European Medicines Agency

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Product name**: Alimta**
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SCIENTIFIC DISCUSSION

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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 as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

This type II variation concerns an extension of indication to include 1st line treatment in combination with cisplatin of patients with non-small cell lung cancer (NSCLC).

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. NSCLC represents about 80% of all lung cancer cases. The most common histologies are epidermoid or squamous cell carcinoma (30-35%), adenocarcinoma (40-45%), and large cell carcinoma (<10%). The frequency of these different histological subsets varies across countries and over time, with a decrease in squamous cell histology in industrialised countries. These histologies are often classified together because approaches to diagnosis, staging, prognosis, and treatment were similar in the past.

Surgery is the preferred treatment of patients with early disease. However, in clinical practice, a high proportion of patients with NSCLC are diagnosed at an advanced stage of the disease (approximately 30% with locally advanced and 40% with metastatic disease) with the remainder 25-30% presenting with early stage disease. Despite recent advances in treatment, the prognosis for patients with lung cancer remains poor. The 5-year survival rate for patients with NSCLC is still only about 15%.

Research over the past decades has proven that chemotherapy has a definite role in the treatment of advanced NSCLC with incremental advances mainly occurring during the last two decades.
One-year survival rates in patients with advanced NSCLC have increased from around 10% without chemotherapy, to 20% with an active single agent, and to 35% with the combination of two active drugs.

Platinum-based chemotherapy has emerged as the standard treatment for advanced NSCLC. In 1995, a large meta-analysis evaluated first- and second-generation platinum-based regimens (developed in the 1980s) and demonstrated a significant increase in median survival of 1.5 months and a 1-year survival rate of 10%, the latter corresponding to a 27% reduction in the probability of death for cisplatin-based therapy, compared with best supportive care.

Thus, the current standard of first-line treatment in patients with advanced disease consists of platinum-based doublet regimens (combination of gemcitabine, vinorelbine, doectaxel or paclitaxel with cisplatin or carboplatin) where 1-year survival rates of 33% and 2-year survival rates of 11% have been reported (Schiller et al.). The use of doublets as compared to cisplatin monotherapy seems to increase the overall survival and the TTP by approximately 2 months (Wozniak et al; Sandler et al.).

Scope of the variation

This type II variation concerns an Extension of Indication to include 1st line treatment in combination with cisplatin of patients with locally advanced or metastatic Non Small Cell Lung Cancer other than predominantly squamous cell histology. In addition, the existing 2nd line monotherapy indication has been amended accordingly. Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SPC have been updated and the Package Leaflet has been updated accordingly.
Further, the Marketing Authorisation Holder (MAH) has updated annex IIB to include a reference to the Pharmacovigilance system (version 2.0) and the Risk Management Plan (version 1.2) agreed with the CHMP.
In addition, the MAH took the opportunity to make a minor change to section 4.5 of the SPC regarding concomitant use with yellow fever vaccine and to make minor editorial changes to the SPC and Package Leaflet.

For this new indication, the proposed posology is similar to the one authorised for pemetrexed in combination with cisplatin in the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma: pemetrexed 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle; cisplatin is 75 mg/m^2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle.

The new first line NSCLC indication is supported by one pivotal, controlled, Phase 3 study, H3E-MC-JMDB (JMDB), which evaluated the efficacy of pemetrexed plus cisplatin (AC) versus gemcitabine plus cisplatin (GC) as the initial treatment of locally advanced or metastatic NSCLC in 1725 patients.

Non-clinical aspects

The non-clinical pharmacology, pharmacokinetics, and toxicology of pemetrexed disodium were evaluated in a battery of non-clinical studies that were discussed as part of the initial Marketing Authorisation application (MAA) for malignant pleural mesothelioma (MPM) and previously treated non-small cell lung cancer (NSCLC). With reference to this new application (II/09), previous findings were summarised by the applicant, followed by a discussion focused on new data. Only the new non-clinical information included in this submission was assessed in this report, including:

Safety Pharmacology:

- 031216-FMD: Effects of LY231514 Disodium (Compound 289739) on Cloned hERG Channels Expressed in Mammalian Cells.

Repeat-dose Toxicology:

- WIL-353055: A Repeat-Dose Study in CD-1 Mice Given LY231514 Disodium (Compound 289739) Weekly by Intraperitoneal Injection for 6 Months

- 500415: A Repeat Dose Toxicity Study in the Beagle Dog Given LY231514 Disodium (Compound 289739) by Intravenous Slow Bolus Injection Every 3 Weeks for 9 Months (14 Doses)

GLP compliance

These safety pharmacology, toxicology, and toxicokinetic studies were performed in accordance with Good Laboratory Practice (GLP) regulations and were consistent with the Organisation for Economic Cooperation and Development (OECD) standards in effect at the time.

Safety pharmacology

The objective of study 031216 was to examine the *in vitro* effects of LY231514 disodium (permetrexed) on IKr current, recapitulated by transfecting the hERG gene in HEK 293 cells. Each of

three concentrations of LY231514 (30, 100 and 300 µM) was applied for 8 min to 3 cells. The results were compared to that of a control solution as well as the positive control E4031 (500 nM). To elicit IKr "tail" currents Chantest used a prepulse to +20 mV followed by a ramp (-0.5 V/sec) to -80 mV, which, in their hands, yields a greater sensitivity than a "step" protocol.
In these conditions, permetrexed neither did significantly block hERG currents nor differ from control [-0.5 to +0.7% blockade as compared to +0.3% for control]. No IC20 or IC50 could be deducted from these experiments due to the lack of effect, confirmed by the fact that a 500 nM concentration of E4031 significantly blocked hERG currents by 89%.
Based on these data, unbound concentrations of up to at least 300 µM permetrexed (~128 µg/ml) or total plasma concentration of ~ 651 µg/ml are not expected to block IKr or induce a QT prolongation subsequent to that mechanism.

Toxicology

Since the initial indication for malignant mesothelioma and previously-treated NSCLC, a 6-month repeat dose study in mice and a 9-month repeat dose study in dogs were conducted to support registration in Japan.
Generally, the toxicity observed in these repeat-dose studies were similar to that observed in shorter duration studies. In mice, the primary effects were on the testis and included decreased testicular weight, degeneration of testicular seminiferous tubules, hyperplasia of interstitial (Leydig) cells, and reduced epididymal spermatozoa. In dogs the effects typical of a cytotoxic agent were observed and included emesis, reduced food consumption resulting in minor fluctuations in body weight, decreases in erythrocytes and/or leukocyte counts and in platelet counts, and hematopoietic hypocellularity in bone marrow. These effects were similar to those observed in the 6-month repeat-dose study in dogs; however, the hematotoxicity was not as severe due to the change in dosing regimen from once a week in the 6-month study to once every 3 weeks in the 9-month study. Additional changes observed in the 9-month study included decreased testes weight with degeneration/necrosis of the seminiferous epithelium and minimal-to-slight renal tubular karyomegaly and degeneration with no organ weight or clinical pathology correlates. The effects on the testes, although not seen in previous studies (possibly due to the age of the dogs), were entirely expected based on the effects in the mouse and the cytotoxic nature of pemetrexed (this finding from Study 500415 has previously been included in the SPC. The effects on the kidney were observed in male dogs only and the overall mild nature of this change was further substantiated by the lack of concurrent compound-related changes in kidney weights, and the absence of any changes in clinical pathology parameters indicative of primary renal injury or dysfunction, even after 9 months of treatment. The effects of pemetrexed on renal function were closely monitored in the pivotal Phase III clinical trials and no adverse findings were observed on renal function.

Discussion on Non-clinical aspects

An extensive series of pharmacodynamic, pharmacokinetic, and toxicology studies in animals have been conducted with pemetrexed disodium and were provided in the initial Marketing Authorisation application. Protocols for the recently completed safety pharmacology and toxicology studies meet current international regulatory guidelines. The format and presentation of the data were appropriate and the studies were performed in line with GLP regulations.

The effects noted in these studies were consistent with the information provided in section 5.3 of the SPC and do not change the safety profile of pemetrexed. The SPC adequately reflects knowledge of the pharmacological and toxicological properties of pemetrexed disodium and includes appropriate advice on reproductive risks and breast feeding and information on genotoxic potential.

Ecotoxicity/environmental risk assessment

The MAH has also provided an environmental risk assessment (ERA) as part of the current application for the use of pemetrexed as first line treatment of non-small cell lung carcinoma. However, this ERA does not completely fulfil the Phase II requirements of the current Guideline on the Environmental

Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00). As a consequence, the MAH has agreed to conduct the requested Phase II studies as a post-opinion commitment.

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

Two Phase I dose-escalation studies with pemetrexed were provided as part of this application; Study H3E-MC-JMAS (JMAS) and Study H3E-JE-1001 (1001).
Further, PK interaction of pemetrexed and cisplatin was investigated in Study H3E-JE-ME01 (ME01) in Japanese patients.
In addition, this application included new PD (sub-) studies in second line treatment of NSCLC (Studies JMGX and NS01) and a Biomarker sub-study of the pivotal study JMDB (Study JMDB-PGX).

- Study H3E-MC-JMAS

Study JMAS was a Phase 1 dose-finding study of pemetrexed administered with high-dose folic acid (FA) or standard-dose FA supplementation through multivitamins (MV) in patients with locally advanced or metastatic cancer.

The **primary objective** of this study was to determine the maximum-tolerated dose (MTD) of pemetrexed when administered as a 10-minute infusion every 3 weeks given with oral folic acid supplementation for 2 days prior, the day of, and for 2 days after study drug administration in patients with locally advanced or metastatic cancer.

The **secondary objectives** of this study were:
-To determine the quantitative and the qualitative toxicities of pemetrexed with folic acid alone or multivitamin supplementation,
-to determine the recommended dose for pemetrexed with folic acid and with multivitamin supplementation for future studies,
-to assess the plasma pharmacokinetics of pemetrexed with folic acid and with multivitamin supplementation,
- to document antitumor activity of pemetrexed with folic acid and with multivitamin supplementation, and
-to determine the folate status of patients.

Patients were classified according to pretreatment status. Lightly pretreated patients (LPT) were those who received no prior treatment, up to 2 courses of mitomycin-C, up to 6 courses of an alkylating agent, or up to 4 courses of carboplatin. Heavily pretreated patients (HPT) were those who previously received more than one of these treatments for their cancer, or any radiotherapy to the pelvic region.
Thus, 4 cohorts of patients (FA_HPT, FA_LPT, MV_HPT, and MV_LPT) were enrolled in the study consisting of 127 patients (72 male and 55 female), of which 99 patients (59 male and 40 female) were included in the pharmacokinetic analyses.
Pemetrexed doses ranging from 600 mg/m^2 to 1400 mg/m^2 were administered as a 10-minute intravenous infusion on Day 1 of a 21-day cycle.

MTD Results

Dose-Limiting Toxicities, Maximum-Tolerated Doses, and Doses Recommended for Phase 2 Study

Cohort	DLTs (n)	MTD	Dose Recommended for Phase 2 Study
FA_HPT	Febrile neutropenia (2) G4 thrombocytopenia (2) G4 neutropenia lasting ≥5 days (1)	925 mg/m2	800 mg/m2
FA_LPT	G4 vomiting with gastritis (1) G4 thrombocytopenia (2) G4 neutropenia lasting ≥5 days (2) G3 rash and fever (1)	1200 mg/m2	1050 mg/m2
MV_HPT	G3 allergic/hypersensitivity reaction (1) Cellulitis associated with G3 neutropenia (1) Febrile neutropenia (1) G4 neutropenia lasting ≥5 days (1)	925 mg/m2	800 mg/m2
MV_LPT	G4 thrombocytopenia (1) G4 neutropenia lasting ≥5 days (1)	1200 mg/m2	1050 mg/m2

Abbreviations: DLTs = dose-limiting toxicities; FA = folic acid; G3 = Grade 3; G4 = Grade 4; HPT = heavily pretreated; LPT = lightly pretreated; MTD = maximum-tolerated dose; MV = multivitamin; n = number of patients with the specified DLT.

Pharmacokinetics results

Plasma concentration versus time data were evaluated using population pharmacokinetic analysis. The pharmacokinetics of pemetrexed administered as a 10-minute intravenous infusion with vitamin supplementation were characterized by a three-compartment model. Population estimates of pemetrexed systemic clearance (CL) and volume of distribution at steady state (Vss) were 88.0 mL/min and 17.0 L, respectively. Pemetrexed (CL) was independent of dose over the dose ranges of 571-1413 mg/m^2 and 888 to 2744 mg m^2; therefore AUC is dose proportional over these dose ranges.

Results from this study demonstrate that pemetrexed pharmacokinetics are linear (that CL is, dose-independent over the range of doses studied). This indicates that pemetrexed total systemic exposure (AUC) and maximum plasma concentration (Cmax) increase proportionally with dose. The data are in accordance with the known PK profile of pemetrexed.

- Study H3E-JE-1001

This was a Phase 1 dose-escalation study of pemetrexed in Japanese patients with locally advanced or metastatic cancer. Patients were classified according to pre-treatment status. Pemetrexed doses ranged from 300 mg/m2 to 1200 mg/m2 and were administered as a 10-minute intravenous infusion on Day 1 of a 21-day cycle. Pharmacokinetic data were available from 31 patients (20 male and 11 female).

The primary pharmacokinetic objective of this trial was to evaluate the pharmacokinetics of LY231514 disodium administered with folic acid and vitamin B12 in Japanese patients.

The secondary objectives of this study were:
▪ To determine the maximum-tolerated dose and recommended dose of LY231514 when administered as a 10-minute infusion every 21 days given with folic acid and vitamin B12 to Japanese patients with locally advanced or metastatic cancer.
▪ To determine the quantitative and qualitative toxicities of LY231514 administered with folic acid and vitamin B12.
▪ To assess the pharmacokinetics of LY231514 when administered with folic acid and vitamin B12.
▪ To investigate antitumor activity of LY231514 administered with folic acid and vitamin B12.

Pharmacokinetics Results
Total plasma clearance of pemetrexed was independent of dose with a mean clearance of 81.9 mL/min (clearance ranged from 61.4 to 109 mL/min across all doses in this study). Steady-state volume of distribution was also consistent across doses and ranged from 10.6 to 14.8 L. Half-life ranged from 2.28 to 3.62 hours and was dose independent. Both $AUC_{(0-\infty)}$ and C_{max} were dose proportional over the dose range of 500 mg/m^2 to 1000 mg/m^2.
The data are in accordance with the known PK profile of pemetrexed.

- Study H3E-JE-ME01

Study ME01 was a Phase 1/2 study of pemetrexed administered in combination with cisplatin in Japanese patients with malignant pleural mesothelioma. Pemetrexed 500 mg/m^2 was administered as an intravenous infusion over 10 minutes followed by a 2-hour cisplatin infusion (60 mg/m^2 or 75 mg/m^2) beginning 30 minutes after the completion of pemetrexed infusion. Doses were administered on Day 1 of each 21-day cycle. Pemetrexed plasma concentration-time data were available from 25 patients.

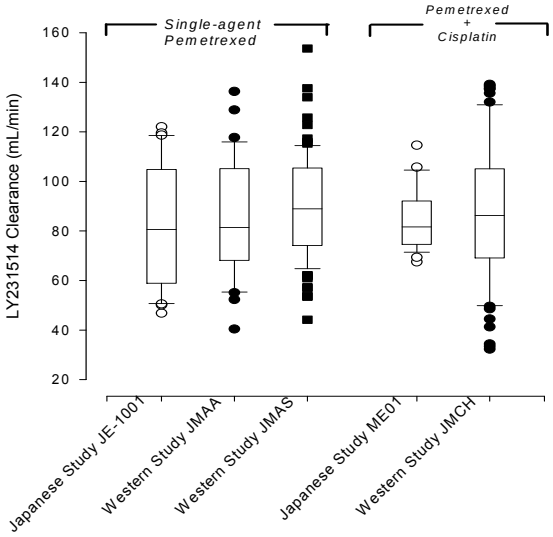
Concomittant Therapy, Dose, and Mode of Administration
-Patients were required to take an oral multivitamin 1 g (containing folic acid 500 µg) once daily from at least 7 days before Day 1 of the scheduled administration of the study drugs in Cycle 1. After discontinuing administration of the study drugs, multivitamin was continuously administered until 22 days after the last dose of the study drugs if possible.
- A vitamin B12 injection at a dose of 1000 µg had to be intramuscularly administered at least 7 days before Day 1 of Cycle 1, and had to be given approximately every 9 weeks (± 7 days) from the date when vitamin B12 was firstly administered until 22 days after the last dose of the study drugs if possible.

The primary pharmacokinetic objective was to characterize the pharmacokinetics of LY231514 and cisplatin when coadministered in Japanese patients and to compare the pharmacokinetics to that characterized in Western patients (Study H3E-MC-JMCH [JMCH]).

Plasma sampling for pharmacokinetic assessment was conducted in Cycles 1 and 3 for characterization of both Alimta and total platinum pharmacokinetics.

Results
Study JMCH was a randomized study of pemetrexed plus cisplatin versus single-agent cisplatin for the treatment of malignant pleural mesothelioma and was provided as a pivotal study in the initial submission of pemetrexed. Pemetrexed data from Study ME01 were combined with data from Study JMCH (N=68) for purposes of pharmacokinetic analysis.

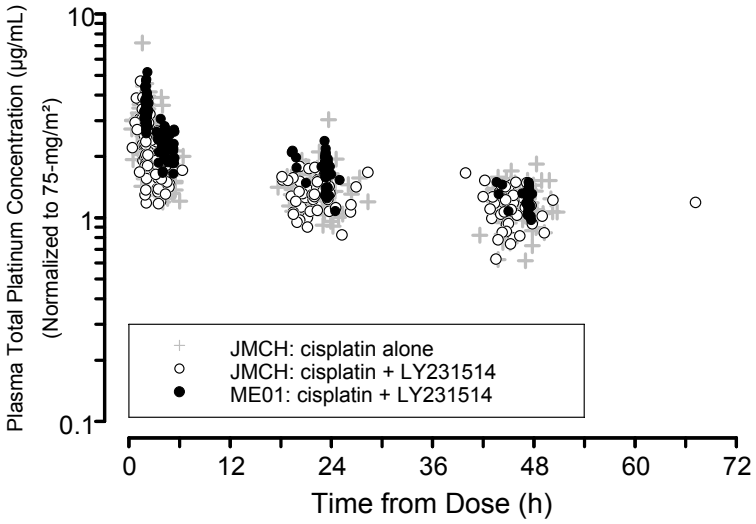
The following plot is comparing pemetrexed plasma clearance in several studies (JMAA, JMAS, 1001, JMCH, and ME01). JMAA was a dose-escalation Phase 1 study included in the initial submission. The range of plasma clearance of pemetrexed is similar whether administered as a single agent or in combination with cisplatin. The median pemetrexed clearance was around 80.0 mL/min and the steady-state volume of distribution was 14.4 L in Study ME01.



Cisplatin data was available from 25 patients in Study ME01. Cisplatin concentration-time data from Study ME01 was combined with data from Study JMCH (63 patients in the combination arm, and 74 patients from the cisplatin single-agent arm) for purposes of cisplatin pharmacokinetic analysis.

The figure below shows the total platinum plasma concentration-time profile in Study ME01 and Study JMCH. In Study JMCH, cisplatin was administered alone or in combination with pemetrexed. The dose-normalized total platinum plasma exposures in Studies JMCH and ME01 are comparable. This suggests that total platinum plasma exposures are comparable whether administered alone or in combination with pemetrexed.

Observed plasma total platinum concentrations versus time from start of infusion: Studies ME01 (•), JMCH, cisplatin + LY231514 (o), and JMCH, cisplatin alone (+):



The results show, as in the original MAA, that the pharmacokinetics of pemetrexed are not altered when administered with cisplatin.

- Study JMDB-PGX (Biomarker Sub-Study of pivotal Study JMDB discussed below)

The pivotal trial of this application, JMDB, provided a biomarker sub-study; participation in this substudy was optional. Of the overall 177 investigators of the main study, 20 main investigators participated in the sub-study. It was anticipated that from the main trial, about 40% of patients (344 patients per treatment arm) should have specimens studied in this sub-study. A total of 366 patients

were consented for this substudy (in both arms) of whom 232 patients had specimens submitted, 113 on AC and 119 on GC.

The study investigated expression levels of several biomarkers known to be involved in pemetrexed, gemcitabine, and cisplatin mechanisms of action and resistance, including genes involved in the activation and transport, as well as genes believed to have prognostic value in NSCLC. Biomarkers of interest included thymidylate synthase (TS), folylpoly-γ-glutamate synthetase (FPGS), γ -glutamyl hydrolase (GGH), ribonucleotide reductase M1 (RRM1), deoxycytidine kinase (dCK), human equilibrative nucleoside transporter (hENT1), multidrug resistance protein 5 (MRP5), excision repair crosscomplementing (ERCC1), and epidermal growth factor receptor (EGFR).

The association between expression levels of biomarkers and survival time was assessed within and between each treatment arm. All patients with clinical outcome data and protein or gene expression data falling within specified reference ranges were included in the analyses.

Samples were obtained from 232 patients, 16 of which had insufficient tumour tissue for analysis.
Patients with IHC data included 90 patients in Treatment Arm AC and 91 patients in Treatment Arm GC.
Patients with gene expression data within reference range included 26 patients in AC and 43 patients in GC.
Patients with both gene and protein data (patients with at least 1 result) included 13 patients in AC and 21 patients in GC.

In this exploratory study, the data analysis of samples received showed statistically significant patterns in a number of analyses that may be of scientific interest for further investigation. Because of the small sample size, results should be considered useful as exploratory analyses but not definitive statements.

- A consistent treatment-independent relationship between higher EGFR expression, both for gene as well as protein, and improved clinical outcome for all time-to-event outcomes and best tumour response was observed.
- All other markers either showed lower levels of statistical significance or association with fewer clinical outcomes.
- For patients treated with AC, there was an association between lower TS mRNA expression and better outcomes (increased time-to-progressive disease [TtPD] and time-to-treatment failure [TtTF]). Conversely for GC, higher TS mRNA levels were associated with increased TtPD and TtTF.
- The analysis uncovered links between high FPGS gene expression and improved TtPD, regardless of treatment.
- For patients treated with AC, lower expression of ERCC1 was associated with increased TtTF. Patients with high ERCC1 expression showed a trend toward improved progression-free survival (PFS) and TtPD. There was a significant interaction between treatment and baseline ERCC1. Expression level-dependent treatment effects for PFS and TtPD were identified.

Due to the small sample size, results should be considered informative but not confirmatory.

- Study JMGX

This was a randomized, open-label, multi-centre, Phase 3 study on second-line patients with NSCLC comparing overall survival following treatment with pemetrexed 500 mg/m^2 (=licensed second line monotherapy schedule) versus pemetrexed 900 mg/m^2 in patients with locally advanced or metastatic (Stage III or IV) NSCLC who had failed a prior platinum-containing chemotherapy.

Of the 629 patients who entered the study, 588 were randomly assigned to treatment and 41 patients were not. Of the 588 patients, 295 patients were randomly assigned to the 500 mg/m^2 arm and 293 to the 900 mg/m^2 arm. Seven patients were randomized but never treated. During this study, the data monitoring committee (DMC) recommended to discontinue further enrolment and to stop treatment with the higher dose (900 mg/m^2) of pemetrexed due to lack of evidence to suggest that there would be

a statistically significant improvement in survival with the higher dose (900 mg/m^2) of pemetrexed compared with the standard dose (500 mg/m^2). Fifty-one patients who were still receiving treatment on the 900 mg/m^2 treatment arm were switched to the 500 mg/m^2 treatment arm (the 900-mg/m^2 and 500-mg/m^2 group).

The final efficacy analyses showed no statistically significant difference in overall survival time between the 2 treatment groups (HR 1.0132; 95% CI 0.837, 1.226; p=0.8930). The median survival time was 6.7 months for the 500 mg/m^2 arm and 6.9 months for the 900 mg/m^2 arm.
Secondary efficacy outcomes included PFS and tumour response rates. The Cox proportional hazards model revealed no statistically significant difference in PFS between the 500 mg/m^2 and 900 mg/m^2 treatment groups. Median PFS time was 2.6 months in the 500 mg/m^2 group and 2.8 months in the 900 mg/m^2 group. The chi-square test showed no statistically significant difference in the tumour response rate between the 500 mg/m^2 and 900 mg/m^2 groups (7.1% versus 4.3%, p=0.1616). Stable disease rates were 50.6% and 53.1%, respectively.

The percentage of serious adverse events (SAEs) was numerically higher (37.9% versus 32.1%) in the 900 mg/m^2 group compared with the 500 mg/m^2 group. The percentage of SAEs among the 51 patients in the 900 to 500 mg/m^2 group was 49%. The percentage of fatal SAEs was 4.5% for the 500 mg/m^2 arm, 5.0% for the 900-mg/m^2 arm, and 5.9% for the 900 to 500-mg/m^2 group. The percentage of drug-related fatal SAEs was 0.7% for the 500-mg/m^2, 1.3% for the 900-mg/m^2, and 2.0% for the 900 to 500-mg/m^2 groups. The percentage of life-threatening adverse events was 2.1% for 500 mg/m^2, 1.7% for the 900 mg/m^2, and 2.0% for the 900 to 500-mg/m^2 groups.

In general, the frequency of adverse events was similar between the low and high dose of pemetrexed. However, for the following adverse events, more than a 5 percentage point difference in frequency between the 900 mg/m^2 and 500 mg/m^2 groups was observed:
Anaemia (32.9% versus 22.1%), fatigue (41.7% versus 32.8%), vomiting (20.0% versus 13.1%), thrombocytopenia (11.3% versus 5.5%), and diarrhoea (15.4% versus 10.0%).

This large monotherapy trial in second line NSCLC patients overall confirms the MA status of Alimta, and suggests that the dosage recommended within the first MA procedure is already near the optimum, both in terms of efficacy and safety.

- Study NS01

This was a multi-centre, randomized, open-label clinical trial involving Japanese patients with advanced NSCLC who previously received systemic chemotherapy (one or two regimens). The planned sample size was 240 patients (120 patients each in the 500 and 1000 mg/m^2 arms).
The actual number of patients assigned to treatment arms was 244. The number of patients actually treated with pemetrexed was 226 patients (114 patients in the 500 mg/m^2 arm and 112 patients in the 1000 mg/m^2 arm).

The primary efficacy endpoint in this study was response rate. Efficacy analyses were performed for the FAS (full analysis set; 216 patients) population based on “best overall response” assessments performed by an independent case judgment committee.
Best overall responses assessed by the case judgment committee for 108 subjects in the 500 mg/m^2 group (who met the criteria for FAS) were as follows: complete response (CR), n=0; partial response (PR), n=20; stable disease (SD), n=40; progressive disease (PD), n=48; and not evaluable (NE), n=0. The response rate (CR+PR rate) was 18.5% (90% confidence interval (CI): 12.6% to 25.8%). The lower limit of one-sided 95% CI was 12.6%.
Best overall responses assessed by the case judgment committee for 108 subjects in the 1000 mg/m^2 group (who met the criteria for FAS) were as follows: CR, n=0; PR, n=16; SD, n=34; PD, n=58; and NE, n=0. The response rate was 14.8% (90% CI: 9.5% to 21.6%).

The median duration of response for 20 subjects with PR in the 500 mg/m^2 group was 4.7 months (95% CI: 3.8 to 6.8 months). The median duration of response for 16 subjects with PR in the 1000 mg/m^2 group was 3.8 months (95% CI: 2.5 to 6.3 months).

The median PFS for 108 subjects in the 500 mg/m^2 was 3.0 months (95% CI: 2.0 to 3.3 months).
The median PFS for 108 subjects in the 1000 mg/m^2 was 2.4 months (95% CI: 1.8 to 3.1 months).

Treatment Emergent Adverse Events (TEAE) which occurred with an incidence of ≥50% in the 500 mg/m^2 group included:
Aspartate aminotransferase increased, n=88 (77.2%); Alanine aminotransferase increased, n=81 (71.1%); White blood cell count decreased, n=80 (70.2%); Rash, n=79 (69.3%); Neutrophil count decreased, n=73 (64.0%); Blood LDH increased, n=71 (62.3%); Nausea, n=64 (56.1%); and Haemoglobin decreased, n=58 (50.9%).

TEAE which occurred with an incidence of ≥50% in the 1000 mg/m^2 group included:
Rash, n=89 (80.2%); Aspartate aminotransferase increased, n=88 (79.3%); Alanine aminotransferase increased, n=82 (73.9%); White blood cell count decreased, n=81 (73.0%); Anorexia, n=78 (70.3%); Neutrophil count decreased, n=72 (64.9%); Blood LDH increased, n=71 (64.0%); Haemoglobin decreased, n=69 (62.2%); Nausea, n=65 (58.6%); and Lymphocyte count decreased, n=64 (57.7%).

Grade 3 or higher TEAE which occurred with an incidence of ≥10% in the 500-mg/m^2 group included:
Neutrophil count decreased, n=23 (20.2%); Alanine aminotransferase increased, n=19 (16.7%); White blood cell count decreased, n=16 (14.0%); and Lymphocyte count decreased, n=16 (14.0%).

Grade 3 or higher TEAE which occurred with an incidence of ≥10% in the 1000 mg/m^2 group included: Neutrophil count decreased, n=27 (24.3%); Lymphocyte count decreased, n=24 (21.6%); White blood cell count decreased, n=23 (20.7%); and Anorexia, n=17 (15.3%).

Results of trial NS01 both in terms of efficacy and safety confirm the findings and conclusions of trial JMGX and support the approved pemetrexed dose of 500 mg/m^2.

Discussion on Clinical pharmacology

The results from Study H3E-MC-JMAS demonstrated that pemetrexed pharmacokinetics are linear (i.e. that CL is dose-independent over the range of doses studied). Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (Cmax) increase proportionally with dose. The data are in accordance with the known PK profile of pemetrexed.

The results from Study H3E-JE-ME01 show, as in the original MAA, that the pharmacokinetics of pemetrexed are not altered when administered with cisplatin.

The small number of patients included in the biomarker sub-study preclude any reliable conclusion although the exploratory results suggest that it would have been valuable to have more reliable data available on e.g. EGFR and TS expression and correlation with efficacy. There are insufficient data at this time to correlate tumour biomarkers with histology and therapeutic outcomes with pemetrexed.

The large monotherapy trial JMGX in second line NSCLC patients confirms that the dosage recommended at the time of the first MAA is already near the optimum, both in terms of efficacy and safety. The results of trial NS01 confirm the findings and conclusions of study JMGX and also support the approved pemetrexed dose of 500 mg/m^2.

Clinical Efficacy

The following clinical efficacy and safety studies were submitted in support of the application:

- Pivotal Study H3E-MC-JMDB (JMDB): a Phase 3 study comparing the efficacy and safety of pemetrexed plus cisplatin combination therapy with that of gemcitabine plus cisplatin in patients with a diagnosis of locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC who have had no prior systemic chemotherapy for lung cancer.

- Supportive Study H3E-MC-JMAY (JMAY): a Phase 2 study assessing the efficacy and safety of pemetrexed in combination with cisplatin in patients with Stage IIIB or Stage IV NSCLC who have had no prior systemic chemotherapy.
- Supportive Study H3E-MC-JMBZ (JMBZ), a Phase 2 study assessing the efficacy and safety of pemetrexed in combination with cisplatin in patients with Stage IIIB or Stage IV NSCLC who have had no prior systemic chemotherapy.

Both supportive studies were previously submitted for evaluation as part of the original Marketing Authorisation application.

Supportive Phase II studies: JMAY and JMBZ

The table below presents key elements of the 2 supportive studies H3E-MC-JMAY (JMAY) and H3E-MC-JMBZ (JMBZ):

Study	Brief Description	N	Regimen	Primary Objective
JMAY	Phase 2, open-label, uncontrolled, initial treatment of Stage IIIB or IV NSCLC	36	Pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 on Day 1 of a 21-day cycle	Tumour response rate
JMBZ	Phase 2, open-label, uncontrolled, initial treatment of Stage IIIB or IV NSCLC	32	Pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 on Day 1 of a 21-day cycle	Tumour response rate

- **Study JMAY** was a multicentre study enrolling 36 patients at 4 study centres: 1 in Austria and 3 in Germany. Of the 36 qualified patients, 29 (80.6%) were male. The median age of the patients was 58 years, with a range of 26 to 73 years. Eighteen patients (50%) had Stage IIIB and 18 patients (50%) had Stage IV disease. All 36 patients had a World Health Organization (WHO) performance status of 0 or 1.

-**Study JMBZ** was a multicentre study, enrolling 31 patients at 5 study centres in Canada. Of the 31 qualified patients, 20 (65%) were male. The median age of the patients was 60 years, with a range of 35 to 75 years. Five patients (16%) had Stage IIIB and 26 patients (84%) had Stage IV disease. Twenty-seven patients (83%) had an ECOG performance status of 0 or 1, and 5 patients (16%) had an ECOG performance status of 2.

The main differences between study populations were in the proportion of patients with Stage IV disease (50% versus 84%, respectively) and performance status (PS); in both studies, a majority of patients had PS 1 (75% versus 77%, respectively), but Study JMAY had a greater number of PS 0 patients (22% versus 6%, respectively), and Study JMAY had no PS 2 patients (0% versus 16%).

Study JMAY and Study JMBZ Summary of Patient Demographic and Disease Characteristics at Baseline

	JMAY	**JMBZ**
Dose (mg/m2)	**Pemetrexed: 500 Cisplatin: 75**	**Pemetrexed: 500 Cisplatin: 75**
N (evaluable)	36	31
Sex: n (%)		
Male	29 (81%)	11 (35%)
Female	7 (19%)	20 (65%)
Median Age: years (range)	58 (26-73)	60 (35-75)
Performance Status* (Visit: 1): n (%)		
0	8 (22%)	2 (6%)
1	27 (75%)	24 (77%)
2	1 (3%)**	5 (16%)
Stage of Disease at Entry (Visit: 0): n (%)		
Stage IIIB	18 (50%)	5 (16%)
Stage IV	18 (50%)	26 (84%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number of patients, n = number of patients per category; N/A = not applicable; WHO = World Health Organization.
*Performance status for Study JMAY based on WHO criteria; performance status for Study JMBZ based on ECOG criteria.
**Patient was enrolled in violation of protocol entry criteria, which required performance status <2.

Efficacy Results

Tumour Response Rate, Time-to-Progressive Disease, and Survival Time H3E-MC-JMAY and H3E-MC-JMBZ

	JMAY	JMBZ
Dose (mg/m2)	Pemetrexed: 500 Cisplatin: 75	Pemetrexed: 500 Cisplatin: 75
N (evaluable)	36	29
ORR (%)	38.9	44.8
Median TtPD (mo)	6.3	N/R
Median survival (mo)	10.9	8.9

Abbreviations: mo = months; N = number of evaluable patients; N/R = not reported; ORR = overall response rate; TtPD = time-to-progressive disease.

Both supportive studies JMAY and JMBZ demonstrated consistent activity for the combination pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 with that shown in the pivotal Study JMDB (ORR 31%) and a similar activity as reported with other platinum-based doublet regimens for NSCLC (Wozniak et al.1998; Sandler et al.2000) .

Pivotal clinical Phase III study – JMDB

Methods

The primary objective of this study was to compare pemetrexed plus cisplatin with gemcitabine plus cisplatin in terms of the Overall Survival (OS) of previously untreated patients with Stage IIIB (not amenable to curative treatment) and Stage IV NSCLC.

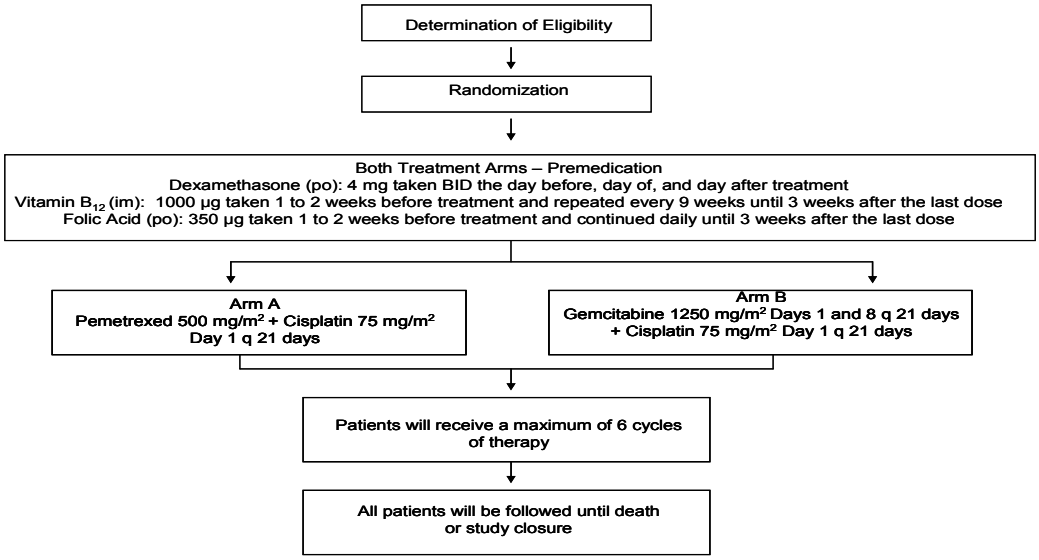
The main secondary objectives of the study were to compare the following between treatment arms:
- time-to-event efficacy variables, including:
  - progression-free survival (PFS)
  - time-to-progressive disease (TtPD)
  - duration of response (DoR)
  - time-to-treatment failure (TtTF)
- objective tumour response
- quantitative and qualitative laboratory and non-laboratory toxicities

Study Design

This was a multicentre, randomized, open-label, phase III, non-inferiority study. Approximately 1700 patients were to be enrolled in this study. Eligible patients were randomized evenly between the experimental treatment arm (pemetrexed plus cisplatin [AC]) and the control treatment arm (gemcitabine plus cisplatin [GC]). Patients in both treatment arms received folic acid and vitamin B12 and dexamethasone pre-treatment supplementation.

Investigational sites involved in Study JMDB were invited to participate in an optional companion biomarker research protocol. Following an initial randomization based on whether the investigative center was participating in the companion biomarker study (yes versus no), randomization was adjusted for baseline factors including disease stage (IIIB versus IV), ECOG performance status (0 versus 1), history of brain metastases (yes versus no), sex (male versus female), basis for initial pathological diagnosis (histological versus cytological), and investigative centre.

Each patient underwent a treatment period and a follow-up period. The treatment period consisted of treatment cycles, each 21 days long. Patients received up to 6 cycles of assigned treatment (control or experimental). The follow-up period began when the treatment period was completed. Patients were to be followed up with periodic tumour response evaluation until disease progression. All patients were followed until death or study closure.



Study Participants

Main inclusion criteria

Patients were eligible to be included in the study only if they met all of the following criteria:

1. histologic or cytologic diagnosis of NSCLC Stage IIIB (not amenable to curative treatment) or IV American Joint Committee on Cancer Staging Criteria for NSCLC;
2. no prior systemic chemotherapy for lung cancer;
3. at least 1 unidimensionally measurable lesion meeting RECIST criteria;
4. performance status of 0 or 1 on the ECOG Scale;
5. at least 18 years of age;
6. adequate organ function.

Main exclusion criteria

Patients were excluded from the study if they met any of the following criteria:

1. had 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;
2. peripheral neuropathy of ≥CTC Grade 1;
3. inability to comply with protocol or study procedures;
4. a serious concomitant systemic disorder that, in the opinion of the investigator, would have compromised the patient's ability to complete the study;

5. a 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;
6. second primary malignancy that was clinically detectable at the time of consideration for study enrolment.

Treatment regimen

Control arm: The cisplatin dose 75 mg/ m^2 in combination with gemcitabine 1250 mg/ m^2 has been tested in a large randomized Phase 3 study (Scagliotti et al. 2003) that produced consistent efficacy and safety data as compared with other gemcitabine/cisplatin studies. The 21-day regimen of gemcitabine in combination with cisplatin was utilized as a control, as this is a clinical standard regimen in patients with NSCLC. In addition, a randomized Phase 2 trial suggested that there was similar efficacy and dose intensity in the 21- versus the 28-day regimen (Soto Parra et al. 2002).

Treatments Administered: Patients were randomized to receive up to 6 cycles of pemetrexed plus cisplatin (AC) or gemcitabine plus cisplatin (GC) combination therapy, as follows:

Experimental Arm A:	pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on Day 1 every 21 days.
Control Arm B:	gemcitabine 1250 mg/m^2 on Day 1 and Day 8 plus cisplatin 75 mg/m^2 on Day 1 every 21 days.

Selection of Doses in the Study: Data from a Phase 1 Study, H3E-MC-JMAP (JMAP) of pemetrexed and cisplatin contributed to the selection of the pemetrexed and cisplatin doses for patients assigned to Treatment Arm A in this study. The maximum-tolerated dose (MTD) for the first cohort was reached at 600 mg/ m^2 pemetrexed and 100 mg/ m^2 cisplatin, with dose-limiting toxicities (DLTs) of thrombocytopenia and febrile neutropenia. The data from this study would have led to a dose of 600 mg/ m^2 and cisplatin 75 mg/m^2 to become the recommended Phase 2 dose. However, because of toxicities observed in other single-agent Phase 2 studies, the recommended Phase 2/3 dose for this combination became 500 mg/ m^2 pemetrexed and 75 mg/ m^2 cisplatin, as used in the pivotal phase 3 study in mesothelioma. The dose of cisplatin in combination with gemcitabine has varied from 75 mg/ m^2 to 100 mg/ m^2 every 21 days. Based on the non-inferiority study design of this study, the cisplatin dose was selected to match the Treatment Arm A cisplatin dose (75 mg/ m^2).

Prior and Concomitant Therapy: Patients in both treatment groups were fully supplemented with folic acid and vitamin B12, as well as dexamethasone prophylaxis. Patients were allowed to receive full supportive-care therapies concomitantly during the study. Antiemetics could be used. Palliative radiation therapy was permitted for irradiating small areas of painful metastases that could not be managed adequately using systemic or local analgesics. Any disease progression requiring other forms of specific antitumor therapy was cause for early discontinuation of study therapy. No other anticancer therapy were permitted while the patients were participating in this study.

Efficacy and safety variables

The following definitions for time-to-event measures will apply:
- **Overall survival (OS)** is measured from the date of randomization to the date of death from any cause.
- **Progression-free survival (PFS)** is measured from the date of randomization to the first date of progression of disease (clinical or objective) or death from any cause.
- **Time to progressive disease** is measured from the date of randomization to the first date of progression of disease (clinical or objective).
- **Duration of tumor response** is measured from the date of the first objective status assessment of a complete or partial response to the first date of progression of disease (clinical or objective) or death from any cause.
- **Time to treatment failure** is measured from the date of randomization until the date of discontinuation from study due to AE, progression of disease (clinical or objective), or death from any cause.

Statistical methods

The statistical hypotheses were:

- H_0: HR $\geq$1.17647 (null hypothesis)
- H_a: HR <1.17647 (alternative, research hypothesis)

The non-inferiority margin of 1.17647 corresponds to GC having a 15% lower survival hazard (that is, risk of death) than that of AC. If this hazard ratio is observed and is assumed to be constant, this non-inferiority margin would translate into a 17.6% longer median survival for the GC arm. Therefore, a statistically significant result implies that the median survival for AC is at least 85% as long as that for GC. As prespecified in the Statistical Analysis Plan, if the 95% confidence interval for HR was found to fall entirely below the margin of 1.17647, the null hypothesis H_0 would be rejected at a one-sided 0.025 significance level and thus support the conclusion that AC is non-inferior to GC.
The study required at least 1190 deaths in accordance with the study design and sample size assumptions.
Two interim analyses for futility were planned and conducted per protocol, in May and September 2005, respectively. The first interim analysis was planned to occur after approximately 700 patients had been enrolled (after a minimum of 200 patients had progressive disease or had died). Dependent on results of the first interim analysis, a second interim analysis was to occur approximately 2 to 3 months after the first interim analysis.

Efficacy analysis

The primary efficacy analysis was a non-inferiority analysis of OS for patients treated with AC compared to patients treated with GC.
The overall survival hazard ratio (HR) of pemetrexed plus cisplatin over gemcitabine plus cisplatin was assumed to be approximately constant from randomization until death. For the primary analysis of this study, HR was estimated from survival data on all randomized patients using a Cox proportional hazards model. This Cox model was used for all time-to-event endpoints. In addition, unadjusted analyses were performed for each time-to-event endpoint, based on Kaplan Meier methods.
Non-inferiority p-values were also calculated for both Cox adjusted and unadjusted analyses at a one-sided, 0.025 significance level. Tumour response rate was also summarized and tested for superiority (two-sided, 0.05 significance level) using normal approximation for the difference in rates.
Time-to-event hazard ratios (HR) were estimated using Cox proportional hazards models using the following baseline covariates: assigned study treatment arm (pemetrexed plus cisplatin [AC] over gemcitabine plus cisplatin [GC]), disease stage (IIIB over IV), ECOG performance status (0 over 1), sex (female over male), basis for initial pathological diagnosis (histopathological over cytological). The covariates listed above were chosen to correspond with the factors involved in randomization, with the exceptions of investigator site, history of brain metastases, and participation in the biomarker research protocol.

Patient Populations for Efficacy Analyses

Four different analysis populations were utilized for the analysis of study JMDB:
- The primary efficacy analyses, as well as baseline characteristics, were based on the **intent-to-treat (ITT) population**, consisting of all patients who were randomized (regardless of whether they were treated or not), and analyzed according to the therapy as randomized (regardless of what they received).
- The tumour response rate and duration of response were analyzed on the **tumour-qualified population**, rather than the ITT population. The tumor-qualified population consisted of patients who had a diagnosis of Stage IIIB or IV NSCLC, did not receive other systemic chemotherapy, had at least 1 measurable lesion at baseline (per the RECIST criteria) and postbaseline, and received at least 1 dose of pemetrexed, gemcitabine, or cisplatin, and analyzed according to the therapy received in the first cycle.

- Sensitivity analyses of key efficacy endpoints were also assessed on the **protocol-qualified population**, which consisted of patients who had a diagnosis of Stage IIIB or IV NSCLC, did not receive other systemic chemotherapy, had at least 1 measurable lesion at baseline (per the RECIST criteria), and received at least 1 dose of pemetrexed, gemcitabine, or cisplatin, and analyzed according to the therapy received in the first cycle.
- Lastly, the safety analyses were performed on the **randomized and treated patients** (received at least one dose of pemetrexed, gemcitabine, or cisplatin), and analyzed according to the therapy received in the first cycle.

Subgroup and Sensitivity Analyses

Subgroup Analyses
The following subgroup analyses of OS were prespecified:
1. randomization factors (disease stage, performance status, sex, basis for initial pathological diagnosis);
2. age and origin as regulatory requirements;
3. ever-smoker versus never-smoker;
4. histology categories of adenocarcinoma, squamous cell, large cell, and other – based on retrospective analyses of other Lilly pemetrexed data in NSCLC.

The analyses were performed using both Cox adjusted and Kaplan Meier analysis.

Main sensitivity Analyses
These sensitivity analyses included:
1. use of protocol-qualified population on key efficacy endpoints to assess robustness of results;
2. use of central blinded review of lesion assessments for determination of progression on a randomly selected subset of approximately 400 patients (from approximately the first 1000 patients enrolled) for PFS;
3. potential impact of post-discontinuation anticancer therapy on PFS.

Efficacy results

Overall, 1833 patients entered trial JMDB at 177 sites in 26 countries. Of these patients, 1725 (94.1%) were randomly assigned to either pemetrexed plus cisplatin (AC arm) or gemcitabine plus cisplatin (GC arm). Of the 1833 patients entered, a total of 108 patients were not randomized; therefore, a total of 1725 patients were enrolled into the study. Of the enrolled patients, 862 patients were randomized to the AC arm, and 863 patients were randomized to the GC arm. A total of 1669 (91.1%) received study treatment consisting of at least 1 dose of pemetrexed, cisplatin, or gemcitabine (AC, n=839; GC, n=830).

Summary of Reasons for Discontinuations- All Patients- H3E-MC-JMDB

Reason for Discontinuation	A/C (N=862) n(%)	G/C (N=863) n(%)	Not Randomized (N=108) n(%)	ALL (N=1833) n(%)
Adverse event	99 (11.5)	117 (13.6)	3 (2.8)	219 (11.9)
Death	3 (3.8)	33 (3.8)	2 (1.9)	68 (3.7)
Death from Study Drug Toxicity	9 (1.0)	6 (0.7)	0 (0.0)	15 (0.8)
Death from study disease	24 (2.8)	21 (2.4)	0 (0.0)	45 (2.5)
Lack of efficacy, patient and physician perception	18 (2.1)	17 (2.0)	0 (0.0)	35 (1.9)
Lack of efficacy, progressive disease	280 (32.5)	253 (29.3)	0 (0.0)	533 (29.1)
Other	3 (0.3)	1 (0.1)	1 (0.9)	5 (0.3)
Patient decision	0 (0.0)	0 (0.0)	17 (15.7)	17 (0.9)
Patient withdrew consent	19 (2.2)	17 (2.0)	0 (0.0)	36 (2.0)
Personal conflict or other patient decision	19 (2.2)	20 (2.3)	0 (0.0)	39 (2.1)
Protocol Violation	2 (0.2)	6 (0.7)	0 (0.0)	8 (0.4)

Protocol completed	305 (35.4)	305 (35.3)	0 (0.0)	610 (33.3)
Protocol entry criteria not met	8 (0.9)	18 (2.1)	84 (77.8)	110 (6.0)
Satisfactory response, patient and physician perception	37 (4.3)	44 (5.1)	0 (0.0)	81 (4.4)
Unable to contact patient (lost to follow-up)	6 (0.7)	5 (0.6)	1 (0.9)	12 (0.7)

- **Abbreviations: A/C = Pemetrexed/Cisplatin; G/C = Gemcitabine/Cisplatin; N = number of patients; n = number of patients with events.**

Patient Characteristics at Baseline by Treatment Group - All Randomized Patients

Variable		AC N=862	GC N=863
Sex	Male n (%)	605 (70.2)	605 (70.1)
	Female n (%)	257 (29.8)	258 (29.9)
Origin	African Decent n (%)	18 (2.1)	18 (2.1)
	Caucasian n (%)	669 (77.6)	680 (78.8)
	East/Southeast Asian n (%)	116 (13.5)	104 (12.1)
	Hispanic n (%)	27 (3.1)	23 (2.7)
	Western Asian n (%)	30 (3.5)	37 (4.3)
	Other n (%)	2 (0.2)	1 (0.1)
Age Group	Age <65 years n (%)	541 (62.8)	577 (66.9)
	Age ≥65 years n (%)	321 (37.2)	286 (33.1)
	Median Age/Range (years)	61.05 (28.8-83.2)	60.95 (26.4-79.4)
Height	Median (cm)	168.0	168.0
Weight	Median (kg)	69.00	68.00
Smoking Status	Ever Smoker n (%)	629 (73.0)	637 (73.8)
	Never Smoker n (%)	128 (14.8)	122 (14.1)
	Unknown	105 (12.2)	104 (12.1)
Performance Status	ECOG PS 0	305 (35.4)	307 (35.6)
	ECOG PS 1	556 (64.5)	554 (64.2)
	Unknown	1 (0.1)	2 (0.2)
Basis for Diagnosis	Cytological n (%)	289 (33.5)	288 (33.4)
	Histological n (%)	573 (66.5)	575 (66.6)
Stage of Disease	Stage IIIB n (%)	205 (23.8)	210 (24.3)
	Stage IV n (%)	657 (76.2)	653 (75.7)
Histology	Adenocarcinoma n (%)	436 (50.6)	411 (47.6)
	Squamous Cell Carcinoma n (%)	244 (28.3)	229 (26.5)
	Large Cell Carcinoma n (%)	76 (8.8)	77 (8.9)
	Other n (%)	106 (12.3)	146 (16.9)

Abbreviations: AC = pemetrexed plus cisplatin; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine plus cisplatin; N = number of patients enrolled; n = number of patients in groups.

Concomitant treatment: For both treatment arms, systemic steroids were the most commonly reported concomitant medication (note that corticosteroids were required as prophylaxis for both treatment arms according to study protocol). Patients on the GC arm received significantly more erythropoietin/darbepoetin than patients on the AC arm (18.1% versus 10.4%; p<0.001) and more iron preparations than patients on the AC arm (7.0% versus 4.3%; p=0.021). Patients on the GC arm also received significantly more G-CSF/GM-CSF than patients on the AC arm (6.1% versus 3.1%; p=0.004).

Primary efficacy endpoints

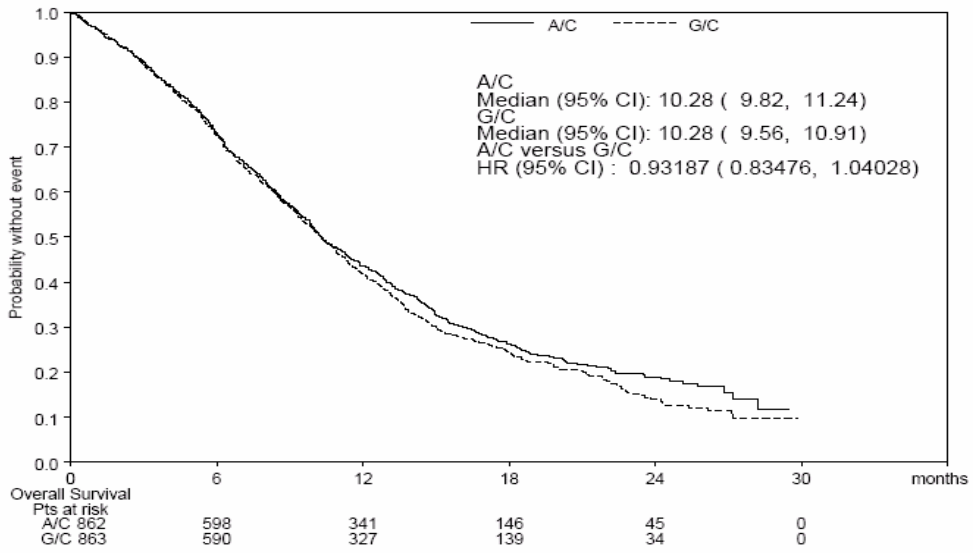
A total of 862 patients on the AC arm and 863 patients on the GC arm were included in the OS analysis of randomized patients.

Results for the Analysis of Overall Survival ITT Population H3E-MC-JMDB

Parameter	AC (N=862)	GC (N=863)
Number of Events (percentage)	623 (72.3%)	647 (75.0%)
Number Censored (percentage)	239 (27.7%)	216 (25.0%)
Median (95% CI)	10.28 (9.82 – 11.24)	10.28 (9.56 – 10.91)
12 mo. Probability (95% CI)	43.5 (40.1 – 46.9)	41.9 (38.5 – 45.4)
24 mo. Probability (95% CI)	18.9 (15.7 – 22.2)	14.0 (10.9 – 17.1)
HR* (95% CI)	0.93 (0.83 – 1.04)	
Noninferiority p-value*	<0.0001	
Log-rank superiority p-value	0.2089	
Adjusted HR** (95% CI):	0.94 (0.84 – 1.05)	
Adjusted Noninferiority p-value**	<0.001	

Abbreviations: AC = pemetrexed plus cisplatin; CI = confidence interval; ECOG PS = Eastern Cooperative Group performance status; GC = gemcitabine plus cisplatin; HR = hazard ratio; ITT = intent to treat; mo. = months; N= total population size.
*Unadjusted HR and p-value from Cox model with treatment as the only cofactor.
**Adjusted HR and p-value from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological)

Kaplan-Meier graph of survival time by treatment group for all randomized patients: H3E-MC-JMDB:



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

Secondary efficacy endpoints

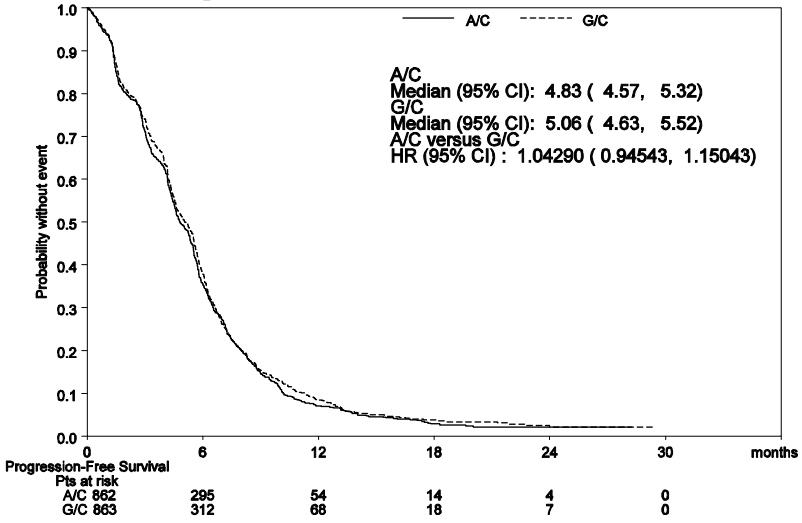
The table below summarises the results of the secondary efficacy endpoints of study JMDB.

Efficacy of Pemetrexed plus Cisplatin versus Gemcitabine plus Cisplatin in First-Line NSCLC ITT Population Study H3E-MC-JMDB

Secondary Efficacy Endpoints	AC (N=862)	GC (N=863)	Adjusted HR (95% CI)	Noninferiority p-Value
PFS				
Median, months	4.83	5.06	1.04	
(95% CI)	(4.57-5.32)	(4.63-5.52)	(0.95-1.15)	0.008
Objective PFS				
Median, months	5.22	5.36	1.06	
(95% CI)	(4.73-5.45)	(4.86-5.59)	(0.96-1.17)	0.019
TtPD				
Median, months	5.19	5.39	1.03	
(95% CI)	(4.73-5.45)	(4.96-5.59)	(0.93-1.14)	0.007
Objective TtPD				
Median, months	5.49	5.62	1.03	
(95% CI)	(5.29-5.62)	(5.49-5.78)	(0.92-1.15)	0.009
TtTF				
Median, months	4.44	4.53	1.05	
(95% CI)	(4.24-4.63)	(4.27-4.76)	(0.92-1.19)	0.050
Response*				
Response rate, %	30.6	28.2		
(95% CI)	(27.3-33.9)	(25.0-31.4)	—	—
Stable disease, %	41.2	45.8		
DoR*				
Median, months	4.50	5.09	1.14	
(95% CI)	(4.27-5.32)	(4.57-5.52)	(0.94-1.38)	0.362

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

Kaplan-Meier graph of progression-free survival time, all progressions without censoring on anticancer therapy, all randomized patients: H3E-MC-JMDB:



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

Progression-Free Survival – Sensitivity Analyses

Sensitivity analyses were conducted on PFS to investigate whether various event and censoring mechanisms for progressive disease had any impact on the interpretation of the PFS results. The main sensitivity analysis (SA1) addressed the potential impact of postdiscontinuation anticancer therapy. In the primary PFS analysis, postdiscontinuation anticancer therapy use was not considered even if it occurred prior to documentation of progression or death. To verify that postdiscontinuation anticancer

therapy did not affect the interpretation of the PFS results, this sensitivity analysis censored patients that received postdiscontinuation anticancer therapy prior to documented disease progression (clinical or objective) or death.

Progression-Free Survival, Sensitivity Analyses All Randomized Patients H3E-MC-JMDB

	Median PFS (95% CI)[a]		Adjusted HR[b]
	AC Arm	GC Arm	(95% CI)
Primary PFS Analysis	4.83 (4.57–5.32)	5.06 (4.63–5.52)	1.04 (0.94–1.15)
PFS Sensitivity Analysis			
SA1: All progressions, censored at date of PDT anticancer therapy	4.83 (4.57–5.32)	5.19 (4.70–5.52)	1.05 (0.95-1.17)

Abbreviations: AC = pemetrexed plus cisplatin; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine plus cisplatin; HR = hazard ratio; PDT = postdiscontinuation; PFS = progression-free survival; SA = sensitivity analysis.

a Unadjusted summary statistics.

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

Post discontinuation anticancer therapy (PDT) use

The table below provides a summary of the types of post discontinuation anticancer therapy received among all randomized patients. Approximately 50% of patients received post discontinuation systemic therapy in each arm.

Patients with any Postdiscontinuation Anticancer Therapy All Randomized Patients H3E-MC-JMDB

Anticancer Therapy[a]	AC (N=862)	GC (N=863)	p-Value[b]
Radiotherapy	273 (31.7%)	289 (33.5%)	0.441
Surgery	28 (3.2%)	26 (3.0%)	0.784
Any postdiscontinuation systemic treatment:	453 (52.6%)	484 (56.1%)	
Chemotherapy:			
Any line	358 (41.5%)	408 (47.3%)	0.018
1 lines	245 (28.4 %)	285 (33.0%)	0.042
2 lines	77 (8.9%)	98 (11.4 %)	0.111
3 or more lines	36 (4.2 %)	25 (2.9 %)	0.154
Targeted therapy	216 (25.1%)	196 (22.7%)	0.259
Immunotherapy	0	0	
Other	31 (3.6%)	37 (4.3%)	0.536

Abbreviations: AC = pemetrexed plus cisplatin; GC = gemcitabine plus cisplatin; N = number of randomized patients.

a Patients could have received more than 1 type of postdiscontinuation anticancer therapy as well as more than 1 type of postdiscontinuation systemic treatment.

b p-value is from Fisher's Exact test.

The post discontinuation systemic anticancer agents received were balanced between treatment arms, with the exception of post-pemetrexed or post-gemcitabine exposure. A very small percentage of patients were reported to receive the same drug (pemetrexed or gemcitabine) post discontinuation as was received according to randomized study treatment, and some patients crossed over to receive the opposite drug in post discontinuation treatment. Overall, fewer patients on the AC arm received post discontinuation systemic anticancer treatment (chemotherapy, targeted therapy, or immunotherapy) than patients on the GC arm (52.6% versus 56.1%), and significantly fewer patients on the AC arm received chemotherapy agents post discontinuation (41.5% versus 47.3%, p=0.018).

Less than 50% of patients in each group completed the 6 cycles of treatment (45.2% for the AC arm and 46.4% for the GC arm). 85.8% of planned mean dose of gemcitabine has been administered compared to 94.8% of pemetrexed, but this is acceptable since the figures are in line with clinical practice and previous studies. Active post-discontinuation treatments were given. The proportion of patients who switched after discontinuation of the initial treatment is not negligible in the context of a non-inferiority trial (16.7% of the AC group received gemcitabine and 13.4% of the GC group received premetrexed). However, the MAH has provided additional OS analyses excluding patients who switched and these analyses are reassuring and support non-inferiority (see below).

Additional efficacy analyses

1. Efficacy Using Randomized Protocol-Qualified Analysis Population:

Additional analyses were performed on the protocol-qualified (PQ) population, which includes patients who had eligible study disease, did not take prohibited anticancer therapy, had baseline lesions, and received at least 1 dose of study treatment. Of the 1725 patients randomized in this study, 1666 were qualified for the PQ analyses (838 patients in the AC arm and 828 patients in the GC arm).

Overall Survival
For the PQ population, the median OS time was 10.38 months for the AC arm and 10.45 months for the GC arm. Using the Cox regression adjusted model, the non-inferiority test of H_0 versus H_a was statistically significant (one-sided $p<0.001$), with the cofactor-adjusted survival HR estimated to be 0.94 (95% CI: 0.84 to 1.05). For sensitivity, an unadjusted estimate of the analysis of the survival HR was found to be similar (HR = 0.93; 95% CI: 0.83 to 1.04), with a non-inferiority p-value of <0.0001.

Progression Free survival:
- Unadjusted HR: 1.04279 (0.94432-1.15152), non-inferiority p=0.0086
- Adjusted HR: 1.04148 (0.94309-1.15015), non-inferiority p=0.008

Time to progressive disease:
- Unadjusted HR: 1.05100 (0.94574-1.16798), non-inferiority p=0.0181
- Adjusted HR: 1.03828 (0.93419-1.15398), non-inferiority p=0.010

Time-to-treatment failure:
- Unadjusted HR: 1.06126 (0.92777-1.21396), non-inferiority p=0.0665
- Adjusted HR: 1.05327 (0.92075-1.20486), non-inferiority p=0.053

2. Independently-Reviewed Progression-Free Survival:

A pre-planned limited independent central review of imaging for determination of objective progressive disease was conducted on a subset of 400 patients randomly selected from the first 1000 patients enrolled. The purpose of this independent review was to look for any evidence of a systematic bias in investigator assessments of progressive disease in terms of the relative efficacy of the 2 treatment arms. As pre-specified in the Statistical Analysis Plan, if the 2 estimates for HR were found to be similar, then there would be no significant bias from investigator-assessed data, and therefore an evaluation to assess agreement and discordance between independently reviewed and investigator-reviewed PFS would not be necessary. Of the 400 patients sampled for review, 333 had reviewable scans. The independent review of 333 patients was consistent with the overall investigator assessment of PFS.

Summary of Progression-Free Survival Time (Months) for Subset of Patients to be Independently Reviewed Investigator and Independent Assessments H3E-MC-JMDB

	Investigator Assessments (N=333)		**Independent Assessments (N=333)**	
	AC n=174	**GC** n=159	**AC** n=174	**GC** n=159
Minimum	0.23	0.30	0.23	0.30
25th percentile	3.06	3.48	1.68	1.91
Median	**5.59**	**5.62**	**4.37**	**4.90**
75th percentile	7.89	8.48	7.79	7.85
Maximum	24.67	29.40	25.72	27.86
Percent censored	5.17	5.03	8.05	7.55
Unadjusted HR* (95% CI)	1.12 (0.90-1.40)		1.07 (0.86-1.34)	
Unadjusted Noninferiority p-value*	0.3427		0.2107	
Adjusted HR** (95% CI)	1.13 (0.92-1.39)		1.11 (0.89-1.39)	
Adjusted Noninferiority p-value**	0.3530		0.3160	

Abbreviations: AC = pemetrexed plus cisplatin; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine plus cisplatin; HR = hazard ratio; N = number of patients in the population; n = number of patients in the treatment arm; PQ = protocol qualified.

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

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

3. Subgroup Analyses Defined by Baseline Characteristics

Preplanned subgroup analyses of OS were performed using Cox and Kaplan-Meier methods. Subgroups were analyzed separately as defined by the following factors: disease stage, performance status, sex, basis for initial pathological diagnosis, smoking status, age, ethnic origin, and NSCLC histology.

The effect on survival of AC relative to GC was similar for disease and patient characteristics; however, a differential effect on survival was seen within histologic groups.

Analysis of Overall Survival in Histologic Subgroups All Randomized Patients H3E-MC-JMDB

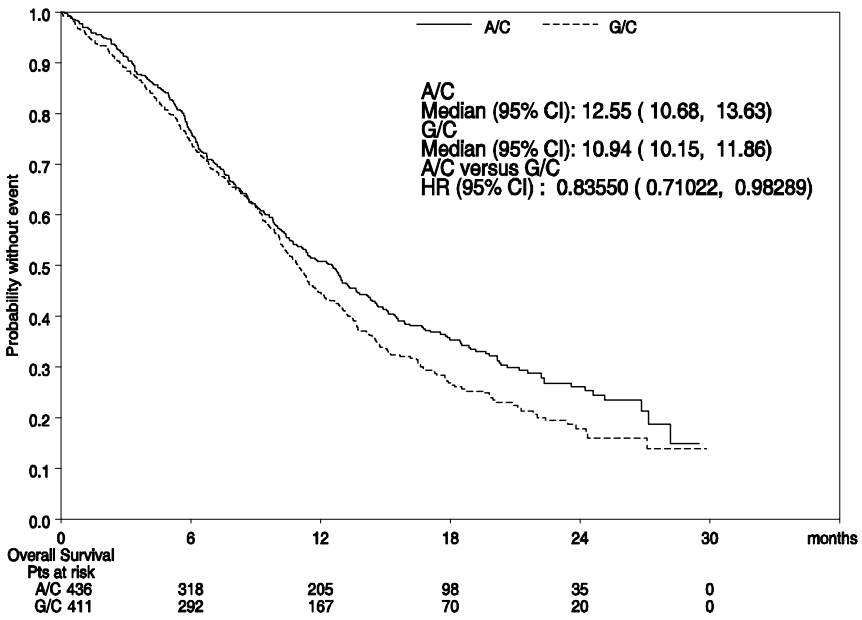
	Median OS (mo)	Adjusted HR[a] (95% CI)	NI p-value[a]	Sup. p-Value[a]
Adenocarcinoma (N=847)				
AC (n=436)	12.55	0.84 (0.71–0.99)	<0.001	0.033
GC (n=411)	10.94			
Large Cell (N=153)				
AC (n=76)	10.38	0.67 (0.48–0.96)	<0.001	0.027
GC (n=77)	6.67			
Squamous Cell (N=473)				
AC (n=244)	9.36	1.23 (1.00–1.51)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

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

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

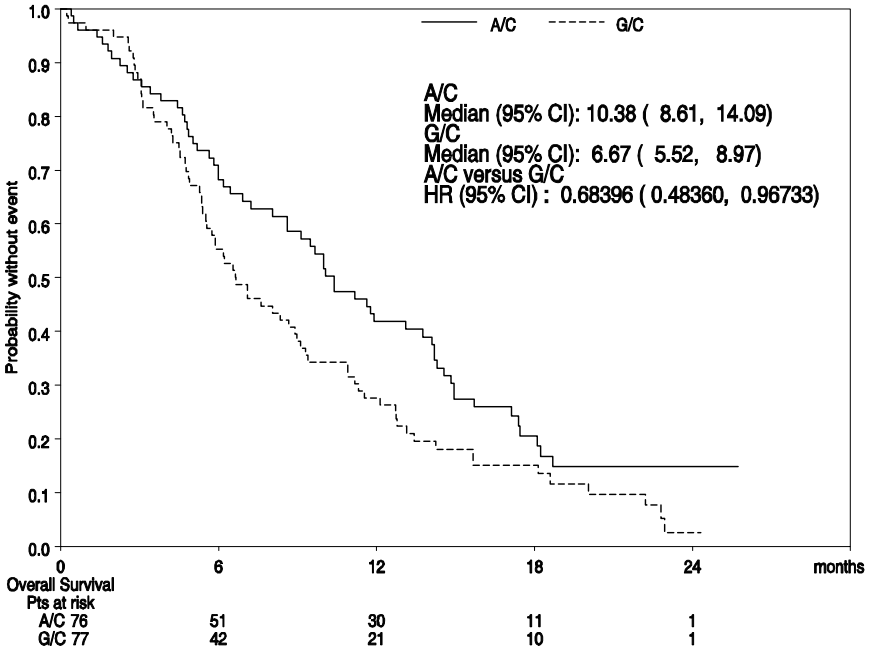
b The subcategory of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

Overall survival in adenocarcinoma subgroup (JMDB ITT population).



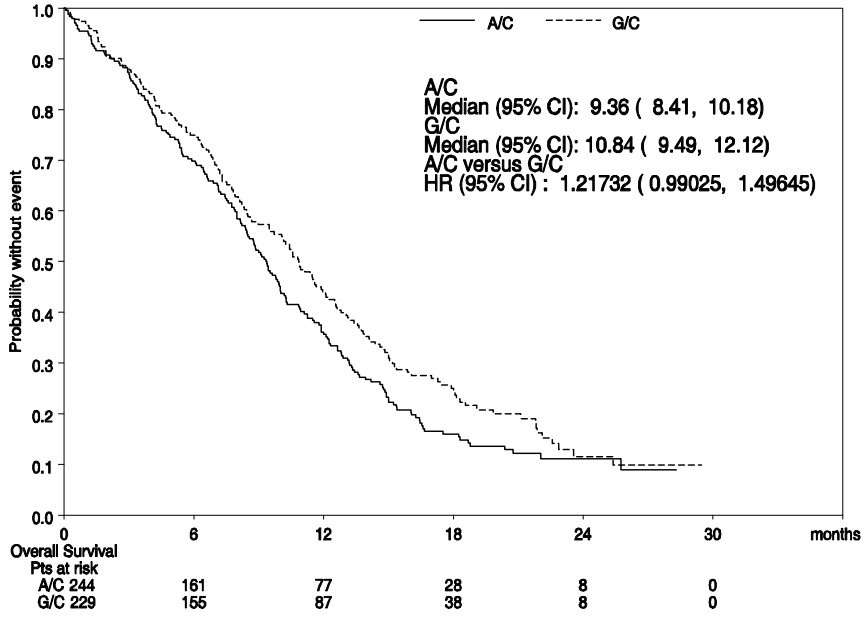
Abbreviations: A/C = pemetrexed plus cisplatin; CI = confidence interval; G/C = gemcitabine plus cisplatin; HR = hazard ratio; ITT = intent to treat; pts = patients.

Overall survival in large cell subgroup (JMDB ITT population).



Abbreviations: A/C = pemetrexed plus cisplatin; CI = confidence interval; G/C = gemcitabine plus cisplatin; HR = hazard ratio; ITT = intent to treat; pts = patients.

Overall survival in squamous cell subgroup (JMDB ITT population).



Abbreviations: A/C = pemetrexed plus cisplatin; CI = confidence interval; G/C = gemcitabine plus cisplatin; HR = hazard ratio; ITT = intent to treat; pts = patients.

After observing differences in the survival hazard ratios for adenocarcinoma, large cell, and squamous cell carcinoma subgroups, a statistical test was performed to assess whether a treatment-by-histology interaction was present.

Since there was the potential for imbalances between arms with respect to prognostic factors within histologic groups, this interaction test was performed using a Cox model of OS with main effects for assigned treatment arm, histology (adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and other histology as 3 indicator variables), and baseline cofactors of performance status (ECOG PS), disease stage, gender, and basis for pathological diagnosis, plus the treatment-by-histology interaction. The interaction was found to be statistically significant (p=0.0058), indicating that there was a significant treatment-by-histology interaction.

Evaluating this interaction as a two-level histology variable as squamous versus non-squamous also resulted in a significant interaction (p=0.0024).

In addition, analyses of PFS and response rate for histologic subgroups were generally consistent with the efficacy results shown on overall survival. There were trends for AC to perform better than GC in adenocarcinoma and large cell carcinoma. In squamous cell carcinoma, GC tended to perform better than AC for both PFS and response rate.

An analysis of overall survival with censoring at PDT was performed upon request by the CHMP, and the censoring rate was much higher for this analysis (74% for AC and 76% for GC) than was observed for PFS. The adjusted HR for this analysis (n=1722) was 1.06 (95% CI: 0.90 to 1.24), and the median survival was 14.2 months for AC versus 13.6 months for GC. With such a high censoring rate, in this case greater than 70%, this analysis is not informative and therefore no conclusions can be drawn, as the estimates are based on very few events.

The table below shows the analyses of overall survival excluding patients who crossed over to the alternate treatment (pemetrexed plus cisplatin [AC] to gemcitabine-containing therapy [G] or gemcitabine plus cisplatin [GC] to pemetrexed-containing therapy [A]), received drug-based post-discontinuation therapy (PDT), and did not receive any drug-based PDT, for the combined subgroups of adenocarcinoma and large cell carcinoma.

Subgroup Analyses of Overall Survival, Based on Systemic PDT Use
All Randomized Patients with Adenocarcinoma or Large Cell Carcinoma.
Intent-to-Treat Analysis H3E-MC-JMDB

	Number of patients with Adenocarcinoma or Large cell carcinoma	AC Median (months)	GC Median (months)	AC vs GC Adj. HR (95% CI)
Overall Population (n=1725)	n=1000	11.83	10.38	0.81 (0.70, 0.94)
Excluding Patients who crossed-over from AC to G or GC to A (n=1465)	n=839	10.38	9.33	0.84 (0.72, 0.99)
Received systemic PDT (n=936)	n=579	15.57	13.01	0.75 (0.62, 0.92)
Did not receive systemic PDT (n=789)	n=421	6.34	6.21	0.83 (0.67, 1.03)

Abbreviations: A = pemetrexed-containing therapy; AC = pemetrexed plus cisplatin; CI = confidence interval; G = gemcitabine-containing therapy; GC = gemcitabine plus cisplatin; HR = hazard ratio; n = number of patients; PDT = postdiscontinuation therapy.

As shown above, the combined subgroups of patients with adenocarcinoma and large cell carcinoma showed a survival advantage for patients treated with Alimta in all categories. The results were consistent, with superiority of survival of AC over GC in nearly all analyses, except for the group of patients who did not receive PDT. In the subset of patients who did not receive PDT, the smaller medians likely reflect the poorer survival of this group of patients; they may not have lived long enough to have had the opportunity to receive PDT. In each of these analyses, the hazard ratio favours AC, and the upper CI is well below the non-inferiority margin of 1.17647.

During the procedure, the CHMP also requested the analyses above be provided for the Protocol-Qualified (PQ) population.

Subgroup Analyses of Overall Survival, Based on Systemic PDT Use All Randomized Protocol-Qualified Patients with Adenocarcinoma or Large Cell Carcinoma Protocol Qualified Analysis H3E-MC-JMDB

	Number of patients with Adenocarcinoma or Large cell carcinoma	AC Median (months)	GC Median (months)	AC vs GC Adj. HR (95% CI)
Overall Population (n=1666)	n=972	11.86	10.48	0.81 (0.70-0.95)
Excluding Patients who crossed-over from AC to G or GC to A (n=1413)	n=815	10.41	9.43	0.84 (0.72, 0.99)
Received systemic PDT (n=921)	n=571	15.57	13.01	0.75 (0.62, 0.92)
Did not receive systemic PDT (n=745)	n=401	6.34	6.41	0.83 (0.66, 1.04)

Abbreviations: A = pemetrexed-containing therapy; AC = pemetrexed plus cisplatin; CI = confidence interval; G = gemcitabine-containing therapy; GC = gemcitabine plus cisplatin; HR = hazard ratio; n = number of patients; PDT = postdiscontinuation therapy.

Discussion on Clinical Efficacy

In the pivotal Study JMDB, patients were randomized to receive 6 cycles of pemetrexed plus cisplatin (AC) or gemcitabine plus cisplatin (GC) combination therapy, as follows:

Experimental Arm A: pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on Day 1 every 21 days.

Control Arm B: gemcitabine 1250 mg/m^2 on Day 1 and Day 8 plus cisplatin 75 mg/m^2 on Day 1 every 21 days.

Demographic and tumour characteristics at baseline were well balanced: a total of 1725 patients were enrolled into the study. Of the enrolled patients, 862 patients were randomized to the AC arm, and 863 patients were randomized to the GC arm. Approximately 70% of the patients were men. The median age of 61 years with a wide age range (26 years to 83 years). At study entry, 24% of patients had Stage IIIB disease and approximately 76% of patients had Stage IV disease. Approximately 36% of patients had an ECOG performance status (PS) of 0, and 64% of patients had an ECOG PS of 1. The arms were well balanced with respect to these well-established prognostic factors, as well as age, history of tobacco use, and histological type (adenocarcinoma about 50%, squamous cell carcinoma about one third, large cell carcinoma about 8%, and other histologies about 15%).

The primary efficacy analysis was a non-inferiority analysis of Overall Survival (OS) for patients treated with AC compared to patients treated with GC based on the ITT population. A non-inferiority fixed margin of 1.17647 was used, which corresponded to GC having a 15% lower hazard than that of AC, and was tested at a one-sided 0.025 alpha level.
This non-inferiority margin may appear large and does not exclude a significant disadvantage when using pemetrexed in the claimed indication. However, a significant tightening of this margin would have resulted in an unrealistic increase in the sample size. More importantly, this margin has to be interpreted in the light of the point estimate and taking into account the respective safety profiles of the compared regimens.

The median OS time was 10.28 months for both treatment arms. The 1 and 2-year survival rates were 43.48% and 18.94%, respectively, for the AC arm and 41.94% and 13.98%, respectively, for the GC arm.

Main efficacy results – study JMDB - ITT Population:

	ALIMTA + Cisplatin (N=862)	Gemcitabine + Cisplatin (N=863)
Median overall survival (95% CI) monts	10.3 (9.8-11.2)	10.3 (9.6-10.9)
Adjusted hazard ratio (HR) (95% CI)	0.94 (0.84-1.05)	
12 month survival probability (95% CI)	43.5% (40.1-46.9)	41.9 % (38.5-45.4)
24 month survival probability (95% CI)	18.9% (15.7-22.2)	14.0% (10.9-17.1)
Median progression free survival (95% CI) months	4.8 (4.6-5.3)	5.1 (4.6-5.5)
Adjusted hazard ratio (HR) (95% CI)	1.04 (0.94-1.15)	
Overall response rate[b] (95% CI)	30.6%(27.3%-33.9%)	28.2% (25.0%-31.4%)

Using the Cox regression adjusted model for the primary analysis, the primary non-inferiority test was statistically significant (one-sided p<0.001), with the primary cofactor-adjusted survival HR estimated to be 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval for HR well below the 1.17645 non-inferiority margin.
The unadjusted estimate of the survival HR was HR = 0.93; 95% CI: 0.83 to 1.04, with a non-inferiority p-value of <0.001.

Thus, study JMDB demonstrated non-inferiority of AC as compared to GC in terms of overall survival when administered as first line treatment in patients with advanced unresectable or metastatic (stage IIIB or IV) NSCLC. The result is rather robust and mature. Reassuring is, in addition, a trend towards improved OS for AC at the end of the Kaplan-Meier curve.
Further, the overall result with reference to the primary endpoint is reflected also in the results for the secondary efficacy endpoints.

As study JMDB is a non-inferiority study, efficacy analyses need to be based on the protocol-qualified (PQ) population. In study JMDB, the primary efficacy analysis was based on the ITT population. Sensitivity analyses of main efficacy endpoints were also assessed on the PQ population. The efficacy analyses using the PQ population follow the same trend as the efficacy analyses for the ITT population and support the non-inferiority of AC versus GC.

However, although this non-inferior efficacy has been demonstrated in the overall group of patients with NSCLC, pre-planned subgroup analyses showed that a qualitative interaction exists between NSCLC histology and treatment effect, with a benefit of AC in patients with adenocarcinoma or large cell carcinoma, and a benefit of GC in patients with squamous cell carcinoma.

Summary of Overall Survival (Months) by Histology Subgroups ITT Population H3E-MC-JMDB

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

Regarding patients with squamous cell carcinoma, the non-inferiority of AC has not been demonstrated as the upper side of the 95% CI exceeds the non-inferiority margin of 1.17647,

suggesting that AC is inferior to GC. Considering that patients with a squamous cell carcinoma histological subtype represent one third of the patients in both arms (453/1725), the efficacy results preclude an indication of AC in this population.

Regarding patients with adenocarcinoma and large cell carcinoma, the non-inferiority of AC was demonstrated, as the upper side of the 95% CI for these populations falls well below the non-inferiority margin of 1.17647. The additional sensitivity analyses on OS provided by the MAH during the procedure also confirm the previously demonstrated non-inferiority of AC vs. GC in patients with adenocarcinoma and large cell carcinoma histologies. They also provide reassurance that non-inferiority is not due to post-discontinuation treatment.

Clinical Safety

In the pivotal JMDB study, the safety profile of AC in NSCLC was consistent with the known safety profile of AC in mesothelioma. In terms of safety, AC can be considered as slightly safer than GC taking into account the better haematotoxicity profile and the slightly worse nephrotoxicity profile of AC vs. GC. There were no clinically relevant differences observed for the safety profile of ALIMTA plus cisplatin within the histology subgroups.

A total of 3648 cycles of AC were administered to 839 patients in the AC arm, and 3626 cycles of GC were administered to 830 patients in the GC arm. A median of 5 cycles of therapy was administered to patients in both arms.
Dose adjustments (delays, reductions, and omissions) were less frequent in patients treated with AC compared to patients treated with GC.
The total number of dose delays (any reason) reported was 815 in the AC arm, and 929 in the GC arm. Scheduling conflict was the most commonly reported reason for dose delays in both treatment arms (486 in the AC arm and 514 in the GC arm). In both treatment arms, the most commonly reported adverse events resulting in dose delays were neutropenia (138 in the AC arm and 188 in the GC arm) and anaemia (25 in the AC arm and 43 in the GC arm).
In the AC arm, the most common reasons for dose reductions were neutropenia (17 for pemetrexed and 17 for cisplatin), fatigue (6 for pemetrexed and 8 for cisplatin), nausea (5 for pemetrexed and 8 for cisplatin), and febrile neutropenia (5 for pemetrexed and 5 for cisplatin).
In the GC arm, the most common reasons for dose reductions were neutropenia (184 for gemcitabine and 59 for cisplatin), thrombocytopenia (82 for gemcitabine and 37 for cisplatin), and febrile neutropenia (15 for gemcitabine and 12 for cisplatin). Dose omissions were permitted per protocol only for Day 8 gemcitabine.

Table JMDB.12.10. Overview of Adverse Events By Treatment Group All Patients Who Received Study Drug H3E-MC-JMDB

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

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

Treatment Emergent Adverse Events (TEAEs)

The percentage of patients experiencing any possibly study-drug related TEAEs (reported in ≥10% of all randomized and treated patients) was similar in both treatment arms: 751 patients (89.5%) in the AC arm and 755 patients (91.0%) in the GC arm. In both treatment arms, the most commonly reported possibly study-drug related TEAEs were anaemia, neutropenia, nausea, vomiting, and fatigue. The GC arm had more categories of TEAEs that were statistically higher as compared to the AC arm. Patients in the GC arm experienced statistically significantly more anaemia, neutropenia, thrombocytopenia, fatigue, pyrexia, febrile neutropenia, alopecia, hypokalaemia, neuropathy, peripheral sensory neuropathy, tinnitus, and epistaxis than patients on the AC arm.
Eye disorders as a whole (mostly conjunctivitis and increased lacrimation), acute renal failure, dry skin, and pigmentation disorder occurred in significantly more patients on the AC arm.

Serious Adverse Events (SAEs)

139 patients in the AC arm (16.6%) and 136 patients in the GC arm (16.4%) experienced possibly related SAEs. Possibly study-drug related serious febrile neutropenia and pyrexia occurred statistically significantly more often in the GC arm, whereas anorexia and acute renal failure occurred statistically more often in the AC arm. 12 patients in the AC arm and 6 patients in the GC arm had a possibly study-drug related renal-failure SAE.
In the AC arm, 11/12 cases presented evidence of gastrointestinal toxicity and/or dehydration prior to developing renal failure, and 6/12 cases presented pre-existing conditions and historical illnesses associated with renal impairment.
The nature and severity of the acute renal failure seen in the AC arm of this study is consistent with the known safety profile of the combination as described in the current product information. Renal failure was primarily pre-renal in nature due to dehydration induced by gastrointestinal toxicity or sepsis.

Table JMDB.12.14. Summary of Selected Serious Adverse Events Possibly Related to Study Drug Patients Who Received Study Drug H3E-MC-JMDB

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

Note: Table JMDB.12.14 summarizes the possibly study-drug related SAEs that were experienced by >=2% of patients or were statistically significantly different between study arms or were otherwise clinically significant.

Discontinuation

15 patients (1.8%) in the AC arm and 23 patients (2.8%) in the GC arm discontinued study treatment due to SAEs that were considered to be possibly related to the study drug. Except for cerebrovascular

accident (AC: 0.1%, GC: 0.8%; p=0.038), there were no significant differences in the numbers of patients who discontinued study drug, regardless of causality, between treatment arms.
57 patients (6.8%) in the AC arm and 60 patients (7.2%) in the GC arm discontinued due to non serious, clinically significant adverse events considered to be possibly related to the study drug.
Among the discontinuations possibly related to the study drug, increased blood creatinine caused significantly more discontinuations in the AC arm than in the GC arm (p=0.004). Haematologic toxicity (anaemia, thrombocytopenia, and neutropenia) caused more discontinuations in the GC arm than in the AC arm.

Grade 3/4 toxicities

Patients in the GC arm experienced statistically significantly more Grade 3 and 4 laboratory toxicities than patients in the AC arm (39.9% versus 22.6%, p<0.001). In both treatment arms, the most frequently reported Grade 3/4 toxicity was neutropenia, which was reported in statistically significantly more patients in the GC arm than in the AC arm (26.7% versus 15.1%, p<0.001). Other Grade 3/4 toxicities experienced by significantly more patients in the GC arm than in the AC arm were also haematologic and included anaemia (9.9% versus 5.6%, p<0.001), leucopenia (7.6% versus 4.8%, p<0.001), and thrombocytopenia (12.7% versus 4.1%, p<0.001).
When CTC Grades 1 through 4 are considered, the incidence of elevated creatinine is statistically significantly higher in the AC arm than in the GC arm (10.1% versus 6.9%, p=0.018).

Overall, patients in the GC arm experienced similar Grade 3 and 4 non-laboratory toxicities as patients in the AC arm (23.5% versus 21.5%, p=0.320).
Patients in the AC arm experienced statistically significantly more study-drug related Grade 3/4 anorexia (2.4% versus 0.7%, p=0.009) and nausea (7.2% versus 3.9%, p=0.004).
Possibly study-drug related Grade 3/4 febrile neutropenia occurred in statistically significantly more patients in the GC arm than in the AC arm (3.7% versus 1.3%, p=0.002).

Deaths

A total of 116 on-therapy deaths were reported: 63 deaths in the AC arm and 53 deaths in the GC arm. These events are categorized as due to study disease, possibly related to study-drug toxicity, and due to other causes. For any category, the difference in the number of deaths was not statistically significant between study arms.
In the AC arm, 9 on-therapy deaths were considered by the investigator to be possibly due to study-drug toxicity, whereas in the GC arm, 6 on-therapy deaths were considered by the investigator to be possibly due to study-drug toxicity.
There were 61 cases of deaths due to other causes, 31 on the AC arm and 30 on the GC arm. Overall, the most commonly reported reasons for deaths due to other causes were pulmonary events and cardiac events.
A total of 27 deaths were reported within 30 days of last study drug dose: 13 deaths in the AC arm and 14 deaths in the GC arm.
A review undertaken by the MAH of patient summaries found possibly study-drug related causes for death in 1 additional patient in the AC arm and 4 additional patients in the GC arm, for a total of 10 deaths possibly due to study-drug toxicity in each arm.

Table JMDB.12.12. Summary of Deaths (On-Therapy or within 30 Days of Last Study Drug Dose)
Patients Who Received Study Drug
H3E-MC-JMDB

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

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

Pharmacovigilance

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

Risk Management Plan

The MAH submitted a 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	• 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
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

Overall, the safety profile of AC in NSCLC was consistent with the known safety profile of AC in mesothelioma. In terms of safety, AC can be considered as slightly safer than GC taking into account the better haematotoxicity profile and the slightly worse nephrotoxicity profile of AC vs. GC. There were no clinically relevant differences observed for the safety profile of ALIMTA plus cisplatin within the histology subgroups.

The GC arm presented a statistically higher hematological toxicity as compared to the AC arm responsible for discontinuation and Grade 3/4 toxicities.
On the other hand, renal toxicity was numerically higher in the AC arm compared to GC arm.
Despite the overall higher toxicity in the GC arm than in the AC arm, the death cases in the AC arm are of great interest, reflecting the known safety profile of the pemetrexed/cisplatin regimen: more deaths due to infection (2 septic shock, 1 sepsis and 1 neutropenia) in the AC arm as compared to GC

arm (1 septicemia); death due to gastro-intestinal toxicity (sigmoides perforation and bleeding gastric); death related to renal toxicity (renal failure and elevated creatinine and urea levels).
Further, although reported as unrelated to the study drug, the 14 death cases classified as pulmonary causes are of great interest, although these were similar in number to the 9 death cases classified as pulmonary causes reported on the GC arm. There were no statistically significant differences between the AC and GC arms in terms of number of deaths reported for study disease, drug toxicity, or "other causes."
The cases of death reported among the 'on-therapy deaths' in the AC arm are in accordance with the seriousness of adverse events mentioned in the SPC of Alimta, and consistent with the known safety profile of pemetrexed when combined with cisplatin.

Pharmacovigilance

The severity of toxicities (grade 3 and 4 ALT and AST elevations, thrombocytopenia, and rash) which were higher in the pemetrexed arm (in study JMEI) will be closely monitored and reported within future PSURs.

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.

A 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

Lung cancer is among the most frequent type of cancer among European men and women and is one of the few that continues to show an increasing incidence. Non small cell lung cancer (NSCLC) accounts for the vast majority of lung cancers (80%). 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.
The current standard of first-line treatment in patients with advanced disease consists of platinum-based doublet regimens (combination of gemcitabine, vinorelbine, doectaxel, or paclitaxel with cisplatin or carboplatin) where 1-year survival rates of 33% and 2-year survival rates of 11% have been reported.

This application for a type II variation to extend the indication of Alimta to include first line treatment of patients with locally advanced or metastatic NSCLC is supported by a well-managed and well-analysed pivotal non-inferiority phase III trial, JMDB.

Study JMDB demonstrated non-inferiority of AC as compared to GC in terms of overall survival when administered as first line treatment in patients with advanced unresectable or metastatic (stage IIIB or IV) NSCLC. The result is rather robust and mature. In addition, a trend towards improved OS for AC at the end of the Kaplan-Meier curve is reassuring.
The overall result with reference to the primary endpoint is reflected also in the results for the secondary efficacy endpoints.

In study JMDB, the primary efficacy analysis was based on the ITT population. Sensitivity analyses of main efficacy endpoints were also assessed on the protocol-qualified (PQ) population. The efficacy analyses using the PQ population follow the same trend as the efficacy analyses in the ITT population and support the non-inferiority of AC versus GC.

In terms of safety, AC can be considered as slightly safer than GC taking into account the better haematotoxicity profile (statistically significantly different) and the slightly worse nephrotoxicity profile of AC vs. GC.

As the comparator GC is a widely accepted standard treatment in advanced NSCLC, it could have been concluded that the benefit/risk assessment of AC in the overall population of NSCLC patients is positive. However, the sub-group analyses of the treatment effect by histology revealed a strong signal.

Retrospective sub-group analyses of two preceding trials investigating pemetrexed as monotherapy in second line treatment of NSCLC (Studies JMEI and NS01, the first part of the original MAA and the second a randomised, dose-optimising trial discussed above) indicated lower efficacy of Alimta in the histological sub-group squamous cell carcinoma. Furthermore, the prospectively planned sub-group analysis by histology of trial JMDB confirmed lower efficacy also in the context of the combination treatment. Similarly, analyses in Studies JMEI and NS01 indicated higher efficacy of Alimta in patients with NSCLC other than predominantly squamous cell histology, and the prospectively planned subgroup analysis in JMDB confirmed higher efficacy for AC in this population .

Therefore, the CHMP concluded that the benefit/risk ratio of AC in squamous cell NSCLC is clearly negative since GC offered prolonged survival compared to AC. However, the benefit/risk ratio in the remainder NSCLC population without predominantly squamous cell histology, i.e. in patients with adenocarcinoma or large cell NSCLC, is clearly positive, where AC offers prolonged survival compared to GC.

In view of the outcome of the CHMP's benefit/risk assessment, the MAH proposed during the procedure to limit the current second line monotherapy indication accordingly and the following final wording of the NSCLC indication in section 4.1 of the SPC was agreed:

"Non-small cell lung cancer

ALIMTA in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1).

ALIMTA is indicated 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 (see section 5.1)."

Section 5.1 of the SPC has been updated to reflect the results of the pivotal study JMDB in first line NSCLC. In addition, the information regarding second line NSCLC has been updated and a statement added to reflect the results of study JMGX investigating the efficacy of pemetrexed after first line treatment with docetaxel.

As the posology of the newly studied combination treatment in first line NSCLC is the same as the posology already granted for the treatment of mesothelioma, and in view of the experience gained in Study JMDB and the post-marketing setting with Alimta, the MAH proposes to provide in section 4.2 of the SPC a single dosage recommendation for the use of Alimta in combination with cisplatin as well as a single table for dose modifications applicable to both monotherapy and combination treatment.
In addition, Common Toxicity Criteria have been clarified in section 4.2 and section 4.8 of the SPC and section 4 of the Package Leaflet for all indications.

All the proposed consequential changes to sections 4.2, 4.4, 4.8 and 5.1 of the SPC and the Package Leaflet can be agreed.

In addition, the MAH took the opportunity to include a minor clarification in section 4.5 regarding concomitant use with yellow fever vaccine and to make minor editorial changes to the SPC and Package Leaflet and these changes are acceptable.

During the procedure, the MAH also submitted the results of user testing of the Package Leaflet and these results were reviewed by the Committee and considered acceptable.

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. However, the severity of toxicities (grade 3 and 4 ALT and AST elevations, thrombocytopenia, and rash) which were higher in the pemetrexed arm (in study JMEI) will be closely monitored and reported within future PSURs.

A 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.

The MAH has updated annex IIB to reflect the latest Pharmacovigilance system (version 2.0) and Risk Management Plan (version 1.2) approved by the CHMP, which is acceptable.

IV. CONCLUSION

On 21 February 2008 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.