SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Alimta. For information on changes after approval please refer to module 8.

Introduction

Malignant pleural mesothelioma

Malignant mesothelioma is a rare tumour affecting mesodermal tissue and whose origin has generally been linked to asbestos exposure. The incidence of malignant pleural mesothelioma has increased steadily since the 1950s and coincides with both the widespread industrial use of asbestos in developed countries and with a highly increased incidence of pleural mesothelioma in men, in Canada [1], the United Kingdom [2], and the United States [3]. Before this time, the incidence was similar in men and women [2]. In addition, asbestos exposure occurs environmentally in certain regions of Turkey, where it is used extensively in building materials [4]. In Turkey, the disease tends to be more equally distributed by gender.

Pleural mesothelioma usually becomes clinically evident by symptoms such as dyspnoea or chest pain from the pleura, chest wall, or *mediastinum*. At the time such symptoms occur, the disease is often locally advanced. The most common sites of origin are the pleura, accounting for 80% of cases, followed by *peritoneum*, *pericardium*, and *tunica vaginalis testis* [5]. Survival of untreated patients is poor, with a median survival time ranging from 6 to 8 months, though the range may be much wider, depending on the characteristics and selection of the population of mesothelioma patients [6]. A number of factors, including histological subtype (epithelial origin as a good prognostic factor), performance status, disease extent at baseline, presence of chest pain, gender, and white blood cell count (WBC), among others, have been suggested as predictors of outcome [7, 8].

Neither surgery nor radiotherapy generally results in increased survival [6]. At the time of submission of the marketing authorization application for Alimta, no approved systemic therapy existed for malignant pleural mesothelioma. In single agent Phase 2 studies response rates seldom exceed 20% [9-18]. Single-arm Phase 2 studies of different combination regimens have demonstrated large variations in response rates [19]. Randomized studies have shown that systemic combination therapy results in somewhat higher response rates than single agent therapy. No significant differences in survival, however, have been observed [20, 21].

Non-small cell lung cancer

Lung cancer is one of the most common malignancies and continues to rise in incidence. One million new cases and over 900,000 lung cancer-related deaths are reported each year worldwide. It is the leading cause of cancer death in men and the third leading cause in women [22]. Almost 80% of lung cancers are classified as non-small cell lung cancer (NSCLC), with 65% to 75% of cases presenting as locally advanced (stage III) or metastatic disease (stage IV) [23-25].

Inoperable patients diagnosed with stage III NSCLC generally receive chemotherapy as part of standard multimodality treatment. stage IIIb and IV patients typically receive chemotherapy alone as first-line therapy. The consensus of chemotherapy in these patients is a platinum-containing regimen. However, the median survival in first-line therapy is approximately 7.9 months, with a 12-month median survival proportion of 33% [26].

Approximately half of the patients treated with a first-line combination regimen will receive single-agent chemotherapy as second-line treatment. Several chemotherapeutic agents were evaluated in phase 2 trials in the second-line setting. Tumour response rates vary from study-to-study. New agents, such as gemcitabine, showed tumour response rates ranging from 0 to 21% [27], while paclitaxel showed a tumour response rate ranging from 0 to 25% depending on various doses, schedules, and patient characteristics [21, 28]. Docetaxel has the largest Phase 2 and Phase 3 experience as a single-agent in second-line NSCLC. In different Phase 2 trials, single-agent docetaxel was given as second-line treatment to 215 patients, and tumour response rate ranged from 10% to 25% with a median survival time from 7.0 to 9.7 months [27].

Two randomized Phase 3 studies of docetaxel were completed. The first trial compared docetaxel 100 mg/m^2 or 75 mg/m^2 with best supportive care (BSC) [29]. Five deaths in the first 49 enrolled patients in the 100 mg/m^2 arm led to discontinuation of this treatment arm. In the 75 mg/m^2 arm docetaxel arm, 7% of the patients had a partial response, with a median survival time of 7.5 months compared with a median survival time of 4.6 months for the patients in the BSC arm (log rank, *P*=0.010). The second trial compared docetaxel with vinorelbine or ifosfamide [30]. A total of 373 patients were randomly assigned to receive docetaxel 100 mg/m^2 or 75 mg/m^2 compared with a control regimen of vinorelbine or ifosfamide. The overall response rate was 10.8% with 100 mg/m^2 docetaxel and 6.7% with 75 mg/m^2 docetaxel. These response rates were each significantly higher than treatment with vinorelbine or ifosfamide (0.8%). The 1-year survival rate in the docetaxel arm was significantly better at 32% compared with 19% in the ifosfamide/vinorelbine arm. However, overall survival time was not significantly different among the groups.

About the product

Pemetrexed disodium (pemetrexed, also referred to during the development as LY231514, multitargeted antifolate, MTA, or Alimta), is a novel pyrrolo[2,3-d]pyrimidine-based folic acid analogue (temporary ATC code: L01BA04). In in vitro studies, pemetrexed inhibited multiple folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase) crucial in the de novo biosynthesis of thymidine and purine nucleotides. Once transported into cells, pemetrexed is rapidly polyglutamated by folylpolyglutamate synthetase, a process that appears to occur more readily in tumour cells than in normal cells. Polyglutamate forms of pemetrexed are retained longer in cells and are more potent inhibitors of thymidylate synthase and glycinamide ribonucleotide formyltransferase than the base compound.

1. Part II: Chemical, pharmaceutical and biological aspects

Composition

Alimta is presented as a sterile single use powder for concentrate for solution for infusion. Each vial contains 500 mg of pemetrexed as pemetrexed disodium. It must be reconstituted with 20 ml sodium chloride 9 mg/ml (0.9 %) solution for injection without preservative. The appropriate volume of required dose is removed from the vial and further diluted to 100 ml with the same diluent.

The other ingredients include mannitol, hydrochloric acid, sodium hydroxide, and nitrogen, low-oxygen.

Alimta is packed in type I clear glass vial closed with a rubber stopper and an aluminium seal with flip-cap.

Active substance

Pemetrexed, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo [2,3-d] pyrimidin-5-yl) ethyl]benzoyl]-L-glutamic acid disodium salt, is a white to almost white freely water soluble solid. It contains a single chiral centre, and is synthesised as the single L-isomer.

Two crystalline hydrate forms of pemetrexed have been identified.

Stress stability studies have shown that the two main degradation pathways for pemetrexed in solid state and in solution are oxidation and hydrolysis.

- Manufacture

Pemetrexed is synthesised from commercially available starting materials. The starting material introducing the active substance chiral centre is controlled for chirality and adequate conditions for the subsequent steps have been set up in order to avoid racemization. Satisfactory in process controls and controls on key intermediates have been established in order to ensure production of an active substance of consistent quality.

- Specification

The active substance specification include tests for appearance, identity, assay, impurities, chiral purity, residual solvents, heavy metals, bacterial endotoxins (PhEur), total aerobic microbial count (PhEur), mold-yeast count (PhEur), water content, pH, colour of solution (PhEur) and clarity of solution (PhEur).

The hydrate form is controlled by water control determination. The formation of the desired isomer of pemetrexed is ensured through chirality control of the key starting material and through the route of synthesis. Moreover, there is a specific limit for the D-isomer.

The specification limits have been adequately justified based on the physico chemical properties of the drug substance and based on batch analysis and stability data of pemetrexed lots used in non-clinical and clinical studies. The analytical methods used in routine controls have been suitably described and validated.

Batch analysis data provided for 5 full-scale batches confirm satisfactory compliance and uniformity with the proposed specifications.

- Stability

Stability data have been provided for 3 full-scale primary stability batches synthesised at the commercial sites. Under accelerated conditions (40°C/75% RH – commercial packaging) and long-term conditions (25°C/60%% RH - commercial packaging), respectively 6-month and 3-year data have been provided. The photostability study performed did not show any significant change in the main stability indicating parameters.

A retest period of 36 months is supported by the presented data when pemetrexed is stored in the commercial packaging

Product development and finished product

A dry powder formulation has been chosen. The pH of the in-process solution was selected based on solubility and stability data. Pemetrexed water solubility is greater than 90 mg/ml at 20°C in pH range of 6.0-10.0.

All the excipients selected are of PhEur quality. Mannitol is present in the formulation as a bulking agent to produce an elegant lyophilisate. Compatibility and acceptability for its use in the drug product has been satisfactorily demonstrated. The pemetrexed filling overage included to compensate vial and syringe retentions is suitable to allow withdrawal and delivery of the labeled dose. Regarding the TSE risk, Alimta does not contain any component of ruminant origin.

The type I glass vials and the rubber stopper used as primary packaging material, as well as the dimethicone used to treat the stoppers, meet the PhEur requirements. Before reconstitution, no incompatibility between the stopper and the finished product has been reported during stability studies. After reconstitution, compatibility of the stopper with the finished product has been satisfactorily addressed from primary stability studies (vials stored in upright and inverted positions). In addition, development studies have evaluated potential extractable from the stopper.

Compatibility of pemetrexed with common i.v. solutions, i.v. bags and administration sets has been evaluated. The drug product is compatible with sodium chloride 9 mg/ml (0.9 %) solution for injection without preservative, but it is incompatible with diluents containing calcium including Ringer's Injection or Lactated Ringer's Injection. The drug product reconstituted and further diluted with sodium chloride 9 mg/ml (0.9 %) solution for injection without preservative is compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags.

The rationale for a sterile filtration followed by an aseptic process has been satisfactorily discussed; the product is sensitive to terminal sterilisation methods.

The manufacturing process was developed to minimize oxidative degradation by reducing exposure of pemetrexed solution to oxygen and upon completion of lyophilization cycle the vacuum is neutralized with sterile filtered nitrogen thus controlling the oxygen level in the drug product vial headspace.

Different variants of a terminally sterilised solution formulation and of the dry powder formulation have been used in clinical trials. They can be all considered as bioequivalent.

- Manufacture of the Product

The manufacturing process involves the following operations: preparation of the bulk solution, sterile filtration, aseptic filling in vials, lyophilization, stoppering and sealing.

Satisfactory in-process controls and holding times/conditions for specific phases of the process have been defined in order to ensure control of the microbiological, chemical and physical attributes of the product.

Process validation data have been provided for three full-scale consecutive batches manufactured at the proposed commercial manufacturing site.

- Product Specification

The product specification includes tests controlled by validated methods for appearance, identity, assay, impurity content, uniformity of mass (PhEur), particulate matter (PhEur), pH (PhEur), water content, reconstitution time, colour of solution (PhEur), clarity of solution (PhEur), oxygen headspace content, sterility (PhEur) and bacterial endotoxins (PhEur).

Batch analysis data provided for one full-scale batch and four half-scale batches manufactured at the proposed commercial manufacturing site comply with the specifications and indicate consistent and reproducible manufacture.

Stability of the product

Stability of the Product before reconstitution: Stability data under long-term (25°C/60%RH - packaging intended for commercialisation) and accelerated conditions (40ºC/75%RH – packaging intended for commercialisation) have been provided for three primary stability batches manufactured at the commercial manufacturing site. Supporting stability studies have been provided for seven batches under long term and under accelerated conditions. Samples have also been stored under stress conditions (excessive heat and humidity, temperature cycling). Photostability studies have shown that the drug product is non-light sensitive. The results presented support the proposed shelf life and storage conditions defined in the SPC.

Stability of the reconstituted solution and of the diluted infusion solution: Reconstituted pemetrexed solutions and diluted infusion solutions have been examined for chemical, physical, and microbiological stability, including photostability and in-use compatibility. The results presented support the proposed reconstitution recommendation and storage conditions defined in the SPC.

- Discussion on chemical, pharmaceutical and biological aspects

The drug substance is well characterised and documented. The drug substance synthesis process as well as the pharmaceutical development has been designed in order to minimize oxidation degradation to which pemetrexed is susceptible. The pharmaceutical form selected is adequate taking into account the properties and stability of pemetrexed. The excipients are commonly used in this kind of formulation and the packaging is well documented. The manufacturing process was developed and optimized to obtain reproducible finished product batches. Stability tests under ICH conditions support the proposed shelf life, storage conditions defined in the SPC. At the time of the CHMP opinion there were some minor unresolved quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

2. Part III: Toxico-pharmacological aspects

Introduction

The pivotal toxicology and toxicokinetic studies, as well as the safety pharmacology studies were performed in accordance with Good Laboratory Practice (GLP) regulations. Other pharmacodynamic and pharmacokinetic studies do not fall under these regulations. Applicable International Conference on Harmonization (ICH) and EMEA guidance documents were referred to during the development of the compound.

Pharmacology

- Primary pharmacodynamics (in vitro/in vivo)

The activity of pemetrexed against a broad range of human tumours was evaluated in two separate colony-forming assays. In the first, dose-dependent responses were observed, including in tumour types generally considered to be chemoresistant. The activity of pemetrexed was similar to that of other agents evaluated concurrently (cisplatin, 5-fluorouracil, irinotecan, and paclitaxel) and was not completely cross-resistant with that of the other agents tested [31]. The applicant presented the results of a second test using a panel of 71 specimens of slightly different tumour spectrum from the first test. At 10 μg/ml, responding tumour types included colon cancer at 21% (3/14), NSCLC at 57% (8/14), breast cancer at 47% (7/15), and ovarian cancer at 18% (3/17). Cisplatin and paclitaxel-resistant mesothelioma and NSCLC were sensitive to pemetrexed.

The activity of pemetrexed against a diverse group of tumour cell lines was tested in 72-hour growth inhibition studies using media that typically contained 1 to 3 μM of folic acid. The IC50 values were found to range from 4 to 220 nM [32-38]. Similar results were reported using a panel of unselected colorectal carcinoma cell lines [39].

According to a study conducted by the applicant, tumour growth inhibition was demonstrated against breast, pancreas, lung, and colon tumour xenografts in mice following 10 daily treatments by pemetrexed at 300 mg/kg, the MTD for this dosing schedule in these animals. Intraperitoneal treatment of a colorectal carcinoma xenograft in CD1 nude mice resulted in >70% tumour growth inhibition measured 5 days after the end of treatment and about 17 days tumour growth delay, compared to vehicle-treated control mice [34].

Against established tumours, the activity of pemetrexed was minimal at doses below 200 mg/kg, especially when given less frequently than ten daily injections. No antitumour effect was observed when three daily intraperitoneal injections of pemetrexed at 100 mg/kg were administered to mice bearing HT-29 colorectal carcinoma xenograft of about 300 mg size [40]. In contrast, antitumor activity could be demonstrated when mice were only given two biweekly intraperitoneal injections of pemetrexed at 500 mg/kg when tumours became palpable (~19 mm^3)[41].

The high circulatory levels of folate and thymidine in murine plasma, which are about 10 and 5 times, respectively, greater than those found in human plasma, can adversely affect the activity of antifolate compounds [34, 35, 42]. Mice fed a low folate diet were also much more sensitive to the toxic effects of pemetrexed, with the MTD being 60- to 250-fold (depending on mouse strain) less than that in mice maintained on a normal (high-folate) diet [35, 42]. In mice on a low-folate diet, the authors found that dietary folic acid protected mice from toxicity without negative influence on the efficacy of pemetrexed [35].

Pharmacodynamic mechanisms

Pemetrexed is a structural analogue of folic acid and uses the same biochemical machinery as natural folates for membrane transport and intracellular polyglutamation. Similar to the natural folates, polyglutamated forms of pemetrexed are better retained in the cell and have higher affinity than parent compound for certain folate-dependent enzymes. Inhibition of several of these enzymes by pemetrexed and its polyglutamates causes depletion of nucleotide pools that is associated with growth inhibition and possibly cell death.

Uptake

The uptake of natural folates into the cell is known to involve several protein carriers, including the reduced folate carrier (RFC), membrane folate binding protein (FBP, also known as folate receptor). RFC is believed to be the major route by which folates and many antifolates gained entry into the cell [32]. Pemetrexed interacted equally well with RFC and FBP compared to their respective cognate folates. However, because of better transport efficiency, RFC is likely to be the main carrier for pemetrexed, as in the case for natural folates. [32]. Studies on the uptake of pemetrexed in NCI-H28 mesothelioma line inferred the existence of an additional novel transport system that was different from both RFC and FBP. The prevalence and significance of this transport system are being investigated [43]. The relative importance of ATP-dependent transporters and RFC in affecting pemetrexed sensitivity is also being investigated [44].

- *Polyglutamation*

RFC is a bidirectional carrier with substrate specificity mainly for the parent compounds of folates and antifolates that contain a single glutamyl residue. Thus, folates and certain antifolates that can be polyglutamated by folylpolyglutamate synthetase (FPGS) are trapped inside the cell. The rate constant (Vm/Km) for pemetrexed in the FPGS catalyzed reaction is about 100 to 400 times greater than for methotrexate [45, 46]. When L1210 murine leukemia cells with functional FPGS were exposed to 1 μM radiolabeled pemetrexed or methotrexate for 2 hours, intracellular radiolabeled compounds were more than two times higher for pemetrexed than for methotrexate [46].

Apart from dihydrofolate reductase (DHFR), polyglutamated forms of pemetrexed were bound significantly more tightly by thymidylate synthase (TS), glycinamide ribonucleotide formyltransferase (GARFT), and aminoimidazocarboxamide formyltransferase (AICARFT) [33, 47]. Pemetrexed polyglutamates were an efficient substrate for the lysosomal enzyme, γ-glutamyl hydrolase (GGH), and were slightly better substrates than the corresponding polyglutamates of methotrexate [48]. Pemetrexed and its polyglutamated metabolites were found to be competitive inhibitors of multiple folate dependent enzymes, including TS, DHFR, GARFT, and, additionally, AICARFT, with respect to the folate cofactor [33].

- *Effects of natural folate cofactors*

The total intracellular folate concentrations and polyglutamation are key factors affecting the potency of an antifolate. The sensitivity of pemetrexed followed an inverse relationship with the size of intracellular folate pool [46]. Changes in the folate source, such as from 5-formyltetrahydrofolate to folic acid, or its corresponding concentration, resulted in various effects depending on the cell lines tested [35].

- *Multiple target inhibition inferred from metabolic end product protection studies*

In vitro, pemetrexed can assert both antithymine (by inhibition of TS and DHFR) as well as antipurine effects (by inhibition of GARFT). TS is the primary target, while DHFR and GARFT are secondary targets for pemetrexed [33, 34, 49, 50].

- *Changes in metabolite pools induced by pemetrexed*

In vitro, pemetrexed induced a rapid depletion in dTTP together with an accumulation of dATP, which is consistent with TS inhibition, and additional effect on GARFT [50]. The inhibition of GARFT by pemetrexed in intact cells was also assessed by direct measurement of the metabolic flux across the purine biosynthesis pathway. According to a report submitted by the applicant, albeit weaker than the GARFT inhibitor LY309887, pemetrexed did cause a decrease in cellular incorporation of radiocarbon from [^{14}C]-formate into purine bases, consistent inhibition on GARFT.

- *Cell-cycle effects of pemetrexed*

The sensitivity to pemetrexed *in vitro* was not completely dependent on p53 status, although it could be favoured by the presence of functional p53 in some cell lines [36]. Exposure to pemetrexed resulted in cell arrest at the G1/S-phase boundary, followed by a synchronous entry into S-phase at 24 hours, and apoptosis and cell disintegration completed by 48 hours [40]. The cell-cycle effects of pemetrexed were thought to contribute to the synergistic interaction observed when pemetrexed was combined with certain DNA damaging agents such as cisplatin [38] and doxorubicin [37].

- *Resistant cell studies*

In cells cultured for several weeks in the presence of pemetrexed, resistant phenotypes emerge with alteration in the levels of the certain enzymes and a decrease in sensitivity to the drug [51].

Secondary pharmacodynamics

No secondary pharmacodynamic studies have been performed with pemetrexed.

Safety pharmacology

The applicant conducted studies to assess the potential of pemetrexed to elicit secondary receptor-mediated autonomic pharmacology by smooth and cardiac muscle tissue bath preparations. *In vivo* assessments included a battery of central nervous system (CNS) and behavioural function tests and a gastrointestinal transit evaluation in mice, a renal assessment in rats, and a cardiovascular and respiratory assessment in anesthetized dogs.

- *Cardiovascular and respiratory effects*

Pemetrexed was administered as a single dose by a 10-minute i.v. infusion at doses of 0, 32, or 105 mg/kg to anesthetized male beagle dogs. Administration of 105 mg/kg produced a mild decrease in peripheral vascular resistance and an increase in stroke volume; however, there were no effects seen on conductivity, as assessed by quantitative electrocardiography. Administration of the 32-mg/kg dose of pemetrexed did not alter any of the cardiovascular parameters.

No statistically significant blockade of the human ether-a-go-go-related gene (HERG) ion channel current was observed at any of the concentrations of pemetrexed tested (up to 300 μM) in an *in vitro* study at near physiological temperature conducted by the applicant.

- *CNS effects*

In CD-1 mice following i.v. administration of pemetrexed of 60, 200, or 600 mg/kg, no overt clinical signs were observed.

- *Renal effects*

Pharmacologic effects on renal function were evaluated in female Fischer 344 rats given a single i.v. dose of 0, 60, 200, or 600 mg pemetrexed/kg. Overall renal function was not adversely affected.

- *Gastrointestinal effects*

Pemetrexed did not alter basal gastrointestinal function at doses up to 600 mg/kg.

Pharmacodynamic drug interactions

A variety of *in vitro* and *in vivo* studies were conducted to investigate the anti-tumour activity of combinations of pemetrexed with cisplatin, as well as other cytotoxic agents and radiotherapy.

The interaction of pemetrexed with cisplatin was studied in the MSTO-211H cell line, which was established from the pleural effusion of a patient with biphasic mesothelioma of the lung [52]. Cells were exposed to pemetrexed or cisplatin as single agents either for the entire culture time of 72 hours, or for 24 followed by 72 hours of drug free incubation for a total culture time of 96 hours. The

simultaneous exposure of both compounds was carried out for 72 hours. The pemetrexed concentration range for each combination assay was 10 nM to 50 nM. The cisplatin concentration range was 4 or 8 times the pemetrexed levels. The results showed that when the cell fraction affected was greater than 0.5, the interaction of pemetrexed with cisplatin was synergistic regardless of the sequence of exposure.

The applicant conducted a study on the interaction of pemetrexed with cisplatin using the NCI-H23 lung carcinoma cell line. Cells were exposed to pemetrexed or cisplatin as single agents for 24 or 168 hours during a total culture time of 168 hours. Simultaneous combinations of both drugs were carried out for 168 hours. The pemetrexed concentration range for each combination assay was 48 nM to 12 μM. The cisplatin concentration range was 0.08 to 1.3 μM. The interaction of pemetrexed with cisplatin, evaluated using the Pritchard-Shipman drug-drug interaction model, was found to be additive regardless of the sequence of exposure.

Other studies demonstrated that the interaction of pemetrexed and cisplatin could be dependent on the sequence of addition as well as the cell line used [38]. In these studies, tumor cells were exposed to pemetrexed and cisplatin either individually or simultaneously for 24 hours, or with one agent for 24 hours followed by the other agent for 24 hours. Simultaneous exposure to pemetrexed and cisplatin produced antagonistic effects in A549 lung and MCF7 breast carcinoma cells, but additive effects in PA1 ovarian and WiDr colon carcinoma cells. In contrast, pemetrexed followed by cisplatin produced synergistic effects in MCF7 cells, greater than additive effects in A549 as well as PA1 cells, and additive effects in WiDr cells. However, cisplatin followed by pemetrexed produced antagonistic effects in A549, MCF7, and PA1 cells but additive effects in WiDr cells. From these data, the applicant concluded that the addition of pemetrexed prior to cisplatin would be the preferred sequence.

The applicant reviewed available pharmacodynamic interaction studies using *in vitro* and *in vivo* colorectal cancer models, including the combination of pemetrexed with 5-fluorouracil, oxaliplatin, and SN38 [41], the combination of pemetrexed and gemcitabine *in vitro* [53, 54] and *in vivo* [40], double and triple combinations of pemetrexed, oxaliplatin, and gemcitabine *in vitro*, pemetrexed combined with paclitaxel or docetaxel [38], 5-FU [55], SN38 [41], CPT11 (conducted by the applicant), and with radiation *in vitro* [56] and *in vivo* [57] (data not shown). The activities of certain of the combinations regimens investigated were characterized as being equal or greater than additive.

Pharmacokinetics

Absorption, distribution, metabolism, and excretion studies for pemetrexed have been conducted in CD-1 mice and beagle dogs. The pharmacokinetics of pemetrexed after a single i.v. or intraperitoneal dose are summarized in Table 1.

- *Methods of analysis*

High performance liquid chromatography with ultraviolet detection or tandem mass spectrometric detection was used for determination of pemetrexed in mouse or dog plasma. The limit of quantification and inter assay precision was 41 ng/ml and 2.6-5.5%, and 10 or 1000 ng/ml, and 2.3-8.2 %, respectively. [^{14}C]-pemetrexed was used in studies to evaluate metabolism, distribution, and excretion of pemetrexed.

- *Absorption- Bioavailability*

Absolute bioavailability following 20 and 200 mg/kg dose by the IP route in mice was significant, thus supporting the comparability of IP and i.v. routes in the toxicology programme. Oral absorption was limited in mice, but at least 13 % of the oral dose was absorbed after oral administration of 20 mg/kg.

- *Distribution*

Plasma levels were measured in Beagle dogs after i.v. administration of single doses of 7.5 or 100 mg/kg pemetrexed. Plasma levels decreased like in a biphasic first order model. No difference between male and female dogs was observed. The AUC levels were proportional to the administered doses.

Following a single i.v. dose of 20 mg/kg in male CD-1 mice, radioactivity was rapidly distributed to tissues and excreted via renal and biliary elimination. Within 1 hour, highest concentrations of radioactivity were present in urine, bile within the gall bladder, feces, intestinal contents, kidney, and liver. Radioactivity was detected only in kidney and liver at times greater than 3 hours after dosing.

Protein binding of [^{14}C]-pemetrexed in plasma was estimated at 2 concentrations (500 and 5000ng/ml) using an ultracentrifugation method. Percentage protein binding was approximately 46%, 53% to 57%, and 81% in dog, mouse, and human plasma, respectively. No dependence of binding on concentration was noted, which is consistent with the magnitude of protein binding.

- *Metabolism*

Metabolism studies of pemetrexed were performed only in urine in female beagle dogs and male CD-1 mice. The dogs were administered a single 7.5-mg/kg i.v. dose of [^{14}C] pemetrexed, and urine was collected for 168 hours as the part of excretion study. The pooled urine from 0 to 24 containing 65.1% of the actual dose of total radioactivity was profiled for identification of metabolites. The mice were given a single 20-mg/kg i.v. dose of [^{14}C] pemetrexed, urine was collected over 0 to 7 hours and 24.7% of the actual dose of total radioactivity was recovered.

The majority of urinary radioactivity found in both species was parent drug, constituting approximately 44% of the total dose in dog (approximately 68% of the [^{14}C] found in the 0- to 24-hour fraction) and approximately 22% in mouse (approximately 90% of the [^{14}C] found in the 0- to 7-hour fraction).

Two minor metabolites were observed, which together accounted for less than 1% (mice) or less than 6% (dog) of the total dose in these urine samples. One of the minor metabolites was identified as compound 338979. Both diastereomers of compound 338979 were observed. In a subsequent study, the other minor metabolite was identified as compound 368962. Unchanged pemetrexed (70% to 90% of the administered dose) and metabolite 338979 were also detected in human urine, but metabolite 368962 could not be detected.

Since pemetrexed is largely excreted unchanged in human urine, and metabolism plays a minor role in clearance of pemetrexed, studies to determine whether pemetrexed is a substrate for CYP450 enzymes have not been carried out (70% to 90% of the administered dose).

- *Excretion*

Half life was 7.0 h in male mice following 20 mg/kg i.v. and 3.7 to 4.4 h in female beagle dogs following 25 mg/kg i.v. Balance studies after administration of [^{14}C] pemetrexed disodium by i.v. to male mice and female beagle dogs demonstrated that feces and urine were major routes of elimination in mice while urine was the major route of elimination of radioactivity in dogs, as in human. In male mice, urine, and feces accounted for 34.9 % and 57.4 % respectively of the recovered radiactivity. Almost 90% was excreted within 24 hours The residual amount in mice 96 hours after dosing was 0.150% ± 0.024%.

In female beagle dogs almost 90% of the administered radioactivity was excreted within 24 hours. From 0 to 168 h, 99.2 % of the radioactivity was recovered, 68.8 % in the urine and 30.6 % in feces.

Table 1. Pharmacokinetics of Pemetrexed After a Single i.v. or Intraperitoneal Dose

Species	Mouse	Mouse	Mouse	Dog	Dog	Human
No./Sex (M/F)	4M	4-5M[a]	4-5M[a]	4F	4F	
Route	IV	IP	IP	IV	IV	IV
Dose (mg/kg)	20	20	200	25	25	500 mg/m^2
Sample	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Assay	HPLC/UV	HPLC/UV	HPLC/UV	LC/MS/MS	LC/MS/MS	LC/MS/MS
PK parameters:						
C_0/C_{max} (ng/ml)[b]	40779	33052	196000	141157	149577	65700
AUC (ng•hr/ml)[c]	30794	43792	216741	119678	125902	NC
$AUC_{0-\infty}$ (ng•hr/ml)	NC	NC	NC	119993	126046	159000
$T_{1/2}$ (hr)	7.0	7.8	10.0	4.4	3.7	3.5
CL (ml/min/kg)	NC	NC	NC	3.53	3.32	91.8
Vd (L/kg)	NC	NC	NC	1.43	1.08	16.1

Abbreviations: # = number, M = male, F = female, NA = not applicable, IV = intravenous, IP = intraperitoneal, HPLC = High Performance Liquid Chromatography, UV = ultraviolet, LC/MS/MS = liquid chromatography with tandem mass spectrometry, C_0/C_{max} = maximal observed plasma concentration, AUC = area under the plasma concentration-time curve, $AUC_{0-\infty}$ = total systemic exposure (area under the plasma concentration-time curve from 0 to infinity), NC = not calculated, $T_{1/2}$ = half-life, CL = clearance, Vd = volume of distribution. [a] 4 animals/timepoint for 0.083-12 hours and 5 animals/timepoint for 12-48 hours. [b] After i.v. administration, the values reported for C_0 were extrapolated to zero; the values reported for C_{max} represent the first time point measured post dose. The concentration at time zero was not extrapolated for the reported C_{max}. [c] AUC = 0-30 hours for dogs, 0-48 hours for mouse and 0-48 hours for human.

- *Pharmacokinetic drug interactions*

See discussion on non-clinical aspects, pharmacokinetics.

Toxicology

Pemetrexed was evaluated in single-dose studies in mice, rats and dogs, and in repeat-dose studies up to 6 weeks in mice, and up to 6 months in dogs using daily, twice weekly, once weekly, or once every 3 week schedules. Reproductive and developmental studies were conducted in mice. Special studies were conducted in dogs to evaluate potential rescue agents.

Single-Dose Toxicity

The i.v. median lethal dose (MLD) for female and male CD-l mice was >1574 mg/kg (4722 mg/m^2) and the i.v. MLD for female and male Fischer 344 rats was >1574 and 1332 mg/kg (approximately 9444 and 7992 mg/m^2), respectively.

In a dose-ranging study, beagle dogs, 1/sex/group, were given a single i.v. dose of 10, 25, 50, or 100 mg/kg (200, 500, 1000, 2000 mg/m²). Dogs were observed for 2 weeks and no animal died within that time. Clinical signs of toxicity were decreased food consumption, emesis, and runny stools in the 50 and 100 mg/kg groups. Also, modest reversible decreases in total leukocyte count were seen in dogs of these groups.

Repeat-Dose Toxicity

In a pilot toxicity study, mice were given daily intraperitoneal doses of 0 to 150 mg/kg (0 to 450 mg/m^2) for 2 weeks. All mice survived to study termination. Effects on bone marrow, testes, and thymus were observed. In a longer duration study, mice were given intraperitoneal doses of 0, 10.6, or 26.2 mg/kg daily, 105 mg/kg twice weekly, or 314.8 mg/kg once weekly for 6 weeks. These doses were equivalent to 31.8, 78.6, 315, or 944.4 mg/m^2. The mice tolerated all doses and dose schedules with no compound-related mortality. In males given daily doses, there was a partially compensated decrease in circulating erythrocytes that was compatible with erythrocyte fragmentation in the microvasculature. In males, mean testes weights from all pemetrexed-treated groups were decreased approximately 70%. Histologically, hypospermatogenesis accompanied these decreases in organ weight. Intestinal necrosis was slight, and was limited to male and female mice treated daily with 10.6 or 26.2 mg pemetrexed/kg.

Studies up to 6 months duration with pemetrexed were conducted in dog.

In a 6-week study, 6 dogs/dose group were given slow-bolus i.v. doses of 0, 0.11, or 0.53 mg pemetrexed/kg daily, 3.15 or 7.87 mg/kg twice weekly, or 104.96 mg/kg once weekly (equivalent to 0, 2.2, 10.6, 63, 157.4, or 2099.2 mg/m^2). In contrast to what seen in the pilot studies, after about 1 week it was apparent that dogs could not tolerate the higher daily (0.53 mg/kg) or the weekly dose (104.96 mg/kg). Dogs in these two groups had their dose lowered to 0.37 and 26.24 mg/kg, respectively (7.4 and 524.8 mg/m^2, respectively). Of the 4 dogs given 26.24 mg pemetrexed/kg once per week, septicemia, secondary to mucositis or pneumonia, was the cause of death in the 2 dogs. One out of 6 dogs administered daily doses of 0.11 mg/kg experienced irreversible toxicity (progressive anorexia, hypoactivity, leukopenia) and death after 4 weeks of treatment. Only 2 of the 6 dogs given 3.15 mg/kg twice weekly completed 6 weeks of treatment. The remaining dogs completed only 3 weeks of treatment.

A one-month study with 3-week reversibility phase in dog was conducted to assess the toxicity of four weekly doses of pemetrexed in beagle dogs. Doses of 0, 10, or 25 mg/kg (0, 200, or 500 mg/m^2) were administered i.v. to 6 dogs/sex/group. The doses of 10 and 25 mg/kg produced measurable hematologic effects, but minimal gastrointestinal effects. All changes, except for the decreased platelet count in the high-dose dogs (25 mg/kg), fully or partially reversed within the 3-week recovery period.

A six-month study in dog was initially conducted to assess the toxicity of weekly doses of pemetrexed in beagle dogs. Doses of 0, 10, or 25 mg/kg (0, 200, or 500 mg/m^2, respectively) were used in the 6-month study and were administered i.v.ly to 4 dogs/sex/group. However, after approximately 3 months, the dosing frequency was changed to once every 3 weeks and dosing was discontinued for the 25-mg/kg group due to hematotoxicity. Pemetrexed given once per week or once 3 weeks caused the expected alterations in clinical observations, hematology parameters, and histopathology: abnormal faeces (watery, mucoid, or soft), decreased food consumption, and skin lesions (erythema, desquamation, excoriation, and exudate or crusts), decreases in neutrophil, platelet, reticulocyte, and lymphocyte counts, non dose-responsive bone marrow hypocellularity and testicular degeneration. Hematotoxicity was the dose-limiting effect and neither 10 nor 25 mg/kg was tolerated when given once per week for more than 7 weeks. Hematologic changes in the 25-mg/kg dogs were reversible, and 10 mg/kg was tolerated for approximately 3 months after the dosing frequency was reduced to once every 3 weeks.

Toxicokinetics were investigated only in the dog. Plasma concentrations increased with the dose, and the increase was proportional to the dose. No gender-effect was observed.

Genotoxicity

Pemetrexed was not mutagenic in *Salmonella typhimurium* and *Escherichia coli*, either with or without metabolic activation, using the Ames test. There was no evidence that pemetrexed induced mammallian cell mutations in the HGPRT+ Chinese hamster ovary (CHO) cell assay, either with or without metabolic activation. Pemetrexed did not produce an increase in chromosomal aberrations in vitro in CHO cells, either with or without metabolic activation, using the chromosome aberration assay.

The potential of pemetrexed to induce micronuclei *in* vivo was investigated in bone marrow of ICR mice. The incidence of micronucleated polychromatic erythrocytes in male and female mice treated with pemetrexed was significantly increased compared to that of animals receiving vehicle control, using the mouse micronucleus test.

Carcinogenicity

Studies to assess the carcinogenic potential of pemetrexed have not been conducted.

Reproductive and Developmental Toxicity

In a segment I reproductive toxicity study in male CD-1 mice, pemetrexed by repeated intraperitoneal injection at doses of 0.1 to 10 mg/kg for 6-weeks resulted in male reproductive toxicity characterised by slightly reduced fertility rates, testicular atrophy and epididymal hypospermia. The no-observed-effect level (NOEL) for these effects was < 0.1 mg/kg.

In the definitive study, pemetrexed was given by injection into one of the caudal veins to mated mice (30 mice/group) at doses of 0.2, 1, or 5 mg/kg (0.6, 3, or 15 mg/m^2, respectively). All treated mice survived until live-phase termination. Foetal weights were reduced from control in the 0.2, 1, and 5 mg/kg groups in a dose-responsive manner. The incidences of foetuses with incomplete ossification of several skeletal structures were higher in the 1- and 5-mg/kg litters relative to controls. The malformation, cleft palate, was observed in approximately 85% and 97% of the 5-mg/kg foetuses and litters, respectively. In this definitive study, the NOEL for maternal toxicity was 1 mg/kg (3 mg/m^2), based on decreased body weight gain. A NOEL for developmental toxicity was not established, because foetal growth retardation was observed at all doses. Foetal malformations were evident only in the group given 5 mg/kg, the highest dose tested.

Studies to assess the prenatal and postnatal toxicity of pemetrexed have not been conducted.

Local tolerance

Specific parenteral tolerance studies were not conducted with pemetrexed. No evidence of irritation was identified at the sites of i.v. and intraperitoneal injection in the repeat-dose toxicity studies. There was no chemical-induced peritonitis in the abdominal cavity of mice following intraperitoneal injection.

Ocular and dermal tolerance tests showed that pemetrexed was considered to be a mild irritant to the ocular tissue of rabbit, and a moderate irritant to the dermal tissue of the rabbit.

Other toxicity studies

Rescue studies

In a folinic acid rescue study in dogs given a potentially lethal dose of pemetrexed (50 mg/kg, or 1000 mg/m^2, $\times 2$, 3 days apart) followed by parenteral folinic acid, the clinical signs of toxicity and haematological alterations induced by pemetrexed treatment were reversed within 4 days after initiation of folinic acid therapy, and leukocyte counts had returned to normal range after 6 days.

Ecotoxicity/environmental risk assessment

The amount of pemetrexed that was estimated to be used and excreted did not warrant a full environmental analysis. Information was gained, though, as part of the development of waste containment guidelines for manufacturing facilities. In this regard, pemetrexed was found to have high water solubility and a wide safety margin for aquatic species.

The K_{ow} of pemetrexed also indicates a low potential for bioaccumulation in aquatic organisms. Further, due to the anticipated volume and usage, substantive excretion of pemetrexed from humans is not expected. The maximum predicted concentration of pemetrexed in the influent of sewage treatment facilities that may be discharged into the aquatic environment is < 0.03 µg/L.

Pemetrexed is highly biodegradable in sewage treatment sludge. Less than 1000 kg of the active ingredient in pemetrexed is expected to be used within a year in Europe, resulting in concentrations in the influent of sewage treatment facilities less than 0.03 µg/L. For these reasons, exposure to concentrations of pemetrexed in the environment would not pose an environmental concern.

Discussion on the non-clinical aspects

Nonclinical reports and bibliographic references, a comprehensive factual synopsis of findings and the implications for the safe use of pemetrexed have been provided following agreed Common Technical Document recommendations [58].

Pharmacodynamics

Pemetrexed was found to have activity against a broad range of tumor cells, including tumor types generally considered to be chemoresistant. In combination with cisplatin a synergistic effect was shown in vitro when given simultaneously. Tumour growth inhibition was demonstrated against breast, pancreas, lung, and colon tumour xenografts. No secondary pharmacodynamic studies have been performed with pemetrexed, which is considered acceptable, as the mechanism of action seems to be specific. Overall, adequate information about the pemetrexed-specific activity profile has been

obtained using well-characterised cell lines and compared with that of standard anticancer agents, in agreement with relevant guidance [59].

The safety pharmacology of pemetrexed was assessed with a limited number of *in vitro* and *in vivo* studies. No reference compounds have been used. However, the models used were all well characterized, and the lack of concurrent positive and negative controls can be justified in agreement with current guidance [59a]. Overall, there were no effects seen in the safety pharmacology studies that would be of concern. From a preclinical perspective, pemetrexed has no effect on QTc prolongation.

Pemetrexed was evaluated in combination with a variety of other anti-tumor agents including platinum compounds, antitubulin agents, and other antimetabolites. The resulting growth inhibitory activities were generally additive or synergistic. From non-clinical results, a clear justification of the sequence of an efficient treatment combination is difficult, due to the wide range of compounds, models and sequence administration used. The pharmacodynamic drug interaction of pemetrexed and cisplatin is of particular interest, and is prompted by indications of therapeutic effect in the treatment of mesothelioma. One *in vitro* investigation showed that simultaneous administration of the combination has synergistic effects on growth inhibition of the mesothelioma tumour cell line. No *in vivo* studies with the cisplatin combination have been submitted. Since extensive clinical data have been available, further animal studies to justify the combination, as generally required [60], are not expected to bring any essential new information on the effects of the combination in humans.

Pharmacokinetics

The oral absorption in mice was very limited. Therefore, the i.v. route of administration was chosen for clinical development. The Beagle dog was found to be an appropriate animal for pharmaco-toxicological studies since the pharmacokinetic parameters of Beagle dogs and humans were in the same order of magnitude. Pemetrexed was rapidly distributed, followed by rapid urinary and biliary elimination. The latter is pronounced in mice whereas urinary excretion is preferred in Beagle dogs and humans. The long retention in liver observed in mice could possibly be due to tissue-specific uptake and retention of polyglutamylated forms of this close folate analog. Metabolism contributed minimally towards the clearance of pemetrexed in mice, dogs, and humans.

The applicant has justified the details of the methods used, their validity and reproducibility, including the specificity, precision and accuracy. The animal species in these studies are those normally used in the laboratory for pharmacological and toxicological investigations. Doses and routes of drug administration are related to the proposed clinical use of the substance. Overall, adequate information has been presented allowing comparison and extrapolation between animal and human, and appropriate conclusions have been drawn from these studies about the time course of the absorption, distribution and excretion of pemetrexed.

Aspirin and ibuprofen are commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) in cancer patients and occasionally fatal adverse events have been reported with the anti-folate methotrexate in combination with NSAIDs. In vivo interaction studies were conducted with aspirin and ibuprofen to determine if single or repeated oral doses of these agents would alter the pharmacokinetics of pemetrexed. No substantive pharmacokinetic interactions were observed, but this may also be due to the small number of animals studied, and the lack of power of the studies detect any effect (data not shown).

Preclinical toxicology studies using concomitant administration of pemetrexed and cisplatin were not conducted, although such studies are encouraged [59]. For combinations involving pemetrexed and cisplatin, preclinical toxicity testing was not considered essential by the applicant because each agent has been fully evaluated for safety in humans, and because of the lack of a pharmacokinetic interaction in humans. It is agreed that coadministration with cisplatin did not alter pemetrexed clearance and pemetrexed did not alter total platinum clearance in the Phase III trial JMCH. Further animal studies to describe any collateral effects of the combination are not expected to bring any essential new information on the effects of the combination in humans. Given the documentation and justifications provided, the toxicology requirements are considered fulfilled.

Toxicology

The number and types of species studied in single-dose tioxicity studies were adequate and the list of tissues examined was extensive and consistent with GLP. In agreement with applicable requirements and guidelines [59-61], adequate presentation of the results and conclusions have been provided. Dogs were more sensitive to the toxic effects of pemetrexed than were mice. This finding was expected, as mice have a "self-rescue" mechanism in a circulating thymidine moiety that can serve as a replacement source in folate-antagonized cells [62]. Additionally, dogs are generally more predictive of systemic toxicity in man than are mice [63, 64]. Despite the rescue mechanism, identification of target organs in the toxicity studies in mice was not confounded by this phenomenon and was confirmed by the findings in the dog. In addition, NOAELs found in the mice were similar to those found in the dog. Thus, the choice of the mouse in pilot toxicology studies is acceptable.

Pemetrexed was administered by the route intended for use in man and the rationale on which the dose levels were selected was presented. Adequate presentation of the results and conclusions have been provided. The duration of the long-term repeat-dose studies is adequate for the conditions of clinical use, and has been adequately justified in view of applicable requirements and guidelines [59, 60, 65].

The main limiting toxicity of pemetrexed following repeated dosing was haematological toxicity followed by necrotising enteropathy. This toxicologic profile is consistent with the antiproliferative activities of folate antimetabolites [66]. Lesions of mucositis, enteropathy, and lymphoid and bone marrow hypocellularity are commonly encountered with folate antimetabolites and other oncolytic agents [66, 67]. Skin, especially the mucosa of the mouth cavity, were affected leading to ulceration of mucosa and sometimes followed by bacterial inflammation. Hypospermatogenesis with necrotised spermatocytes were also seen in pathological investigations at the end of the study. Usually these effects were reversible, however, this is not clear with regard to hypospermatogenesis.

Due to the extreme toxic effects in beagle dogs it was not possible to determine safety margins which were comparable to humans. Doses of 25 mg/kg (500 mg/m²) every 3 weeks seemed to be tolerated in dogs poorly but the same dose of pemetrexed is given to humans.

Pemetrexed was clastogenic in the *in* vivo mouse micronucleus test. This finding might be explained by the TS inhibition caused by pemetrexed. TS methylates uridine to thymidine and is dependent on folate metabolism. TS inhibition by pemetrexed will result in accumulation of uridine along with a decrease in thymidine levels. Absence of folic acid and thymidine in the medium, greatly enhanced micronucleus formation in proliferating lymphocyte cultures from normal individuals [68]. Increased levels of uridine with decreased levels of thymidine also result in cycles of urdine insertion and excision into the DNA, eventually leading to DNA strand breakage and cell death [69, 70]. Pemetrexed was not mutagenic in the Ames test and tested negative in the *in vitro* chromosome aberration test in CHO cells. The clastogenic potential of pemetrexed is adequately described in the SPC (Section 5.3).

Pemetrexed can have genetically damaging effects. Adequate warnings have been included in the SPC (Section 4.4, and 4.6). Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended. Women of childbearing potential must use effective contraception during treatment with pemetrexed.

Overall, the genotoxicity of pemetrexed has been adequately investigated and standard test have been conducted and described in compliance with regulatory guidance and requirements [58-61, 71].

Carcinogenicity studies with pemetrexed have not been conducted. Such studies are not needed with unequivocally genotoxic compounds, as they are presumed to be transspecies carcinogens, implying a hazard to humans. No long-term carcinogenicity studies are required taking into account the life expectancy of patients with unresectable malignant pleural mesothelioma or locally advanced or metastatic NSCLC after prior chemotherapy [58-61]. The lack of such studies has been adequately reflected in the SPC (Section 5.3).

Although generally not required for anticancer agents (these products are are assumed to cause reproductive disturbances), studies elucidating the potential for reproductive toxicity are encouraged [59]. Administration of pemetrexed to male mice resulted in reproductive toxicity suggesting that pemetrexed may impair male fertility. The applicant did not conduct any female fertility study as the

results obtained from such a study with pemetrexed would not provide any additional insights given the magnitude of embryolethality already described in the pregnant mouse. The reproductive toxicity observed is consistent with the known antiproliferative activities of folate antimetabolites. These observations are not unexpected findings for a drug that affects rapidly dividing cells, are commonly seen with anticancer drugs, and are adequately reflected in the SPC (Section 5.3). Owing to the possibility of pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment, and this has been reflected in the SPC (Section 4.4).

Pemetrexed, like other anti-metabolites, is suspected to cause serious birth defects when administered during pregnancy (see SPC, section 4.6). Administration of pemetrexed to pregnant mice resulted in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate. As a class, folic acid antimetabolites have been demonstrated to produce three manifestations of developmental toxicity: growth retardation, embryolethality, and malformations [72]. Exencephaly, omphalocele, ectrodactyly, and cleft palate have been observed in mouse fetuses exposed to methotrexate during organogenesis [73]. Based on the pilot and the definitive developmental toxicity studies with pemetrexed, growth retardation was observed at doses ≥0.2 mg/kg, malformations at doses ≥5 mg/kg, and embryolethality at doses ≥50 mg/kg. Pemetrexed should not be used during pregnancy unless clearly necessary, after a careful consideration of the needs of the mother and the risk for the foetus. Adequate warnings are provided in the SPC (Section 4.6 and 5.3)

Studies to assess the prenatal and postnatal toxicity of pemetrexed have not been conducted. Lack of these studies has been justified in view of the nature of the disease, cyclic nature of pemetrexed administraton, duration of treatment, and poor life expectancy of the proposed patient population.

In summary, the developmental toxicity profile of pemetrexed and the types of foetal effects observed are consistent with effects reported in rodents for other folic acid anti-metabolites [63]. A nonrodent species was not tested in a segment II study based on the significant positive findings observed in the mouse study. Female fertility studies were not conducted as such a study would not provide any additional insights given the magnitude of embryolethality observed. Studies to assess the prenatal and postnatal toxicity of pemetrexed have not been conducted, in view of nature of the disease, cyclic nature of pemetrexed administration, duration of treatment, and poor life-expectancy of the proposed patient population. Overall, the reproductive and developmental toxicity of pemetrexed has been adequately investigated and reported, and the omission of further reproductive and developmental toxicity studies has been adequately justified, in line with applicable guidelines and regulatory requirements [59, 60, 74].

The lack of local tolerance testing has been justified based on the findings of other toxicity studies, in line with applicable guidance [59]. It is unlikely that the formulated pemetrexed would pose a risk for reaction at the site of injection. Pemetrexed has potential to be an ocular and dermal irritant. Appropriate cautionary statements and preparation and administration precautions are included in the SPC (Section 6.6). Extravasation should be managed by local standard practice as with other non-vesicants.

The mechanism of reversal of antifolate toxicity by the active folates at the cellular level is complex and is the subject of continuous research (see discussion on clinical pharmacology). In vitro studies have confirmed that the toxic effect of pemetrexed can be reversed efficiently by folinic acid [75]. According to a study conducted by the applicant, leucovorin was able to rescue dogs from lethal acute toxicity. Folinic acid should be considered as an antidote for overdose (see SPC Section 4.9).

3. Part IV: Clinical aspects

Introduction

Efficacy data are presented by indication. Based on the information provided, all trials were conducted according to the principles of GCP. In MPM one pivotal Phase 3 study was performed comparing the test regimen of pemetrexed plus cisplatin with cisplatin monotherapy. Supporting studies include a Phase 1 dose-finding study of pemetrexed plus cisplatin, a Phase 1 dose-finding study of pemetrexed plus carboplatin, and a Phase 2 study of single-agent pemetrexed in chemotherapy-naive MPM

patients (Table 2A). In NSCLC after prior chemotherapy, one pivotal Phase 3 study was performed. This study compared the test regimen of pemetrexed with docetaxel, the only drug currently approved for second-line treatment of NSCLC. Supporting studies include Phase 2 studies of single-agent pemetrexed in previously treated, or untreated, NSCLC patients (Table 2B). Scientific Advice was sought from the Committee for Proprietary Medicinal Products (CPMP) in 2000. Pemetrexed is currently under development for several oncology indications.

Table 2A. Main studies submitted for clinical efficacy (MPM indication)

Study Identifier	Brief Description	Regimen	Primary Objective
H3E-MC-JMCH	Phase 3, randomized, single-blind, controlled	Pemetrexed + cisplatin vs. cisplatin monotherapy	Comparison of overall survival time
H3E-MC-JMDR	Phase 2, open-label, uncontrolled	Pemetrexed	Estimation of tumor response rate
H3E-MC-JMAP	Phase 1, open-label, uncontrolled	Pemetrexed + cisplatin	Dose-finding
H3E-MC-JMAU	Phase 1, open-label, uncontrolled	Pemetrexed + carboplatin	Dose-finding

ALIMTA must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy (see section 4.2 of the SPC). In patients treated for malignant pleural mesothelioma, the recommended dose of ALIMTA is 500 mg/m^2 of body surface area (BSA) administered as an i.v. infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of 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. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin (see SPC section 4.2). In patients treated for NSCLC, the recommended dose of ALIMTA is 500 mg/m^2 BSA administered as an i.v. infusion over 10 minutes on the first day of each 21-day cycle.

Table 2B. Main studies submitted for clinical efficacy (NSCLC indication)

Study Identifier	Brief Description	Regimen	Primary Objective
H3E-MC-JMEI	Phase 3, randomized, open-label, controlled, second-line NSCLC	Pemetrexed vs. Docetaxel	Comparison of overall survival time
H3E-MC-JMBR	Phase 2, open-label, uncontrolled, second-line NSCLC patients who were highly refractory	Pemetrexed	Tumor response rate
H3E-MC-JMAL	Phase 2, open-label, uncontrolled, first-line NSCLC	Pemetrexed	Tumor response rate
H3E-MC-JMAN	Phase 2, open-label, uncontrolled, first-line NSCLC	Pemetrexed	Tumor response rate

Since December 1999, folic acid and vitamin B12 supplementation have been introduced for all patients treated with pemetrexed, to reduce toxicity (see SPC section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Accordingly, patients must also receive an intramuscular injection of vitamin B_{12} (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.

Pharmacology

- *Analytical methods*

For the measurement of pemetrexed concentrations in plasma and urine, a reverse-phase HPLC method using electrospray tandem mass spectrometry detection was primarily employed. For the measurement of total platinum (for cisplatin and carboplatin) concentrations in plasma, a standard graphite furnace atomic absorption spectroscopic method was used.

- *Pharmacokinetics*

The pharmacokinetic properties of pemetrexed following single-agent administration have been evaluated in 426 cancer patients with a variety of solid tumours at doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period.

Pemetrexed was administered as a single agent in Phase 1 dose-escalation studies JMAA, JMAB, and BP001. Pemetrexed was administered as a 10-minute i.v. infusion every 21 days over a dose range of 50 to 700 mg/m^2 in Study JMAA, once weekly (every 7 days) for 4 weeks followed by two weeks of rest over a dose range of 10 to 40 mg/m^2 in Study JMAB, and once daily for 5 consecutive days followed by 16 days of rest to complete a 21-day cycle over a dose range of 0.2 to 5.2 mg/m^2 in Study BP001. Clinical evaluation demonstrated that the once every 21-day dosing regimen (Study JMAA) was the most promising dosing regimen to explore for subsequent development.

In Study JMAA, dose escalation was performed using the modified continual reassessment method. Only 1 or 2 patients were assigned to each dose until the presence of toxicity was observed. More patients were enrolled at the three highest doses (525, 600, and 700 mg/m^2). The MTD from this dosage regimen was determined to be 600 mg/m^2. The main DLTs were neutropenia, thrombocytopenia, and chronic fatigue. Doses of 500 and 600 mg/m^2 were evaluated in a variety of subsequent Phase 2 studies in various solid tumor types. The pharmacokinetic parameters for study JMAA are summarized in Table 2C. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed were consistent over multiple treatment cycles.

Table 2C. Summary (mean [%CV]) of Single Agent Phase 1 Pemetrexed Pharmacokinetic Parameters in Cancer Patients (Study JMAA, i.v. route of administration)

Dose (mg/m^2)	C_{max} (μg/ml)	T_{max} (hr)[a]	V_{ss} (L/m^2)	AUC (μg·hr/ml)	$t_{1/2}$ (hr)	Urinary Excretion (% dose)	CL_p ($ml/min/m^2$)	CL_r ($ml/min/m^2$)
50	11.9	0.25	6.88	21.9	2.5	70	38.1	26.8
(n=1)			12.7[d]				70.5[d]	49.6[d]
75	10.0	0.25	9.58	13.6	1.5	41	92.1	38.1
(n=1)			20.9[d]				201[d]	83.0[d]
100	27.3	0.25	5.92	39.5	2.4	80	42.2	NA
(n=1)			11.3[d]				80.7[d]	
150	12.9	0.5	5.3 – 11.8	40.1 - 53.9	2.2 - 2.4	108	46.4 - 62.4	50.1
(n=2)	39.5	0.25	7.63 – 30.7[d]				67.4 - 163[d]	72.6[d]
225	64.4	0.25	5.50	121	2.7	70.0	31.2	21.8
(n=2)			10.6[d]				59.8[d]	41.9[d]
350	91.4	0.25	5.68	158	2.7	67	36.8	24.8
(n=1)			9.88[d]				64.1[d]	43.1[d]
525	121	0.08 – 0.25	6.85	231	3.9	70[b]	40.7	27.4[c]
(n=3)	(13%)		(12%)	(32%)		(29%)	(33%)	(52%)
			13.6[d]				80.7[d]	54.7[d]
			(12%)				(31%)	(50%)
600	137	0.08 – 0.25	7.00	266	3.1	83[b]	40.0	35.9[b]
(n=20)	(33%)		(20.0%)	(27%)		(15%)	(24%)	(41%)
			13.8[d]				77.7[d]	62.8[d]
			(27%)				(26%)	(25%)
700	175	0.08 – 0.25	6.39	398	3.7	88[b]	33.6	29.9[c]
(n=5)	(27%)		(7.7%)	(43%)		(20%)	(39%)	(12%)
			12.5[d]				65.7[d]	62.4[d]
			(11%)				(42%)	(79%)

Abbreviations: AUC = area under the curve; CL_p = plasma clearance; CL_r = renal clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation = [standard deviation/mean] × 100%; NA = not applicable; T_{max} = observed sampling time of C_{max}; $t_{1/2}$ = apparent terminal elimination half-life; V_{ss} = distribution volume at steady state. [a] T_{max} reported as range. [b] n = 4. [c] n = 3. [d] non BSA normalized units (ml/min for CL_p, CL_r, and L for V_{SS}).

- *Absorption – Bioavailability*

Alimta is intended for i.v. administration, and absorption studies are not relevant.

- *Distribution*

In Study JMAA, mean plasma concentration-time profiles at the three highest doses (525, 600 and 700 mg/m^2) demonstrated a sharp decline of approximately three orders of magnitude from the maximum over a 24-hour period. Maximum plasma concentrations (Cmax) occurred at or near termination of the infusion and ranged from 67.4 to 251.3 μg/ml at a 600 mg/m^2 dose. Total plasma clearance (CL_p) and steady-state volume of distribution (V_{ss}) were consistent across the dose range and ranged from 52.3 to 136 ml/min and 8.5 to 23.0 L at 600 mg/m^2, respectively. Inter-patient variability of CL_p and V_{ss} was moderate at 23% and 26%, respectively. The apparent $t_{1/2}$ was short, ranging from 2 to 7 hours for all doses. Within each of the three Phase 1 studies there were no clinically significant deviations from dose proportionality for both AUC and C_{max}.

Pemetrexed demonstrated a relatively small volume of distribution in both noncompartmental pharmacokinetic evaluations based on data from Phase 1 studies, and population pharmacokinetic analyses based on data from Phase 2 and 3 studies, suggesting that the compound has limited tissue distribution. In population pharmacokinetic analyses, distribution volume at steady state (V_{ss}) was

16.1 L, or approximately 9 L/m^2 (based on median BSA of 1.74 m^2). Of this volume, approximately 80% was associated with the volume of the central compartment (V_1). Body size as quantified by body surface area (BSA) was identified in the population pharmacokinetics analyses to be the only significant predictor of V_1 as described by the relationship $V_1 = 6.13 \bullet BSA^{1.32}$. Because V_1 probably represents a combination of total blood volume and well-perfused organs, it is reasonable that larger individuals have greater blood volume and organ size and thus a larger volume of distribution. The relationship identified between V_1 and BSA is consistent with this assumption. No relationships were established between distribution volume of the second (that is, peripheral) compartment (V_2) and the potential covariates investigated.

The protein binding of [^{14}C] pemetrexed in plasma was estimated using an ultracentrifugation method. In vitro pemetrexed protein binding at concentration of 0.5, 100 and 200 µg/ml was assessed in pre-dose human plasma samples from Study JMAW using ultracentrifugation. Subjects were classified into treatment groups according to varying degrees of renal impairment as measured by GFR. In a concentration range from 0.5 to 200 µg/ml, pemetrexed was approximately 80.3% to 83.9% bound to plasma proteins. No notable differences were observed for different degrees of pemetrexed plasma concentration and of renal impairment.

- *Metabolism*

Non-clinical studies revealed minimal metabolism of pemetrexed. Two minor metabolites were observed from non-clinical studies but neither metabolite is pharmacologically active. Unchanged pemetrexed and metabolite LY338979 were also detected in human urine collected from subjects participating in the renal insufficiency Study JMAW using liquid chromatography with tandem mass spectrometry (LC/MS/MS). Unchanged pemetrexed accounted for the majority of the drug-related material in urine. Metabolite LY368962 could not be detected in human urine samples.

The ability of pemetrexed to inhibit the metabolism of marker catalytic activities for the cytochromes P450 CYP3A, CYP2D6, CYP2C9, and CYP1A2 was examined. Slight inhibition by pemetrexed of the form-selective biotransformation for CYP3A, the 1'-hydroxylation of midazolam, was observed. At a midazolam concentration of 5 µM, 21% inhibition of CYP3A mediated midazolam metabolism was observed at the highest concentration of pemtrexed (885 µM) examined. At a bufuralol concentration of 5 µM, little change in CYP2D6 mediated bufuralol metabolism was observed at concentrations of pemetrexed ranging from 400 to 1000 µM. At a diclofenac concentration of 2.5 µM, slight inhibition of the CYP2C9 mediated metabolism was observed at the highest pemetrexed concentration (1000 µM) examined. Metabolism of phenacetin to acetaminophen, the form-selective biotransformation for CYP1A2 catalytic activity, was slightly inhibited in the presence of up to 1000 µM pemetrexed when a 12.5 µM phenacetin concentration was used. Since peak circulating levels of pemetrexed approach 200 µg/ml (468 µM) in humans, these in vitro studies predict that pemetrexed would not cause clinically significant inhibition of the metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

- *Excretion*

Study JMAA showed that pemetrexed is eliminated primarily by urinary excretion of unchanged drug. Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered dose being recovered unchanged in urine within the first 24 hours following administration. Urinary excretion started to reach a plateau at approximately 12 hours after start of infusion, consistent with the short elimination half-life (t1/2).

The fraction excreted unchanged into urine appeared to decrease progressively with severity of renal insufficiency (see also pharmacokinetics in special populations). Indeed, a positive correlation between pemetrexed CLp and estimated creatinine clearance was observed for Studies JMAA and JMAB. Plasma clearance increased with improved renal function, as expected for a drug that is eliminated primarily by urinary excretion.

Pemetrexed total systemic clearance was estimated to be 91.8 ml/min and the elimination half-life from plasma was 3.5 hours for a “typical” patient with normal renal function (creatinine clearance of 90 ml/min calculated using the standard Cockcroft and Gault formula or measured GFR using the

Tc99m-DPTA serum clearance method). Active tubular secretion contributes significantly to the renal elimination of pemetrexed. The product of the fraction unbound (f_u) and GFR ($f_u \bullet$GFR; 0.19•120 ml/min = 23 ml/min), represents the filtration capacity of the kidney to eliminate pemetrexed. Therefore, the estimate of pemetrexed clearance (CL) (91.8 ml/min) is approximately 4 times the estimated clearance by filtration (23 ml/min). Between patient variability in clearance was moderate at 19.3 % in cancer patients receiving single-agent pemetrexed at a dose of 500 mg/m^2.

Population pharmacokinetics

Methods

A population pharmacokinetic model was developed using data from 8 of 10 Phase II studies (Studies JMAC, JMAD, JMAG, JMAH, JMAI, JMAJ, JMAK, JMAM, construction set). The predictive ability of the model was then evaluated using the data from the remaining 2 studies (JMAL and JMBR, validation set). The primary objective for each of the nonrandomized single-arm studies without controls was to determine the response rate in each tumor type for patients treated with pemetrexed. In each of the studies, pemetrexed was administered as a 10-minute i.v. infusion every 21 days. Initial doses (Cycle 1) were 500 to 600 mg/m^2. Dose adjustment (reduction) at the start of subsequent courses of therapy were based on nadir counts or maximal nonhematologic toxicity from the preceding cycle of therapy. The studies were prospectively designed to include a sparse blood sampling strategy for evaluation using population pharmacokinetic techniques. Plasma concentration-time data were analyzed by population pharmacokinetic methods using the NONMEM software [76].

Results

The analyses included data from 287 (209 and 78 for the construction and validation sets, respectively) patients receiving pemetrexed as a 10-minute continuous infusion every 21 days. A total of 1596 observations from 287 patients receiving pemetrexed and 441 treatment cycles with doses ranging from 244 mg to 1494 mg were collected at various times during Cycles 1 and 3 for analysis of pemetrexed concentrations in plasma to cover the entire plasma concentration-time profile. The pharmacokinetics of pemetrexed were best characterized using an open two-compartment model parameterized in terms of clearance (CL), central volume of distribution (V_1), intercompartmental clearance (Q), and peripheral volume of distribution (V_2).

Various patient demographic and physiologic factors were evaluated with respect to each pharmacokinetic parameter. The final population pharmacokinetic model indicated that pemetrexed clearance was dependent on creatinine clearance as estimated by the standard Cockcroft-Gault formula ($CrCl_{CG,std}$) incorporating age, body weight, and serum creatinine concentration. The volume of distribution of the central compartment was dependant on body surface area (BSA). Between-patient variability in CL, Central Volume of Distribution (V1), and Peripheral Volume of Distribution V2 in the final population model are summarised in Table 3.

The “typical value” (population central tendency) for pemetrexed CL was 90.2 ml/min, and for pemetrexed V_{SS} was 16.1 L. The apparent $t_{1/2}$ of pemetrexed from plasma for the typical patient was determined to be approximately 3.5 hours. Each of these values are consistent with the results obtained from the Phase 1 study, JMAA. Similarly, estimates of between-patient variability were consistent with those obtained from Study JMAA and were well-characterized based on precision of variance parameter estimates (19.3% [14.1 %SEE] for CL, 16.6% [29.3 %SEE] for V_1, 24.5% [24.6 %SEE] for V_2, and 28.4% [8.22 %SEE] residual variability).

Table 3. Pharmacokinetic and covariate parameters in final population model for pemetrexed

Parameter Description	Population Estimate (% SEE)	Between-Patient Variability (% SEE)
Clearance		
TVCL, base parameter for CL (ml/min)	43.0 (16.6)	19.3 % (14.1)
Θ_1, parameter for effect of CGCL on CL (ml/min) [a]	47.2 (14.8)	
Central Volume of Distribution		
TVV1, base parameter for V_1 (L)	6.13 (9.04)	16.6 % (29.3)
Θ_2, parameter for effect of BSA on V_1 [b]	1.32 (11.6)	
Intercompartmental Clearance		
Parameter for Q (ml/min)	14.5 (17.6)	---
Peripheral Volume of Distribution		
Parameter for V_2 (L)	3.38 (10.9)	24.5 % (24.6)
Residual Error (proportional)	28.4 % (8.22)	

[a] $CL = TVCL + \Theta_1 \times CGCL/92.6$ where 92.6 is the median baseline CGCL.
[b] $V1 = TVV1 \times BSA^{\Theta_2}$
Abbreviations : SEE = standard error of the estimate
Method : FOCE with interaction

Dose proportionality was also evaluated using population pharmacokinetics over the dose range of 244 to 1494 mg (126 to 838 mg/m^2). Results from this analysis demonstrated that pemetrexed pharmacokinetics were linear (that is, dose-independent over the range of doses studied). This indicates that pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose.

The influence of duration of therapy was evaluated and indicated that pemetrexed clearance decreased 4.3% and V_1 increased 10% for later treatment cycles (Cycle 3 or 4) relative to Treatment Cycle 1. These differences, although statistically significant, are small (not clinically relevant) and are much less than within-patient variability.

Special populations

Impaired renal function

Pemetrexed pharmacokinetics were evaluated in 47 patients who had varying degrees of renal function (Study JMAW). Glomerular filtration rate, measured by Tc99m-DPTA serum clearance, varied from 19 ml/min to 151 ml/min. The study was initiated without vitamin supplementation; the protocol was amended during the study to include folic acid and vitamin B_{12} supplementation. Creatinine clearance calculated by the standard Cockcroft-Gault method ($CrCl_{CG,std}$) [77] was found to provide a better approximation to the measured renal function using Tc99m-DPTA serum clearance than compared to lean body mass formula ($CrCl_{CG,LBM}$). A proportional relationship was observed between pemetrexed plasma clearance and renal clearance with measured GFR and $CrCl_{CG,std}$ in patients with renal impairment (GFR 19 to 79 ml/min). No statistically significant relationship was observed for patients with normal renal function (GFR >80 ml/min). Mean plasma and renal clearance values exhibited over a 2-fold decrease in patients with moderate renal impairment relative to patients with normal renal function. Additionally, the ratio of mean renal clearance to the product of the fraction of drug unbound in plasma (f_u) with GFR ($f_u \bullet GFR$) values increased from 1.5 to 2.1 with an improvement in renal function in patients with moderate renal impairment to the lower limit of normal renal function. Therefore, it appears that tubular secretion became more prominent as renal function improved or the contribution of reabsorption decreased as renal function improved. Mean percent bound ranged from 73.4% to 81.0%. Although pemetrexed clearance varied almost 10 fold over the range of renal function, pemetrexed given at the recommended clinical dose of 500 mg/m^2 was well-tolerated in patients with GFR as low as 40 ml/min.

The final population pharmacokinetic model indicated that pemetrexed clearance was dependent on creatinine clearance as estimated by the $CrCl_{CG,std}$ incorporating age, body weight, and serum

creatinine concentration. A combined evaluation of pemetrexed pharmacokinetics in patients with renal insufficiency included 127 patients with reduced renal function from the 10 single-agent Phase 2 studies, the pivotal Phase 3 study in combination with cisplatin (JMCH), and the Phase 1 renal impairment study (JMAW). Estimates of pemetrexed CL and total systemic exposure (AUC) following a 500 mg/m^2 dose for the "typical" patient (population average; creatinine clearance based on the $CrCl_{CG,std}$ 90 ml/min) and a renally impaired ($CrCl_{CG,std}$ 45 ml/min) patient are provided in Table 4. A patient with a creatinine clearance of 45 ml/min would be expected to have 36% lower pemetrexed clearance relative to the population average, which would result in a 56% increase in overall exposure.

Table 4. Summary of mean predicted pemetrexed cl and AUC for a 500 mg/m^2 dose by renal function

Creatinine Clearance [a] (ml/min)	Study JMAW		Combined	
	Pemetrexed CL	Pemetrexed AUC	Pemetrexed CL	Pemetrexed AUC
90	82.1	178	91.8	159
45	46.2	316	58.8	248

Abbreviations: AUC = area under the curve; CL = clearance.

[a] Estimated creatinine clearance using standard Cockcroft-Gault method (Cockcroft and Gault 1976).

Impaired liver function

Because the drug is eliminated primarily by renal excretion of unchanged drug, and metabolism plays a negligible role in clearance of the drug, no specific study was performed in patients with hepatic dysfunction. The relationships between ALT (SGPT), AST (SGOT), and total bilirubin as indicators of hepatic dysfunction, and pemetrexed pharmacokinetics were evaluated in the population pharmacokinetics analyses. No association was observed between pemetrexed disposition and ALT over a range from 5 to 495 upper limit (U/L), AST over a range from 5 to 204 U/L, or total bilirubin over a range of 3 to 34.2 μmol/L (data not shown).

Gender, race, weight, age

No important association between gender or age (range 26 to 80 years) and pemetrexed pharmacokinetics was observed. No data in children are available. The index dataset consisted of predominantly Caucasian 160 (77%) patients with 35 (11%) of African descent, 2 (1%) Asian, 2 (1%) Hispanic, and 10 (11%) having undefined ethnic origin. No important association between ethnic origin and pemetrexed disposition was observed. Pemetrexed central volume of distribution is dependant on body surface area in an exponential fashion (see Clinical aspects, Pharmacokinetics, *Distribution*). Because BSA is a predictor of V1 and not CL, the effect of BSA is reflected in peak pemetrexed concentration and not on overall exposure to the drug (AUC).

Extrinsic factors, and interaction studies

No associations between smoking or self-reported alcohol consumption and pemetrexed disposition were observed.

Studies to determine whether pemetrexed is a substrate for CYP450 enzymes have not been carried out. The ability of pemetrexed to inhibit the metabolism of marker catalytic activities for the main cytochrome P450 isoenzymes was performed in vitro with human liver microsomes (see Metabolism).

The effect of aspirin and non steroidal anti-inflammatory drugs on pemetrexed clearance were investigated because of the established interaction between aspirin/NSAIDs and methotrexate, and due to the structural similarity of pemetrexed with methotrexate. Study JMAW was a phase I dose-finding study in patients with advanced cancers of various types having varying degrees of renal function. Pursuant to Protocol Addendum JMAW2b, additional patients (24) with glomerular filtration rate (GRF ≥ 60ml/min) received pemetrexed 500 mg/m^2 alone and in combination with aspirin (325 mg orally every 6 hours) or ibuprofen (2×200mg orally every 6 hours). Aspirin and ibuprofen were administered 2 days prior to pemetrexed administration and the last dose given 1 hour prior pemetrexed administration. The assessment of the influence of pemetrexed on aspirin and ibuprofen was not performed.

No significant association between co-administration of aspirin 325mg every 6 hours and pharmacokinetics of pemetrexed was observed. Interactions between pemetrexed and aspirin administered at high doses have not been investigated.

When pemetrexed is administered concomitantly with ibuprofen 1.6 mg daily, a statistically significant increase in pemetrexed AUC (20%) and Cmax, (15%) occured as well as a a statistically significant reduction in clearance (CL) (17%).

Discussion on pharmacokinetics

Pemetrexed pharmacokinetics are linear. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose.

Pemetrexed is approximately 81% bound to plasma proteins. The binding of pemetrexed to individual components of plasma such as albumin, alpha-1 glycoprotein, etc. was not evaluated. Pemetrexed did not appear to influence total platinum plasma clearance (CL_p) and steady state volume of distribution (V_{ss}), Nevertheless, since cisplatin is 98% bound to albumin in plasma, there is a concern that if pemetrexed is also bound to albumin and has a high affinity for this protein, a displacement of cisplatin to albumin may occur and lead to an increase of cisplatin exposure and toxicity. The applicant has committed to evaluate the protein binding of pemetrexed to individual principal components of human plasma such as albumin and p-alpha glycoprotein.

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Caution should be used with concomitant administration of pemetrexed and nephrotoxic drugs (e.g. aminoglycoside, loop diuretics, platinum compounds, cyclosporin) or substances that are also tubularly secreted (e.g. probenecid, penicillin). If necessary, creatinine clearance should be closely monitored. Adequate warnings have been included in the SPC (see section 4.5).

The fraction excreted unchanged into urine appeared to decrease progressively with severity of renal insufficiency. Renal function is the best predictor of overall systemic exposure. Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal (and hepatic) function. No dosing adjustments are required as long as patients have creatinine clearance of at least 45 ml/min. Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, when pemetrexed is combined with cisplatin, patients must receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving cisplatin. There are insufficient data on the use of pemetrexed in patients with creatinine clearance below 45 ml/min; therefore the use of pemetrexed is not recommended. These recommendations are adequately reflected in the SPC (see section 4.2). Overall, pemetrexed pharmacokinetics in patients with impaired renal function have been adequately investigated, and reported [78].

Pemetrexed undergoes limited hepatic metabolism. Results from *in vitro* studies with human liver microsomes indicated that pemetrexed would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2, as reflected in the SPC (section 4.5). Enzyme induction studies with pemetrexed have not been carried out. Lack of specific pharmacokinetic studies in patients with hepatic dysfunction has been adequately justified because pemetrexed is primarily eliminated unchanged by renal excretion, and metabolism plays a negligible role. No relationships between AST (SGOT), ALT (SGPT), or total bilirubin and pemetrexed pharmacokinetics were identified. However patients with hepatic impairment such as bilirubin > 1.5 times the upper limit of normal and/or transaminase > 3.0 times the upper limit of normal (hepatic metastases absent) or > 5.0 times the upper limit of normal (hepatic metastases present) have not been specifically studied. This has been reflected in the SPC (see section 4.2).

It is known that the combination of methotrexate with aspirin or non steroidal anti-inflammatory drugs as ibuprofen, decreases the renal clearance of methotrexate, and consequently, increases the haematoxicity of methotrexate.

In patients with normal renal function (creatinine clearance $\geq$ 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and aspirin at higher dosage ($\geq$ 1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of

pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or aspirin at higher dosage, concurrently with pemetrexed to patients with normal function (creatinine clearance $\geq$ 80 ml/min). In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min), the concomitant administration of pemetrexed with NSAIDs (e.g. ibuprofen) or aspirin at higher dosage should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration. In the absence of data regarding potential interaction with NSAIDs having longer half-lives as piroxicam or rofecoxib, the concomitant administration with pemetrexed should be avoided for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration (see SPC section 4.4 and 4.5).

European PK Guidelines recommend to assess the absence of interaction between two drugs indicated to be used in association [79]. Pharmacokinetics analyses of pemetrexed and cisplatin were performed in the Phase I study JMAP, and in a population pharmacokinetic analysis from the phase III study JMCH in MPM. No significant influence of concomitant cisplatin administration on pemetrexed clearance was observed (data not shown). The pharmacokinetics of total platinum were consistent with published literature values for single-agent cisplatin administration [80-82]. However, a specific analysis of the pharmacokinetic profile of ultrafilterable platinum allowing to predict a potential interaction between the two agents was lacking.

No significant influence of folic acid or vitamin B_{12} administration on pemetrexed clearance was identified (data not shown).

In conclusion, the pharmacokinetics of pemetrexed have been adequately investigated and reported, in agreement with applicable guidelines and requirements [60, 83]. Potential pharmacokinetic drug interaction have been adequately investigated and reported [79].

Pharmacodynamics

Pharmacodynamic analyses for pemetrexed focused on exploring relationships between measures of hematologic toxicity (nadirs of neutrophil counts) with indices of systemic drug exposure (Cmax and AUC0-∞). In 8 Phase 2 studies included in the population pharmacodynamic analyses, pemetrexed was administered as a 10-minute i.v. infusion every 21 days. Initial doses (Cycle 1) were 500 to 600 mg/m^2. Dose adjustment (reduction) at the start of subsequent courses of therapy were based on nadir counts or maximal nonhematologic toxicity from the preceding cycle of therapy. The time course of ANC was adequately characterized by a seven-compartment semi-physiologic mechanistic pharmacokinetic/ pharmacodynamic model [84].

Between-patient variability was adequately characterized based on precision of variance parameter estimates (30.3% with 32.7 %standard error of the estimate, SEE for BAS, 9.85% with 28.7 %SEE for MTT, 45.6% with 29.0 %SEE for the DS parameter, and 27.6% with 38.4 %SEE for the FP). The "typical" patient receiving 500 mg/m^2 pemetrexed was predicted to have a nadir absolute neutrophil count (NANC) of $1.77 \bullet 10^9$/L and had approximately 50% probability of remaining at CTC Grade 0 toxicity (above $2 \bullet 10^9$/L) following pemetrexed administration. Systemic drug exposure was the dominant predictor of absolute neutrophil response to pemetrexed. Increased homocysteine and cystathionine were associated with lower NANC. There appeared to have been no change in the effect of pemetrexed on NANC following multiple treatment cycles.

Gender had no significant effect on absolute neutrophil response to pemetrexed administration. Age (range 26 to 79 years) had no significant effect on absolute neutrophil response to pemetrexed administration. Caucasians and patients of African descent had similar absolute neutrophil response to pemetrexed administration. Insufficient data were available to generalize for other ethnic groups (for example, Asian, Hispanic). Alcohol consumption did not affect absolute neutrophil response to pemetrexed administration. Smoking did not affect absolute neutrophil response to pemetrexed administration.

Discussion on pharmacodynamics

Systemic drug exposure was the dominant predictor of absolute neutrophil response to pemetrexed. Dosing based on renal function (creatinine clearance) has been considered. Safety results from the clinical studies (See Clinical Safety) have shown that there was no evidence that decreasing renal function was associated with increasing toxicities when pemetrexed was administered alone or in

combination with cisplatin. Hence, no dosing adjustments are required as long as patients have creatinine clearance of at least 45 ml/min. A minimum CrCl of 45 ml/min is recommended before pemetrexed administration for all patients (including patients with decreased renal function due to age). Adequate dosing recommendations and warnings have been provided in the SPC (see Section 4.2 and 4.4)

Increased homocysteine and cystathionine, which are predictive of vitamin B_{12} and folate deficiency [85, 86], were associated with lower nadir absolute neutrophil count (NANC) with pemetrexed. A correlation between high serum homocysteine and increased risk of Grade 4 neutropenia with Grade 3 or 4 infection, and Grade 3 or 4 diarrhea for pemetrexed has been reported [87]. Exploratory analyses of study JMCH showed that overall Grade 3/4 toxicities were reported less frequently in the fully supplemented patients than the non-supplemented patients with statistically significant differences occurring for leukocytes, nausea, vomiting, and febrile neutropenia. Integrated safety analyses of single-agent pemetrexed showed significanct differences in Grade 3 or 4 neutropenia and thrombocytopenia when supplemented patients are compared with nonsupplemented patients at either 500 or 600 mg/m^2 dose of pemetrexed.

In conclusion, the results from these analyses support the use of vitamin supplementation to ensure normal vitamin B_{12} and folate status to control hematologic toxicity secondary to pemetrexed administration. Folinic acid and folic acid are both systemically metabolized to active folate cofactors. Folinic acid, or folic acid in high doses, result in supranormal plasma concentrations of active folate cofactors that can cause the displacement of accumulated antifolate compounds from tissues. Conversely, low-dose folic acid supplementation providing adequate pools of active cofactors in tissues can prevent uptake, polyglutamation and target interaction of antifolates. Low-dose supplementation has been shown to reduced pemetrexed toxicity with preservation of pemetrexed antitumor activity [88]. Normal tissues have lower folate requirements than tumor tissues [89, 90]. Vitamin supplementation might satisfy the need in normal tissue but not in tumor tissue. This theory might explain how dose limiting toxicity of pemetrexed can be reduced by folic acid while at the same preserving pemetrexed efficacy.

Clinical efficacy

Dose-finding studies, and the clinical studies submitted to support the demonstration efficacy in the MPM and NSCLC indications are reviewed and discussed separately in the following sections.

Dose finding studies

Single-agent pemetrexed

Three Phase 1 dose-escalation studies were conducted (JMAA, JMAB, BP-001) The initially recommended dose of pemetrexed for Phase 2 trials was 600 mg/m^2 on Day 1 every 21 days was based on study JMAA [91]. Pemetrexed was administered as a 10-minute i.v. infusion every 21 days over a dose range of 50 to 700 mg/m^2, without folic acid and vitamin B_{12} supplementation. The MTD from this dosage regimen was determined to be 600 mg/m^2. The main dose-limiting toxicities (DLTs) were neutropenia, thrombocytopenia, and chronic fatigue.

Doses of 500 and 600 mg/m^2 were evaluated in a variety of subsequent Phase 2 studies in various solid tumor types. However, toxicities observed in a Phase 2 colorectal study led to a decrease in the pemetrexed dose to 500 mg/m^2 on Day 1 every 21 days. Initial analyses using a multiple logistic regression model were able to quantify the relative risk of developing toxicities with pemetrexed and generated a validated clinical hypothesis on ways to improve the safety profile of pemetrexed. Levels of pretreatment total plasma homocysteine and methylmalonic acid significantly predicted Grade 4 neutropenia, Grade 4 thrombocytopenia, Grade 3/4 diarrhea, and Grade 3/4 mucositis. Thus, it was postulated that reducing homocysteine levels with folic acid and vitamin B_{12} supplementation would reduce severe toxicities. Further prospective trials with vitamin supplementation demonstrated that the pemetrexed safety profile was improved [87].

Study JMAB was a Phase 1 study in patients with various solid tumors of pemetrexed administered as a bolus intravenously every 7 days, over a dose range of 10 to 40 mg/m^2, without folic acid and vitamin B_{12} supplementation. The MTD was determined to be 30 mg/m^2. Inability to maintain weekly treatment due to neutropenia limited dose escalation in this study. Study BP001 was a Phase 1 study in

patients with various solid tumors of pemetrexed administered as a 10-minute i.v. infusion once a day for 5 consecutive days, followed by 16 days of rest, to complete a 21-day cycle, over a dose range of 0.2 to 5.2 mg/m^2. The MTD was determined to be 4.0 mg/m^2, with neutropenia as the most predominant DLT. This dosing regimen was not studied further due to lack of efficacy.

Pemetrexed in combination with cisplatin

H3E-MC-JMAP was a single-center Phase 1 study of pemetrexed and cisplatin on Day 1 every 21 days in patients with locally advanced or metastatic solid tumors who could have received prior chemotherapy. The study was extended and additional patients were enrolled in order to collect data regarding the administration of pemetrexed on Day 1 and cisplatin on Day 2. Pemetrexed was administered at dose levels ranging from 300 mg/m^2 to 600 mg/m^2 in conjunction with varying dose levels of cisplatin (from 60 mg/m^2 to 100 mg/m^2). A total of 54 patients were enrolled in the study and of these 51 patients received study drug. The majority of patients were male and had a Performance Status of 1. In the initial treatment schedule (both pemetrexed and cisplatin administered on Day 1), the MTD-defining toxicity of CTC Grade 4 thrombocytopenia was at Dose Level 6 (600 mg/m^2 pemetrexed and 100 mg/m^2 cisplatin). Dose Level 5 was initially chosen for Phase 2 studies. However, due to toxicities observed in two National Cancer Institute Canada Clinical Trials Group single-agent Phase 2 studies (H3EMC-JMAO and H3E-MC-JMAN), the recommended Phase 2/3 dose for this combination became 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin. In the study extension segment (pemetrexed administered on Day 1 and cisplatin administered on Day 2), the MTD and the recommended Phase 2 dose for the study extension segment is Dose Level 4 (500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin). Myelosuppression was noted at all dose levels and, in all cases, was considered to be possibly or probably related to study therapy but not dose-related. One study drug-related death occurred at each of the 2 levels tested in this extended cohort compared with no study drug-related deaths in the original cohort. Thus, the schedule investigated in Cohort 2 – pemetrexed on Day 1 and cisplatin on Day 2 – was concluded to be more toxic. Therefore, the recommended schedule for further studies was administration of pemetrexed in combination with cisplatin on Day 1. Of the 51 patients who received study drug, 1 patient experienced a complete response, 14 patients had a partial response, 21 patients had stable disease, and 10 patients had progressive disease as their best response. In 11 patients with MPM evaluable for response, 5 partial responses were observed. Plasma concentration data were collected on 15 patients (10 males and 5 females) in this study. 4 patients received initial treatment schedule and 11 patients received extended treatment schedule. Although the sample size was small, the applicant claimed that concomitant administration of pemetrexed and cisplatin regimen did not appear to alter the pharmacokinetics profile of each drug.

H3E-MC-JMAU was a dose-finding Phase 1 study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma [92-96].

Main studies (malignant pleural mesothelioma)

Study JMCH ("EMPHACIS"), was an international, multicenter, single-blind, randomized Phase 3 trial of pemetrexed in combination with cisplatin versus cisplatin monotherapy in patients with MPM who had received no prior chemotherapeutic regimens [97].

Patients and methods

- Study participants – eligibility criteria

Patients with histologically proven pleural mesothelioma who were not candidates for curative surgery were assessed for eligibility. Histological diagnosis was based on local pathology; however, independent centralized pathology review was carried out on all patients, if feasible.

Eligibility requirements included uni- or bidimensionally measurable disease, age ≥18 years with life expectancy ≥12 weeks, and a Karnofsky performance status of ≥ 70, signed informed consent from the patient. Patients were not eligible if they had prior chemotherapy, a second primary malignancy, or brain metastases, or if they were unable to interrupt nonsteroidal anti-inflammatory drugs. Patients had to have adequate organ function (ANC ≥1.5×10^9/L, platelets ≥100×10^9/L, hemoglobin ≥9 g/dL, bilirubin ≤1.5 times the ULN, alkaline phosphatase, AST and ALT ≤3.0 times the ULN, or ≤5 times the ULN if there was tumor involvement in the liver, albumin ≥2.5 g/dL, CrCl ≥45 ml/min by using

the lean body mass formula only) [98]. Patients with reproductive potential must have been using an approved contraceptive method if appropriate during and for 3 months after the study.

- Treatments

Pemetrexed was administered i.v. at 500 mg/m^2 over 10 minutes, followed 30 minutes later by cisplatin 75 mg/m^2 i.v. over 2 hours on day 1 of a 21-day cycle. Patients assigned to the cisplatin arm were treated likewise, except normal saline was given in the place of pemetrexed at equivalent volume. For both arms a regimen was defined as six cycles of therapy. In response to an unacceptable level of toxicity (particularly Grade 4 neutropenia with Grade 3 or 4 infection, and Grade 3 or 4 diarrhea) and pemetrexed-related death, the applicant conducted several analyses to illustrate the relationship between folate status and severe pemetrexed-related toxicity [87]. Using homocysteine level as a marker for folate deficiency, the applicant showed this marker to be highly correlated with several key toxicities. The applicant then decided, with the guidance of experts in folate metabolism, to require all patients in pemetrexed trials to take folic acid and vitamin B12 for supplementation (JMCH protocol amendment C). Folic acid 350 to 1,000 μg was taken orally daily beginning 1 to 3 weeks before the first chemotherapy doses, continued throughout study and for 1 to 3 weeks after the patient discontinued the treatment. Vitamin B12 1,000 μg was given intramuscularly 1 to 3 weeks before the first dose of study therapy and repeated every 9 weeks until the patient discontinued the study therapy. In addition, based on the early clinical experience with pemetrexed and reported cutaneous toxicity, dexamethasone was chosen as primary prophylaxis for skin rash. Dexamethasone (4 mg orally twice a day) was given the day before, day of, and day after pemetrexed dosing to reduce the risk of severe skin rash. Both vitamin supplementation and dexamethasone were given to patients in both arms to maintain patient blinding to study therapy. Other chemotherapy, immunotherapy, or hormonal therapy was not permitted. Supportive care therapies were allowed per protocol during the study.

Dose adjustments for hematologic toxicity were based on a stepwise reduction schedule. Grade 3 or 4 mucositis, diarrhea requiring hospitalization, or grade 3 or 4 nonhematologic effects also resulted in dose reduction for subsequent doses. Dose escalations were not allowed.

- Objectives / Endpoints

The primary objective of this study was to compare survival in chemonaive patients with malignant pleural mesothelioma (MPM) when treated with pemetrexed plus cisplatin combination therapy to survival in the same patient population when treated with cisplatin alone. Survival was defined as the time from randomization to time of death from any cause.

The secondary objectives were to compare tumor response rate, duration of response, time to progressive disease, time to treatment failure between treatment arms. The response criteria were define using a combination of modified Southwest Oncology Group (SWOG) [99] criteria and RECIST [100] response criteria, for bidimensionally and unidimensionally measurable lesions, respectively. A responder was defined as any patient who had a complete response (CR) or a partial response (PR). All responses were documented by using appropriate diagnostic tests that were repeated approximately every 6 weeks to continue evaluation using consistent methods and independent response review. The duration of response was defined as the time from first objective assessment of response to disease progression, or death because of any cause.

Other secondary endpoints were clinical benefit (CB) response rate was evaluated by using an algorithm of performance status, analgesic consumption, patient-reported pain intensity, and dyspnea. Lung Cancer Symptom Scale (LCSS), pulmonary function test scores (forced vital capacity, vital capacity, forced expiratory volume), lung density, toxicity. Additional secondary objectives of this study were to assess toxicity between patients who received folic acid and vitamin B12 supplementation and patients who did not, to assess PK effects, and to collect information regarding vitamin deficiency markers (homocysteine, methylmalonic acid, cystathionine)

- Sample size and Interim analysis

The sample size indicated in the first protocol is 150 total patients (75 per treatment arm) with tumour response as primary endpoint. Thereafter, prior to enrollment of the first patient, the primary endpoint was amended to overall survival. The sample size was changed to ensure 80% power to detect a

hazard ratio of .67 (a 33% reduction in the hazard ratio) based on a two-sided log rank test ($\alpha = 0.05$). The number of deaths required is 197, and an enrolment of 280 patients (140 patients per arm) was planned. Supplementation was implemented after 118 patients had been randomized, of these 117 were treated. After supplementation was implemented, enrollment was extended to ensure that at least 280 fully supplemented (FS) patients were included, allowing adequate power for a secondary subgroup analysis (the population for the interim and final analysis remained the entire population, regardless of supplementation status). For this purpose, two distinct patient groups were defined. One group of patients was classified as FS if they were randomized to a treatment group on or after 02 December 1999. The intent was that these patients would begin supplementation during the baseline period and continue during their entire course of treatment. The second group included patients who were partially supplemented (PS) and who were never supplemented (NS); this group was classified as non supplemented (PS+NS) if they were randomized to a treatment group before 02 December 1999.

A prospectively planned interim analysis of survival was conducted and presented on 23 July 2001 to the Data Monitoring Board (DMB). This analysis was based on 296 patients who received therapy (FS, PS, and NS patients).

- Randomization

Randomization was dynamically balanced [101] for the following factors: performance status (KPS ≥90 *v.* <90), degree of measurability of disease (unidimensional *v.* other), histologic subtype (epithelial *v.* other), baseline WBC (WBC ≥8.3 10^9/L *v.* <8.3 10^9), pain intensity at entry (baseline score <20 mm on the visual analog scale of Question 6 in the LCSS patient scale *v.* ≥20 mm), analgesic consumption at entry (baseline score <60 mg morphine equivalents per day, only NSAIDs, or no analgesic consumption *v.* ≥60 mg), dyspnea at entry (baseline score <20 mm on the VAS of Question 4 in the LCSS patient scale *v.* ≥20 mm), baseline homocysteine levels (baseline homocysteine ≥12 μmol/L v.<12 μmol/L), gender, country, and treatment center. It was anticipated that most patients enrolled into study JMCH would be stage III/IV patients. Therefore, stratifying at randomisation for stage I/II versus stage III/IV was not considered useful.

- Methods of efficacy analyses / statistical analysis

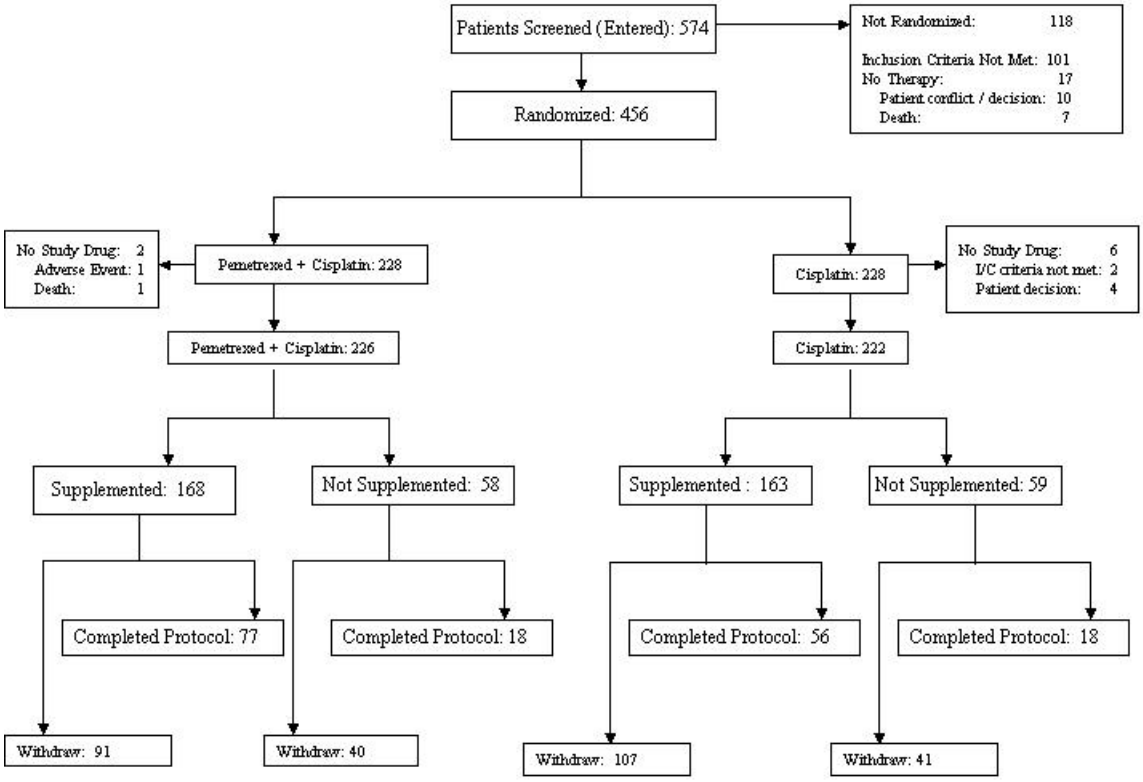
The primary analysis was comparison of survival time between the study arms in the RT population. The RT population was defined as all patients randomly assigned to a treatment arm and who started to receive at least one dose of study therapy. Differences were assessed using a two-sided log rank test. Because an interim analysis of efficacy ($\alpha = 0.01$) was conducted (resulting in a decision to continue the trial to planned completion), the comparison of survival was tested at the α=0.0476 level.

Results

- Participant flow and numbers analysed

Study JMCH included 88 investigational sites. The majority of patients enrolled into this study were from the United States, Germany, France, and Australia. Of the 456 patients randomly assigned to a treatment arm, 448 (98.2%) received LY/cis (n=226) or cisplatin monotherapy (n=222) (Figure 1).

Figure 1. Disposition of patients who entered Study JMCH



These patients constitute the RT population. Treatment arms were well balanced with respect to baseline characteristics. Patients were predominantly male and white, with a median age of 61 years (range, 19 to 85 years). Approximately two thirds of the patients had epithelial histology, whereas 78% had stage III or stage IV disease (Table 5). The most common site of disease included was pleural rind (98.3% in the tested arm and 97.8% in the control arm).

Table 5. Baseline characteristics for the analysis populations (Study JMCH)

		All randomized and treated (RT)		Full supplementation (FS)		Full or partial supplementation (FS+PS)	
		Pem/Cisp (n = 226)	Cisp (n =222)	Pem/Cisp (n = 168)	Cisp (n =163)	Pem/Cisp (n=194)	Cisp (n=184)
Age, years	Median	61	60	60	60	61	60
	Range	29-85	19-84	29-85	19-82	29-85	19-82
Gender	Male No. (%)	184 (81.4)	181 (81.5)	136 (81)	134 (82.2)	158 (81.4)	152 (82.6)
	Female No. (%)	42 (18.6)	41 (18.5)	32 (19)	29 (17.8)	36 (18.6)	32 (17.4)
Race	White No. (%)	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)	173 (89.2)	172 (93.5)
	Other* No. (%)	22 (9.7)	16 (7.2)	18 (10.7)	10 (6.1)	21 (10.8)	12 (6.5)
Performance status	70 No. (%)	37 (16.4)	31 (14)	25 (14.9)	22 (13.5)	28 (14.4)	25 (13.6)
	80 No. (%)	72 (31.9)	66 (29.7)	58 (34.5)	47 (28.8)	65 (33.5)	54 (29.3)
	90/100 No. (%)	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)	101 (52.1)	105 (57.1)

Histology [a]	Epithelial No. (%)	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)	135 (69.6)	127 (69)
	Sarcomatoid No. (%)	18 (8)	25 (11.3)	14 (8.3)	17 (10.4)	16 (8.2)	20 (10.9)
	Mixed cell No. (%)	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)	29 (14.9)	29 (15.8)
	Unspecified No. (%)	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)	14 (7.2)	8 (4.3)
Stage	I No. (%)	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)	16 (8.2)	12 (6.5)
	II No. (%)	35 (15.6)	33 (15)	27 (16.2)	27 (16.8)	32 (16.5)	29 (15.8)
	III No. (%)	73 (32.4)	68 (30.9)	51 (30.5)	49 (30.4)	63 (32.5)	58 (31.5)
	IV No. (%)	102† (45.1)	107† (48.2)	75† (44.6)	75† (46)	83 (42.8)	85 (46.2)

* Includes Hispanics, Asians, and patients of African descent. . [a] According to local diagnosis.
† Includes patients with unspecified stage (one patient in Pem/Cisp arm and two patients in Cisp arm).
Abbreviations: Pem, pemetrexed; Cisp, cisplatin.

- Efficacy results

At the cut-off for the primary analysis for survival, the median follow up was 9.3 months (range 0.1-29.2 months). The median overall survival time was 12.1 months *versus* 9.3 months, for pemetrexed/cisplatin *versus* cisplatin, respectively in the RT population. A statistically significant difference in the distribution of survival times was observed abetween the two treatments (log-rank P=0.020).

Cox regression was used to perform a secondary analysis of survival time, adjusting for important prognostic factors. As per protocol, 14 baseline variables were considered as potential prognostic factors. After model selection based on likelihood testing, a statistically significant treatment effect was shown (P =0.002). Other factors significantly (P <0.05) associated with increased survival time were supplementation (fully or partially), good KPS (KPS 90 or 100), early disease stage (stage I or II), and epithelial histological subtype. Baseline factors associated with decreased survival time were elevated WBC, and elevated cystathionine. No important association between homocysteine and survival was observed. The size of the treatment effect was consistent across levels of homocysteine (adjusted hazard ratio = 0.73, 95%CI: 0.46-1.15 and 0.65 95%CI: 0.49-0.87, for the ≥12 μmol/L and <12 μmol/L groups, respectively).

Efficacy results for primary and selected secondary analyses are summarised in Table 6 and Figure 2. Two assessments of tumor response rate were conducted, one on the basis of the investigators' determination and the second on the basis of an independent peer review. The results of the investigator assessment are consistent with those for the independent reviewer assessment. The median duration of response for responders in the RT population (n=130) was 5.75 versus 4.7 months, for pemetrexed+cisplatin *v.* cisplatin, respectively. The duration of investigator-determined responses was used for this analysis.

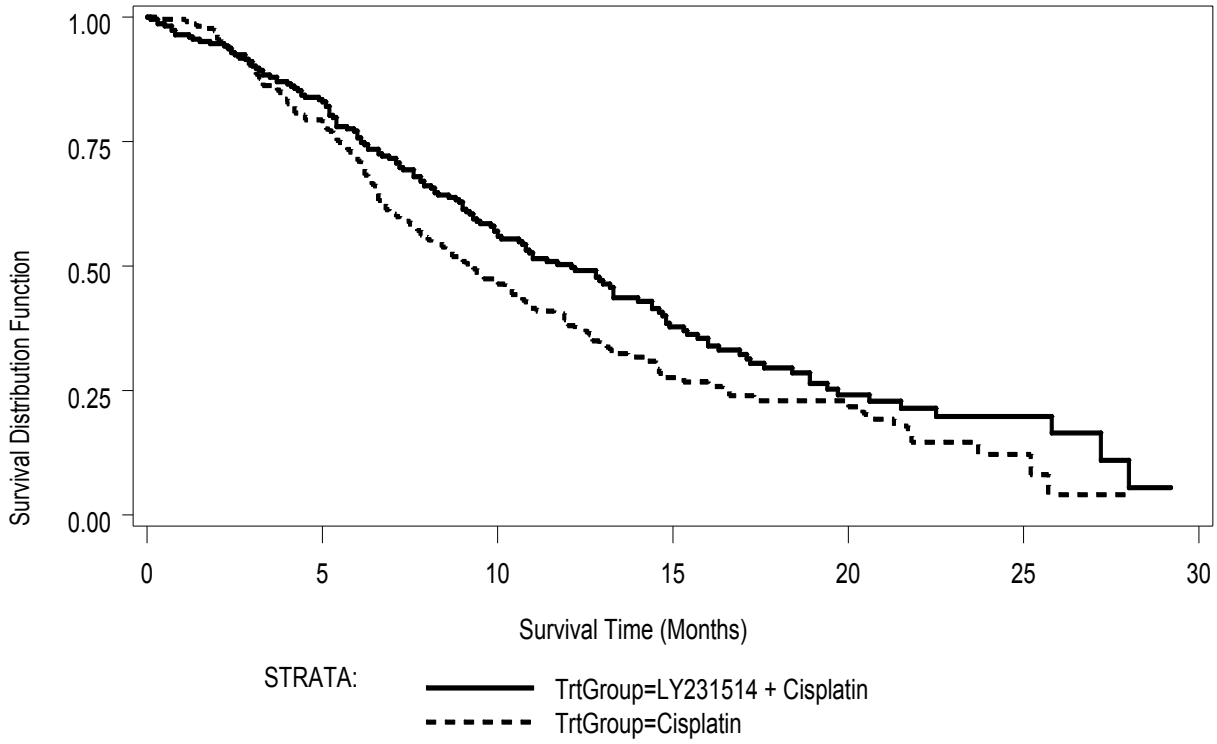
The analysis of individual parameters and especially for dyspnea and pain, showed that dyspnea was relatively unchanged in the pemetrexed/cisplatin arm, but increased in the cisplatin alone arm. This difference reached statistical significance at Cycle 6 in the RT population. A similar pattern was also seen in the FS groups. Pain decreased in the pemetrexed/cisplatin arm and increased in the cisplatin alone arm. From Cycle 3 through Cycle 6, scores were significantly different. A similar pattern was seen in the FS subgroup, although differences in scores did not reach statistical significance between arms. In the PS+NS subgroup, the cisplatin alone arm had a greater increase in pain with scores statistically different from the pemetrexed/cisplatin arm at Cycles 4 and 5. Concerning pulmonary function test, for each parameter (SVC, FVC, and FEV1), averaging over the entire treatment period, the pemetrexed/cisplatin arm had statistically significantly greater pulmonary function for all three parameters.

Table 6. Survival Time, Time to Progressive Disease, and Tumor Response Rate RT Population, FS, and FS+PS Subgroups H3E-MC-JMCH

	RT Population		FS Subgroup		FS+PS Subgroup	
	Pem/Cis (N=226)	Cisplatin (N=222)	Pem/Cis (N=168)	Cisplatin (N=163)	Pem/Cis (N=194)	Cisplatin (N=184)
Median survival (mo)	12.1	9.3	13.3	10.0	13.2	9.4
95% CI	10.0–14.4	7.8–10.7	11.4–14.9	8.4–11.9	10.9–14.8	8.4–11.6
Hazard ratio	0.77		0.75		0.71	
Log rank *P*-value	0.020		0.051		0.022	
12 month survival	0.50	0.38	0.57	0.42	0.54	0.41
P-value[a]	0.012		0.011		0.014	
TTPD (mo)	5.7	3.9	6.1	3.9	6.1	4.3
95% CI	4.9–6.5	2.8–4.4	5.3–7.0	2.8–4.5	5.4–6.7	3.0–4.9
Hazard ratio	0.68		0.64		0.70	
Log rank *P*-value	0.001		0.008		0.003	
Response rate (%) (Inv.)	41.3	16.7	45.5	19.6	45.6	19.0
95% CI	34.8–48.1	12.0–22.2	37.8–53.4	13.8–26.6	38.4–52.9	13.6–25.4
Fisher exact *P*-value	< 0.001		< 0.001		< 0.001	

Abbreviations: CI = confidence interval; Inv. = investigator assessed; mo=months; Pem/Cis = pemetrexed/cisplatin; TTPD = time to progressive disease. [a] Two-sided *P*-value based on the normal approximation.

Figure 2. Kaplan-Meier estimates of survival time for pemetrexed + cisplatin and cisplatin alone, RT population. H3E-MC-JMCH



Supportive studies (malignant pleural mesothelioma)

H3E-MC-JMDR was a Phase 2 study of single-agent pemetrexed in patients with MPM who had received no prior chemotherapeutic pemetrexed [102, 103]. Pemetrexed was administered as a 10-minute i.v. infusion at 500 mg/m^2 on Day 1 of a 21-day period. Prophylactic dexamethasone was administered. In order to improve patient safety the applicant amended the study protocol to add supplementation with low-dose folic acid (350 μg to 1000 μg) and vitamin B12 (1000 μg). As a consequence, the protocol-specified sample size was increased from 41 to 61 qualified patients. A total of 64 patients were enrolled in the study and received at least one dose of the study drug. The median age of patients enrolled was 65 years, and 82.8% of the patients were male. Most patients had a Karnofsky Performance Status of 90, a diagnosis of epitheloid pleural mesothelioma, and either stage III or stage IV disease. According to investigator assessment the overall tumor response rate was 9 / 64 (14.1% 95% CI: 6.6% to 25.0%), with 7 responders among patients who were enrolled in the study and assigned to receive low-dose folic acid and vitamin B12. The response rate was 17.9% (95% CI 8.9%, 30.4%), according to independent response review. Supplemented patients completed a median of 6 cycles of therapy, compared with a median of 2 cycles for nonsupplemented patients. Fever and leukopenia were the most commonly reported adverse events that led to reduction in the dose of pemetrexed. Supplementation was associated with less severe hematologic toxicity, particularly a lower incidence of Grade 4 neutropenia and leukopenia. Furthermore the trend suggested that supplementation may be associated with some improvement in Grade 3 and Grade 4 nonlaboratory toxicity.

Discussion on clinical efficacy in MPM

The MPM indication is supported by one phase III study, JMCH. This study was the first large trial performed in MPM which included more than 400 patients. The observed hazard ratio of 0.77, and a median difference in survival of 2.8 months in favour of pemetrexed in addition to cisplatin is of great clinical relevance in a disease for which currently no life prolonging treatment is known. In the subgroup of fully supplemented patients, the survival advantage was equally relevant. The effect of pemetrexed on survival can be explained by its outstanding antineoplastic activity against malignant mesothelial tumours when added to cisplatin. The effect was consistent across secondary efficacy endpoints such as objective response rate and progression-free survival. The effect was comparable across subgroups with different supplementation status.

The primary objective of this study, overall survival, is adequate in such a disease when expected overall survival is short. Concerning secondary objectives, the difficulties with assessing response and progression objectively are well known in this disease. The sample size is adequately justified after the protocol amendment requiring vitamin supplementation.

Baseline patient characteristics reflect what one would expect in the general MPM population i.e. most patients are male, had epithelial histology, a pleural mesothelioma localisation, and stage III or IV for their disease. The dynamic randomisation used was efficient in balancing the marginal distribution of important prognostic factors between treatment arms.

The conduct of the trial was complex, with several protocol amendments including changes from tumor response rate to a hard primary endpoint of survival, more than doubling of the sample-size due to the addition of vitamin supplementation. Although such changes would generally have prompted the conduct of a different trial, in the context of a rare disease such as mesothelioma, once centres recruiting effectively patients with MPM are available, it is acknowledged that to continue with the ongoing trial may have been the most efficient option available.

The population for the primary efficacy analysis defined in the protocol included only randomised patients that had started treatment, a definition, which is generally used for safety and not primary efficacy analyses. The exclusion of randomized patients from the population for the primary analysis violates fundamental statistical principles and cannot be considered an intent-to-treat analysis. However, in view of the small number of patients actually excluded, it is unlikely that a re-analysis on all randomized patients would result in radically different conclusions. A re-analysis of the data was therefore not requested but the methodological pitfall was noted.

The choice of the control group also required careful consideration. At the time when the study was designed, no established chemotherapy for MPM was available [19]. Concerning agents which had shown some activity, certain combination regimens such as with anthracycline / cisplatin reported better responses rates in phase II trials than single-agent therapy [104, 105]. No randomised trials have clearly established the role of combination regimen over single-agent chemotherapy (or indeed the clinical benefit of single-agent chemotherapy). Thus, the choice of a single therapy rather than a combined therapy as comparator is acceptable.

The 75 mg/m^2 every 3 weeks cisplatin regimen was used in place of more intense cisplatin dosing (e.g., 100 mg/m^2 every 3 weeks) in the control arm of trial JMCH. So far no clear dose-response effect has been shown in for single-agent cisplatin in the treatment of mesothelioma [106, 107]. Similar results were observed in NSCLC within a range of of 60 mg/m^2 to 120 mg/m^2 [108, 109]. In conclusion, the choice of control arm in the JMCH trials is acceptable.

The dose of 500 mg/m^2 pemetrexed, in combination with 75 mg/m^2 cisplatin, was selected because of toxicities observed in single-agent Phase 2 studies (without vitamin supplementation). It is possible that the 500 mg/m^2 of pemetrexed in combination with 75 mg/m^2 of cisplatin might not be the optimal dose with the addition of vitamin supplementation, and further studies are warranted. For the time being, the current dosing recommendation as described in the SPC are adequate, and are justified based on the efficacy and safety results from the main phase III trial.

Studies of pemetrexed (without the supplementation of folic acid and vitamin B12) identified myelosuppression as the principal dose-limiting toxicity, although nonhematologic toxicities of mucositis, diarrhea, vomiting and infection were also significant. This toxicity profile is consistent with those of other antifolates. During the trial, toxicities such as Grade 4 neutropenia with Grade 3 or 4 infection, and Grade 3 or 4 diarrhea, and pemetrexed-related death in patients receiving pemetrexed resulted in a decision to add folic acid and vitamin B12 supplementation in both treatment arms. Folic acid 350 to 1,000 μg was taken orally and Vitamin B12 1,000 μg was given intramuscularly. The supplementation regimen was chosen based on a combination of theoretical, and practical considerations. From the data obtained thus far in the clinical development of pemetrexed, no definitive conclusions can be drawn regarding the contribution of supplementation to efficacy. Concerning safety, since vitamin supplementation considerably improves the toxicity profile, albeit in a non-randomised comparison pragmatically, it has been proposed that all patients (regardless of homocysteine plasma level) might benefit from vitamin supplementation.

There are limited data in patients with malignant pleural mesothelioma treated with pemetrexed alone. The uncontrolled phase II study JMDR (see Dose finding for MPM) showed that pemetrexed when administered as single agent to patients with malignant pleural mesothelioma has an antitumor activity in the range of such data published for other single agents as cisplatin, doxorubicin and gemcitabine. Most of the patients who responded were fully supplemented. The safety profile was also improved in supplemented patients with a lower incidence of haematologic toxicity, particularly Grade 3 and Grade 4 neutropenia and leukopenia.

Main studies (NSCLC)

Study JMEI, was a multi-center, randomized, phase III trial comparing pemetrexed vs docetaxel in previously treated patients with histologic or cytologic diagnosis of locally advanced or metastatic (stage III or IV) NSCLC [110].

Patients and methods

- Study participants – eligibility criteria

The main inclusion criteria were designed to select patients at least 18 years of age with histologic or cytologic diagnosis of NSCLC with locally measurable and/or evaluable advanced or metastatic disease (stage IIIA, IIIB or IV at entry) that was not amenable to curative therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients should have received previous treatment consisting of neoadjuvant chemotherapy, neoadjuvant followed by adjuvant chemotherapy (only a single regimen was allowed), adjuvant chemotherapy or chemotherapy for advanced disease. Patients were also eligible if they had received one chemotherapy regimen as neoadjuvant, neoadjuvant followed by adjuvant, or adjuvant chemotherapy and a different

chemotherapy regimen for advanced disease. Only a single regimen was allowed for prior therapy of advanced disease. Patients had to have, adequate organ function including the following: absolute neutrophil (segmented and bands) count (ANC $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥9 g/dL, bilirubin ≤ ULN, AST and ALT ≤ 1.5 ULN, alkaline phosphatase ≤ 5 ULN. CrCl ≥45 ml/min using the lean body mass formula only) [98]. Patients with symptomatic brain metastases, or with presence of clinically detectable (by physical exam) third-space fluid collections that cannot be controlled by drainage or other procedures prior to study entry, or with significant weight loss (ie, ≥10%) over the previous 6 weeks before study entry, with prior treatment with either pemetrexed or docetaxel, CTC Grade 3 or 4 peripheral neuropathy were not eligible. Patients with reproductive potential must have been using an approved contraceptive method if appropriate during and for 3 months after the study. Females with childbearing potential must have had a negative serum pregnancy test within 7 days prior to study enrollment.

- Treatments

Pemetrexed was administered at 500 mg/m^2 as a 10-minute i.v. infusion on Day 1 of a 21-day cycle. All Pemetrexed patients were required to take folic acid, vitamin B12, and prophylactic dexamethasone (4 mg, orally BID on the day before, the day of and the day after each dose of pemetrexed, unless clinically contraindicated).

No other chemotherapy, immunotherapy, hormonal cancer therapy, surgery for cancer, or experimental medications (with the exception of thymidine) was permitted while the patients were receiving study therapy. Palliative radiation therapy was permitted for irradiating small areas of painful metastasis that could not be managed adequately using systemic or local analgesics. Routine use of colony-stimulating factors (CSFs) was not permitted. Patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) or salicylates were not permitted the NSAID or salicylate on the 2 days before, the day of, and the 2 days after receiving pemetrexed. If a patient was taking an NSAID or salicylate with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone), it should not have been taken on the 5 days before, the day of, and the 2 days after receiving pemetrexed. Leucovorin was allowed for CTC Grade 4 leukopenia, CTC Grade 4 neutropenia lasting greater than 3 days, or immediately for CTC Grade 4 thrombocytopenia, or bleeding associated with Grade 3 thrombocytopenia.

Docetaxel was administered at 75 mg/m^2 as a 1-hour i.v. infusion on Day 1 of a 21-day cycle. Dexamethasone 16 mg orally, was administered daily (eg, 8 mg BID) for 3 days starting 1 day prior to each dose of docetaxel (or equivalent regimen), unless clinically contraindicated, to reduced the severity of fluid retention and hypersensitivity reaction. The docetaxel regimen was chosen as the active control based on two randomized Phase 3 studies of docetaxel [29, 30].

Antiemetic therapy was to be administered according to standard local practice.

- Outcomes/endpoints

The primary objective of study JMEI was to show non-inferiority in overall survival following treatment with pemetrexed versus docetaxel in patients with locally advanced or metastatic (stage IIIA, IIIB or IV) NSCLC who had been previously treated with chemotherapy. Overall survival time was defined as the time from the date of randomization to date of death due to any cause, or censoring.

Secondary endpoints included toxicity, progression-free survival, time to documented disease progression, time to treatment failure, objective tumor response, duration of response, and changes in the average symptom burden index between the pemetrexed and docetaxel arms by using the Lung Cancer Symptom Scale (LCSS). Time-to-event efficacy variables were compared between treatment arms using the Cox proportional hazards model. Tumor response measurement was done according to Southwest Oncology Group (SWOG) criteria [99].

- Sample size and Interim analysis

A sample size of 520 randomized patients was chosen assuming no more than 26% censoring in order to oberve 385 deaths necessary based on consideration of the primary comparison of overall survival between treatment arms using the Cox proportional hazard model with treatment as the only factor. From the Cox model, a two tailed 95% confidence interval for HR was used to simultaneously evaluate the null hypotheses of HR≥1.00 (pemetrexed not superior) and HR≥1.11 (pemetrexed

inferior). This sample size ensured about 80% chance of demonstrating statistically significant superiority of pemetrexed for a true value of HR of 0.75, or noninferiority for a true value of HR of 0.83. Statistical power was calculated using methods developed for the log-rank statistic [111, 112], and using the asymptotic equivalence of the Cox model to one form of the log-rank statistic [113]. No interim analyses of efficacy were planned.

- Randomization

The algorithm of Pocock and Simon [101], using a probability factor of 0.75, was applied to balance the treatment arms for the following factors: ECOG Performance Status (2 *v.* 0 or 1), prior platinum-containing chemotherapy (Yes *v.* No), prior paclitaxel-containing chemotherapy (Yes *v.* No), baseline homocysteine level (<12 μM *v.* ≥12 μM), number of prior chemotherapy regimens (1 *v.* 2), time since last chemotherapy (<3 months *v.* ≥3 months), best response to last prior chemotherapy (CR/PR/SD *v.* PD or unknown, disease stage (III *v.* IV), investigational centre.

- Methods of efficacy analyses / statistical analysis

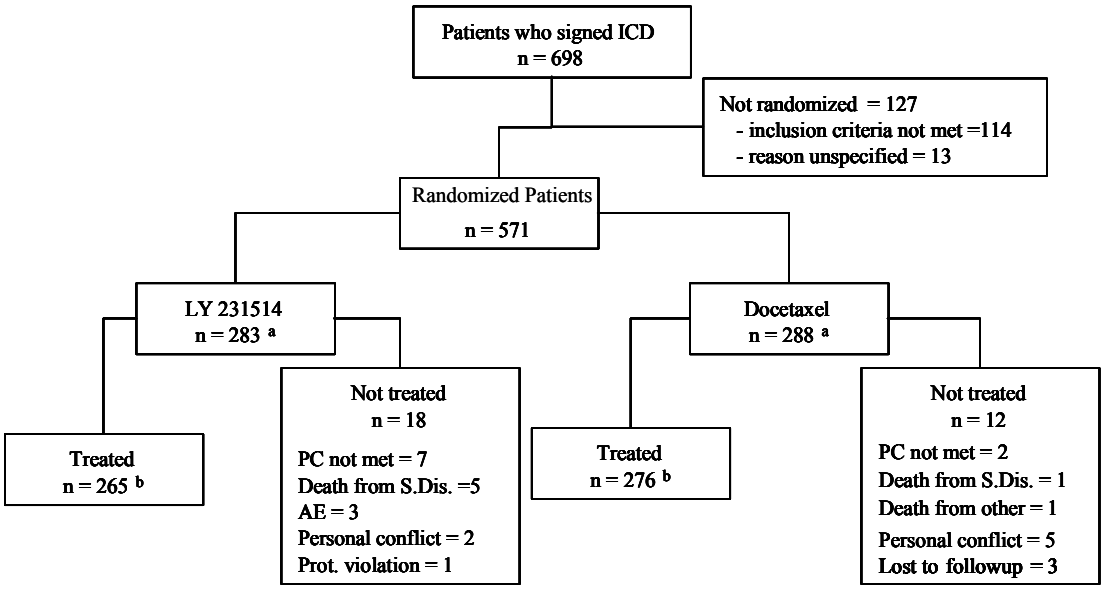
Noninferiority of PEMETREXED over docetaxel in overall survival was defined by HR <1.11. Prior to unblinding of the trial data, another (secondary) noninferiority criterion was defined in the analysis plan, whereby noninferiority was defined by HR <1.21. This new margin was determined by the Rothmann method [114], so as to preserve a study-wide type I error rate of about 0.025 for testing for the retention by pemetrexed of 50% of the assumed efficacy of docetaxel over BSC in the trial population. In terms of HR of docetaxel over BSC this was assumed to be 0.56 (95% CI, 0.35 to 0.88), based on a previous study [29]. The HR and the 95% confidence interval (CI) for pemetrexed over docetaxel were calculated based on the Cox proportional hazards model with therapy arm as the only variable. From the Cox model, a two-tailed 95% confidence interval for HR was used to evaluate the null hypotheses (the resulting non-inferiority tests can be viewed as one-tailed at the 0.025 level). The primary analysis was conducted in the intent-to-treat population (ITT), defined as all patients randomly assigned to a treatment arm whether or not they received study drug. Secondary analyses for overall survival were performed on patients who were randomized and treated (RT) with at least one cycle of therapy.

Results

- Participant flow and numbers analysed

Study JMEI screened 698 patients at 135 investigational sites in 23 countries. The ITT population consists of 571 patients randomized to either pemetrexed (n=283) or to docetaxel (n=288) (Figure 3) and constitute the ITT population. This includes all randomized patients, except for all patients (n=4) from one centre that was excluded from all analyses of efficacy (and safety) before analysis, because the investigator at this site did not meet applicable regulatory requirements for participating in the study.

Figure 3. Disposition of patients while on-study and until 30 days after the last dose of study drug. H3E-MC-JMEI



Abbreviations: AE = adverse event; CD = Informed Consent Document; LY231514 = pemetrexed; PC =protocol criteria; S. Dis = study disease. [a] intent to treat (ITT) population. [b] randomized and treated (RT) population.

- Baseline characteristics

Baseline characteristics are summarised in Table 7-8. In order to allow the comparison between the Shepherd trial [29] and study JMEI by the percent retention method, patient baseline demographics and disease characteristics of these two trial have been compared. Age and stage of disease at baseline were similar. In the Shepherd trial, more patients had an ECOG Performance Status 2, more patients had prior chemotherapy (with at least 2 regimens), and fewer responders to prior chemotherapy than when compared with the JMEI study. Also, all patients had prior platinum therapy, and no patients received prior taxane in the Shepherd study.

Table 7. Summary of patient characteristics and Baseline Stratification Factors Used for Randomization ITT Population H3E-MC-JMEI

		Pemetrexed n=283	Docetaxel n=288	ALL N=571
Sex No. (%)	Female	89 (31.4)	71 (24.7)	160 (28.0)
	Male	194 (68.6)	217 (75.3)	411 (72.0)
Origin No. (%)	African Descent	8 (2.8)	8 (2.8)	16 (2.8)
	Western Asian	20 (7.1)	23 (8.0)	43 (7.5)
	Caucasian	203 (71.7)	200 (69.4)	403 (70.6)
	East/Southeast A	44 (15.5)	49 (17.0)	93 (16.3)
	Hispanic	4 (1.4)	6 (2.1)	10 (1.8)
	Other	4 (1.4)	2 (0.7)	6 (1.1)
Age (years)	Mean	58.44	58.05	58.24
	Median	59.00	57.00	58.00
	Standard Dev.	10.47	9.49	9.98
	Minimum	22.00	28.00	22.00
	Maximum	81.00	87.00	87.00
Histological subtype No. (%)	Adenocarcinoma	154 (54.4)	142 (49.3)	296 (51.8)
	Bronchoalveolar	4 (1.4)	1 (0.3)	5 (0.9)
	Squamous	78 (27.6)	93 (32.3)	171 (29.9)

	Other	47 (16.6)	52 (18.1)	99 (17.3)
Stage of disease No. (%)	Stage IIIA	14 (4.9)	13 (4.5)	27 (4.7)
	Stage IIIB	57 (20.1)	60 (20.8)	117 (20.5)
	Stage IV	212 (74.9)	215 (74.7)	427 (74.8)
Homocysteine No. (%)	*No. patients*	*283 (49.7)*	*286 (50.3)*	*569*
	LOW (< 12 umol/L)	202 (71.4)	197 (68.9)	399 (70.1)
	HIGH (>= 12 umol/L)	81 (28.6)	89 (31.1)	170 (29.9)
ECOG PS No. (%)	*No. patients*	*264 (49.1)*	*274 (50.9)*	*538*
	0	52 (19.7)	48 (17.5)	100 (18.6)
	1	182 (68.9)	192 (70.1)	374 (69.5)
	2	30 (11.4)	34 (12.4)	64 (11.9)

Table 8. Summary of prior treatment patient characteristics ITT Population H3E-MC-JMEI

		Pemetrexed n=283	**Docetaxel n=288**	**ALL N=571**
Prior Chemo No. (%)	1 Regimen	270 (95.4)	268 (93.1)	538 (94.2)
	2 Regimens	13 (4.6)	20 (6.9)	33 (5.8)
Prior Platinum No. (%)	Had No Prior Platinum	21 (7.4)	29 (10.1)	50 (8.8)
	Had Prior Platinum	262 (92.6)	259 (89.9)	521 (91.2)
Prior Taxane No. (%)	Had No Prior Taxane	210 (74.2)	208 (72.2)	418 (73.2)
	Had Prior Taxane	73 (25.8)	80 (27.8)	153 (26.8)
Best response to prior chemo. No. (%)	Complete Response	12 (4.2)	4 (1.4)	16 (2.8)
	Partial Response	89 (31.4)	101 (35.1)	190 (33.3)
	Stable Disease	106 (37.5)	93 (32.3)	199 (34.9)
	Progressive Disease	67 (23.7)	73 (25.3)	140 (24.5)
	Unknown or Not Done	4 (1.4)	11 (3.8)	15 (2.6)
	Not Evaluable	5 (1.8)	6 (2.1)	11 (1.9)
Time since last chemo No. (%)	*No. patients*	*278 (49.4)*	*285 (50.6)*	*563*
	<3 mos since last chemo	140 (50.4)	137 (48.1)	277 (49.2)
	>3 mos since last chemo	138 (49.6)	148 (51.9)	286 (50.8)

- Study outcome

A total of 283 patients on the pemetrexed arm and 288 patients on the docetaxel arm were included in the survival analysis of the ITT population. The median overall survival time for patients treated with pemetrexed was 8.3 months compared with 7.9 months for those treated with docetaxel. The HR was 0.99, (95% CI of 0.82 to 1.20) with a noninferiority *P*-value of 0.226 for testing HR of <1.11. This means that the noninferiority criteria were not met using the fixed margin method. The estimate of the percentage of survival benefit (docetaxel over BSC) retained by pemetrexed was 102% with the lower 95% CI bound of 52% (*P*=0.047). The results of overall survival time analyses for the RT population were consistent with those of the ITT population. Key primary and secondary efficacy results are presented in Table 9-10 and Figure 4-5.

Table 9. Summary of Survival Time (Months), ITT and RT Patients (H3E-MC-JMEI)

	ITT Patients (N=571)		RT Patients (N=541)	
	Pemetrexed (N=283)	Docetaxel (N=288)	Pemetrexed (N=265)	Docetaxel (N=276)
Median	8.3	7.9	8.4	8.0
95% CI for median	(7.0-9.4)	(6.3–9.2)	(7.4–9.4)	(6.7–9.2)
6 months	61.5	57.6	62.9	58.3
12 months	29.7	29.7	30.6	29.8
Percent censored	27.2	29.5	27.6	28.3
Hazard ratio	0.99		0.97	
95% CI for hazard ratio	(0.82–1.20)		(0.80–1.18)	
NI *P*-value for testing HR of <1.11	0.226		0.155	
% Retention Method				
% efficacy retained by pemetrexed	102%		105%	
95% CI of % benefit retained	(52%-157%)		(58%-168%)	
NI *P*-value for testing 50% retention	0.047		0.036	

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; N = number of patients in the population; n = number of patients in the treatment arm; NI = noninferiority; RT = randomized and treated.

Figure 4. Summary of Survival Time (Months), ITT and RT Patients (JMEI)

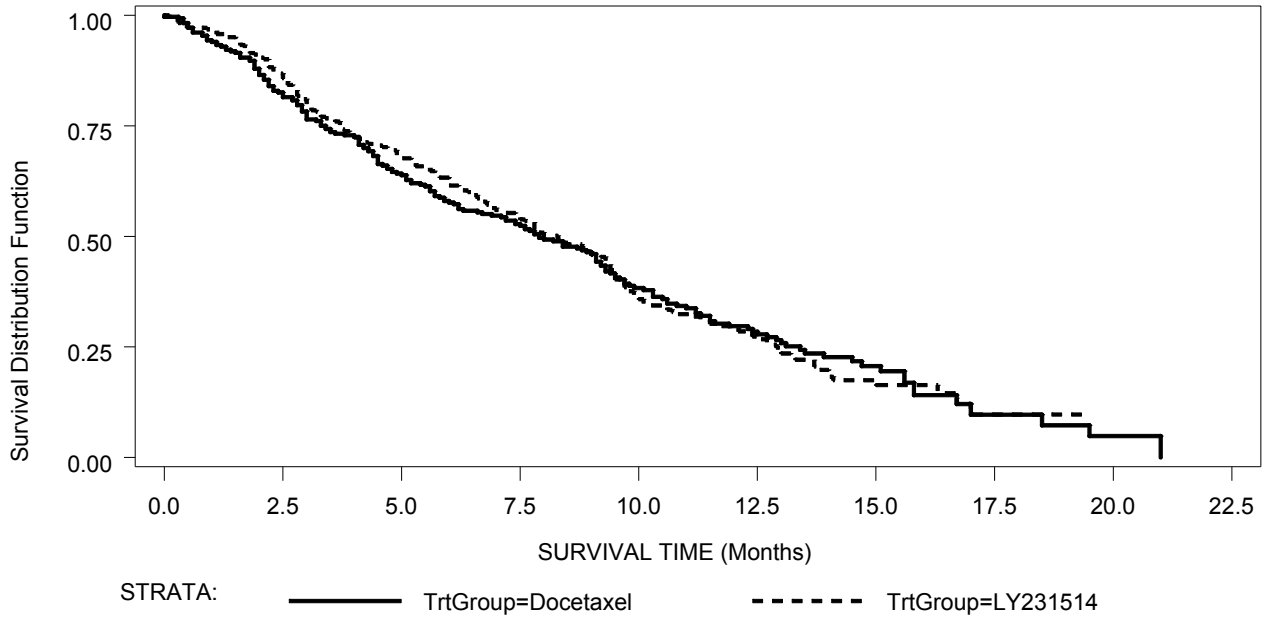
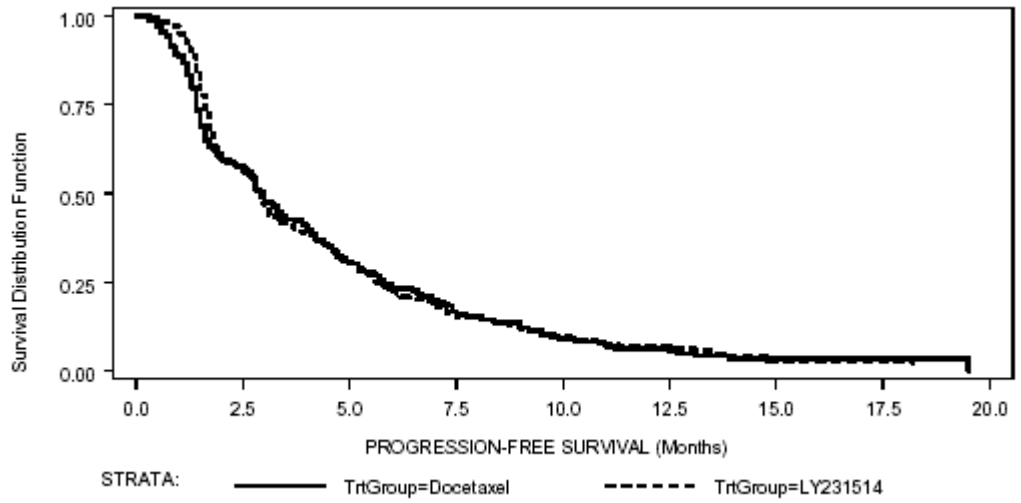


Table 10. Efficacy of Pemetrexed versus Docetaxel in NSCLC ITT Population

		Pemetrexed	Docetaxel
Progression-free Survival (months)	No. of patients evaluated	283	288
	Median	2.9	2.9
	HR (95% CI)	0.97 (0.82–1.16)	
	Wald *P*-value	0.759	
Time to progressive disease (months)	No. of patients evaluated	283	288
	Median	3.4	3.5
	HR (95% CI)	0.97 (0.80 – 1.17)	
	Wald *P*-value	0.721	
Time to Treatment Failure (months)	No. of patients evaluated	282	288
	Median	2.3	2.1
	HR (95% CI)	0.84 (0.71–.997)	
	Wald *P*-value	0.046	
Response	No. of patients evaluated	264	274
	Response rate (%) (95% CI)	9.1 (5.9–13.2)	8.8 (5.7–12.8)
	Stable disease (%)	45.8	46.4
Duration of tumor response (months)	No. of patients evaluated	24	24
	Median	4.6	5.3
	HR (95% CI)	0.77 (0.40– 1.47)	
	Wald *P*-value	0.427	

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat.

Figure 5. Progression-free survival RT population



Thirty % of the patients in the pemetrexed arm received docetaxel after failure of pemetrexed therapy. Post hoc analyses of overall survival in subgroups of patients who did not receive poststudy chemotherapy, those who received docetaxel poststudy chemotherapy, and those who received other poststudy chemotherapy were performed and summarized in Table 11. In the pemetrexed arm, the median survival of patients who received poststudy docetaxel was 1.0 months lower than the median survival of patients who received other poststudy chemotherapy.

Table 11. Survival based on poststudy chemotherapy (JMEI RT population)

Poststudy Therapy	Pemetrexed (n=265)		Docetaxel (n=276)	
	Pts (%)	Median Survival (mo)	Pts (%)	Median Survival (mo)
No poststudy chemotherapy	139 (52.4)	6.2	169 (61.2)	5.0
Poststudy docetaxel-containing therapy	85 (32.1)	9.6	11 (4.0)	10.1
Poststudy chemotherapy regimens not containing docetaxel	41 (15.5)	10.6	96 (34.8)	11.2

Duration of Clinical Benefit

The duration of clinical benefit was defined as the time since randomization to the progressive disease or death for patients who had a CR, PR (measurable or non-measurable disease), or stable disease. A total of 145 patients in the pemetrexed arm and 151 patients in the docetaxel arm were qualified for this analysis. Duration of clinical benefit for patients treated with pemetrexed was similar to that for the docetaxel patients (median time 5.4 months compared with 5.2 months). The HR was 0.91 with the 95% HR CI of 0.71 to 1.16.

Lung Cancer Symptoms Scale

Compliance was 89.0% (3317 of 3726 of expected questionnaires) for the pemetrexed arm and 85.1% (2995 of 3519 of expected questionnaires) for the docetaxel arm. The most commonly reported reason for not completing the LCSS was failure by the site to administer the questionnaire. Compliance may have been underestimated if patients had discontinued therapy before the end of the 3-week cycle.

A total of 507 randomized patients completed at least the six symptom items of the patient LCSS at baseline. The mean average symptom burden index at baseline for these patients was 27.7 mm with a standard deviation of 16.2 mm. Baseline mean average symptom burden indices for the two treatment arms were not different (27.8 mm for pemetrexed, 27.6 mm for docetaxel).

LCSS data from 227 patients (80.2%) in the pemetrexed arm and 247 (85.8%) in the docetaxel arm were included in average symptom burden index analysis.

Data from 239 patients (84.5%) in the pemetrexed arm and 233 (80.9%) in the docetaxel arm were included in the observer scale analysis. Patients were only included in the analysis if they had data for the baseline period and had data from at least one cycle.

A summary of changes in observer LCSS scores by treatment arm is presented in Table 12.

Table 12. Summary of LCSS Observer Scale Response (ITT Population Qualified for LCSS Analysis, JMEI)

LCSS Observer Scores		Pemetrexed (N=239) n(%)	Docetaxel (N=233)1 n(%)	*P*-value[2]
Anorexia	Improved	35 (14.6)	38 (16.3)	
	Stable	98 (41.0)	104 (44.6)	
	Failure	46 (19.2)	37 (15.9)	0.337
	Insufficient Data	60 (25.1)	54 (23.2)	
Fatigue	Improved	34 (14.2)	40 (17.2)	
	Stable	97 (40.6)	92 (39.5)	
	Failure	48 (20.1)	47 (20.2)	0.589
	Insufficient Data	60 (25.1)	54 (23.2)	
Cough	Improved	42 (17.6)	37 (15.9)	
	Stable	110 (46.0)	113 (48.5)	
	Failure	27 (11.3)	29 (12.4)	0.545
	Insufficient Data	60 (25.1)	54 (23.2)	
Dyspnea	Improved	27 (11.3)	30 (12.9)	
	Stable	125 (52.3)	109 (47.0)	
	Failure	27 (11.3)	39 (16.8)	0.416
	Insufficient Data	60 (25.1)	54 (23.3)	
Hemoptysis	Improved	11 (4.6)	8 (3.4)	

	Stable	157 (65.7)	162 (69.8)	
	Failure	11 (4.6)	8 (3.4)	1.000
	Insufficient Data	60 (25.1)	54 (23.3)	
Pain	Improved	38 (15.9)	44 (19.0)	
	Stable	115 (48.1)	100 (43.1)	
	Failure	25 (10.5)	34 (14.7)	0.800
	Insufficient Data	61 (25.5)	54 (23.3)	
Total (average)	Improved	64 (26.8)	65 (28.0)	
	Stable	44 (18.4)	48 (20.7)	
	Failure	70 (29.3)	65 (28.0)	0.712
	Insufficient Data	61(25.5)	54(23.3)	

Abbreviations: ITT = intention to treat; LCSS = Lung Cancer Symptom Scale; N = number of patients in the treatment arm; n = number of patients with observer scores. 1 N = 232 for dyspnea, hemoptysis, pain, total. 2 Mantel-Haenszel chi-square.

Ancillary analyses

A prospectively planned, stepwise Cox regression model of the JMEI survival data was constructed starting with seven of the nine baseline randomization factors (excluding homocysteine and center). Baseline homocysteine level was excluded as one of the factors because homocysteine had been shown at the time the study was started to be a predictor of toxicity and not of efficacy; a high baseline homocysteine level most clearly distinguished patients with an increased risk of severe hematologic and/or nonhematologic toxicities following treatment with pemetrexed. In addition, the omission of center from this model (because of modeling difficulties of including 135 centers in the model) is appropriate because the influence of center is always through other risk factors, and the important risk factors have all been included. The stepwise Cox procedure resulted in three significant cofactors (performance status, stage, and time since last chemotherapy) among the original seven (Table 13). When treatment arm is added to these three significant factors in the model, the survival comparison to the 10% margin very nearly reached statistical significance (*P*=0.051; hazard ratio upper confidence bound of 1.13). Additionally, this adjusted margin is equivalent to retaining at least 73% of the docetaxel survival benefit over BSC. Treatment effect was added to the final model with the above three significant factors to test for any difference and this analysis showed that there was no statistically significant difference in progression-free survival between the treatment groups (*P*=0.608).

Table 13. Summary of Model Selection on Overall Survival Time (ITT Population, H3E-MC-JMEI)

Variable	*P*-value	HR	95% Lower Limit	95% Upper Limit
Treatment (Pemetrexed over docetaxel)	0.051*	0.93	0.76	1.13
Performance status (0/1 over 2)	<.001	0.25	0.19	0.34
Time since last chemotherapy (≥3 months over <3 months)	0.004	0.74	0.60	0.90
Stage (III over IV)	0.026	0.77	0.60	0.97

Abbreviations: HR = hazard ratio (adjusted); ITT = intent to treat.

* Testing noninferiority for HR of 1.11.

Exploratory subgroup analyses were performed. No subgroup by treatment interactions was observed with either age or sex for overall survival time. Overall survival time was similar between the treatment arms in the subcategories of age (< 65 yrs., ≥65 yrs.) or sex (female, male). No significant prognostic factor (performance status, stage of disease and time since last chemotherapy) by treatment interactions were observed for overall survival.

Supportive studies (NSCLC)

Study JMBR was a phase 2 study of pemetrexed in second-line treatment of NSCLC. Pemetrexed was administered at 500 mg/m^2 by 10-min i.v. infusion once every 21 days. The investigators concluded

that pemetrexed has manageable side effects and may be considered to have sufficient activity to be developed further as a first or second-line treatment in NSCLC [115].

The applicant also conducted two trials in first-line NSCLC with single-agent pemetrexed (Study JMAL and Study JMAN) [116, 117]. Two additional studies were conducted to assess the effectiveness of pemetrexed plus cisplatin combination therapy in first-line patients with NSCLC (Study JMAY and Study JMBZ) [118, 119]. Trials JMBR, JMAL, JMAN, JMAY, and JMBZ were completed before the programmatic addition of folic acid and vitamin B_{12} supplementation.

Discussion on clinical efficacy- NSCLC

The survival data from trial H3E-MC-JMEI failed the test for non-inferiority in the main efficacy analysis (*P*-value of 0.226 for testing HR of 1.11). The non-inferiority margin of 10% had been chosen according to a Scientific Advice of the CPMP. After model selection and adjustments for selected prognostic factors (as secondary analysis), this test showed a borderline statistical significance (*P*=.051). Although the pre-specified non-inferiority criterion was not met, further analyses have shown that at least 52% (lower 95% CI) of the (historical) survival benefit of docetaxel over BSC was retained by pemetrexed of the survival benefit of docetaxel over BSC, assuming that a similar effect would have been observed in the population under study, i.e., a hazard ratio survival of docetaxel over BSC 0.56 (95% CI, 0.35 to 0.88), which corresponded to an observed median survival of 7.0 v 4.6 months. In comparison, a non-inferiority margin of 10% would correspond to a more stringent 78% retention of such an effect. It is noted that this estimates only refer to the subgroup which has received 75 mg/m² of docetaxel, not those patients which have received 100 mg/m² of docetaxel [29], and furthermore does not consider active comparators such as vinorelbine or ifosfamide [30]. These considerations weaken the relevance of the proposed noniferiority margin. Adjusted and unadjusted survival analyses have shown upper confidence limits between 1.13 and 1.20 (depending on the analysis). This range corresponds to a worst-case scenario of pemetrexed retaining 52% to 73% of docetaxel's historical benefit over BSC. Notably, this corresponds to at most a 16.1 to 3.6 days difference in median survival from the protocol-defined 10% margin. Thus, although inferiority of pemetrexed has not formally been excluded, based on the data provided it is still possible to rule out striking differences.

Clinical safety

Clinical safety of combination therapy of pemetrexed and cisplatin (MPM studies)

- Patient exposure

Among all patients in study JMCH, 1066 cycles were administered to patients on the LY/cis arm while 877 cycles were administered to patients on the cisplatin alone arm. In the RT population, a median of six cycles (range: 1 to 12 cycles) was completed on the pemetrexed/cisplatin arm compared with four cycles (range: 1 to 9 cycles) completed on the cisplatin alone arm.

Among FS patients, a median of 6 cycles of therapy was delivered on the pemetrexed/cisplatin arm compared with 4 cycles delivered on the cisplatin alone arm. Concerning vitamin supplementation, in the pemetrexed/cisplatin arm, FS patients received a median of 6 cycles compared with 5 cycles among PS+NS patients, and 2 cycles among NS patients.

Dose reductions occurred more often in the pemetrexed/cisplatin arm (2.6 to 3.4% of doses administered) than in the cisplatin-alone arm (0.3% of doses administered). The most common reasons for dose reductions in the pemetrexed/cisplatin arm were neutropenia, diarrhea, thrombocytopenia, and stomatitis.

Dose delays were reported for 308 (28.9%) cycles on the LY/cis arm, and for 171 (19.5%) cycles on the cisplatin alone arm. Scheduling conflicts (difficulty to schedule the drug infusion due to reasons such as vacation, holiday, delayed lab collection, etc.) constituted the majority of the dosing delays in both groups. The most common clinical causes of delay on both arms were firstly neutropenia, and secondly decreased creatinine renal clearance.

On the LY/cis arm, the most frequent reason for dose reduction was neutropenia, followed by diarrhea, thrombocytopenia, and stomatitis. On the cisplatin alone arm, 3 (0.3%) dose reductions were reported for neutropenia, hyponatremia, and neurotoxicity. On both arms, dose reductions occurred most frequently in Cycle 2.

Of the FS patients on the LY/cis arm, the most frequent reasons for pemetrexed dose reductions were diarrhea, neutropenia, and stomatitis (each 17.4%).

- Adverse events

A total of 226 patients on the LY/cis arm and 222 patients on the cisplatin alone arm were qualified for safety analyses. On the LY/cis arm, 223 (98.7%) patients reported at least one Treatment Emergent Adverse Events (TEAE). On the cisplatin alone arm, a total of 218 (98.2%) patients reported at least one TEAE. On both treatment arms, nausea, vomiting, and fatigue were the most commonly reported TEAEs. In addition, on the LY/cis arm, neutropenia and leukopenia were reported for >50% of all patients and significantly greater ($p<0.001$) than those events reported for the cisplatin alone arm.

Concerning fully supplemented patients, frequency and severity of undesirable effects that have been reported in > 5 % of patients (RT/FS population mesothelioma) are summarised in Table 14. Clinically relevant CTC toxicities that were reported in > 1 % and ≤ 5 % (common) of the patients that were randomly assigned to receive cisplatin and pemetrexed include: increased AST, ALT, and GGT, infection, pyrexia, febrile neutropenia, renal failure, chest pain, and urticaria. Clinically relevant CTC toxicities that were reported in ≤ 1 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include arrhythmia and motor neuropathy.

Among FS patients on the LY/cis arm, there were significantly fewer reports of vomiting, stomatitis, neutropenia, anorexia, and rash than reported by the PS+NS patients (data not shown). This finding suggests that supplementation may have played a role in decreasing the episodes of these toxicities among patients randomized to the LY/cis arm.

Table 14. Frequency and severity of undesirable effects that have been reported in > 5 % of patients (RT/FS population mesothelioma)

System Organ Class	Event*	Pemetrexed/cisplatin (N = 168)		Cisplatin (N = 163)	
		All Grades Toxicity (%)	Grade 3 - 4 Toxicity (%)	All Grades Toxicity (%)	Grade 3 - 4 Toxicity (%)
Blood and Lymphatic System	Neutrophils/granulocytes decreased	56.0	23.2	13.5	3.1
	Leukocytes decreased	53.0	14.9	16.6	0.6
	Haemoglobin decreased	26.2	4.2	10.4	0.0
	Platelets decreased	23.2	5.4	8.6	0.0
Eye	Conjunctivitis	5.4	0.0	0.6	0.0
Gastrointestinal	Nausea	82.1	11.9	76.7	5.5
	Vomiting	56.5	10.7	49.7	4.3
	Stomatitis/Pharyngitis	23.2	3.0	6.1	0.0
	Anorexia	20.2	1.2	14.1	0.6
	Diarrhoea	16.7	3.6	8.0	0.0
	Constipation	11.9	0.6	7.4	0.6
	Dyspepsia	5.4	0.6	0.6	0.0
General	Fatigue	47.6	10.1	42.3	9.2
Metabolism/Nutrition	Dehydration	6.5	4.2	0.6	0.6
Nervous System	Neuropathy-Sensory	10.1	0.0	9.8	0.6
	Dysgeusia	7.7	0.0	6.1	0.0
Renal & urinary disorders	Creatinine elevation	10.7	0.6	9.8	1.2
	Other: Creatinine clearance decreased	16.1	0.6	17.8	1.8
Skin and subcutaneous Tissue	Rash	16.1	0.6	4.9	0.0
	Alopecia	11.3	0.0	5.5	0.0

* National Cancer Institute CTC version 2 for each grade of toxicity except the term "creatinine clearance decreased"** which is derived from the term "renal/genitourinary other".

- Serious adverse event/deaths/other significant events

In the RT population, there were more SAEs experienced by patients on the LY/cis arm (36.7%) than on the cisplatin alone arm (21.6%). In the FS subgroup, 62/168 (36.9%) patients reported serious adverse events in the LY/cis arm and 34/163 (20.9%) in the cisplatin alone arm.

The most frequently reported drug-related SAEs (among those reported in >2% of patients) in the RT population for the LY/cis arm were nausea (8.4%), vomiting (8.4%) and dehydration (5.8%). The most frequently reported SAEs in the cisplatin alone arm were vomiting (2.3%) and nausea (1.4%). Drug-related SAEs by supplementation status are summarised in Table 15.

Table 15. Summary of Serious Adverse Events (>2% Incidence) Possibly or Probably Related to Study Drug RT Population by Supplementation Status H3E-MC-JMCH

	Pemetrexed/cisplatin				Cisplatin			
	FS (n=168)		PS+NS (n=58)		FS (n=163)		PS+NS (n=59)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
≥1 event	35	(20.8)	16	(27.6)	15	(9.2)	1	(1.7)
Vomiting NOS	8	(4.8)	11	(19.0)	4	(2.5)	1	(1.7)
Nausea	8	(4.8)	11	(19.0)	2	(1.2)	1	(1.7)
Dehydration	8	(4.8)	5	(8.6)	0	(0.0)	0	(0.0)
Neutropenia	4	(2.4)	5	(8.6)	0	(0.0)	0	(0.0)
Fatigue	2	(1.2)	5	(8.6)	1	(0.6)	0	(0.0)
Stomatitis	4	(2.4)	4	(6.9)	0	(0.0)	0	(0.0)
Diarrhoea	4	(2.4)	3	(5.2)	0	(0.0)	0	(0.0)
Anaemia	4	(2.4)	2	(3.4)	0	(0.0)	0	(0.0)
Anorexia	2	(1.2)	3	(5.2)	0	(0.0)	0	(0.0)
Leukopenia	3	(1.8)	2	(3.4)	0	(0.0)	0	(0.0)

A total of 22 deaths occurred while patients were on-study (LY/cis: 14; cisplatin alone: 8). Three deaths on the LY/cis arm were considered to be possibly related to study drug. Febrile neutropenia was present in all 3 cases. Most deaths (eight in the LY/cis arm and three in the cisplatin alone arm) occurred in the first two cycles of therapy or in the 30 days following the last infusion of study drug (five in the LY/cis arm and three in the cisplatin alone arm). The proportion of on-study deaths in the LY/cis arm was lower in the FS subgroup (8/168 (4.8%)) compared to the PS+NS subgroup (6/58 (10.3%)).

- Laboratory findings

In both arms, Common Toxicity Criteria (CTC) Grade 3 or 4 neutropenia was the most commonly reported hematologic toxicity. Grade 3/4 neutropenia was more frequent among PS+NS patients compared with the FS patients (Table 16).

The incidence of CTC Grade 3/4 neutropenia was significantly more common among PS+NS patients (24/58 (41.4%)) compared with FS (39/168 (23.2%)) patients in the LY/cis arm (P=0.011).

Table 16. Summary of Maximum CTC Grade 3/4 Toxicity Grades for Hematologic Toxicity RT Population by Patient Supplementation Status H3E-MC-JMCH

	Pemetrexed/cisplatin				Cisplatin			
	FS (n=168)		PS+NS (n=58)		FS (n=163)		PS+NS (n=59)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Hemoglobin	7	(4.2)	4	(6.9)	0		0	
Leukocytes	25	(14.9)	15	(25.9)	1	(0.6%	1	(1.7)
Lymphocytes	1	(0.6)	0		1	(0.6)	0	
Neutrophils	39	(23.2)	24	(41.4)	5	(3.1)	0	
Platelet Count	9	(5.4)	4	(6.9)	0		0	

On the LY/cis arm, CTC Grade 3 or 4 neutropenia occurred in 125 of 1066 cycles of study drug administered (11.7%). By contrast, only five episodes of CTC Grade 3/4 neutropenia occurred among 877 cycles given in the cisplatin alone arm (0.6%). For all parameters, the percent of cycles of Grade 3/4 toxicity are higher among the cycles not supplemented when compared with the supplemented cycles for patients in the LY/cis arm, reaching statistical significance for neutrophils (*P*=0.001).

Three episodes of non-haematologic Grade 4 toxicity occurred, all in the LY/cis arm (two CrCl decreased and one GGT). With the exception of 3 patients, all other patients who experienced any CTC Grade 3 or Grade 4 nonhematologic laboratory toxicities also received supplementation.

- Safety in special populations

Patients randomized and treated on the LY/cis treatment arm who were ≥65 years of age demonstrated a significantly greater frequency of nausea (*P*=0.008) when compared with patients on the cisplatin alone arm.

- Safety related to drug-drug interactions and other interactions

No safety data related to drug-drug interactions and other interactions have been reported, with the exception of supplementation.

- Post marketing experience

No post marketing experience data have been available.

Clinical safety of single-agent therapy with pemetrexed (NSCLC studies)

There were 5 completed clinical trials where single-agent pemetrexed was used along with low-dose folic acid and vitamin B_{12} supplementation. Of these 5 clinical trials, a total of 472 patients were treated with pemetrexed. The data of the JMEI study are the most relevant to the safety assessment and the primary focus hereafter.

- Safety Measurements and analyses

Patients were rated for toxicity prior to each cycle by using the NCI CTC scale (version 2.0). All patients who received at least one dose of pemetrexed or docetaxel (RT population) were evaluated for safety except for the patients previously mentioned for the centre excluded from the study.

Treatment-emergent adverse events (TEAE) were defined as events that first occurred or became worse after baseline. Nonserious, clinically significant adverse events were defined as any nonserious adverse event that caused discontinuation from the study.

- Patient exposure

A total of 265 patients received at least one dose of pemetrexed and 276 patients received at least one dose of docetaxel. Patients of the both treatment arms completed a median of 4 cycles of therapy: from 1 to 20 cycles on pemetrexed, and from 1 to 14 on docetaxel. A total of 90 (34%) patients on the pemetrexed arm and 88 (32%) patients on the docetaxel arm completed at least six cycles of therapy. The percent of planned dose-intensity was 98.8% and 94.4% for pemetrexed and docetaxel, respectively.

A total of 231 dose delays were reported for patients on the pemetrexed arm and 193 for patients on the docetaxel arm (19.8% and 17.8% of doses administered, respectively). Most of the dose delays on both treatment arms were due to scheduling conflict and not due to study drug toxicity. Decreased CrCl was the second most common reason for dose delay in the pemetrexed arm. Infection was the second most common reason for dose delay in the docetaxel arm.

There were 14 dose reductions (1.2% of doses administered) on the pemetrexed arm compared with 61 (5.6% of doses administered) on the docetaxel arm (p<.001). Neutropenia and febrile neutropenia were the cause of >50% of reductions in the docetaxel arm. No single reason was the main cause of dose reductions in the pemetrexed arm.

- Adverse events

A total of 259 patients on pemetrexed (97.7%) and 272 patients on docetaxel (98.6%) reported at least one treatment-emergent adverse event. The five most commonly reported events in pemetrexed arm

were fatigue (50.2%), anorexia (40%), nausea (37%), dyspnea (31.3%) and anemia (28.7%). The five most commonly reported events in the docetaxel arm were neutropenia (43.8%), fatigue (41.7%), alopecia (39.1%), dyspnea (35.1%) and leukopenia (33.7%). Neutropenia, febrile neutropenia, alopecia, leukopenia, myalgia, diarrhoea, arthralgia and neurotoxicity were significantly more frequent for docetaxel, whilst the incidence of thrombocytopenia, fatigue, nausea, increased transaminases, decreased creatinine clearance, vomiting, constipation and rash was significantly higher for pemetrexed.

Frequency and severity of undesirable effects that have been reported in > 5 % of patients are reported in Table 17. Clinically relevant CTC toxicities that were reported in > 1 % and $\leq$ 5 % (common) of the patients that were randomly assigned to pemetrexed include: sensory neuropathy, motor neuropathy, abdominal pain, increased creatinine, febrile neutropenia, infection without neutropenia, allergic reaction/hypersensitivity and erythema multiforme.

Clinically relevant CTC toxicities that were reported in $\leq$ 1 % of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single agent pemetrexed studies (n = 164) and the Phase 3 single agent pemetrexed study described above, with the exception of neutropenia (12.8 % versus 5.3 %, respectively) and alanine transaminase elevation (15.2 % versus 1.9 %, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included both chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

Fifty patients on the pemetrexed arm received more than 6 cycles of drug. In this population a slight cumulative toxicity regarding anemia, lymphopenia, ALAT and fatigue was observed.

Table 17. Frequency and severity of undesirable effects that have been reported in > 5 % of 265 patients randomly assigned to receive single agent pemetrexed with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single agent docetaxel.

System Organ Class	Event*	Pemetrexed (N=265)		Docetaxel (N=276)	
		All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Blood and Lymphatic System	Haemoglobin decreased	19.2	4.2	22.1	4.3
	Leukocytes decreased	12.1	4.2	34.1	27.2
	Neutrophils/ Granulocytes decreased	10.9	5.3	45.3	40.2
	Platelets decreased	8.3	1.9	1.1	0.4
Gastrointestinal	Nausea	30.9	2.6	16.7	1.8
	Anorexia	21.9	1.9	23.9	2.5
	Vomiting	16.2	1.5	12.0	1.1
	Stomatitis/ Pharyngitis	14.7	1.1	17.4	1.1
	Diarrhoea	12.8	0.4	24.3	2.5
	Constipation	5.7	0.0	4.0	0.0
General	Fatigue	34.0	5.3	35.9	5.4
	Fever	8.3	0.0	7.6	0.0
Hepatobiliary	SGPT (ALT) elevation	7.9	1.9	1.4	0.0
	SGOT (AST) elevation	6.8	1.1	0.7	0.0
Skin and Sub-cutaneous tissue	Rash/ desquamation	14.0	0.0	6.2	0.0
	Pruritus	6.8	0.4	1.8	0.0
	Alopecia	6.4	0.4	37.7	2.2

* National Cancer Institute CTC version 2

- Serious adverse events and deaths

The five most frequently reported SAE regardless of causality in the pemetrexed arm were pneumonia (6.8%), dyspnea (4.9%), pyrexia (4.5%), anemia (3.8%) and abdominal pain (2.3%).

The five most frequently reported SAE regardless of causality in the docetaxel arm were febrile neutropenia (11.2%), dyspnea (9.1%), neutropenia (6.2%), pneumonia (5.1%) and pyrexia (3.6%).

The serious drug related AE included febrile neutropenia, anaemia and pyrexia in the pemetrexed arm and febrile neutropenia, neutropenia, anaemia and pyrexia in the docetaxel arm. The incidence of drug related febrile neutropenia and neutropenia was statistically higher in the docetaxel arm.

Among the SAE, one case of serious decreased of creatinine clearance after cycle 4 (017-1614), a grade 3 cytolysis on day 7 cycle 1 (303-3031) and a grade 3 supra-ventricular arrhythmia on day 12 cycle 1 (801-8020) were reported.

Three deaths in the pemetrexed arm and five deaths in the docetaxel arm were considered possibly drug related.

- ECG findings

Electrocardiographic data from patients treated in the phase III study JMEI were collected. Two baseline ECG recording were performed. One ECG recording was performed during the peak concentration oif the first pemetrexed infusion. One ECG recording was performed prior to the next cycle. A total of 163 patients had evaluable ECGs. Five patients experienced a QTc prolongation between 30 to 60 msec at peak concentration of pemetrexed. Two other patients experienced QTc prolongation from 30 to 60 msec 21 days after pemetrexed infusion, probably due to electrolyte imbalances.

- Laboratory findings

The incidence of drug related febrile neutropenia and neutropenia was significantly higher in the docetaxel arm (Table 17). Except for neutropenia, the biological toxicity of pemetrexed and docetaxel were not significantly different.

- Discussion on clinical safety

In combination with cisplatin in patients treated for MPM, the main toxicities are gastrointestinal and haematological. Vitamin supplementation in MPM patients has a favourable effect on global toxicity. Combination therapy with pemetrexed/cisplatin (MPM studies) presented more toxicity and SAEs, than cisplatin alone in patients treated for malignant pleural mesothelioma, which is expected. In the combination arm, significantly more severe nausea, vomiting, diarrhoea, dehydration, and stomatitis were observed. Haematological toxicity of the combination appears acceptable. Grade ¾ neutropenia did not present frequent clinically significant complications such as febrile neutropenia and sepsis. Nausea, vomiting, and fatigue are the most frequent non-haematological toxicity. The TEAE of stomatitis and diarrhea were significantly more frequently reported in the LY/cis arm compared to the cisplatin arm alone. Grade 3 or 4 nausea, vomiting, diarrhea, and stomatitis were also significantly more frequently reported in the LY/cis arm compared to the cisplatin arm alone. The TEAE of rash was significantly more frequently reported in the LY/cis arm compared to the cisplatin arm alone. In 3 cases on the pemetrexed arm, death can be considered as drug-related. All these patients were never supplemented. SAEs with cerebral ischemia, angina pectoris and pulmonary embolism were observed in the combination arm but not in the cisplatin alone arm. In the pemetrexed/cisplatin arm, 18/226 patients (8%) compared to 5/222 (2.3%) in the cisplatin alone arm presented depression as TEAEs. This was severe in one case, where depression with suicide attempt led to withdrawal from the study. In general, depression was not reported as study drug- or procedure-related. Due to the gastro-intestinal toxicity of pemetrexed, the combination pemetrexed + cisplatin significantly increases the risk of dehydration compared to the cisplatin alone and this has been reflected in a warning in section 4.4 of the SPC.

The safety profile of single-agent pemetrexed is close to the safety profile of docetaxel, regarding asthenia and gastrointestinal toxicity. The incidence of drug related febrile neutropenia and neutropenia was significantly higher in the docetaxel arm. Pemetrexed is associated with a slight grade 3/4 hepatotoxicity and nephrotoxicity which was not observed with docetaxel during study JMEI. Since pemetrexed is excreted by the kidney, a control of renal function at baseline and before pemetrexed administration is necessary (see SPC section 4.2). Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single agent pemetrexed studies (n = 164) and the Phase 3 single agent pemetrexed study, with the exception of

neutropenia (12.8 % versus 5.3 %, respectively) and alanine transaminase elevation (15.2 % versus 1.9 %, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included both chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident and transient ischaemic attack have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors. A full review of cardiovascular, cerebrovascular toxicity and heart failure adverse event reports, which were reported during ongoing and completed pemetrexed clinical trials was submitted. Among the 128 patients who had cardiovascular events issued of 42 studies in a total of 4963 patients, 30 patients had events that were reported as related to pemetrexed. Among these 30 patients 28 myocardial toxicities and 8 cerebrovascular events were recorded. Five of these patients received monotherapy. These findings are adequately reflected in the SPC, which includes a warning about the risk of cardiovascular event in patients with associated cardiovascular risk factors (see SPC section 4.4 and 4.8).

Six cases of colitis were recorded with pemetrexed (5 related, out of 7949 patients included in an updated safety database), although 4 occurred prior to the vitamin supplementation. A full review of hepatobiliary adverse event reports during pemetrexed clinical trials was conducted. The hepatotoxicity profile of pemetrexed includes cytolytic hepatitis or cholestatic hepatitis, jaundice and hepatic failure. The incidence of hepatobiliary events seen in pemetrexed clinical trials is 1.5%, with the majority of the events occurring in patients with underlying liver metastases or other pre-existing disease. Appropriate dose modifications in case of hepatobiliary disorders have been provided (see SPC section 4.2). The occurrence of rare cases of hepatitis, potentially serious, with pemetrexed has been noted in the SPC (see section 4.8).

A full review of skin and subcutaneous tissue adverse event reportsfrom pemetrexed clinical trials (n=42) was conducted. Among the 92 patients who had skin toxicity related to pemetrexed, 3 cases of urticaria and three cases of bullous toxicity including one case of Stevens Johnson syndrome in association with cisplatin were reported. To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day (see SPC section 4.4).

In clinical studies, there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions other than those recommended for all patients are necessary. ALIMTA is not recommended for use in patients under 18 years of age, as safety and efficacy have not been established in this group of patients. This has been reflected in the SPC (see section 4.2).

Interactions and conditions relevant for all cytotoxics (oral anticoagulants, Yellow fever vaccine, other live attenuated vaccines, immunosuppression) are expected for pemetrexed as well, and adequate contraindications and warnings have been provided in the SPC (see section 4.3, 4.4, and 4.5).

Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: Absolute Neutrophil Count (ANC) should be ≥ 1500 cells/mm^3 and platelets should be $\geq 100{,}000$ cells/mm^3. Creatinine clearance should be ≥ 45 ml/min. The total bilirubin should be ≤ 1.5 times upper limit of normal. Alkaline phosphatase (AP), aspartate transaminase (AST or SGOT) and alanine transaminase (ALT or SGPT) should be ≤ 3 times upper limit of normal. Alkaline phosphatase, AST and ALT ≤ 5 times upper limit of normal is acceptable if liver has tumour involvement (see SPC section 4.2).

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Dose adjustments for toxicity are adequately described in the SPC (see section 4.2).

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to pemetrexed administration (see SPC section 4.4).

There are no data from the use of pemetrexed in pregnant women but pemetrexed, like other anti-metabolites, is suspected to cause serious birth defects when administered during pregnancy. Pemetrexed should not be used during pregnancy unless clearly necessary, after a careful consideration of the needs of the mother and the risk for the foetus. Effective contraception during treatment with pemetrexed must be used as applicable, and men are advised to seek counselling on sperm storage before starting treatment (see also discussion on non-clinical aspects and section 4.6 of the SPC). It is not known whether pemetrexed is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during pemetrexed therapy (see SPC section 4.6).

Pemetrexed may cause fatigue and patients should be cautioned against driving or operating machines if this event occurs (see SPC section 4.7).

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia and anaemia. In addition, infection with or without fever, diarrhoea, and/or mucositis may be seen. In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary (see SPC section 4.9).

4. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Pemetrexed is a novel multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

Pemetrexed behaves as a multitargeted antifolate by inhibiting key folate-dependent enzymes for the *de novo* biosynthesis of thymidine and purine nucleotides. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms. The polyglutamate forms are retained in cells and are even more potent inhibitors. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells. In mice on a low-folate diet, dietary folic acid protected mice from toxicity without negative influence on the efficacy of pemetrexed.

Gastrointestinal and haematotoxicity were the dose-limiting effects in dogs, and the toxicity observed in non-clinical models was predictive of the toxicity observed in clinical studies. Pemetrexed has been shown to be clastogenic in the *in vivo* micronucleus test in the mouse. Pemetrexed was not mutagenic using the Ames test and did not increase chromosomal aberrations in the CHO cell assay. Carcinogenicity studies have not been conducted.

Administration of pemetrexed to pregnant mice resulted in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate. Pemetrexed should not be used during pregnancy unless clearly necessary, after a careful consideration of the needs of the mother and the risk for the foetus. Administration of pemetrexed to male mice resulted in reproductive toxicity suggesting that pemetrexed may impair male fertility.

Efficacy

A multicentre, randomised, phase 3 study of pemetrexed plus cisplatin versus cisplatin in chemonaive patients with malignant pleural mesothelioma, has shown that patients treated with pemetrexed and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone. A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the pemetrexed/cisplatin arm versus the cisplatin arm alone was demonstrated using the Lung Cancer Symptom Scale. Statistically significant differences in pulmonary function tests were also observed. The separation between the treatment arms was achieved by improvement in lung function in the pemetrexed/cisplatin arm and deterioration of lung function over time in the control arm.

A multicentre, randomised, open label phase 3 study of pemetrexed versus docetaxel in patients with locally advanced or metastatic NSCLC after prior chemotherapy has shown median survival times of 8.3 months for patients treated with pemetrexed and 7.9 months for patients treated with docetaxel. Although non-inferiority was not formally established, the data submitted are robust enough to conclude that a clinically significant inferiority of pemetrexed to docetaxel in terms of efficacy in this population is unlikely.

Safety

The most common side effects when pemetrexed is used in combination with cisplatin are disorders of the blood and lymphatic system, gastrointestinal disorders, fatigue, sensory disorders of the nervous system, renal and urinary disorders, rash and alopecia. Clinically relevant CTC toxicities that were reported in > 1 % and $\leq$ 5 % (common) of the patients that were randomly assigned to receive cisplatin and pemetrexed include: increased AST, ALT, and GGT, infection, pyrexia, febrile neutropenia, renal failure, chest pain, and urticaria. Clinically relevant CTC toxicities that were reported in $\leq$ 1 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include arrhythmia and motor neuropathy.

The most common side effects when pemetrexed is used as monotherapy are disorders of the blood and lymphatic system, gastrointestinal disorders, fatigue, rash and desquamation. Clinically relevant CTC toxicities that were reported in > 1 % and $\leq$ 5 % (common) of the patients that were randomly assigned to pemetrexed include: sensory neuropathy, motor neuropathy, abdominal pain, increased creatinine, febrile neutropenia, infection without neutropenia, allergic reaction/hypersensitivity and erythema multiforme. Clinically relevant CTC toxicities that were reported in $\leq$ 1 % of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

Benefit/risk assessment

Malignant pleural mesothelioma

The MPM indication is supported by one phase III study, JMCH. In this trial, a clinically relevant and statistically significant difference in survival was observed. The median survival time for patients treated with pemetrexed/cisplatin was longer than for patients receiving cisplatin alone: 12.1 months versus 9.3 months. Consistent results were observed in terms of secondary endpoints and across relevant patient subgroups. In terms of safety, pemetrexed in combination with cisplatin is, as expected, more toxic than cisplatin alone. The frequencies of adverse events were lower in the fully supplemented subgroup when compared to the non-supplemented subgroup. The main toxicities are haematological and gastrointestinal, regardless of supplementation and are considered to be manageable. Overall, the benefit/risk profile for pemetrexed is considered favourable in combination with cisplatin for chemotherapy naïve patients with unresectable MPM.

Non-small cell lung cancer

Non-inferiority of pemetrexed over docetaxel was not formally established in the primary efficacy analysis. Nonetheless, any possible differences in efficacy between pemetrexed and docetaxel are likely to be marginal. The rationale for the vitamin supplementation and the proposed dose are considered acceptable. Altogether, the co-administration of pemetrexed and vitamin supplementation as second line treatment in patients with locally advanced or metastatic NSCLC reduces the toxicity of

pemetrexed, particularly nausea, vomiting, grade III/IV haematotoxicity and infections. The safety profile of pemetrexed appears to be manageable, and existing safety concerns have been adequately reported in the SPC.

Overall, the benefit/risk ratio of pemetrexed compared to docetaxel puts the two products on the same line given the fact that efficacy can be considered as similar (although formally not ruling out the possibility of a marginal loss of efficacy), and given that safety is slightly better.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of ALIMTA in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma, and that the benefit/risk ratio of ALIMTA as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy was favourable, and therefore recommended the granting of the marketing authorisation.

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