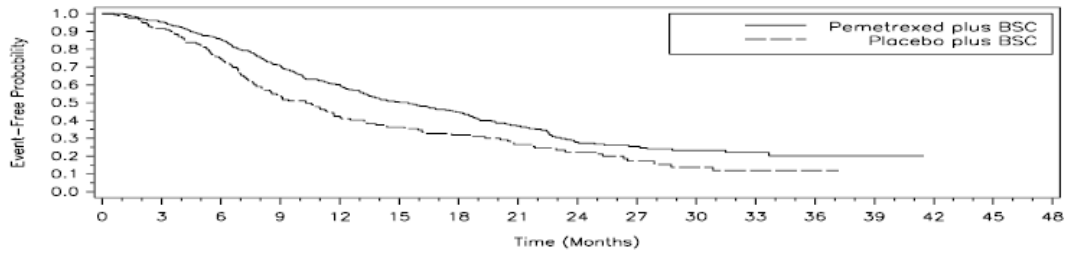
The final OS results in the non-squamous population indicated a significant improvement of OS for the pemetrexed arm, with a hazard ratio of 0.70 (95% CI: 0.56 to 0.88; p = 0.00196), representing a 30% reduction in the risk of death for patients receiving pemetrexed. Median OS was 15.5 months for nonsquamous patients receiving pemetrexed and 10.3 months for non-squamous patients receiving placebo. The 1-year survival rate in the non-squamous population was estimated at 60% for the pemetrexed arm and 42% for the placebo arm.

Table 14: Analysis of Final Overall Survival by Study Arm and Histologic Subgroups All Randomised Patients. Study JMEN

	Number of Events/ Number Censored	Median OS (mo)	Unadjusted HRa (95% CI)	p-Value[a]
Nonsquamous Histology[b] (N = 482)				
Pemetrexed (n = 325)	213/112	15.47	0.701 (0.56-0.88)	0.00196
Placebo (n = 156)	119/37	10.28		
Adenocarcinoma (N = 328)				
Pemetrexed (n = 222)	143/79	16.82	0.732 (0.56-0.96)	0.02632
Placebo (n = 106)	79/27	11.53		
Large Cell Carcinoma (N = 20)				
Pemetrexed (n = 10)	8/2	8.39	0.977 (0.36-2.65)	0.96406
Placebo (n = 10)	8/2	7.87		
Other Histology[c] (N = 133)				
Pemetrexed (n = 93)	62/31	11.27	0.611 (0.40-0.94)	0.02507
Placebo (n = 40)	32/8	7.66		
Squamous Cell (N = 182)				
Pemetrexed (n = 116)	90/26	9.89	1.074 (0.77-1.50)	0.67776
Placebo (n = 66)	55/11	10.84		

Abbreviations: CI = confidence interval; HR = hazard ratio; mo = months; N= number of patients per histologic subgroup; n = number of patients per study arm (within histologic subgroup); OS = overall survival.
a Unadjusted HR and p-values from Cox model with treatment as the only cofactor. HR < 1.0 favors pemetrexed study arm, HR > 1.0 favors placebo.
b Nonsquamous histology includes adenocarcinoma, large cell carcinoma, and other histologies.
c 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.

Figure 5 Overall survival in the non-squamous subgroup (adenocarcinoma, large cell carcinoma, and other histology), Study JMEN.



Pemetrexed pts at risk: 325	265	178	117	51	25	9	0	0
Placebo pts at risk: 156	112	63	42	20	7	3	0	0

Table 15: Comparison of final OS from start of induction therapy all randomised patients Overall Population and Non-squamous Subgroup.

	JMEN N = 663	
Overall Population	**Pemetrexed**	**Placebo**
	N = 441	**N = 222**
OS (months)	16.53	13.93
Nonsquamous Populationa	**Pemetrexed**	**Placebo**
	N = 325	**N = 156**
OS (months)	18.56	13.60

Abbreviations: N= number of randomised patients; OS = overall survival.
a Nonsquamous histology includes adenocarcinoma, large cell carcinoma, and other histology.

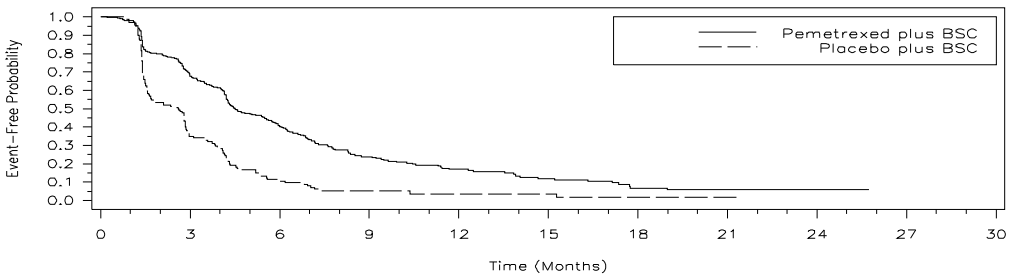
Table 16: Summary of Tumor Response and Disease Control Rate by Histologic Subgroups

	Tumor Response (CR+PR)		**Disease Control (CR+PR+SD)**	
	Pemetrexed (N = 441) %	**Placebo (N = 222) %**	**Pemetrexed (N = 441) %**	**Placebo (N = 222) %**
Histologic Subgroup	**p-Value**		**p-Value**	
Nonsquamous (n = 482)	7.4	1.9	57.7	32.7
	0.018		< 0.001	
Adenocarcinoma (n = 329)	8.1	2.8	61.0	33.0
	0.090		< 0.001	
Large Cell (n = 20)	9.1	0.0	45.5	33.3
	> 0.999		0.670	
Other/Indeterminate (n = 133)	5.4	0.0	51.1	31.7
	0.323		0.041	
Squamous (n = 181)	5.2	1.5	34.8	34.8
	0.425		> 0.999	

Abbreviations: CR = complete response; N = number of randomized patients; n = number of patients in category; PR = partial response; SD = stable disease.

Figure 6: Kaplan-Meier graph of objective progression-free survival for patients with non-squamous histology

PRODUCTION DATA – PRODUCTION MODE 06DEC2007 00:19
Kaplan–Meier Graph of Progression Free Survival
Histology Subgroup: Adenocarcinoma, Large Cell Lung Cancer & Other or Indeterminate Histology
All Randomized Patients
H3E–MC–JMEN

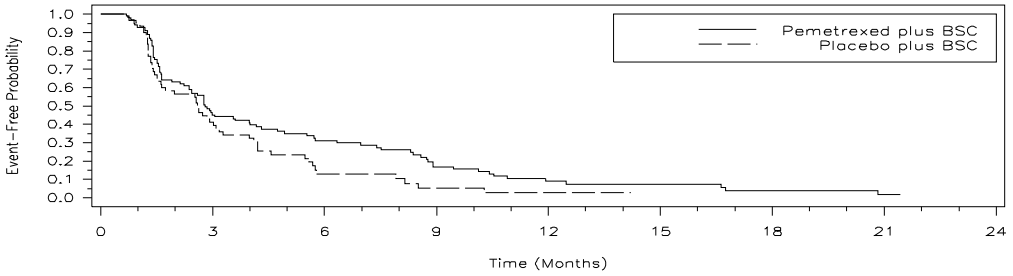


Pemetrexed pts at risk:	326	187	98	49	27	16	7	4	1	0	0
Placebo pts at risk:	156	46	13	4	2	2	1	1	0	0	0

Program Location : CABINETS\SPREE\RMP\Clinical\Oncology\Alimta\NSCLC\H3E–MC–JMEN\CSR\PROGRAMS\KMPFSA1.sas
Output Location : CABINETS\SPREE\RMP\Clinical\Oncology\Alimta\NSCLC\H3E–MC–JMEN\CSR\OUTPUTS\KMPFSA17
Data Set Location : RMP.SAS.H3ES.L.MCJMEN.ADS.INTRM1

Figure 7: Kaplan-Meier graph of objective progression-free survival for patients with squamous histology

PRODUCTION DATA – PRODUCTION MODE 06DEC2007 00:19
Kaplan–Meier Graph of Progression Free Survival
Histology Subgroup: Squamous Cell Lung Cancer
All Randomized Patients
H3E–MC–JMEN



Pemetrexed pts at risk:	115	42	24	13	6	4	2	1	0
Placebo pts at risk:	66	24	6	2	1	0	0	0	0

Program Location : CABINETS\SPREE\RMP\Clinical\Oncology\Alimta\NSCLC\H3E–MC–JMEN\CSR\PROGRAMS\KMPFSA1.sas
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Data Set Location : RMP.SAS.H3ES.L.MCJMEN.ADS.INTRM1

Cofactor-Adjusted Efficacy Analyses in Specific Histologic Subgroups

The treatment effect for non-squamous patients (HR = 0.45; 95% CI: 0.36 to 0.56; p < 0.0001) was similar to that observed in the unadjusted analysis of PFS for this population (HR = 0.44; 95% CI: 0.36 to 0.55; p < 0.00001). Results of cofactor-adjusted analyses for squamous cell patients (HR = 0.70; 95% CI: 0.49 to 1.01; p = 0.055) were also consistent with the unadjusted PFS results for this population (HR = 0.69; 95% CI: 0.49 to 0.98; p = 0.039). The only cofactor with a statistically significant effect on PFS was gender (female *versus* male) in the non-squamous population (HR = 0.77; 95% CI: 0.59 to 0.99; p = 0.040).

In terms of cofactor-adjusted analyses for OS, treatment effect for non-squamous (HR = 0.64; 95% CI: 0.48 to 0.86; p = 0.003) and squamous cell patients (HR = 1.26; 95% CI: 0.82 to 1.94; p = 0.296) were also consistent with those observed in the unadjusted analyses.

Table 17: Cofactor-Adjusted Summary Statistics for PFS by Non-squamous and Squamous Histology

Variable (N = 475[a,b], 359 events)	Nonsquamous (N = 475[a,b], 359 events) HR (95% CI)	(p-Value)[c]	Squamous (N = 180[a,b], 139 events) HR (95% CI)	(p-Value)[c]
Study Treatment Arm (Pemetrexed vs Placebo)	0.45 (0.36-0.56)	< 0.0001	0.70 (0.49-1.01)	0.055
ECOG PS (1 vs 0)	1.04 (0.84-1.29)	0.725	0.83 (0.58-1.20)	0.331
Induction response (PR/CR vs SD)	1.04 (0.83-1.30)	0.739	0.96 (0.68-1.36)	0.824
East Asian (yes vs no)	1.12 (0.87-1.42)	0.383	1.45 (0.92-2.29)	0.113
Nonsmoker (yes vs no)	1.02 (0.78-1.34)	0.861	0.98 (0.59-1.64)	0.946
Gender (Female vs Male)	0.77 (0.59-0.99)	0.040	1.12 (0.69-1.84)	0.643
Age (< 65 vs ≥ 65)	1.19 (0.94-1.50)	0.153	0.87 (0.61-1.25)	0.459

Abbreviations: CI = confidence interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; N = number of patients; PFS = progression-free survival; PR = partial response; SD = stable disease; vs = versus.

a Stratified by nonplatinum component of induction therapy (gemcitabine versus paclitaxel/docetaxel).

b Eight patients were excluded due to missing values for 1 or more cofactors (7 nonsquamous patients and 1 squamous patient).

c p-value is from the Mantel-Haenszel chi-square test.

Quality of life- Overall Population

The Lung Cancer Symptom Scale (LCSS) consists of nine 100-mm visual analogue scales, and scores are reported from 0 to 100, with 0 representing the best score. The Average Symptom Burden Index (ASBI) was calculated from the average of the 6 symptom items (loss of appetite, fatigue, cough, dyspnea, hemoptysis, and pain). A total score was calculated from the average of all 9 LCSS values (including the 6 symptom items, symptom distress, interference with activity level, and global quality of life).

Table 18: Baseline LCSS Patient Scale Scores Randomized Patients Qualified for LCSS Analysis

	Pemetrexed N = 441			**Placebo N = 222**		
LCSS Variable	**n**	**Mean Score**	**Median Score**	**n**	**Mean Score**	**Median Score**
Loss of appetite	423	**23.0**	14.0	211	**25.3**	19.0
Fatigue	423	**33.5**	30.0	211	**33.9**	28.0
Cough	421	**19.9**	9.0	211	**19.6**	9.0
Dyspnea	420	**21.4**	10.0	210	**20.1**	8.0
Hemoptysis	422	**2.8**	0	210	**3.5**	0
Pain	420	**14.8**	4.0	211	**15.5**	5.0
Symptom distress	421	**20.9**	11.0	210	**23.2**	14.0
Interference with activity level	420	**32.9**	25.5	211	**33.3**	27.0
Global quality of life	421	**33.5**	30.0	209	**33.3**	31.0
Total LCSS	407	**22.2**	20.1	207	**23.2**	21.7
ASBI	411	**19.1**	16.0	209	**19.7**	17.7

Abbreviations: ASBI = Average Symptom Burden Index; LCSS = Lung Cancer Symptom Scale; N = number of randomized patients; n = number of patients in population.

Time to Worsening of Symptoms- Overall Population

Time to worsening of symptoms (TWS) was measured from the date of randomization to the first date of worsening in each of the 6 symptoms and 3 summary items of the patient-reported LCSS. Due to a high rate of censoring, median TWS of hemoptysis was not calculated. There were no differences in any of the other TWS variables. Results were generally consistent with results for the analysis of TWS for the overall population.

Table 19: Summary of Time to Worsening of Symptoms (months)

	Pemetrexed N = 441		**Placebo N = 222**			
Individual LCSS Score	**% censored n (%)**	**Median (95% CI)**	**% censored n (%)**	**Median (95% CI)**	**HR[a] (95% CI)**	**p-Value[a]**
Any symptom	113 (25.6)	**1.41** (1.31-1.51)	65 (29.3)	**1.41** (1.05-1.48)	0.92 (0.76-1.12)	0.402
Loss of appetite	236 (53.5)	**3.78** (2.86-4.44)	140 (63.1)	**4.40** (2.96-15.61)	1.12 (0.87-1.45)	0.374
Fatigue	237 (53.7)	**3.06** (2.63-5.29)	130 (58.6)	**3.09** (2.43-3.98)	0.98 (0.77-1.26)	0.886
Cough	274 (62.1)	**6.05** (4.21-7.82)	146 (65.8)	**4.67** (3.06-15.61)	0.90 (0.69-1.19)	0.470
Dyspnea	271 (61.5)	**5.36** (4.21-10.87)	143 (64.4)	**4.40** (2.83-15.61)	0.93 (0.71-1.22)	0.596
Hemoptysis[b]	404 (91.6)	-	198 (89.2)	-	0.58 (0.34-0.97)	0.038
Pain	271 (61.5)	**6.11** (4.57-9.56)	135 (60.8)	**4.63** (3.32-5.98)	0.76 (0.59-0.99)	0.041
Symptom distress	247 (56.0)	**4.21** (3.58-5.55)	141 (63.5)	**3.78** (2.99-18.53)	1.00 (0.77-1.29)	0.972
Interference with activity level	267 (60.5)	**6.51** (4.34-8.18)	141 (63.5)	**3.98** (2.83-15.61)	0.92 (0.70-1.19)	0.512
Global quality of life	262 (59.4)	**5.75** (4.37-8.41)	137 (61.7)	**3.71** (2.99-5.49)	0.86 (0.66-1.12)	0.267

Abbreviations: CI = confidence interval; HR = hazard ratio; LCSS = Lung Cancer Symptom Scale; N = number of randomized patients; n = number of patients; TWS = time to worsening of symptoms.

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

b Median TWS for hemoptysis was not calculated due to the high level of censoring.

Summary of Additional Analyses of LCSS Data

Mean maximum improvement for each of the 9 LCSS items, the ASBI, and the total score were compared statistically between study arms. Patients treated with pemetrexed had similar improvement in LCSS scores compared to those receiving placebo.

Table 20: Summary of Maximum Improvement Over Baseline LCSS Patient Scale Scores Randomized Patients Qualified for LCSS Analysis

	Pemetrexed N = 441			Placebo N =222			p-Values	
	n (%)	Mean (SD)	LS Mean (SE)	n (%)	Mean (SD)	LS Mean (SE)	ANCOVA p-Value[a]	p-Value[b]
Loss of appetite	403 (91.4)	**7.3** (25.90)	7.9 (9.97)	197 (88.7)	**10.6** (25.25)	9.5 (1.40)	0.350	0.136
Fatigue	403 (91.4)	**10.2** (27.10)	10.3 (1.06)	197 (88.7)	**10.4** (23.92)	10.2 (1.51)	0.982	0.959
Cough	402 (91.2)	**7.6** (20.09)	7.7 (0.80)	197 (88.7)	**6.7** (23.81)	6.5 (1.15)	0.417	0.192
Dyspnea	400 (90.7)	**7.6** (22.50)	7.4 (0.85)	196 (88.3)	**5.4** (20.44)	5.9 (1.22)	0.315	0.204
Pain	401 (90.9)	**5.4** (20.96)	5.6 (0.79)	197 (88.7)	**4.3** (21.93)	3.9 (1.12)	0.233	0.039
Hemoptysis	402 (91.2)	**1.5** (9.41)	1.7 (0.28)	196 (88.3)	**2.1** (9.23)	1.7 (0.40)	0.985	0.831
Symptom distress	401 (90.9)	**6.5** (21.13)	7.0 (0.85)	196 (88.3)	**8.2** (22.55)	7.1 (1.21)	0.960	0.533
Interference with activity level	400 (90.7)	**10.8** (27.08)	10.7 (1.06)	197 (88.7)	**9.3** (25.50)	9.4 (1.48)	0.441	0.592
Global quality of life	401 (90.9)	**10.7** (24.94)	10.6 (0.99)	195 (87.8)	**10.5** (22.98)	10.8 (1.42)	0.900	0.897
Total LCSS	388 (88.0)	**4.07** (12.76)	4.17 (0.61)	193 (86.9)	**4.04** (13.03)	3.82 (0.86)	0.739	0.720
ASBI	392 (88.9)	**3.7** (12.34)	3.77 (0.58)	195 (87.8)	**3.8** (13.24)	3.59 (0.83)	0.861	0.713

Abbreviations: ANCOVA = analysis of covariance; ASBI = Average Symptom Burden Index; LCSS = Lung Cancer Symptom Scale; LS = least square; N = number of randomized patients; n = number of patients in each category; SD = standard deviation; SE = standard error.

a p-value from ANCOVA adjusted for baseline value.

b p-value from Mann-Whitney-Wilcoxon test.

Discussion on Clinical Efficacy

The new NSCLC maintenance treatment indication is supported by a multicentre, randomised, double-blind, placebo-controlled Phase 3 study (JMEN), that compared the efficacy and safety of maintenance treatment with Alimta plus best supportive care (BSC) (n = 441) with that of placebo plus BSC (n= 222) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC who did not progress after 4 cycles of first line doublet therapy containing Cisplatin or Carboplatin in combination with Gemcitabine, Paclitaxel, or Docetaxel. First line doublet therapy containing Alimta was not included because the results of the first-line study with Alimta-cisplatin were not yet available.

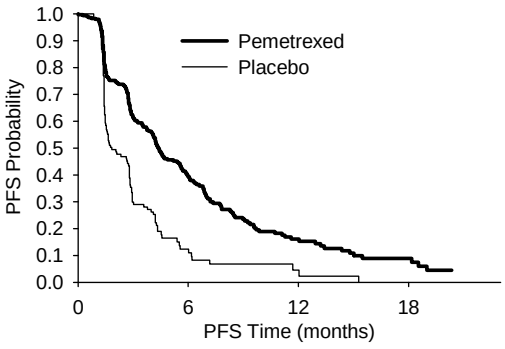
All patients included in this study had an ECOG performance status of 0 or 1. Patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomisation after completion of first line (induction) therapy. Patients received a median of 5 cycles of maintenance treatment with Alimta and 3.5 cycles of placebo. A total of 213 patients (48.3%) completed ≥ 6 cycles and a total of 103 patients (23.4%) completed ≥ 10 cycles of treatment with Alimta.

The study met its primary endpoint and showed a statistically significant improvement in PFS in the Alimta arm over the placebo arm (n = 581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (hazard ratio = 0.60, 95% CI: 0.49-0.73, $p < 0.00001$). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. The median OS for the overall population (n = 663) was 13.4 months for the Alimta arm and 10.6 months for the placebo arm, hazard ratio = 0.79 (95% CI: 0.65 to 0.95; $p = 0.01192$).

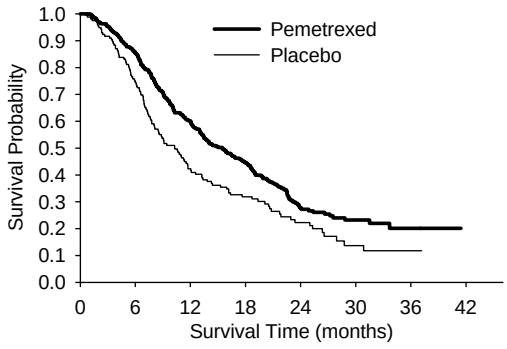
Consistent with other Alimta studies, a difference in efficacy according to NSCLC histology was observed in JMEN. For patients with NSCLC other than predominantly squamous cell histology (n= 430, independently reviewed population) median PFS was 4.4 months for the Alimta arm and 1.8 months for the placebo arm, hazard ratio = 0.47, 95% CI: 0.37-0.60, p= 0.00001. The median OS for patients with NSCLC other than predominantly squamous cell histology (n = 481) was 15.5 months for the Alimta arm and 10.3 months for the placebo arm (hazard ratio = 0.70, 95% CI: 0.56-0.88, p=0.002). Including the induction phase the median OS for patients with NSCLC other than predominantly squamous cell histology was 18.6 months for the Alimta arm and 13.6 months for the placebo arm (hazard ratio =0.71, 95% CI: 0.56-0.88, p=0.002).
The PFS and OS results in patients with squamous cell histology suggested no advantage for Alimta over placebo.

Kaplan Meier Plots of Progression-Free Survival (PFS) and Overall Survival ALIMTA versus Placebo in Patients with NSCLC other than Predominantly Squamous Cell Histology:

Progression-Free Survival



Overall Survival



Clinical Safety

Exposure

Pivotal study JMEN is a multicentric trial that entered 741 patients from 83 investigational sites in 20 countries. Of these 741 patients, a total of 663 (89.5%) patients were randomized in the study: 441 to the pemetrexed arm and 222 to the placebo arm. Of the 441 patients randomized to the pemetrexed arm, 432 received at least 1 cycle of treatment. Of the 222 patients randomized to the placebo arm, 221 received at least 1 cycle of treatment.

In accordance with the protocol and statistical analysis plan, all safety variables were evaluated at the time of the primary analysis for progression-free survival (PFS). A second safety analysis was performed approximately 6 months after the primary safety analysis. The purpose of the updated analysis was to assess event rates and determine if there were any new safety signals from patients with additional follow-up.

At the time of the second safety analysis, patients in the pemetrexed arm received a median of 5 cycles, whereas patients in the placebo arm received a median of 3.5 cycles.
The percentage of patients exposed to pemetrexed for at least 6 cycles was 48.3%, which is significantly greater than those in the placebo-treated group (27.5%) ($p<0.0001$).
Ninety-eight (22.2%) patients in the pemetrexed arm and 19 (8.6%) patients in the placebo arm completed at least 10 cycles ($p < 0.001$) at the time of the updated safety analysis.

Table 21: Patient Exposure to Study Drug

	Primary safety analysis		Updated safety analysis	
	Pemetrexed (N = 441)	**Placebo (N = 222)**	**Pemetrexed (N = 441)**	**Placebo (N = 222)**
Mean number of cycles	6.1	4.2	6.9	4.5
Median number of cycles	4.0	3.0	5.0	3.5
n (%) completing at least 6 cycles	189(42.9)	56 (25.2)	213 (48.3)	61 (27.5)
n (%) completing at least 10 cycles	80 (18.1)	13 (5.9)	98 (22.2)	19 (8.6)

Dose delays

A larger percentage of dose delays related to AEs occurred in the pemetrexed arm (71 patients; 16.1%) than in the placebo arm (13 patients; 5.9%). A total of 100 cycles of pemetrexed (0.6% of total cycles administered) and 18 cycles of placebo (0.5% of total cycles administered) were delayed due to AEs, regardless of causality. Taken together, AEs related to decreased renal function (creatinine clearance decreased, glomerular filtration rate decreased, blood creatinine increased, renal function test abnormal, and renal failure) accounted for the largest number of dose delays in the pemetrexed arm. Other commonly reported AEs causing dose delays in the pemetrexed arm included fatigue, asthenia, and bronchitis.

Table 22: Summary of reasons for dose delays by study arm

Reason for delay[a]	**Pemetrexed** N = 441 n (%)	**Placebo** N = 222 n (%)
Cycle Delay (any reason)	290 (65.8)	96 (43.2)
Scheduling Conflict	218 (49.4)	83 (37.4)
Any Adverse Event	71 (16.1)	13 (5.9)
Inadequate vitamin supplementation	2 (0.5)	4 (1.8)

Adverse events (AEs)

Table 23: Overview of Adverse Events by study arm- All randomized patients (Study JMEN)

Adverse Events During Safety Reporting Period	Number of Patients (%) with Adverse Event			
	Pemetrexed		Placebo	
	N = 441		N = 222	
	Primary Analysis	Safety Update	Primary Analysis	Safety Update
Adverse events				
All	378(85.7)	**391 (88.7)**	180 (81.1)	**186 (83.8)**
Possibly related to study drug	280 (63.5)	**291 (66.0)**	78 (35.1)	**81 (36.5)**
Deaths				
All	39 (8.8)	**43 (9.8)**	21 (9.5)	**22 (9.9)**
Possibly related to study drug	0	**0**	0	**0**
Serious adverse events				
All	71 (16.1)	**78 (17.7)**	31 (14.0)	**33 (14.9)**
Possibly related to study drug	19 (4.3)	**22 (5.0)**	0	**0**
Serious, unexpected, and reportable events	0	**0**	0	**0**
Adverse events resulting in discontinuation				
All	29 (6.6)	**35 (7.9)**	5 (2.3)	**5 (2.3)**
Possibly related to study drug	17 (3.9)	**21 (4.8)**	3 (1.4)	**3 (1.4)**

Treatment Emergent Adverse Events (TEAEs)

In the pemetrexed arm, 63% of patients experienced at least 1 possibly related study drug-related TEAEs compared to 35.1% of patients in the placebo arm ($p<0.001$). In both study arms, the most commonly reported possibly study drug-related TEAEs were nausea, fatigue, anorexia, and anaemia. Patients receiving pemetrexed experienced statistically significantly more clinically relevant drug-related TEAEs including anaemia, leukopenia, neutropenia, thrombocytopenia, nausea, stomatitis, vomiting, fatigue, anorexia, pyrexia, increased alanine transaminase (ALT), increased aspartate transaminase (AST), peripheral sensory neuropathy, rash, and decreased creatinine clearance.

Table 24: Study Drug-Related TEAEs by SOC, clinically significant or occurring in more than 5% of Patients

System Organ Class Preferred Term	Pemetrexed (N = 441)	Placebo (N = 222)	
	n (%)	n (%)	p-Value
Patients with at least 1 TEAE	**278 (63.0)**	**78 (35.1)**	**< 0.001**
Blood and lymphatic system disorders			
Anemia	44 (10.0)	5 (2.3)	**< 0.001**
Febrile neutropenia	4 (0.9)	0	0.307
Leukopenia	20 (4.5)	3 (1.4)	**0.041**
Neutropenia	19 (4.3)	0	**0.001**
Thrombocytopenia	16 (3.6)	1 (0.5)	**0.016**
Cardiac disorders			
Atrial tachycardia	1 (0.2)	0	> 0.999
Eye disorders			
Conjunctivitis	10 (2.3)	1 (0.5)	0.110
Gastrointestinal disorders			
Constipation	18 (4.1)	6 (2.7)	0.509
Diarrhea	21 (4.8)	6 (2.7)	0.297
Nausea	79 (17.9)	9 (4.1)	**< 0.001**
Stomatitis	13 (2.9)	0	**0.006**
Vomiting	36 (8.2)	3 (1.4)	**< 0.001**
General disorders and administration site conditions			
Edema	3 (0.7)	0	0.555
Edema - face	2 (0.5)	0	0.554
Edema - localized	3 (0.7)	0	0.555
Edema – peripheral	8 (1.8)	0	0.057
Fatigue	79 (17.9)	16 (7.2)	**< 0.001**
Pyrexia	13 (2.9)	0	**0.006**
Immune system disorders			
Hypersensitivity	3 (0.7)	0	0.555
Investigations			
ALT increased	38 (8.6)	6 (2.7)	**0.003**
AST increased	31 (7.0)	5 (2.3)	**0.010**
Hemoglobin decreased	12 (2.7)	2 (0.9)	0.158
Blood creatinine decreased	3 (0.7)	0	0.555
Creatinine renal clearance decreased	13 (2.9)	1 (0.5)	**0.043**
Glomerular filtration rate decreased	3 (0.7)	0	0.555
Renal function test abnormal	1 (0.2)	0	> 0.999
Metabolism and nutrition disorders			
Anorexia	77 (17.5)	11 (5.0)	**< 0.001**
Nervous system disorders			
Peripheral sensory neuropathy	14 (3.2)	0	**0.004**
Renal and urinary disorders			
Renal failure	2 (0.5)	0	0.554
Respiratory, thoracic, and mediastinal Disorders			
Dyspnea	7 (1.6)	0	0.102
Skin and subcutaneous tissue disorders			
Alopecia	14 (13.2)	2 (0.9)	0.105
Pruritus	12 (2.7)	2 (0.9)	0.158

System Organ Class Preferred Term	Pemetrexed (N = 441)	Placebo (N = 222)	
	n (%)	n (%)	p-Value
Patients with at least 1 TEAE	**278 (63.0)**	**78 (35.1)**	**< 0.001**
Rash	50 (11.3)	9 (4.1)	**0.001**

Bold text indicates statistically significant difference between study arms.

Deaths

Table 25: Summary of Deaths On Study or Within 30 Days of discontinuation - All Randomized Patients

	Pemetrexed n (%) (N = 441)		Placebo n (%) (N = 222)		p-Value	
	Primary Analysis	Safety Update	Primary Analysis	Safety Update	Primary Analysis	Safety Update
All deaths	**39 (8.8)**	**43 (9.8)**	**21 (9.5)**	**22 (9.9)**	**0.776**	**>0.999**
Deaths on study or ≤ 30 days after last dose	**11 (2.5)**	**12 (2.7)**	**10 (4.5)**	**10 (4.5)**	**0.167**	**0.253**
On-therapy deaths	**4 (0.9)**	**5 (1.1)**	**6 (2.7)**	**6 (2.7)**	**0.093**	**0.195**
Study disease	1 (0.2)	1 (0.2)	4 (1.8)	4 (1.8)	0.045	0.045
Adverse event	3 (0.7)	4 (0.9)	2 (0.9)	2 (0.9)	>0.999	>0.999
Aspiration	0	0	1 (0.5)	1 (0.5)	0.335	0.335
Chest pain	1 (0.2)	1 (0.2)	0	0	>0.999	> 0.999
Aspiration pneumonia	0	0	1 (0.5)	1 (0.5)	0.335	0.335
Pneumonia	0	1 (0.2)	0	0	--	> 0.999
Respiratory failure	2 (0.5)	2 (0.5)	0	0	0.554	0.554
Deaths within 30 days of last dose	**7 (1.6)**	**7 (1.6)**	**4 (1.8)**	**4 (1.8)**	**> 0.999**	**> 0.999**
Study disease	6 (1.4)	6 (1.4)	4 (1.8)	4 (1.8)	0.739	0.739
Adverse event: dyspnea	1 (0.2)	1 (0.2)	0	0	> 0.999	> 0.999
Deaths > 30 days after last dose but ≤ 30 days after discontinuation	**28 (6.3)**	**31 (7.0)**	**11 (5.0)**	**12 (5.4)**	**0.600**	**0.505**
Study disease	27 (6.1)	30 (6.8)	10 (4.5)	11 (5.0)	0.475	0.397
Not study related	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)	> 0.999	> 0.999

According to the safety update analysis, a total of 65 patients died during the safety reporting period (while on study therapy or within 30 days after discontinuation). Of the 65 reported deaths, there were 22 deaths (12 [2.7%] in the pemetrexed arm and 10 [4.5%] in the placebo arm) that occurred while patients were on study or within 30 days of the last study dose. The remaining 43 deaths (31 [6.8%] in the pemetrexed arm and 12 [5.4%] in the placebo arm) occurred greater than 30 days after the last study dose but within 30 days of study discontinuation. There were 11 deaths during study treatment (5 [1.1%] in the pemetrexed arm and 6 [2.7%] in the placebo arm]. Of the on-study treatment deaths, 5 (1 [0.2%] in the pemetrexed arm and 4 [1.8%] in the placebo arm) were attributed to disease progression. The remaining 6 deaths were caused by AEs not attributed to study drug by the investigator.

There were 11 additional deaths within 30 days of last study dose administered (7 [1.6%] in the pemetrexed arm and 4 [1.8%] in the placebo arm). With the exception of 1 death in the pemetrexed arm with a primary event of dyspnea, the cause of death for these patients was listed as disease progression.

The remaining 43 deaths occurred within the 30-day post discontinuation time period and were > 30 days after last study dose; these deaths were primarily related to disease progression.

As assessed by the investigator, no deaths were considered to be related to pemetrexed or placebo.

Serious Adverse Events (SAEs) Possibly Related to Study Treatment

All study-drug-related SAEs occurred in the pemetrexed arm, with 5.0% of patients in the pemetrexed arm experiencing at least 1 event ($p < 0.001$). However, no statistically significant differences were observed in the incidence of any individual SAE. The most frequently reported SAE was anemia, which occurred in 1.4% of patients in the pemetrexed arm; all other SAEs occurred in less than 1% of patients. No serious, unexpected, reportable events (SURs) were reported.

Table 26: Summary of SAEs Possibly Related to Study Drug All Randomized Patients

	Primary safety analysis	Safety update analysis	
	Number (%) of Patients		
System Organ Class Preferred Term	**Pemetrexed (N = 441)**	**Pemetrexed (N = 441)**	**Placebo (N = 222)**
	n (%)	n (%)	n (%)
Patients with at least 1 event	19 (4.3)	22 (5.0)	0
Anemia	6 (1.4)	6 (1.4)	0
Febrile neutropenia	4 (0.9)	4 (0.9)	0
Anorexia	4 (0.9)	4 (0.9)	0
Thrombocytopenia	3 (0.7)	3 (0.7)	0
Asthenia	2 (0.5)	2 (0.5)	0
Mucosal inflammation	2 (0.5)	2 (0.5)	0
Pneumonia	2 (0.5)	3 (0.7)	0
Erysipelas	1 (0.2)	1 (0.2)	0
Infection	1 (0.2)	1 (0.2)	0
Leukopenia	1 (0.2)	1 (0.2)	0
Nausea	1 (0.2)	1 (0.2)	0
Neutropenia	1 (0.2)	2 (0.5)	0
Oral candidiasis	1 (0.2)	1 (0.2)	0
Pelvic venous thrombosis	1 (0.2)	1 (0.2)	0
Renal failure	1 (0.2)	1 (0.2)	0
Urosepsis	1 (0.2)	1 (0.2)	0
Weight decreased	1 (0.2)	1 (0.2)	0
Pulmonary fibrosis	-	1 (0.2)	0

Discontinuation due to Adverse Events (AEs)

The incidence of discontinuation from study therapy due to AEs related to study drug was statistically significantly higher in the pemetrexed arm: 21 (4.8%) patients in the pemetrexed arm and 3 (1.4%) patients in the placebo ($p = 0.027$). The majority of non-serious drug-related AEs causing discontinuation (10 patients) from the pemetrexed arm were attributed to a decrease in renal function. Two patients discontinued from pemetrexed therapy because of study-drug-related SAEs (thrombocytopenia and pulmonary fibrosis). In the placebo arm, reason for discontinuation was aspiration pneumonia and death.

Table 27: Discontinuations Due to Adverse Events All Randomized Patients

	Regardless of Causality			**Possibly Related to Study Drug**[b]		
	Pemetrexed (N = 441)	Placebo (N = 222)		Pemetrexed (N = 441)	Placebo (N = 222)	
Preferred Term[a]	**n (%)**	**n (%)**	**p-Value**[c]	**n (%)**	**n (%)**	**p-Value**[c]
Patients who discontinued due to adverse events	**29 (6.6)**	**5 (2.3)**	**0.016**	**17 (3.9)**	**3 (1.4)**	**0.093**
Anemia	1 (0.2)	0	> 0.999	1 (0.2)	0	> 0.999
Chest pain	2 (0.5)	0	0.554	0	0	-
Death	0	1 (0.5)	0.335	0	0	-
Dyspnea	4 (0.9)	0	0.307	0	0	-
Fatigue	3 (0.7)	1 (0.5)	> 0.999	2 (0.5)	1 (0.5)	> 0.999
Lung infection	1 (0.2)	0	> 0.999	1 (0.2)	0	> 0.999
Myalgia	0	1 (0.5)	0.335	0	1 (0.5)	0.335
Paraparesis	1 (0.2)	0	> 0.999	1 (0.2)	0	> 0.999
Platelet count decreased/ thrombocytopenia	1 (0.2)	1 (0.5)	> 0.999	1 (0.2)	1 (0.5)	> 0.999
Pneumonia	1 (0.2)	0	> 0.999	0	0	-
Pneumonia aspiration	0	1 (0.5)	0.335	0	0	-
Rash	1 (0.2)	0	> 0.999	1 (0.2)	0	> 0.999
Respiratory failure	2 (0.5)	0	0.554	0	0	0.554
Renal toxicities	12 (2.7)	0	-	10 (2.3)	0	-
Creatinine renal clearance decreased	4 (0.9)	0	0.307	3 (0.7)	0	0.555
Blood creatinine decreased	2 (0.5)	0	0.554	1 (0.2)	0	> 0.999
Blood creatinine increased	2 (0.5)	0	0.554	2 (0.5)	0	0.554
GFR decreased	2 (0.5)	0	0.554	2 (0.5)	0	0.554
Hypercreatininaemia	1 (0.2)	0	> 0.999	1 (0.2)	0	> 0.999
Renal function test abnormal	1 (0.2)	0	> 0.999	1 (0.2)	0	> 0.999

Analysis of laboratory and non-laboratory toxicities

The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that were reported in > 5% of patients in the pivotal study. Clinical relevance was assessed according to several factors, including severity, treatment emergence, reporting in previous studies, and frequency compared to placebo arm.

Table 28: Frequency and severity of undesirable effects considered possibly related to study drug that were reported in > 5% of patients in the pivotal study

System Organ Class	Frequency[a]	Event[b]	Pemetrexed (N = 441)		Placebo (N = 222)	
			All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Blood and Lymphatic System Disorders	Very Common	Hemoglobin	15.2	2.7	5.4	0.5
	Common	Leukocytes	6.1	1.6	1.4	0.5
		Neutrophils	5.9	2.9	0.0	0.0
Gastrointestinal Disorders	Very Common	Nausea	18.8	0.9	5.4	0.5
		Anorexia	18.6	1.8	5.0	0.0
	Common	Vomiting	8.6	0.2	1.4	0.0
		Mucositis/stomatitis	7.0	0.7	1.8	0.0
	Common	Diarrhoea	5.2	0.5	2.7	0.0
General	Very Common	Fatigue	24.5	5.0	10.4	0.5
Hepatobiliary Disorders	Common	ALT (SGPT)	9.5	0.2	3.6	0.0
		AST (SGOT)	8.2	0.0	3.6	0.0
Infections and Infestations	Common	Infection	5.2	1.6	1.8	0.0
Skin and Subcutaneous Tissue Disorders	Very Common	Rash/desquamation	10.0	0.0	3.2	0.0
Nervous System Disorders	Common	Neuropathy-sensory	8.8	0.7	4.1	0.0

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CTCAE = Common Terminology Criteria for Adverse Event; NCI = National Cancer Institute; SGOT = serum glutamic oxaloacectic transaminase; SGPT = serum glutamic pyruvic transaminase.

a Definition of frequency terms: Very common - ≥ 10%; Common - > 5% and < 10%. For the purpose of this table, a cutoff of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

b Refer to NCI CTCAE Criteria (Version 3.0; NCI 2003) for each grade of toxicity

Clinically relevant CTC toxicity of any grade that was reported in ≥1% and ≤5% (common) of the patients that were randomly assigned to pemetrexed include: decreased platelets, decreased creatinine clearance, constipation, edema, alopecia, increased creatinine, pruritis/itching, fever (in the absence of neutropenia), ocular surface disease (including conjunctivitis), increased lacrimation, and decreased glomerular filtration rate.

Clinically relevant CTC toxicity that was reported in <1% (uncommon) of the patients that were randomly assigned to pemetrexed include: febrile neutropenia, allergic reaction/hypersensitivity, motor neuropathy, erythema multiforme, renal failure, and supraventricular arrhythmia.

Grade 3/4 Toxicities Possibly Related to Study Treatment

The incidence of study- drug-related Grade 3/4 toxicities was statistically significantly higher for pemetrexed versus placebo. Only neutropenia (2.9% versus 0.5%; p = 0.006) was statistically significantly different between the 2 treatment arms. Consistent with the higher incidence of anemia in the pemetrexed arm, use of transfusions was significantly higher for patients receiving pemetrexed (42 -9.5%) compared to placebo (7 -3.2%).

Non laboratory Toxicities

The incidence of non-laboratory toxicities is statistically significantly higher in the pemetrexed arm than in the placebo arm (57.4% versus 28.4%; $p < 0.001$). Individual drug-related non-laboratory toxicities of any grade occurring significantly more frequently for patients in the pemetrexed arm included alopecia, anorexia, fatigue, fever without neutropenia, mucositis/stomatitis, nausea, vomiting, sensory neuropathy, oedema of the limb, rash, and renal/genitourinary – other (decreased creatinine clearance). For combined drug-related CTCAE Grade 3 and Grade 4 toxicities, the incidence of patients with at least 1 adverse event was also significantly higher for patients in the pemetrexed arm (10.7%) compared to patients in the placebo arm (1.4%; $p < 0.001$). The only statistically significant difference in the incidence of individual drug-related Grade 3/4 CTCAE non-laboratory toxicities was for fatigue. No other statistically significant differences were observed between study arms for any other category of any grade or of Grade 3/4 non-laboratory toxicities.

Adverse Events Related to Decreased Renal Function were specifically reviewed

A total of 36 patients were identified as having at least 1 event associated with decreased renal function, which was possibly related to study drug. Thirty three patients in the pemetrexed arm (7.5%) were reported to have an AE associated with decreased renal function, which was possibly related to study drug according to investigator report. Of these 33 patients, 10 (2.3%) were discontinued from pemetrexed due to their drug-related renal AE, and 1 patient was reported to have a SAE of renal failure (Grade 3) that required hospitalization.
Only 3 patients in the placebo arm (1.4%) were reported to have an adverse event signifying decreased renal function and possibly related to study treatment. None of these were reported as Grade 3 or 4, none resulted in discontinuation from study treatment, and none were reported as an SAE.

Safety in subgroups

Analysis of toxicities by age, gender, and ethnic origin revealed the following significant results:

- Patients < 65 years of age receiving pemetrexed experienced significantly higher rates of neutropenia and fatigue compared to patients receiving placebo (3.1% versus 0; $p = 0.032$ for both toxicities). The rate of individual Grade 3/4 laboratory and non-laboratory toxicities possibly related to study treatment was compared between age groups (< 65 years versus ≥ 65 years).

- No statistically significant differences were observed in the pemetrexed arm between patients < 65 years of age and those ≥ 65 years of age.

- For both males and females, a statistically significantly higher percentage of patients treated with pemetrexed, compared to patients receiving placebo, experienced at least 1 Grade 3/4 non-laboratory toxicity. Men receiving pemetrexed experienced statistically significantly higher rates of any Grade 3/4 nonlaboratory toxicity, neutropenia, and fatigue, compared to men receiving placebo. No other statistically significant differences were observed between study arms for either male or female patients.

- No statistically significant differences were observed between male and female patients treated with pemetrexed.

- For patients of Caucasian origin, the only significant differences were observed in the incidence of Grade 3/4 toxicities of neutrophils/granulocytes decreased ($p = 0.017$) and fatigue ($p = 0.001$), with significantly more patients in the pemetrexed arm than in the placebo arm reporting these toxicities.

- Statistically significantly more pemetrexed-treated patients of Caucasian origin reported Grade 3/4 fatigue than those in the Other subgroup: 6.45% versus 0.62%; $p = 0.003$. No other statistically significant differences were observed.

- Analyses of safety for histological subgroups were generally consistent with the safety profiles for pemetrexed and placebo observed in the entire patient population. No clinically significant safety trends were identified that would suggest that 1 subgroup experienced a different toxicity profile of pemetrexed compared to other subgroups, or to the randomized or treated population as a whole.

Effect on long-term exposure on patient safety

The safety profile of pemetrexed has been well characterized in previous studies for patient exposures up to a median of 6 cycles.
With regard to long-term maintenance therapy, 29.5% of patients in the pemetrexed arm completed more than 6 cycles. Additional analysis of possibly drug-related Grade 3 and Grade 4 CTCAE toxicities comparing patients receiving ≤ 6 cycles and patients receiving > 6 cycles of pemetrexed did not show any statistical difference between these groups. In addition, no statistically significant differences were seen in any individual categories of laboratory or non-laboratory toxicities between the 2 groups.

Key supportive studies

Study JMEI is included as a key supportive study because it is a single-agent study in patients with NSCLC after prior chemotherapy treatment. Study JMEI was the pivotal study for approval of pemetrexed as a second-line, single-agent therapy for NSCLC. The study used the same dosage of pemetrexed as in Study JMEN, and patients received the same vitamin supplementation regimen.
The eligibility criteria were similar between the studies, with notable exceptions. Study JMEN excluded patients with a best response of progressive disease (PD) to induction (first-line) chemotherapy. In contrast, Study JMEI included patients who had failed prior chemotherapy. While Study JMEN only enrolled patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, Study JMEI also included patients with an ECOG performance status of 2. These differences may help explain some variations in safety observed between the 2 studies.

In addition to the differences between the patient populations in Studies JMEN and JMEI, laboratory assessments for potential toxicity were also different. In Study JMEI, haematology laboratory assessments were performed on Day 1 (prior to therapy), Day 8, and Day 15, and serum chemistries were performed on Day 1 (prior to therapy) and Day 8 of each 21-day cycle. The JMEN protocol required that haematology and serum chemistry assessments be performed only once during each 21-day cycle, prior to study drug administration. As a result, the incidence and severity of laboratory toxicity in Study JMEN could be lower than that observed in Study JMEI, in part due to less frequent assessments in Study JMEN.

The percentage of patients completing at least 6 cycles of pemetrexed was higher in Study JMEN (48.3%) than in Study JMEI (34.0%), which may in part be explained by differences between the study populations. Further, the overall incidence of Grade ¾ toxicities was lower in Study JMEN than in Study JMEI.

Table 29: Overview of Adverse Events - Studies JMEN and JMEI

Adverse Events During Safety Reporting Period	Number of Patients (%) with Adverse Event		
	Study JMEN		Study JMEI
	Pemetrexed N = 441 n (%)	Placebo N = 222 n (%)	Pemetrexed N = 265 n (%)
Adverse events			
All	391 (88.7)	186 (83.8)	259 (97.7)
Possibly related to study drug	291 (66.0)	81 (36.5)	207 (78.1)
Deaths			
All	43 (9.8)	22 (9.9)	31 (11.7)
Possibly related to study drug	0	0	3 (1.1)
Serious adverse events			
All	78 (17.7)	33 (14.9)	99 (37.4)
Possibly related to study drug	22 (5.0)	0	27 (10.2)
Serious, unexpected, and reportable events	0	0	5 (1.9)
Adverse events resulting in discontinuation			
All	35 (7.9)	5 (2.3)	5 (1.9)
Possibly related to study drug	21 (4.8)	3 (1.4)	4 (1.5)

Pharmacovigilance

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk Management Plan

The MAH submitted an updated risk management plan, which included a risk minimisation plan.

Summary of the Risk Management Plan for Alimta

Safety Concern	Pharmacovigilance Activities (Routine and Additional)	Risk Minimisation Activities
Noncompliance with vitamin supplementation manifested mainly as haematological and gastrointestinal toxicities	• routine pharmacovigilance • monitoring of cases for compliance to supplementation regimen	• advice in SPC to supplement with vitamins • Lilly-sponsored programs related to pemetrexed to include information on the need for vitamin supplementation
• Serious Renal Events • Gastrointestinal Disorders • Interstitial Pneumonitis • Radiation Pneumonitis • Radiation Recall.	• routine pharmacovigilance • ongoing surveillance of these events, with special topic reports produced as needed • possible changes to prescribing information based on data analyzed	• advice in SPC about occurrence of events and measures to minimise risk
• Cardiovascular events, • Oesophagitis • Peripheral vascular disorders • Serious skin disorders • Hearing loss/Hypoacusis	• routine pharmacovigilance • ongoing surveillance of these events, with special topic reports produced as needed • possible changes to prescribing information based on data analyzed	• advice in SPC about occurrence of cardiovascular events
Toxicities due to administration to patients with third-space fluid collections	• routine pharmacovigilance • clinical study to assess the safety of pemetrexed in patients with third-space fluid collections	• advice in SPC to drain third-space fluids
Safety and efficacy in paediatric patients is not known	• routine pharmacovigilance • clinical study to assess the safety of pemetrexed in paediatric patients	• advice in SPC not to administer to children

Abbreviation: SPC = Summary of Product Characteristics.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Discussion on Clinical Safety

The safety results observed in the pemetrexed arm of Study JMEN are consistent with the known safety profile of pemetrexed. The incidence of toxicities in Study JMEN is generally lower than the incidence observed in the pemetrexed arm of Study JMEI and is likely to be reflective of the differences between the 2 studies patient populations and study designs.

In the pivotal study JMEN, out of the 65 reported deaths (9.8% in the pemetrexed arm and 9.9% in the placebo arm), 2.7% occurred while on study therapy or less than 30 days after last dose in the pemetrexed arm *versus* 4.5% in the placebo arm. No study drug-related deaths were reported for either study arm. However, according to the provided narratives, data for causality assessment are

missing in some cases and a causal relationship between adverse events leading to death and study drug can therefore not be definitely excluded in some cases.

Overall, more patients treated with pemetrexed than patients treated with placebo had dose adjustments (4.8% in the pemetrexed arm/ 0.9% in the placebo arm). All pemetrexed dose adjustments were a result of adverse events. The incidence of drug-related toxicities was statistically higher in the pemetrexed arm compared to the placebo arm. Neutropenia and fatigue were statistically significantly different between the 2 treatment arms.

The most common toxicities were of haematologic origin, gastro-intestinal disorders (nausea, vomiting, stomatitis), increased ASAT and ALAT and neuropathy. Renal toxicity was more common in the pemetrexed arm; 33 patients in the pemetrexed arm (7.5%) were reported to have a possibly drug-related adverse event associated with decreased renal function.

The most frequently reported SAE was anaemia, which occurred in 1.4% of patients in the pemetrexed arm; all other SAEs occurred in less than 1% of patients. No serious, unexpected, reportable events (SURs) were reported.

With regard to long-term maintenance therapy, there were no statistically or clinically relevant differences in the safety profile reported for patients receiving more than 6 cycles of pemetrexed compared to those receiving 6 cycles or less. However, given the small number of patients remaining on treatment after 6 cycles, no conclusion can be drawn.

Overall, the safety results for pemetrexed as a maintenance treatment were consistent with the known safety profile of pemetrexed. All the adverse reactions reported in clinical trials and post-marketing have been included in the SPC. The CHMP does not consider that any change to the PSUR cycle is necessary following this extension of indication.

Pharmacovigilance

An updated risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Benefit-risk assessment

Efficacy

The new NSCLC maintenance treatment indication is supported by a multicentre, randomised, double-blind, placebo-controlled Phase 3 study (JMEN), that compared the efficacy and safety of maintenance treatment with Alimta plus best supportive care (BSC) (n = 441) with that of placebo plus BSC (n= 222) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC who did not progress after 4 cycles of first line doublet therapy containing Cisplatin or Carboplatin in combination with Gemcitabine, Paclitaxel, or Docetaxel. First line doublet therapy containing Alimta was not included because the results of the first-line study with Alimta-cisplatin were not yet available.

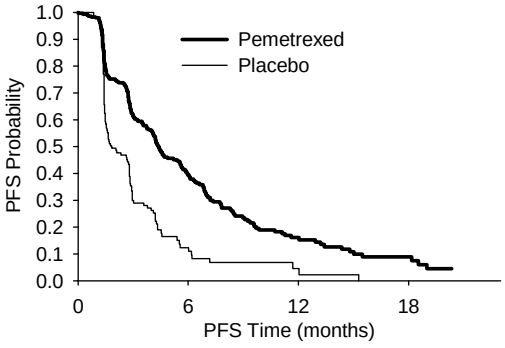
All patients included in this study had an ECOG performance status of 0 or 1. Patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomisation after completion of first line (induction) therapy. Patients received a median of 5 cycles of maintenance treatment with Alimta and 3.5 cycles of placebo. A total of 213 patients (48.3%) completed ≥ 6 cycles and a total of 103 patients (23.4%) completed ≥ 10 cycles of treatment with Alimta.

The study met its primary endpoint and showed a statistically significant improvement in PFS in the Alimta arm over the placebo arm (n = 581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (hazard ratio = 0.60, 95% CI: 0.49-0.73, p < 0.00001). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. The median OS for the overall population (n = 663) was 13.4 months for the Alimta arm and 10.6 months for the placebo arm, hazard ratio = 0.79 (95% CI: 0.65 to 0.95; p = 0.01192). All time-to-event parameters were measured from the date of randomization upon completion of induction therapy.

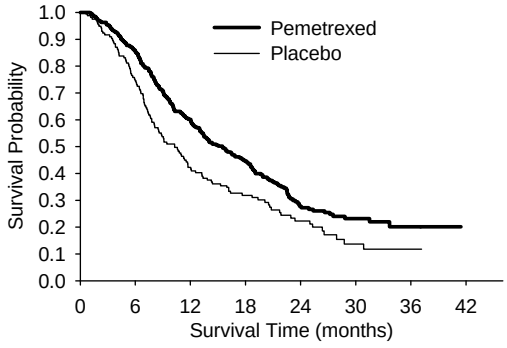
Consistent with other Alimta studies, a difference in efficacy according to NSCLC histology was observed in JMEN. For patients with NSCLC other than predominantly squamous cell histology (n= 430, independently reviewed population) median PFS was 4.4 months for the Alimta arm and 1.8 months for the placebo arm, hazard ratio = 0.47, 95% CI: 0.37-0.60, p= 0.00001. The median OS for patients with NSCLC other than predominantly squamous cell histology (n = 481) was 15.5 months for the Alimta arm and 10.3 months for the placebo arm (hazard ratio = 0.70, 95% CI: 0.56-0.88, p=0.002). Including the induction phase the median OS for patients with NSCLC other than predominantly squamous cell histology was 18.6 months for the Alimta arm and 13.6 months for the placebo arm (hazard ratio =0.71, 95% CI: 0.56-0.88, p=0.002).
The PFS and OS results in patients with squamous cell histology suggested no advantage for Alimta over placebo.

Kaplan Meier Plots of Progression-Free Survival (PFS) and Overall Survival ALIMTA versus Placebo in Patients with NSCLC other than Predominantly Squamous Cell Histology:

Progression-Free Survival



Overall Survival



Safety

The safety results observed in the pemetrexed arm of Study JMEN are consistent with the known safety profile of pemetrexed. The incidence of toxicities in Study JMEN is generally lower than the incidence observed in the pemetrexed arm of Study JMEI and is likely to be reflective of the differences between the 2 studies patient populations and study designs.

In the pivotal study JMEN, out of the 65 reported deaths (9.8% in the pemetrexed arm and 9.9% in the placebo arm), 2.7% occurred while on study therapy or less than 30 days after last dose in the pemetrexed arm *versus* 4.5% in the placebo arm. No study drug-related deaths were reported for either study arm. However, according to the provided narratives, data for causality assessment are missing in some cases and a causal relationship between adverse events leading to death and study drug can therefore not be definitely excluded in some cases.

Overall, more patients treated with pemetrexed than patients treated with placebo had dose adjustments (4.8% in the pemetrexed arm/ 0.9% in the placebo arm). All pemetrexed dose adjustments were a result of adverse events. The incidence of drug-related toxicities was statistically higher in the

pemetrexed arm compared to the placebo arm. Neutropenia and fatigue were statistically significantly different between the 2 treatment arms.

The most common toxicities were of haematologic origin, gastro-intestinal disorders (nausea, vomiting, stomatitis), increased ASAT and ALAT and neuropathy. Renal toxicity was more common in the pemetrexed arm; 33 patients in the pemetrexed arm (7.5%) were reported to have a possibly drug-related adverse event associated with decreased renal function.

The most frequently reported SAE was anaemia, which occurred in 1.4% of patients in the pemetrexed arm; all other SAEs occurred in less than 1% of patients. No serious, unexpected, reportable events (SURs) were reported.

With regard to long-term maintenance therapy, there were no statistically or clinically relevant differences in the safety profile reported for patients receiving more than 6 cycles of pemetrexed compared to those receiving 6 cycles or less. However, given the small number of patients remaining on treatment after 6 cycles, no conclusion can be drawn.

Overall, the safety results for pemetrexed as a maintenance treatment were consistent with the known safety profile of pemetrexed. With reference to the safety database, all adverse reactions reported in clinical trials and post-marketing have been included in the SPC. The CHMP did not consider that any change to the current PSUR cycle was necessary following this extension of indication.

An updated risk management plan was provided. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Overall Benefit/Risk

Following the overall assessment of the efficacy and safety data provided, the CHMP concluded that the benefit/risk ratio of Alimta is positive for maintenance treatment of NSCLC and agreed on the following final wording of the indication in section 4.1 of the SPC:

"Alimta is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel (see Section 5.1)."

All the proposed consequential changes to sections 4.8 and 5.1 of the SPC and the Package Leaflet can be agreed.

Further, the MAH has updated annex IIB to reflect the latest version of the Risk Management Plan (version 2.1) agreed with the CHMP, which is acceptable.

IV. CONCLUSION

On 29 May 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.