

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALIMTA safely and effectively. See full prescribing information for ALIMTA.

ALIMTA (pemetrexed disodium) Injection, Powder, Lyophilized, For Solution for Intravenous Use

Initial U.S. Approval: 2004

INDICATIONS AND USAGE

ALIMTA® is a folate analog metabolic inhibitor indicated for:

- Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer:
 - Initial treatment in combination with cisplatin. (1.1)
 - Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.2)
 - After prior chemotherapy as a single-agent. (1.3)
- Mesothelioma: in combination with cisplatin. (1.4)

Limitations of Use:

- ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer. (1.5)

DOSAGE AND ADMINISTRATION

- Combination use in Non-Small Cell Lung Cancer and Mesothelioma: Recommended dose of ALIMTA is 500 mg/m² i.v. on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m² i.v. beginning 30 minutes after ALIMTA administration. (2.1)
- Single-Agent use in Non-Small Cell Lung Cancer: Recommended dose of ALIMTA is 500 mg/m² i.v. on Day 1 of each 21-day cycle. (2.2)
- Dose Reductions: Dose reductions or discontinuation may be needed based on toxicities from the preceding cycle of therapy. (2.4)

DOSAGE FORMS AND STRENGTHS

- 100 mg vial for injection (3)
- 500 mg vial for injection (3)

CONTRAINDICATIONS

History of severe hypersensitivity reaction to pemetrexed. (4)

WARNINGS AND PRECAUTIONS

- Premedication regimen: Instruct patients to take folic acid and vitamin B₁₂. Pretreatment with dexamethasone or equivalent reduces cutaneous reaction. (5.1)
- Bone marrow suppression: Reduce doses for subsequent cycles based on hematologic and nonhematologic toxicities. (5.2)
- Renal function: Do not administer when CrCl <45 mL/min. (2.4, 5.3)
- NSAIDs with renal insufficiency: Use caution in patients with mild to moderate renal insufficiency (CrCl 45-79 mL/min). (5.4)
- Lab monitoring: Do not begin next cycle unless ANC ≥1500 cells/mm³, platelets ≥100,000 cells/mm³, and CrCl ≥45 mL/min. (5.5)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised to use effective contraception measures to prevent pregnancy during treatment with ALIMTA. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥20%) with single-agent use are fatigue, nausea, and anorexia. Additional common adverse reactions when used in combination with cisplatin include vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- NSAIDs: Use caution with ibuprofen or other NSAIDs. (7.1)
- Nephrotoxic drugs: Concomitant use of these drugs and/or substances which are tubularly secreted may result in delayed clearance. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 00/0000

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FULL PRESCRIBING INFORMATION

1 **1 INDICATIONS AND USAGE**

2 **1.1 Nonsquamous Non-Small Cell Lung Cancer - Combination with Cisplatin**

3 ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or
4 metastatic nonsquamous non-small cell lung cancer.

5 **1.2 Nonsquamous Non-Small Cell Lung Cancer - Maintenance**

6 ALIMTA is indicated for the maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small
7 cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

8 **1.3 Nonsquamous Non-Small Cell Lung Cancer - After Prior Chemotherapy**

9 ALIMTA is indicated as a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous
10 non-small cell lung cancer after prior chemotherapy.

11 **1.4 Mesothelioma**

12 ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose
13 disease is unresectable or who are otherwise not candidates for curative surgery.

14 **1.5 Limitations of Use**

15 ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer. [see *Clinical Studies*
16 (14.1, 14.2, 14.3)]

17 **2 DOSAGE AND ADMINISTRATION**

18 **2.1 Combination Use with Cisplatin**

19 Nonsquamous Non-Small Cell Lung Cancer and Malignant Pleural Mesothelioma

20 The recommended dose of ALIMTA is 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each
21 21-day cycle. The recommended dose of cisplatin is 75 mg/m² infused over 2 hours beginning approximately 30 minutes after the end
22 of ALIMTA administration. Patients should receive appropriate hydration prior to and/or after receiving cisplatin. See cisplatin
23 package insert for more information.

24 **2.2 Single-Agent Use**

25 Nonsquamous Non-Small Cell Lung Cancer

26 The recommended dose of ALIMTA is 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each
27 21-day cycle.

28 **2.3 Premedication Regimen**

29 Vitamin Supplementation

30 To reduce toxicity, patients treated with ALIMTA must be instructed to take a low-dose oral folic acid preparation or
31 multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the
32 first dose of ALIMTA; and dosing should continue during the full course of therapy and for 21 days after the last dose of ALIMTA.
33 Patients must also receive one (1) intramuscular injection of vitamin B₁₂ during the week preceding the first dose of ALIMTA and
34 every 3 cycles thereafter. Subsequent vitamin B₁₂ injections may be given the same day as ALIMTA. In clinical trials, the dose of folic
35 acid studied ranged from 350 to 1000 mcg, and the dose of vitamin B₁₂ was 1000 mcg. The most commonly used dose of oral folic
36 acid in clinical trials was 400 mcg [see *Warnings and Precautions (5.1)*].

37 Corticosteroid

38 Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone
39 (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth
40 twice daily the day before, the day of, and the day after ALIMTA administration [see *Warnings and Precautions (5.1)*].

41 **2.4 Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations**

42 Monitoring

43 Complete blood cell counts, including platelet counts, should be performed on all patients receiving ALIMTA. Patients should
44 be monitored for nadir and recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each cycle.
45 Patients should not begin a new cycle of treatment unless the ANC is ≥ 1500 cells/mm³, the platelet count is $\geq 100,000$ cells/mm³, and
46 creatinine clearance is ≥ 45 mL/min. Periodic chemistry tests should be performed to evaluate renal and hepatic function [see
47 *Warnings and Precautions (5.5)*].

48 Dose Reduction Recommendations

49 Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic
50 toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients
51 should be retreated using the guidelines in Tables 1-3, which are suitable for using ALIMTA as a single-agent or in combination with
52 cisplatin.

Nadir ANC <500/mm ³ and nadir platelets ≥50,000/mm ³ .	75% of previous dose (pemetrexed and cisplatin).
Nadir platelets <50,000/mm ³ without bleeding regardless of nadir ANC.	75% of previous dose (pemetrexed and cisplatin).
Nadir platelets <50,000/mm ³ with bleeding ^a , regardless of nadir ANC.	50% of previous dose (pemetrexed and cisplatin).

^a These criteria meet the CTC version 2.0 (NCI 1998) definition of ≥CTC Grade 2 bleeding.

If patients develop nonhematologic toxicities (excluding neurotoxicity) ≥Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in Table 2.

Table 2: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Nonhematologic Toxicities^{a,b}

	Dose of ALIMTA (mg/m ²)	Dose of Cisplatin (mg/m ²)
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

^a NCI Common Toxicity Criteria (CTC).

^b Excluding neurotoxicity (see Table 3).

In the event of neurotoxicity, the recommended dose adjustments for ALIMTA and cisplatin are described in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 3: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Neurotoxicity

CTC Grade	Dose of ALIMTA (mg/m ²)	Dose of Cisplatin (mg/m ²)
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Discontinuation Recommendation

ALIMTA therapy should be discontinued if a patient experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Renally Impaired Patients

In clinical studies, patients with creatinine clearance ≥45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients [see *Clinical Pharmacology (12.3)*]. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:

$$\begin{aligned} \text{Males:} & \quad \frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} = \text{mL/min} \\ \text{Females:} & \quad \text{Estimated creatinine clearance for males} \times 0.85 \end{aligned}$$

Caution should be exercised when administering ALIMTA concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min [see *Drug Interactions (7.1)*].

2.5 Preparation and Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of ALIMTA. The use of gloves is recommended. If a solution of ALIMTA contacts the skin, wash the skin immediately and thoroughly with soap and water. If ALIMTA contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available [see *References (15)*].

ALIMTA is not a vesicant. There is no specific antidote for extravasation of ALIMTA. To date, there have been few reported cases of ALIMTA extravasation, which were not assessed as serious by the investigator. ALIMTA extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

2.6 Preparation for Intravenous Infusion Administration

1. Use aseptic technique during the reconstitution and further dilution of ALIMTA for intravenous infusion administration.
2. Calculate the dose of ALIMTA and determine the number of vials needed. Vials contain either 100 mg or 500 mg of ALIMTA. The vials contain an excess of ALIMTA to facilitate delivery of label amount.
3. Reconstitute each 100-mg vial with 4.2 ml of 0.9% Sodium Chloride Injection (preservative free). Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives a solution containing 25 mg/mL ALIMTA. Gently swirl each vial until the powder is completely dissolved. The resulting

solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted ALIMTA solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.

4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.
5. An appropriate quantity of the reconstituted ALIMTA solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml. ALIMTA is administered as an intravenous infusion over 10 minutes.
6. Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature [see USP Controlled Room Temperature] and lighting. When prepared as directed, reconstitution and infusion solutions of ALIMTA contain no antimicrobial preservatives. Discard any unused portion.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). ALIMTA is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Coadministration of ALIMTA with other drugs and diluents has not been studied, and therefore is not recommended. ALIMTA is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags.

3 DOSAGE FORMS AND STRENGTHS

ALIMTA, pemetrexed for injection, is a white to either light-yellow or green-yellow lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg pemetrexed.

4 CONTRAINDICATIONS

ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any other ingredient used in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Premedication Regimen

Need for Folate and Vitamin B₁₂ Supplementation

Patients treated with ALIMTA must be instructed to take folic acid and vitamin B₁₂ as a prophylactic measure to reduce treatment-related hematologic and GI toxicity [see *Dosage and Administration* (2.3)]. In clinical studies, less overall toxicity and reductions in Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B₁₂ was administered.

Corticosteroid Supplementation

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid in clinical trials. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction [see *Dosage and Administration* (2.3)].

5.2 Bone Marrow Suppression

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia) [see *Adverse Reactions* (6.1)]; myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle [see *Dosage and Administration* (2.4)].

5.3 Decreased Renal Function

ALIMTA is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance ≥ 45 mL/min. Insufficient numbers of patients have been studied with creatinine clearance < 45 mL/min to give a dose recommendation. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is < 45 mL/min [see *Dosage and Administration* (2.4)].

One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B₁₂ died of drug-related toxicity following administration of ALIMTA alone.

5.4 Use with Non-Steroidal Anti-Inflammatory Drugs with Mild to Moderate Renal Insufficiency

Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Other NSAIDs should also be used with caution [see *Drug Interactions* (7.1)].

5.5 Required Laboratory Monitoring

Patients should not begin a new cycle of treatment unless the ANC is ≥ 1500 cells/mm³, the platelet count is $\geq 100,000$ cells/mm³, and creatinine clearance is ≥ 45 mL/min [see *Dosage and Administration* (2.4)].

5.6 Pregnancy Category D

Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. Pemetrexed administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic and teratogenic in mice at greater than 1/833rd the recommended human dose. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid

becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with ALIMTA [see Use in Specific Populations (8.1)].

5.7 Third Space Fluid

The effect of third space fluid, such as pleural effusion and ascites, on ALIMTA is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to ALIMTA administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

In clinical trials, the most common adverse reactions (incidence $\geq 20\%$) during therapy with ALIMTA as a single-agent were fatigue, nausea, and anorexia. Additional common adverse reactions (incidence $\geq 20\%$) during therapy with ALIMTA when used in combination with cisplatin included vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Non-Small Cell Lung Cancer (NSCLC) - Combination with Cisplatin

Table 4 provides the frequency and severity of adverse reactions that have been reported in $>5\%$ of 839 patients with NSCLC who were randomized to study and received ALIMTA plus cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus cisplatin. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B₁₂.

Table 4: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in NSCLC^a

Reaction ^b	ALIMTA/cisplatin (N=839)		Gemcitabine/cisplatin (N=830)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	90	37	91	53
Laboratory				
Hematologic				
Anemia	33	6	46	10
Neutropenia	29	15	38	27
Leukopenia	18	5	21	8
Thrombocytopenia	10	4	27	13
Renal				
Creatinine elevation	10	1	7	1
Clinical				
Constitutional Symptoms				
Fatigue	43	7	45	5
Gastrointestinal				
Nausea	56	7	53	4
Vomiting	40	6	36	6
Anorexia	27	2	24	1
Constipation	21	1	20	0
Stomatitis/Pharyngitis	14	1	12	0
Diarrhea	12	1	13	2
Dyspepsia/Heartburn	5	0	6	0
Neurology				
Neuropathy-sensory	9	0	12	1
Taste disturbance	8	0 ^c	9	0 ^c
Dermatology/Skin				
Alopecia	12	0 ^c	21	1 ^c
Rash/Desquamation	7	0	8	1

^a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

^b Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity.

^c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.

In addition to the lower incidence of hematologic toxicity on the ALIMTA and cisplatin arm, use of transfusions (RBC and platelet) and hematopoietic growth factors was lower in the ALIMTA and cisplatin arm compared to the gemcitabine and cisplatin arm.

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive ALIMTA plus cisplatin.

Incidence 1% to 5%

Body as a Whole — febrile neutropenia, infection, pyrexia

General Disorders — dehydration

Metabolism and Nutrition — increased AST, increased ALT

Renal — creatinine clearance decrease, renal failure

Special Senses — conjunctivitis

Incidence Less than 1%

Cardiovascular — arrhythmia

General Disorders — chest pain

Metabolism and Nutrition — increased GGT

Neurology — motor neuropathy

Non-Small Cell Lung Cancer (NSCLC) - Maintenance

Table 5 provides the frequency and severity of adverse reactions that have been reported in >5% of 438 patients with NSCLC who received ALIMTA and 218 patients with NSCLC who received placebo. All patients received study therapy immediately following 4 cycles of platinum-based treatment for locally advanced or metastatic NSCLC. Patients in both study arms were fully supplemented with folic acid and vitamin B₁₂.

Table 5: Adverse Reactions in Patients Receiving ALIMTA versus Placebo in NSCLC^a

Reaction ^b	ALIMTA (N=438)		Placebo (N=218)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	66	16	37	4
Laboratory				
Hematologic				
Anemia	15	3	6	1
Neutropenia	6	3	0	0
Leukopenia	6	2	1	1
Hepatic				
Increased ALT	10	0	4	0
Increased AST	8	0	4	0
Clinical				
Constitutional Symptoms				
Fatigue	25	5	11	1
Gastrointestinal				
Nausea	19	1	6	1
Anorexia	19	2	5	0
Vomiting	9	0	1	0
Mucositis/stomatitis	7	1	2	0
Diarrhea	5	1	3	0
Infection	5	2	2	0
Neurology				
Neuropathy-sensory	9	1	4	0
Dermatology/Skin				
Rash/Desquamation	10	0	3	0

^a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

^b Refer to NCI CTCAE Criteria version 3.0 for each Grade of toxicity.

No clinically relevant differences in Grade 3/4 adverse reactions were seen in patients based on age, gender, ethnic origin, or histology except a higher incidence of Grade 3/4 fatigue for Caucasian patients compared to non-Caucasian patients (6.5% versus 0.6%).

Safety was assessed by exposure for patients who received at least one dose of ALIMTA (N=438). The incidence of adverse reactions was evaluated for patients who received ≤6 cycles of ALIMTA, and compared to patients who received >6 cycles of

ALIMTA. Increases in adverse reactions (all grades) were observed with longer exposure; however no clinically relevant differences in Grade 3/4 adverse reactions were seen.

Consistent with the higher incidence of anemia (all grades) on the ALIMTA arm, use of transfusions (mainly RBC) and erythropoiesis stimulating agents (ESAs; erythropoietin and darbepoetin) were higher in the ALIMTA arm compared to the placebo arm (transfusions 9.5% versus 3.2%, ESAs 5.9% versus 1.8%).

The following additional adverse reactions were observed in patients with non-small cell lung cancer who received ALIMTA.

Incidence 1% to 5%

Dermatology/Skin — alopecia, pruritis/itching

Gastrointestinal — constipation

General Disorders — edema, fever (in the absence of neutropenia)

Hematologic — thrombocytopenia

Renal — decreased creatinine clearance, increased creatinine, decreased glomerular filtration rate

Special Senses — ocular surface disease (including conjunctivitis), increased lacrimation

Incidence Less than 1%

Cardiovascular — supraventricular arrhythmia

Dermatology/Skin — erythema multiforme

General Disorders — febrile neutropenia, allergic reaction/hypersensitivity

Neurology — motor neuropathy

Renal — renal failure

Non-Small Cell Lung Cancer (NSCLC) – After Prior Chemotherapy

Table 6 provides the frequency and severity of adverse reactions that have been reported in >5% of 265 patients randomly assigned to receive single-agent ALIMTA with folic acid and vitamin B₁₂ supplementation and 276 patients randomly assigned to receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic NSCLC and received prior chemotherapy.

Table 6: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA versus Docetaxel in NSCLC^a

Reaction ^b	ALIMTA (N=265)		Docetaxel (N=276)	
	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)
Laboratory				
Hematologic				
Anemia	19	4	22	4
Leukopenia	12	4	34	27
Neutropenia	11	5	45	40
Thrombocytopenia	8	2	1	0
Hepatic				
Increased ALT	8	2	1	0
Increased AST	7	1	1	0
Clinical				
Gastrointestinal				
Nausea	31	3	17	2
Anorexia	22	2	24	3
Vomiting	16	2	12	1
Stomatitis/Pharyngitis	15	1	17	1
Diarrhea	13	0	24	3
Constipation	6	0	4	0
Constitutional Symptoms				
Fatigue	34	5	36	5
Fever	8	0	8	0
Dermatology/Skin				
Rash/Desquamation	14	0	6	0
Pruritis	7	0	2	0
Alopecia	6	1 ^c	38	2 ^c

^a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

^b Refer to NCI CTC Criteria for lab values for each Grade of toxicity (version 2.0).

^c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.
Clinically relevant adverse reactions occurring in <5% of patients that received ALIMTA treatment but >5% of patients that received docetaxel include CTC Grade 3/4 febrile neutropenia (1.9% ALIMTA, 12.7% docetaxel).

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive ALIMTA.

Incidence 1% to 5%

Body as a Whole — abdominal pain, allergic reaction/hypersensitivity, febrile neutropenia, infection

Dermatology/Skin — erythema multiforme

Neurology — motor neuropathy, sensory neuropathy

Renal — increased creatinine

Incidence Less than 1%

Cardiovascular — supraventricular arrhythmias

Malignant Pleural Mesothelioma (MPM)

Table 7 provides the frequency and severity of adverse reactions that have been reported in >5% of 168 patients with mesothelioma who were randomly assigned to receive cisplatin and ALIMTA and 163 patients with mesothelioma randomly assigned to receive single-agent cisplatin. In both treatment arms, these chemo-naïve patients were fully supplemented with folic acid and vitamin B₁₂.

Table 7: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in MPM^a

Reaction ^b	ALIMTA/cisplatin (N=168)		Cisplatin (N=163)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
Laboratory				
Hematologic				
Neutropenia	56	23	13	3
Leukopenia	53	15	17	1
Anemia	26	4	10	0
Thrombocytopenia	23	5	9	0
Renal				
Creatinine elevation	11	1	10	1
Creatinine clearance decreased	16	1	18	2
Clinical				
Eye Disorder				
Conjunctivitis	5	0	1	0
Gastrointestinal				
Nausea	82	12	77	6
Vomiting	57	11	50	4
Stomatitis/Pharyngitis	23	3	6	0
Anorexia	20	1	14	1
Diarrhea	17	4	8	0
Constipation	12	1	7	1
Dyspepsia	5	1	1	0
Constitutional Symptoms				
Fatigue	48	10	42	9
Metabolism and Nutrition				
Dehydration	7	4	1	1
Neurology				
Neuropathy-sensory	10	0	10	1
Taste Disturbance	8	0 ^c	6	0 ^c
Dermatology/Skin				
Rash	16	1	5	0
Alopecia	11	0 ^c	6	0 ^c

^a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

^b Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity except the term “creatinine clearance decreased” which is derived from the CTC term “renal/genitourinary-other”.

^c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

The following additional adverse reactions were observed in patients with malignant pleural mesothelioma randomly assigned to receive ALIMTA plus cisplatin.

Incidence 1% to 5%

- Body as a Whole* — febrile neutropenia, infection, pyrexia
- Dermatology/Skin* — urticaria
- General Disorders* — chest pain
- Metabolism and Nutrition* — increased AST, increased ALT, increased GGT
- Renal* — renal failure

Incidence Less than 1%

- Cardiovascular* — arrhythmia
- Neurology* — motor neuropathy

Effects of Vitamin Supplementations

Table 8 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B₁₂ from the time of enrollment in the study (fully supplemented) with the incidence in patients who never received vitamin supplementation (never supplemented) during the study in the ALIMTA plus cisplatin arm.

Table 8: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the ALIMTA plus Cisplatin arm (% incidence)

Adverse Event ^a (%)	Fully Supplemented Patients (N=168)	Never Supplemented Patients (N=32)
Neutropenia/granulocytopenia	23	38
Thrombocytopenia	5	9
Vomiting	11	31
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	0	6
Diarrhea	4	9

^a Refer to NCI CTC criteria for lab and non-laboratory values for each grade of toxicity (Version 2.0).

The following adverse events were greater in the fully supplemented group compared to the never supplemented group: hypertension (11%, 3%), chest pain (8%, 6%), and thrombosis/embolism (6%, 3%).

Subpopulations

No relevant effect for ALIMTA safety due to gender or race was identified, except an increased incidence of rash in men (24%) compared to women (16%).

Across clinical trials, sepsis, which in some cases was fatal, occurred in approximately 1% of patients.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of ALIMTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These reactions have occurred with ALIMTA when used as a single-agent and in combination therapies.

- Gastrointestinal* — colitis
- General Disorders and Administration Site Conditions* — edema

Injury, poisoning, and procedural complications — Radiation recall has been reported in patients who have previously received radiotherapy.

Respiratory — interstitial pneumonitis

Skin — Bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis, which in some cases were fatal.

7 DRUG INTERACTIONS

7.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥80 mL/min). Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) [see *Clinical Pharmacology* (12.3)].

Other NSAIDs

Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA.

In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If

concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

7.2 Nephrotoxic Drugs

ALIMTA is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of ALIMTA. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of ALIMTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects - Pregnancy Category D [see *Warnings and Precautions* (5.6)]

Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies of ALIMTA in pregnant women. Pemetrexed was embryotoxic, fetotoxic, and teratogenic in mice. In mice, repeated intraperitoneal doses of pemetrexed when given during organogenesis caused fetal malformations (incomplete ossification of talus and skull bone; about 1/833rd the recommended intravenous human dose on a mg/m² basis), and cleft palate (1/33rd the recommended intravenous human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use effective contraceptive measures to prevent pregnancy during the treatment with ALIMTA.

8.3 Nursing Mothers

It is not known whether ALIMTA or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ALIMTA, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

8.4 Pediatric Use

Efficacy of ALIMTA in pediatric patients has not been demonstrated. ALIMTA was administered as an intravenous infusion over 10 minutes on Day 1 of a 21 day cycle to pediatric patients with recurrent solid tumors in a Phase 1 study (32 patients) and a Phase 2 study (72 patients). All patients received pretreatment with vitamin B₁₂ and folic acid supplementation and dexamethasone. The dose escalation in the Phase 1 study determined the maximum tolerated dose was 1910 mg/m² and this dose (or 60 mg/kg for patients <12 months old) was evaluated in the Phase 2 study of patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high grade glioma. No responses were observed among the 72 patients in this Phase 2 trial. The most common toxicities reported were hematological (leukopenia, neutropenia/granulocytopenia, anemia, thrombocytopenia, and lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea.

The single dose pharmacokinetics of ALIMTA administered in doses ranging from 400 to 2480 mg/m² were evaluated in the Phase 1 trial in 22 patients (13 males and 9 females) aged 4 to 18 years (average age 12 years). Pemetrexed exposure (AUC and C_{max}) appeared to increase proportionally with dose. The average pemetrexed clearance (2.30 L/h/m²) and half-life (2.3 hours) in pediatric patients were comparable to values reported in adults.

8.5 Geriatric Use

ALIMTA is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Renal function monitoring is recommended with administration of ALIMTA. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older [see *Dosage and Administration* (2.4)].

In the initial treatment non-small cell lung cancer clinical trial, 37.7% of patients treated with ALIMTA plus cisplatin were ≥65 years and Grade 3/4 neutropenia was greater as compared to patients <65 years (19.9% versus 12.2%). For patients <65 years, the HR for overall survival was 0.96 (95% CI: 0.83, 1.10) and for patients ≥65 years the HR was 0.88 (95% CI: 0.74, 1.06) in the intent to treat population.

In the maintenance non-small cell lung cancer trial 33.3% of patients treated with ALIMTA were ≥65 years and no differences were seen in Grade 3/4 adverse reactions as compared to patients <65 years. For patients <65 years, the HR for overall survival was 0.74 (95% CI: 0.58, 0.93) and for patients ≥65 years the HR was 0.88 (95% CI: 0.65, 1.21) in the intent to treat population.

In the non-small cell lung cancer trial after prior chemotherapy, 29.7% patients treated with ALIMTA were ≥65 years and Grade 3/4 hypertension was greater as compared to patients <65 years. For patients <65 years, the HR for overall survival was 0.95 (95% CI: 0.76, 1.19), and for patients ≥65 years the HR was 1.15 (95% CI: 0.79, 1.68) in the intent to treat population.

The mesothelioma trial included 36.7% patients treated with ALIMTA plus cisplatin that were ≥65 years, and Grade 3/4 fatigue, leukopenia, neutropenia, and thrombocytopenia were greater as compared to patients <65 years. For patients <65 years, the HR for overall survival was 0.71(95% CI: 0.53, 0.96) and for patients ≥65 years, the HR was 0.85 (95% CI: 0.59, 1.22) in the intent to treat population.

8.6 Patients with Hepatic Impairment

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed [see *Clinical Pharmacology* (12.3)].

375 Dose adjustments based on hepatic impairment experienced during treatment with ALIMTA are provided in Table 2 [see
376 *Dosage and Administration (2.4)*].

377 8.7 Patients with Renal Impairment

378 ALIMTA is known to be primarily excreted by the kidneys. Decreased renal function will result in reduced clearance and
379 greater exposure (AUC) to ALIMTA compared with patients with normal renal function [see *Dosage and Administration (2.4)* and
380 *Clinical Pharmacology (12.3)*]. Cisplatin coadministration with ALIMTA has not been studied in patients with moderate renal
381 impairment.

382 8.8 Gender

383 In the initial treatment non-small cell lung cancer trial, 70% of patients were males and 30% females. For males the HR for
384 overall survival was 0.97 (95% CI: 0.85, 1.10) and for females the HR was 0.86 (95% CI: 0.70, 1.06) in the intent to treat population.

385 In the maintenance non-small cell lung cancer trial, 73% of patients were males and 27% females. For males the HR for
386 overall survival was 0.78 (95% CI: 0.63, 0.96) and for females the HR was 0.83 (95% CI: 0.56, 1.21) in the intent to treat population.

387 In the non-small cell lung cancer trial after prior chemotherapy, 72% of patients were males and 28% females. For males the
388 HR for overall survival was 0.95 (95% CI: 0.76, 1.19) and for females the HR was 1.28 (95% CI: 0.86, 1.91) in the intent to treat
389 population.

390 In the mesothelioma trial, 82% of patients were males and 18% females. For males the HR for overall survival was 0.85
391 (95% CI: 0.66, 1.09) and for females the HR was 0.48 (95% CI: 0.27, 0.85) in the intent to treat population.

392 8.9 Race

393 In the initial treatment non-small cell lung cancer trial, 78% of patients were Caucasians, 13% East/Southeast Asians, and
394 9% others. For Caucasians, the HR for overall survival was 0.92 (95% CI: 0.82, 1.04), for East/Southeast Asians the HR was 0.86
395 (95% CI: 0.61, 1.21), and for others the HR was 1.24 (95% CI: 0.84, 1.84) in the intent to treat population.

396 In the maintenance non-small cell lung cancer trial, 65% of patients were Caucasians, 23% East Asian, and 12% others. For
397 Caucasians the HR for overall survival was 0.77 (95% CI: 0.62, 0.97), for East Asians was 1.05 (95% CI: 0.70, 1.59) and for others
398 the HR was 0.46 (95% CI: 0.26, 0.79) in the intent to treat population.

399 In the non-small cell lung cancer trial after prior chemotherapy, 71% of patients were Caucasians and 29% others. For
400 Caucasians the HR for overall survival was 0.91 (95% CI: 0.73, 1.15) and for others the HR was 1.27 (95% CI: 0.87, 1.87) in the
401 intent to treat population.

402 In the mesothelioma trial, 92% of patients were Caucasians and 8% others. For Caucasians, the HR for overall survival was
403 0.77 (95% CI: 0.61, 0.97) and for others the HR was 0.86 (95% CI: 0.39, 1.90) in the intent to treat population.

404 10 OVERDOSAGE

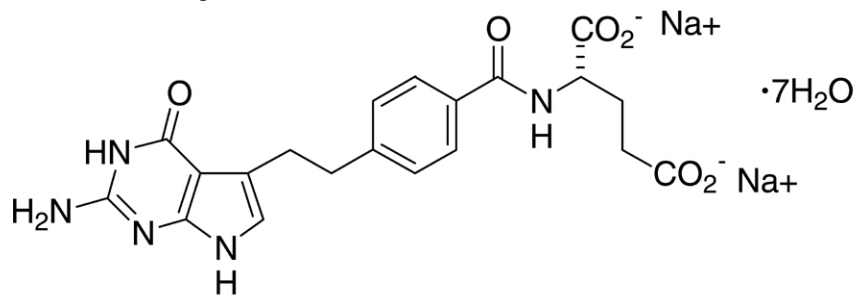
405 There have been few cases of ALIMTA overdose. Reported toxicities included neutropenia, anemia, thrombocytopenia,
406 mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia,
407 thrombocytopenia, and anemia. In addition, infection with or without fever, diarrhea, and mucositis may be seen. If an overdose
408 occurs, general supportive measures should be instituted as deemed necessary by the treating physician.

409 In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting ≥ 3 days, CTC Grade 4 neutropenia lasting
410 ≥ 3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3
411 or 4 mucositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100 mg/m²,
412 intravenously once, followed by leucovorin, 50 mg/m², intravenously every 6 hours for 8 days.

413 The ability of ALIMTA to be dialyzed is unknown.

414 11 DESCRIPTION

415 Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-
416 pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white to almost-white solid with a molecular formula
417 of C₂₀H₁₉N₅Na₂O₆•7H₂O and a molecular weight of 597.49. The structural formula is as follows:



418 ALIMTA is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a
419 white to either light yellow or green-yellow lyophilized solid. Each 100-mg or 500-mg vial of ALIMTA contains pemetrexed
420 disodium equivalent to 100 mg pemetrexed and 106 mg mannitol or 500 mg pemetrexed and 500 mg mannitol, respectively.
421 Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.
422

423 12 CLINICAL PHARMACOLOGY

Reference ID: 2919227

424 **12.1 Mechanism of Action**

425 ALIMTA, pemetrexed for injection, is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent
426 metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS),
427 dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes
428 involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as
429 the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to
430 polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of
431 TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to
432 a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in
433 prolonged drug action in malignant cells.

434 **12.2 Pharmacodynamics**

435 Preclinical studies have shown that pemetrexed inhibits the in vitro growth of mesothelioma cell lines (MSTO-211H,
436 NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined
437 concurrently with cisplatin.

438 Absolute neutrophil counts (ANC) following single-agent administration of ALIMTA to patients not receiving folic acid and
439 vitamin B₁₂ supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as
440 measured by the depth of the ANC nadir, correlates with the systemic exposure, or area under the curve (AUC) of pemetrexed. It was
441 also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or homocysteine concentrations. The
442 levels of these substances can be reduced by folic acid and vitamin B₁₂ supplementation. There is no cumulative effect of pemetrexed
443 exposure on ANC nadir over multiple treatment cycles.

444 Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days over a range of exposures from
445 38.3 to 316.8 mcg•hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

446 **12.3 Pharmacokinetics**

447 **Absorption**

448 The pharmacokinetics of ALIMTA administered as a single-agent in doses ranging from 0.2 to 838 mg/m² infused over a
449 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed total systemic
450 exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of pemetrexed
451 do not change over multiple treatment cycles.

452 **Distribution**

453 Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed is approximately
454 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

455 **Metabolism and Excretion**

456 Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose
457 recovered unchanged within the first 24 hours following administration. The clearance decreases, and exposure (AUC) increases, as
458 renal function decreases. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is
459 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min).

460 The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in controlled and single arm
461 studies.

462 **Effect of Age**

463 No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26 to 80 years.

464 **Effect of Gender**

465 The pharmacokinetics of pemetrexed were not different in male and female patients.

466 **Effect of Race**

467 The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. Insufficient data are
468 available to compare pharmacokinetics for other ethnic groups.

469 **Effect of Hepatic Insufficiency**

470 There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of
471 hepatically impaired patients have not been conducted [see *Dosage and Administration (2.4) and Use in Specific Populations (8.6)*].

472 **Effect of Renal Insufficiency**

473 Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed
474 decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and
475 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with
476 creatinine clearance of 100 mL/min [see *Warnings and Precautions (5.4) and Dosage and Administration (2.4)*].

477 **Effect of Ibuprofen**

478 Ibuprofen doses of 400 mg four times a day reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in
479 patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown [see *Drug*
480 *Interactions (7.1)*].

481 **Effect of Aspirin**

482 Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed.
483 The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Reference ID: 2919227

Effect of Cisplatin

Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum are unaltered by pemetrexed.

Effect of Vitamins

Coadministration of oral folic acid or intramuscular vitamin B₁₂ does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes

Results from in vitro studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m² basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer (NSCLC) - Combination with Cisplatin

A multi-center, randomized, open-label study in 1725 chemo-naïve patients with Stage IIIb/IV NSCLC was conducted to compare the overall survival following treatment with ALIMTA in combination with cisplatin (AC) versus gemcitabine in combination with cisplatin (GC). ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m² with cisplatin administered intravenously at a dose of 75 mg/m² after ALIMTA administration, on Day 1 of each 21-day cycle. Gemcitabine was administered at a dose of 1250 mg/m² on Day 1 and Day 8, and cisplatin was administered intravenously at a dose of 75 mg/m² after administration of gemcitabine, on Day 1 of each 21-day cycle. Treatment was administered up to a total of 6 cycles, and patients in both treatment arms received folic acid, vitamin B₁₂, and dexamethasone [see *Dosage and Administration (2.3)*].

Patient demographics of the intent to treat (ITT) population are shown in Table 9. The demographics and disease characteristics were well balanced.

Table 9: First-Line Therapy: Summary of Patient Characteristics in Study of NSCLC

Patient characteristic	ALIMTA plus Cisplatin (AC) (N=862)	Gemcitabine plus Cisplatin (GC) (N=863)
Age (yrs)		
Median (range)	61.1 (28.8-83.2)	61.0 (26.4-79.4)
Gender		
Male/Female	70.2%/29.8%	70.1%/29.9%
Origin		
Caucasian	669 (77.6%)	680 (78.8%)
Hispanic	27 (3.1%)	23 (2.7%)
Asian	146 (16.9%)	141 (16.3%)
African descent	18 (2.1%)	18 (2.1%)
Stage at Entry		
IIIb/IV	23.8%/76.2%	24.3%/75.7%
Histology		
Nonsquamous NSCLC ^a	618 (71.7%)	634 (73.5%)
Adenocarcinoma	436 (50.6%)	411 (47.6%)
Large cell	76 (8.8%)	77 (8.9%)
Other ^b	106 (12.3%)	146 (16.9%)
Squamous	244 (28.3%)	229 (26.5%)
ECOG PS^{c,d}		
0/1	35.4%/64.6%	35.6%/64.3%
Smoking History^e		
Ever/never smoker	83.1%/16.9%	83.9%/16.1%

^a Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

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

^c Eastern Cooperative Oncology Group Performance Status.

^d ECOG PS was not reported for all randomized patients. Percentages are representative of N=861 for the ALIMTA plus cisplatin arm, and N=861 for the gemcitabine plus cisplatin arm.

^e Smoking history was collected for 88% of randomized patients (N=757 for the ALIMTA plus cisplatin arm and N=759 for the gemcitabine plus cisplatin arm).

Patients received a median of 5 cycles of treatment in both study arms. Patients treated with ALIMTA plus cisplatin received a relative dose intensity of 94.8% of the protocol-specified ALIMTA dose intensity and 95.0% of the protocol-specified cisplatin dose intensity. Patients treated with gemcitabine plus cisplatin received a relative dose intensity of 85.8% of the protocol-specified gemcitabine dose intensity and 93.5% of the protocol-specified cisplatin dose intensity.

The primary endpoint in this study was overall survival. The median survival time was 10.3 months in the ALIMTA plus cisplatin treatment arm and 10.3 months in the gemcitabine plus cisplatin arm, with an adjusted hazard ratio of 0.94.

Table 10: First-Line Therapy: Efficacy in NSCLC - ITT Population

	ALIMTA plus Cisplatin (N=862)	Gemcitabine plus Cisplatin (N=863)
Median overall survival (95% CI)	10.3 mos (9.8-11.2)	10.3 mos (9.6-10.9)
Adjusted hazard ratio (HR) ^{a,b} (95% CI)	0.94 (0.84-1.05)	
Median progression-free survival (95% CI)	4.8 mos (4.6-5.3)	5.1 mos (4.6-5.5)
Adjusted hazard ratio (HR) ^{a,b} (95% CI)	1.04 (0.94-1.15)	
Overall response rate (95% CI)	27.1% (24.2-30.1)	24.7% (21.8-27.6)

^a Adjusted for gender, stage, basis of diagnosis, and performance status.

^b A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

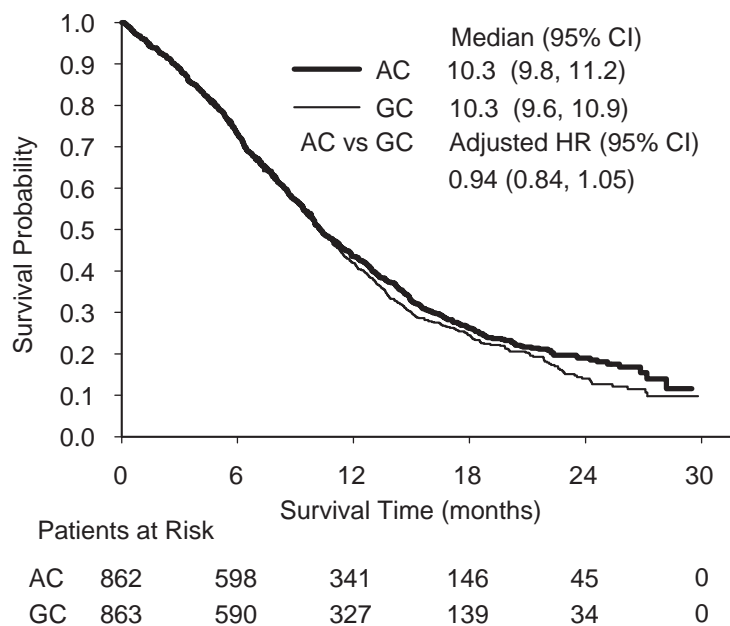


Figure 1: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC - ITT Population.

A pre-specified analysis of the impact of NSCLC histology on overall survival was examined. Clinically relevant differences in survival according to histology were observed and are shown in Table 11. This difference in treatment effect for ALIMTA based on histology demonstrating a lack of efficacy in squamous cell histology was also observed in the single-agent, second-line study and the maintenance study [see *Clinical Studies (14.2, 14.3)*].

Table 11: First-Line Therapy: Overall Survival in NSCLC Histologic Subgroups

Histology Subgroup	Median Overall Survival in Months (95% CI)				Unadjusted Hazard Ratio (HR) ^{a,b} (95% CI)	Adjusted Hazard Ratio (HR) ^{a,b,c} (95% CI)
	ALIMTA plus Cisplatin		Gemcitabine plus Cisplatin			
Nonsquamous NSCLC ^d (N=1252)	11.0 (10.1-12.5)	N=618	10.1 (9.3-10.9)	N=634	0.84 (0.74-0.96)	0.84 (0.74-0.96)
Adenocarcinoma (N=847)	12.6 (10.7-13.6)	N=436	10.9 (10.2-11.9)	N=411	0.84 (0.71-0.98)	0.84 (0.71-0.99)
Large Cell	10.4	N=76	6.7	N=77	0.68	0.67

(N=153)	(8.6-14.1)		(5.5-9.0)		(0.48-0.97)	(0.48-0.96)
Other ^c (N=252)	8.6 (6.8-10.2)	N=106	9.2 (8.1-10.6)	N=146	1.12 (0.84-1.49)	1.08 (0.81-1.45)
Squamous Cell (N=473)	9.4 (8.4-10.2)	N=244	10.8 (9.5-12.1)	N=229	1.22 (0.99-1.50)	1.23 (1.00-1.51)

^a A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

^b Unadjusted for multiple comparisons.

^c HRs adjusted for ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

^d Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

^e The subgroup of “other” represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

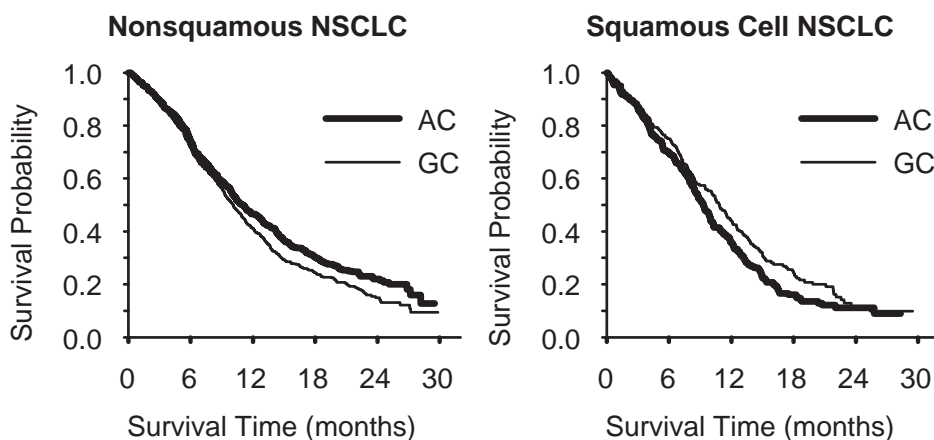


Figure 2: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC - Nonsquamous NSCLC and Squamous Cell NSCLC.

14.2 Non-Small Cell Lung Cancer - Maintenance

A multi-center, randomized, double-blind, placebo-controlled study was conducted in 663 patients with Stage IIIb/IV NSCLC who did not progress after four cycles of platinum-based chemotherapy. Patients who did not progress were randomized 2:1 to receive ALIMTA or placebo immediately following platinum-based chemotherapy. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m² on Day 1 of each 21-day cycle, until disease progression. Patients in both study arms received folic acid, vitamin B₁₂, and dexamethasone [see *Dosage and Administration* (2.3)].

The study was designed to demonstrate superior progression-free survival and overall survival of ALIMTA over placebo. Progression-free survival (PFS) was assessed by independent review. Patient characteristics of the intent to treat (ITT) population are shown in Table 12. The demographics and baseline disease characteristics were well balanced between study arms.

Table 12: Maintenance Therapy: Summary of Patient Characteristics in Study of NSCLC

Patient characteristic	ALIMTA (N=441)	Placebo (N=222)
Age (yrs)		
Median (range)	60.6 (25.6-82.6)	60.4 (35.4-78.5)
Gender		
Male/Female	73.0%/27.0%	72.5%/27.5%
Ethnic Origin		
Caucasian	279 (63.3%)	149 (67.1%)
East Asian	104 (23.6%)	50 (22.5%)
Other	58 (13.2%)	23 (10.4%)
Stage at Entry^a		
IIIb/IV	18.0%/82.0%	21.2%/78.8%
Histology (%)		
Nonsquamous NSCLC ^b	325 (73.7%)	156 (70.3%)
Adenocarcinoma	222 (50.3%)	106 (47.7%)
Large cell	10 (2.3%)	10 (4.5%)

Other ^c	93 (21.1%)	40 (18.0%)
Squamous	116 (26.3%)	66 (29.7%)
ECOG PS^d		
0/1	40.1%/59.9%	38.3%/61.7%
Smoking History^e		
Ever/never smoker	74.1%/25.9%	71.5%/28.5%
Time from start of induction therapy to study randomization (months)		
Median (range)	3.25 (1.6-4.8)	3.29 (2.7-5.1)

^a Stage at Entry was not reported for all randomized patients. Percentages are representative of N=440 for the ALIMTA arm and N=222 for the placebo arm.

^b Includes patients with adenocarcinoma, large cell, and other histologic diagnoses.

^c The subgroup of “Other” represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

^d Eastern Cooperative Oncology Group Performance Status (ECOG PS) was not reported for all randomized patients. Percentages are representative of N=439 for the ALIMTA arm, and N=222 for the placebo arm.

^e Smoking history was not reported for all randomized patients. Percentages are representative of N=437 for the ALIMTA arm and N=221 for the placebo arm.

Patients received a median of 5 cycles of ALIMTA and 3.5 cycles of placebo. Patients randomized to ALIMTA received a relative dose intensity of 95.7%. A total of 213 patients (48.3%) completed ≥6 cycles and a total of 98 patients (22.6%) completed ≥10 cycles of treatment with ALIMTA.

In the overall study population, ALIMTA was statistically superior to placebo in terms of overall survival (OS) (median 13.4 months versus 10.6 months, HR=0.79 (95% CI: 0.65-0.95), p-value=0.012) and PFS (median 4.0 months versus 2.0 months, HR=0.60 (95% CI: 0.49-0.73), p-value<0.00001). A difference in treatment outcomes was observed according to histologic classification. For the population of patients with nonsquamous NSCLC, ALIMTA was superior to placebo for OS (median 15.5 months versus 10.3 months, HR=0.70 (95% CI: 0.56-0.88)) and PFS (median 4.4 months versus 1.8 months, HR=0.47 (95% CI: 0.37-0.60)). For the population of patients with squamous NSCLC, ALIMTA did not improve OS compared to placebo (median 9.9 months versus 10.8 months, HR=1.07 (95% CI: 0.77-1.50)) or PFS (median 2.4 months versus 2.5 months, HR=1.03 (95% CI: 0.71-1.49)). This difference in treatment effect for ALIMTA based on histology demonstrating lack of benefit in squamous cell histology was also observed in the first-line and second line studies. [see *Clinical Studies (14.1, 14.3)*]

Efficacy results for the overall patient population are presented in Table 13 and Figure 3, and efficacy results by pre-specified histologic subgroups are presented in Table 14 and Figure 4, below.

Table 13: Maintenance Therapy: Efficacy of ALIMTA versus Placebo in NSCLC - ITT Population

Efficacy Parameter ^{a,b}	ALIMTA (N=441)	Placebo (N=222)
Median overall survival ^c (95% CI)	13.4 mos (11.9-15.9)	10.6 mos (8.7-12.0)
Hazard ratio (HR) ^c (95% CI)	0.79 (0.65-0.95)	
p-value	p=0.012	
Median progression-free survival (95% CI)	4.0 mos (3.1-4.4)	2.0 mos (1.5-2.8)
Hazard ratio (HR) ^c (95% CI)	0.60 (0.49-0.73)	
p-value	p<0.00001	

^a PFS and OS were calculated from time of randomization, after completion of 4 cycles of induction platinum-based chemotherapy.

^b Values for PFS given based on independent review (ALIMTA N=387, Placebo N=194).

^c Unadjusted hazard ratios are provided. A HR <1.0 indicates that the result is better in the ALIMTA arm than in the placebo arm.

Table 14: Maintenance Therapy: Efficacy in NSCLC by Histologic Subgroups^a

	Overall Survival		Progression-Free Survival ^b	
	ALIMTA	Placebo	ALIMTA	Placebo
	Median (months) HR ^c (95% CI)	Median (months) HR ^c (95% CI)	Median (months) HR ^c (95% CI)	Median (months) HR ^c (95% CI)
Nonsquamous NSCLC^d N=481	15.5 0.70 (0.56-0.88)	10.3	4.4 0.47 (0.37-0.60)	1.8
Adenocarcinoma N=328	16.8 0.73 (0.56-0.96)	11.5	4.6 0.51 (0.38-0.68)	2.7
Large cell carcinoma N=20	8.4 0.98 (0.36-2.65)	7.9	4.5 0.40 (0.12-1.29)	1.5
Other ^e N=133	11.3 0.61 (0.40-0.94)	7.7	4.1 0.44 (0.28-0.68)	1.6

Squamous cell N=182	9.9 1.07 (0.77-1.50)	10.8	2.4 1.03 (0.71-1.49)	2.5
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- ^a PFS and OS were calculated from time of randomization, after completion of 4 cycles of induction platinum-based chemotherapy. All results unadjusted for multiple comparisons.
- ^b Values for PFS are given based on independent review (ALIMTA N=387, Placebo N=194).
- ^c Unadjusted hazard ratios are provided. A HR <1.0 indicates that the result is better in the ALIMTA arm than in the placebo arm. A HR >1.0 indicates that the result is better in the placebo arm than in the ALIMTA arm.
- ^d Includes patients with adenocarcinoma, large cell carcinoma, and other histology.
- ^e The subgroup of "Other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

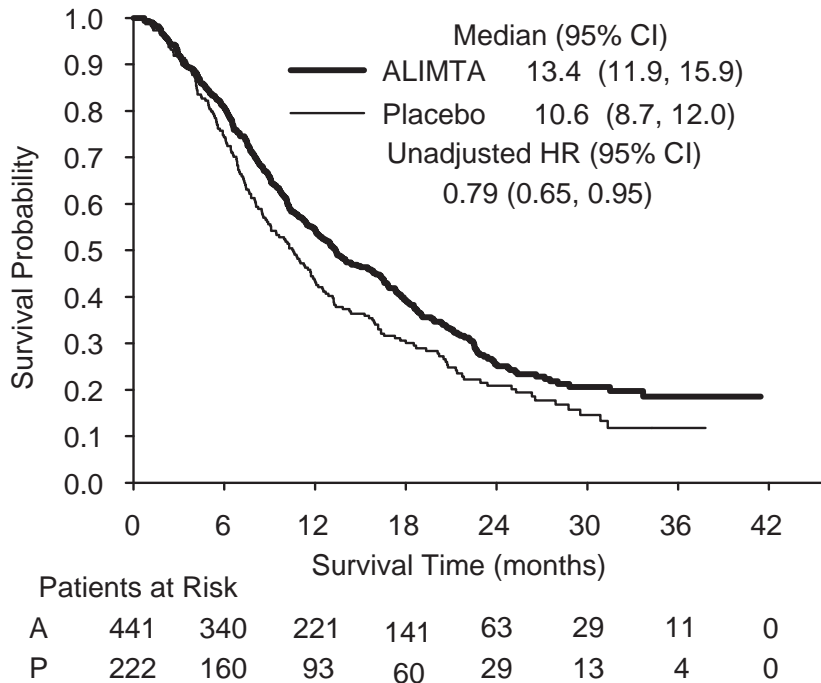


Figure 3: Kaplan-Meier Curve for Overall Survival ALIMTA (A) versus Placebo (P) in NSCLC - ITT Population.

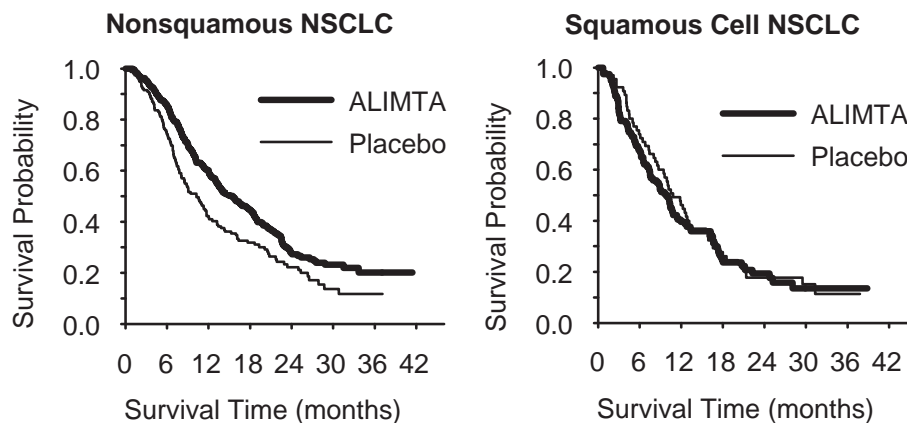


Figure 4: Kaplan-Meier Curves for Overall Survival ALIMTA versus Placebo in NSCLC - Nonsquamous NSCLC and Squamous Cell NSCLC.

14.3 Non-Small Cell Lung Cancer - After Prior Chemotherapy

A multi-center, randomized, open label study was conducted in patients with Stage III or IV NSCLC after prior chemotherapy to compare the overall survival following treatment with ALIMTA versus docetaxel. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m² and docetaxel was administered at 75 mg/m² as a 1-hour intravenous infusion. Both drugs were given on Day 1 of each 21-day cycle. All patients treated with ALIMTA received vitamin supplementation with folic acid and

vitamin B₁₂. The study was intended to show either an overall survival superiority or non-inferiority of ALIMTA to docetaxel. Patient demographics of the intent to treat (ITT) population are shown in Table 15.

Table 15: Second-Line Therapy: Summary of Patient Characteristics in NSCLC Study

Patient characteristic	ALIMTA (N=283)	Docetaxel (N=288)
Age (yrs)		
Median (range)	59 (22-81)	57 (28-87)
Gender (%)		
Male/Female	68.6/31.4	75.3/24.7
Stage at Entry (%)		
III/IV	25.1/74.9	25.3/74.7
Diagnosis/Histology (%)		
Adenocarcinoma	154 (54.4)	142 (49.3)
Squamous	78 (27.6)	94 (32.6)
Bronchoalveolar	4 (1.4)	1 (0.3)
Other	47 (16.6)	51 (17.7)
Performance Status (%)^a		
0-1	234 (88.6)	240 (87.6)
2	30 (11.4)	34 (12.4)

^a Performance status was not reported for all randomized patients. Percentages are representative of N=264 for the ALIMTA arm and N=274 for the docetaxel arm.

The primary endpoint in this study was overall survival. The median survival time was 8.3 months in the ALIMTA treatment arm and 7.9 months in the docetaxel arm, with a hazard ratio of 0.99 (see Table 16). The study did not show an overall survival superiority of ALIMTA.

Table 16: Efficacy of ALIMTA versus Docetaxel in Non-Small Cell Lung Cancer - ITT Population

	ALIMTA (N=283)	Docetaxel (N=288)
Median overall survival (95% CI)	8.3 mos (7.0-9.4)	7.9 mos (6.3-9.2)
Hazard ratio (HR) (95% CI)	0.99 (0.82-1.20)	
Median progression-free survival (95% CI)	2.9 mos (2.4-3.1)	2.9 mos (2.7-3.4)
Hazard ratio (HR) (95% CI)	0.97 (0.82-1.16)	
Overall response rate (95% CI)	8.5% (5.2-11.7)	8.3% (5.1-11.5)

A retrospective analysis of the impact of NSCLC histology on overall survival was examined. Clinically relevant differences in survival according to histology were observed and are shown in Table 17. This difference in treatment effect for ALIMTA based on histology demonstrating a lack of efficacy in squamous cell histology was also observed in the first-line combination study and in the maintenance study [see *Clinical Studies (14.1, 14.2)*].

Table 17: Second Line Therapy: Overall Survival of ALIMTA versus Docetaxel in NSCLC by Histologic Subgroups

Histology Subgroup	Median Overall Survival in Months (95% CI)				Unadjusted Hazard Ratio (HR) ^{a,b} (95% CI)	Adjusted Hazard Ratio (HR) ^{a,b,c} (95% CI)
	ALIMTA		Docetaxel			
Nonsquamous NSCLC ^d (N=399)	9.3 (7.8-9.7)	N=205	8.0 (6.3-9.3)	N=194	0.89 (0.71-1.13)	0.78 (0.61-1.00)
Adenocarcinoma (N=301)	9.0 (7.6-9.6)	N=158	9.2 (7.5-11.3)	N=143	1.09 (0.83-1.44)	0.92 (0.69-1.22)
Large Cell (N=47)	12.8 (5.8-14.0)	N=18	4.5 (2.3-9.1)	N=29	0.38 (0.18-0.78)	0.27 (0.11-0.63)
Other ^c (N=51)	9.4 (6.0-10.1)	N=29	7.9 (4.0-8.9)	N=22	0.62 (0.32-1.23)	0.57 (0.27-1.20)
Squamous Cell (N=172)	6.2 (4.9-8.0)	N=78	7.4 (5.6-9.5)	N=94	1.32 (0.93-1.86)	1.56 (1.08-2.26)

^a A HR that is less than 1.0 indicates that survival is better in the ALIMTA arm than in the docetaxel arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the docetaxel arm than in the ALIMTA arm.

^b Unadjusted for multiple comparisons.

^c Other includes bronchoalveolar and adenocarcinoma.

^d Includes large cell and other.

Reference ID: 2919227

- ^c HRs adjusted for ECOG PS, time since prior chemotherapy, disease stage, and gender.
^d Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.
^e The subgroup of “other” represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

14.4 Malignant Pleural Mesothelioma

A multi-center, randomized, single-blind study in 448 chemo-naïve patients with malignant pleural mesothelioma (MPM) compared survival in patients treated with ALIMTA in combination with cisplatin to survival in patients receiving cisplatin alone. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m² and cisplatin was administered intravenously over 2 hours at a dose of 75 mg/m² beginning approximately 30 minutes after the end of administration of ALIMTA. Both drugs were given on Day 1 of each 21-day cycle. After 117 patients were treated, white cell and GI toxicity led to a change in protocol whereby all patients were given folic acid and vitamin B₁₂ supplementation.

The primary analysis of this study was performed on the population of all patients randomly assigned to treatment who received study drug (randomized and treated). An analysis was also performed on patients who received folic acid and vitamin B₁₂ supplementation during the entire course of study therapy (fully supplemented), as supplementation is recommended [see *Dosage and Administration* (2.3)]. Results in all patients and those fully supplemented were similar. Patient demographics are shown in Table 18.

Table 18: Summary of Patient Characteristics in MPM Study

Patient characteristic	Randomized and Treated Patients		Fully Supplemented Patients	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Age (yrs)				
Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
Gender (%)				
Male	184 (81.4)	181 (81.5)	136 (81.0)	134 (82.2)
Female	42 (18.6)	41 (18.5)	32 (19.0)	29 (17.8)
Origin (%)				
Caucasian	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)
Hispanic	11 (4.9)	12 (5.4)	10 (6.0)	7 (4.3)
Asian	10 (4.4)	4 (1.9)	7 (4.2)	3 (1.8)
African descent	1 (0.4)	0	1 (0.6)	0
Stage at Entry (%)				
I	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)
II	35 (15.6)	33 (15.0)	27 (16.2)	27 (16.8)
III	73 (32.4)	68 (30.6)	51 (30.5)	49 (30.4)
IV	101 (44.9)	105 (47.2)	74 (44.3)	73 (45.3)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.2)
Diagnosis/Histology^a (%)				
Epithelial	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)
Mixed	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)
Sarcomatoid	18 (8.0)	25 (11.3)	14 (8.3)	17 (10.4)
Other	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)
Baseline KPS^b (%)				
70-80	109 (48.2)	97 (43.7)	83 (49.4)	69 (42.3)
90-100	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)

^a Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review.

^b Karnofsky Performance Scale.

Table 19 and Figure 5 summarize the survival results for all randomized and treated patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrollment in the trial.

Table 19: Efficacy of ALIMTA plus Cisplatin versus Cisplatin in Malignant Pleural Mesothelioma

Efficacy Parameter	Randomized and Treated Patients		Fully Supplemented Patients	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Median overall survival (95% CI)	12.1 mos (10.0-14.4)	9.3 mos (7.8-10.7)	13.3 mos (11.4-14.9)	10.0 mos (8.4-11.9)
Hazard ratio	0.77		0.75	

Log rank p-value ^a	0.020	0.051
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^a p-value refers to comparison between arms.

Similar results were seen in the analysis of patients (N=303) with confirmed histologic diagnosis of malignant pleural mesothelioma. There were too few non-white patients to assess possible ethnic differences. The effect in women (median survival 15.7 months with the combination versus 7.5 months on cisplatin alone), however, was larger than the effect in males (median survival 11 versus 9.4 respectively). As with any exploratory analysis, it is not clear whether this difference is real or is a chance finding.

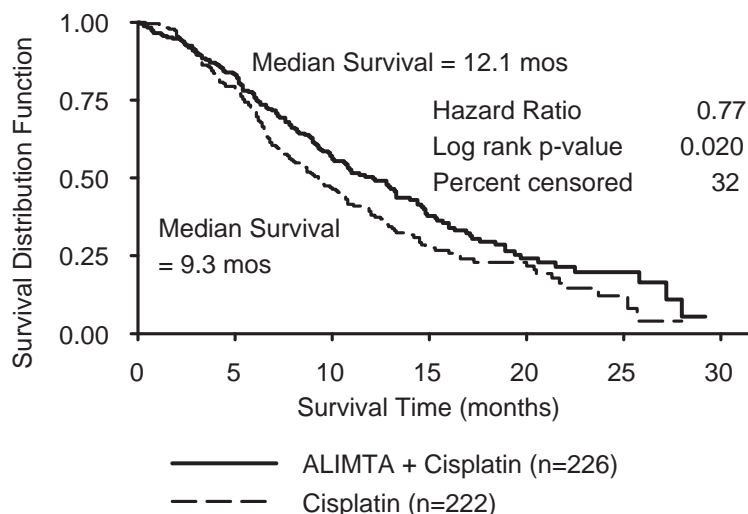


Figure 5: Kaplan-Meier Estimates of Survival Time for ALIMTA plus Cisplatin and Cisplatin Alone in all Randomized and Treated Patients.

Objective tumor response for malignant pleural mesothelioma is difficult to measure and response criteria are not universally agreed upon. However, based upon prospectively defined criteria, the objective tumor response rate for ALIMTA plus cisplatin was greater than the objective tumor response rate for cisplatin alone. There was also improvement in lung function (forced vital capacity) in the ALIMTA plus cisplatin arm compared to the control arm.

Patients who received full supplementation with folic acid and vitamin B₁₂ during study therapy received a median of 6 and 4 cycles in the ALIMTA/cisplatin (N=168) and cisplatin (N=163) arms, respectively. Patients who never received folic acid and vitamin B₁₂ during study therapy received a median of 2 cycles in both treatment arms (N=32 and N=38 for the ALIMTA/cisplatin and cisplatin arm, respectively). Patients receiving ALIMTA in the fully supplemented group received a relative dose intensity of 93% of the protocol specified ALIMTA dose intensity; patients treated with cisplatin in the same group received 94% of the projected dose intensity. Patients treated with cisplatin alone had a dose intensity of 96%.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ALIMTA, pemetrexed for injection, is available in sterile single-use vials containing 100 mg pemetrexed.

NDC 0002-7640-01 (VL7640): single-use vial with ivory flip-off cap individually packaged in a carton.

ALIMTA, pemetrexed for injection, is available in sterile single-use vials containing 500 mg pemetrexed.

NDC 0002-7623-01 (VL7623): single-use vial with ivory flip-off cap individually packaged in a carton.

16.2 Storage and Handling

ALIMTA, pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

705 Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were demonstrated for up to 24 hours
706 following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to
707 15-30°C (59-86°F) [see USP Controlled Room Temperature]. When prepared as directed, reconstituted and infusion solutions of
708 ALIMTA contain no antimicrobial preservatives. Discard unused portion [see *Dosage and Administration (2.5)*].
709 ALIMTA is not light sensitive.

710 **17 PATIENT COUNSELING INFORMATION**

711 See FDA-Approved Patient Labeling

712 Patients should be instructed to read the patient package insert carefully.

713 **17.1 Need for Folic Acid and Vitamin B₁₂**

714 Patients treated with ALIMTA must be instructed to take folic acid and vitamin B₁₂ as a prophylactic measure to reduce
715 treatment-related hematologic and gastrointestinal toxicity [see *Dosage and Administration (2.3)*].

716 **17.2 Low Blood Cell Counts**

717 Patients should be adequately informed of the risk of low blood cell counts and instructed to immediately contact their
718 physician should any sign of infection develop including fever. Patients should also contact their physician if bleeding or symptoms of
719 anemia occur.

720 **17.3 Gastrointestinal Effects**

721 Patients should be instructed to contact their physician if persistent vomiting, diarrhea, or signs of dehydration appear.

722 **17.4 Concomitant Medications**

723 Patients should be instructed to inform the physician if they are taking any concomitant prescription or over-the-counter
724 medications including those for pain or inflammation such as non-steroidal anti-inflammatory drugs [see *Drug Interactions (7.1)*].

725 Literature revised month dd, yyyy

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727 **Indianapolis, IN 46285, USA**

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INFORMATION FOR PATIENTS AND CAREGIVERS

ALIMTA[®] (uh-LIM-tuh) (pemetrexed for injection)

Read the Patient Information that comes with ALIMTA before you start treatment and each time you get treated with ALIMTA. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about ALIMTA.

What is ALIMTA?

ALIMTA is a treatment for:

- **Malignant pleural mesothelioma.** This cancer affects the inside lining of the chest cavity. ALIMTA is given with cisplatin, another anti-cancer medicine (chemotherapy).
- **Nonsquamous non-small cell lung cancer.** This cancer is a disease in which malignant (cancer) cells form in the tissues of the lung. If you are having initial treatment for your lung cancer, ALIMTA may be given alone or in combination with another chemotherapy drug. If this is the first time you have been treated for your lung cancer, ALIMTA may be given with another anti-cancer drug called cisplatin. If you have completed initial treatment for your lung cancer, ALIMTA may be given alone immediately following your initial treatment. If you are being treated because your cancer has come back or you had trouble tolerating a prior treatment, ALIMTA may be given alone. Your doctor will speak to you about whether ALIMTA is appropriate for your specific type of non-small cell lung cancer.

To lower your chances of side effects of ALIMTA, you must also take folic acid and vitamin B₁₂ prior to and during your treatment with ALIMTA. Your doctor will prescribe a medicine called a “corticosteroid” to take for 3 days during your treatment with ALIMTA. Corticosteroid medicines lower your chances of getting skin reactions with ALIMTA.

In children, ALIMTA has not been shown to be effective. No important differences in side effects were seen in children compared to adults (see “**What are the possible side effects of ALIMTA?**”).

What should I tell my doctor before taking ALIMTA?

Tell your doctor about all of your medical conditions, including if you:

- **are pregnant or planning to become pregnant.** ALIMTA may harm your unborn baby.
- **are breastfeeding.** It is not known if ALIMTA passes into breast milk. You should stop breastfeeding once you start treatment with ALIMTA.
- **are taking other medicines,** including prescription and nonprescription medicines, vitamins, and herbal supplements. ALIMTA and other medicines may affect each other causing serious side effects. Especially, tell your doctor if you are taking medicines called “nonsteroidal anti-inflammatory drugs” (NSAIDs) for pain or swelling. There are many NSAID medicines. If you are not sure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

How is ALIMTA given?

- ALIMTA is slowly infused (injected) into a vein. The injection or infusion will last about 10 minutes. You will usually receive ALIMTA once every 21 days (3 weeks).
- If you are being treated with ALIMTA and cisplatin for the initial treatment of either mesothelioma or non-small cell lung cancer, ALIMTA will be given first as a 10 minute infusion into your vein and cisplatin (another anti-cancer drug) will also be given through your vein starting about 30 minutes after ALIMTA and ending about 2 hours later.

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- If you have completed initial treatment for your non-small cell lung cancer, you may receive ALIMTA alone, given as a 10 minute infusion into your vein.
- If you are being treated because your non-small cell lung cancer has returned, you may receive ALIMTA alone, given as a 10 minute infusion into your vein.
- Your doctor will prescribe a medicine called a “corticosteroid” to take for 3 days during your treatment with ALIMTA. Corticosteroid medicines lower your chances for getting skin reactions with ALIMTA.
- **It is very important to take folic acid and vitamin B₁₂ during your treatment with ALIMTA to lower your chances of harmful side effects.** You must start taking 350-1000 micrograms of folic acid every day for at least 5 days out of the 7 days before your first dose of ALIMTA. You must keep taking folic acid every day during the time you are getting treatment with ALIMTA, and for 21 days after your last treatment. You can get folic acid vitamins over-the-counter. Folic acid is also found in many multivitamin pills. Ask your doctor or pharmacist for help if you are not sure how to choose a folic acid product. Your doctor will give you vitamin B₁₂ injections while you are getting treatment with ALIMTA. You will get your first vitamin B₁₂ injection during the week before your first dose of ALIMTA, and then about every 9 weeks during treatment.
- You will have regular blood tests before and during your treatment with ALIMTA. Your doctor may adjust your dose of ALIMTA or delay treatment based on the results of your blood tests and on your general condition.

What should I avoid while taking ALIMTA?

- **Women who can become pregnant should not become pregnant during treatment with ALIMTA.** ALIMTA may harm the unborn baby.
- **Ask your doctor before taking medicines called NSAIDs.** There are many NSAID medicines. If you are not sure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

What are the possible side effects of ALIMTA?

Most patients taking ALIMTA will have side effects. Sometimes it is not always possible to tell whether ALIMTA, another medicine, or the cancer itself is causing these side effects. **Call your doctor right away if you have a fever, chills, diarrhea, or mouth sores.** These symptoms could mean you have an infection which may be severe and could lead to death.

The most common side effects of ALIMTA when given alone or in combination with cisplatin are:

- **Stomach upset, including nausea, vomiting, and diarrhea.** You can obtain medicines to help control some of these symptoms. Call your doctor if you get any of these symptoms.
- **Low blood cell counts:**
 - **Low red blood cells.** Low red blood cells may make you feel tired, get tired easily, appear pale, and become short of breath.
 - **Low white blood cells.** Low white blood cells may give you a greater chance for infection. If you have a fever (temperature above 100.4°F) or other signs of infection, call your doctor right away.
 - **Low platelets.** Low platelets give you a greater chance for bleeding. Your doctor will do blood tests to check your blood counts before and during treatment with ALIMTA.
- **Tiredness.** You may feel tired or weak for a few days after your ALIMTA treatments. If you have severe weakness or tiredness, call your doctor.
- **Mouth, throat, or lip sores** (stomatitis, pharyngitis). You may get redness or sores in your mouth, throat, or on your lips. These symptoms may happen a few days after ALIMTA treatment. Talk with your doctor about proper mouth and throat care.
- **Loss of appetite.** You may lose your appetite and lose weight during your treatment. Talk to your doctor if this is a problem for you.
- **Rash.** You may get a rash or itching during treatment. These usually appear between treatments with ALIMTA and usually go away before the next treatment. Rarely, these reactions may be severe (can

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91 lead to Stevens-Johnson Syndrome or Toxic epidermal necrolysis) and could lead to death. Call your
92 doctor if you get a severe rash, itching, or blistering.

93 Talk with your doctor, nurse or pharmacist about any side effect that bothers you or that doesn't go away.

94 These are not all the side effects of ALIMTA. For more information, ask your doctor, nurse or pharmacist.

95 **General information about ALIMTA**

96 Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets.
97 ALIMTA was prescribed for your medical condition.

98 This leaflet summarizes the most important information about ALIMTA. If you would like more
99 information, talk with your doctor. You can ask your doctor or pharmacist for information about ALIMTA that
100 is written for health professionals. You can also call 1-800-LILLY-RX (1-800-545-5979) or visit
101 www.ALIMTA.com.

102 Patient information revised month dd, yyyy

103 **Eli Lilly and Company**
104 **Indianapolis, IN 46285, USA**

105 **www.ALIMTA.com**
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