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 for injection), for Intravenous Use

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Indications and Usage (1.1)	06/2018
Dosage and Administration (2.1)	06/2018

INDICATIONS AND USAGE

ALIMTA® is a folate analog metabolic inhibitor indicated:

- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). (1.1)
- in combination with carboplatin and pembrolizumab for the initial treatment of patients with metastatic, non-squamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1)
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. (1.1)

Limitations of Use: ALIMTA is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. (1.1)

- initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. (1.2)

DOSAGE AND ADMINISTRATION

- The recommended dose of ALIMTA, administered as a single agent or with cisplatin or with carboplatin and pembrolizumab, in patients with creatinine clearance of 45 mL/minute or greater, is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. (2.1, 2.2)
- Initiate folic acid 400 mcg to 1000 mcg orally, once daily, beginning 7 days prior to the first dose of ALIMTA and continue until 21 days after the last dose of ALIMTA. (2.4)
- Administer vitamin B_{12}, 1 mg intramuscularly, 1 week prior to the first dose of ALIMTA and every 3 cycles. (2.4)
- Administer dexamethasone 4 mg orally, twice daily the day before, the day of, and the day after ALIMTA administration. (2.4)

DOSAGE FORMS AND STRENGTHS

For Injection: 100 mg or 500 mg lyophilized powder in single-dose vial. (3)

CONTRAINDICATIONS

History of severe hypersensitivity reaction to pemetrexed. (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression: Can cause severe bone marrow suppression resulting in cytopenia and an increased risk of infection. Do not administer ALIMTA when the absolute neutrophil count is less than 1500 cells/mm^3 and platelets are less than 100,000 cells/mm^3. Initiate supplementation with oral folic acid and intramuscular vitamin B_{12} to reduce the severity of hematologic and gastrointestinal toxicity of ALIMTA. (2.6, 5.1)
- Renal Failure: Can cause severe, and sometimes fatal, renal failure. Do not administer when creatinine clearance is less than 45 mL/min. (2.3, 5.2)
- Bullous and Exfoliative Skin Toxicity: Permanently discontinue for severe and life-threatening bullous, blistering or exfoliating skin toxicity. (5.3)
- Interstitial Pneumonitis: Withhold for acute onset of new or progressive unexplained pulmonary symptoms. Permanently discontinue if pneumonitis is confirmed. (5.4)
- Radiation Recall: Can occur in patients who received radiation weeks to years previously; permanently discontinue for signs of radiation recall. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥20%) of ALIMTA, when administered as a single agent are fatigue, nausea, and anorexia. (6.1)
- The most common adverse reactions (incidence ≥20%) of ALIMTA when administered with cisplatin are vomiting, neutropenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation. (6.1)
- The most common adverse reactions (incidence ≥30%) of ALIMTA when administered in combination with carboplatin and pembrolizumab are fatigue, nausea, constipation, rash, vomiting, dyspnea, diarrhea, headache, and decreased appetite.

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

Ibuprofen increased risk of ALIMTA toxicity in patients with mild to moderate renal impairment. Modify the ibuprofen dosage as recommended for patients with a creatinine clearance between 45 mL/min and 79 mL/min. (2.5, 5.6, 7)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

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

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

ALIMTA® is indicated:

- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC).
- in combination with carboplatin and pembrolizumab for the initial treatment of patients with metastatic, non-squamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.

Limitations of Use: ALIMTA is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer *[see Clinical Studies 14.1].*

1.2 Mesothelioma

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Non-Squamous NSCLC

- The recommended dose of ALIMTA when administered with cisplatin for initial treatment of NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes administered prior to cisplatin on Day 1 of each 21-day cycle for up to six cycles in the absence of disease progression or unacceptable toxicity.

- The recommended dose of ALIMTA for maintenance treatment of NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity after four cycles of platinum-based first-line chemotherapy.

- The recommended dose of ALIMTA for treatment of recurrent NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity.

- The recommended dose of ALIMTA when administered with carboplatin and pembrolizumab for the initial treatment of NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 administered as an intravenous infusion over 10 minutes prior to carboplatin on Day 1 of each 21-day cycle for 4 cycles. Following completion of platinum-based therapy, ALIMTA may be administered as maintenance therapy,

alone or with pembrolizumab, until disease progression or unacceptable toxicity. Pembrolizumab should be administered prior to ALIMTA when given on the same day. Please refer to the full prescribing information for pembrolizumab and for carboplatin.

2.2 Recommended Dosage for Mesothelioma

- The recommended dose of ALIMTA, administered when administered with cisplatin, in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity.

2.3 Renal Impairment

- ALIMTA dosing recommendations are provided for patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater *[see Dosage and Administration (2.1, 2.2)]*. There is no recommended dose for patients whose creatinine clearance is less than 45 mL/min *[see Use in Specific Populations (8.6)]*.

2.4 Premedication and Concomitant Medications to Mitigate Toxicity

Vitamin Supplementation

- Initiate folic acid 400 mcg to 1000 mcg orally once daily, beginning 7 days before the first dose of ALIMTA and continuing until 21 days after the last dose of ALIMTA *[see Warnings and Precautions (5.1)]*.

- Administer vitamin $B_{12,}$ 1 mg intramuscularly, 1 week prior to the first dose of ALIMTA and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with ALIMTA *[see Warnings and Precautions (5.1)]*. **Do not substitute oral vitamin B_{12} for intramuscular vitamin B_{12}.**

Corticosteroids

- Administer dexamethasone 4 mg orally twice daily for three consecutive days, beginning the day before each ALIMTA administration.

2.5 Dosage Modification of Ibuprofen in Patients with Mild to Moderate Renal Impairment Receiving ALIMTA

In patients with creatinine clearances between 45 mL/min and 79 mL/min, modify administration of ibuprofen as follows *[see Warnings and Precautions (5.6), Drug Interactions (7) and Clinical Pharmacology (12.3)]*:

- Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA.
- Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

2.6 Dosage Modifications for Adverse Reactions

Obtain complete blood count on Days 1, 8, and 15 of each cycle. Assess creatinine clearance prior to each cycle. Do not administer ALIMTA if the creatinine clearance is less than 45 mL/min.

Delay initiation of the next cycle of ALIMTA until:

- recovery of non-hematologic toxicity to Grade 0-2,
- absolute neutrophil count (ANC) is 1500 cells/mm^3 or higher, and
- platelet count is 100,000 cells/mm^3 or higher.

Upon recovery, modify the dosage of ALIMTA in the next cycle as specified in Table 1.

For dosing modifications for cisplatin, refer to the prescribing information for cisplatin.

Table 1: Recommended Dosage Modifications for Adverse Reactions[a]

Toxicity in Most Recent Treatment Cycle	ALIMTA Dose Modification for Next Cycle
Myelosuppressive toxicity *[see Warnings and Precautions (5.1)]*	
ANC less than 500/mm^3 **and** platelets greater than or equal to 50,000/mm^3 OR Platelet count less than 50,000/mm^3 without bleeding.	75% of previous dose
Platelet count less than 50,000/mm^3 with bleeding	50% of previous dose
Recurrent Grade 3 or 4 myelosuppression after 2 dose reductions	Discontinue
Non-hematologic toxicity	
Any Grade 3 or 4 toxicities EXCEPT mucositis or neurologic toxicity OR Diarrhea requiring hospitalization	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose
Renal toxicity *[see Warnings and Precautions (5.2)]*	Withhold until creatinine clearance is 45 mL/min or greater
Grade 3 or 4 neurologic toxicity	Permanently discontinue
Recurrent Grade 3 or 4 non-hematologic toxicity after 2 dose reductions	Permanently discontinue
Severe and life-threatening Skin Toxicity *[see Warnings and Precautions (5.3)]*	Permanently discontinue
Interstitial Pneumonitis *[see Warnings and Precautions (5.4)]*	Permanently discontinue

[a] National Cancer Institute Common Toxicity Criteria for Adverse Events version 2 (NCI CTCAE v2).

2.7 Preparation for Administration

- ALIMTA is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]
- Calculate the dose of ALIMTA and determine the number of vials needed.
- Reconstitute ALIMTA to achieve a concentration of 25 mg/mL as follows:
  - Reconstitute each 100-mg vial with 4.2 mL of 0.9% Sodium Chloride Injection, USP (preservative-free)
  - Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection, USP (preservative-free)
  - Do not use calcium-containing solutions for reconstitution.
- 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. FURTHER DILUTION IS REQUIRED prior to administration.
- Store reconstituted, preservative-free product under refrigerated conditions [2-8°C (36-46°F)] for no longer than 24 hours from the time of reconstitution. Discard vial after 24 hours.
- Inspect reconstituted product visually for particulate matter and discoloration prior to further dilution. If particulate matter is observed, discard vial.
- Withdraw the calculated dose of ALIMTA from the vial(s) and discard vial with any unused portion.
- Further dilute ALIMTA with 0.9% Sodium Chloride Injection (preservative-free) to achieve a total volume of 100 mL for intravenous infusion.
- Store diluted, reconstituted product under refrigerated conditions [2-8°C (36-46°F)] for no more than 24 hours from the time of reconstitution. Discard after 24 hours.

3 DOSAGE FORMS AND STRENGTHS

For injection: 100 mg or 500 mg pemetrexed as a white to light-yellow or green-yellow lyophilized powder in single-dose vials for reconstitution.

4 CONTRAINDICATIONS

ALIMTA is contraindicated in patients with a history of severe hypersensitivity reaction to pemetrexed *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression and Increased Risk of Myelosuppression without Vitamin Supplementation

ALIMTA can cause severe myelosuppression resulting in a requirement for transfusions and which may lead to neutropenic infection. The risk of myelosuppression is increased in patients who do not receive vitamin supplementation. In Study JMCH, incidences of Grade 3-4 neutropenia (38% versus 23%), thrombocytopenia (9% versus 5%), febrile neutropenia (9% versus 0.6%), and neutropenic infection (6% versus 0) were higher in patients who received ALIMTA plus cisplatin without vitamin supplementation as compared to patients who were fully supplemented with folic acid and vitamin B_{12} prior to and throughout ALIMTA plus cisplatin treatment.

Initiate supplementation with oral folic acid and intramuscular vitamin B_{12} prior to the first dose of ALIMTA; continue vitamin supplementation during treatment and for 21 days after the last dose of ALIMTA to reduce the severity of hematologic and gastrointestinal toxicity of ALIMTA *[see Dosage and Administration (2.4)]*. Obtain a complete blood count at the beginning of each cycle. Do not administer ALIMTA until the ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3. Permanently reduce ALIMTA in patients with an ANC of less than 500 cells/mm^3 or platelet count of less than 50,000 cells/mm^3 in previous cycles *[see Dosage and Administration (2.6)]*.

In Studies JMDB and JMCH, among patients who received vitamin supplementation, incidence of Grade 3-4 neutropenia was 15% and 23%, the incidence of Grade 3-4 anemia was 6% and 4%, and incidence of Grade 3-4 thrombocytopenia was 4% and 5%, respectively. In Study JMCH, 18% of patients in the ALIMTA arm required red blood cell transfusions compared to 7% of patients in the cisplatin arm *[see Adverse Reactions (6.1)].* In Studies JMEN, PARAMOUNT, and JMEI, where all patients received vitamin supplementation, incidence of Grade 3-4 neutropenia ranged from 3% to 5%, and incidence of Grade 3-4 anemia ranged from 3% to 5%.

5.2 Renal Failure

ALIMTA can cause severe, and sometimes fatal, renal toxicity. The incidences of renal failure in clinical studies in which patients received ALIMTA with cisplatin were: 2.1% in Study JMDB and 2.2% in Study JMCH. The incidence of renal failure in clinical studies in which patients received ALIMTA as a single agent ranged from 0.4% to 0.6% (Studies JMEN, PARAMOUNT, and JMEI *[see Adverse Reactions (6.1)]*. Determine creatinine clearance before each dose and periodically monitor renal function during treatment with ALIMTA. Withhold ALIMTA in patients with a creatinine clearance of less than 45 mL/minute *[see Dosage and Administration (2.3)]*.

5.3 Bullous and Exfoliative Skin Toxicity

Serious and sometimes fatal, bullous, blistering and exfoliative skin toxicity, including cases suggestive of Stevens-Johnson Syndrome/Toxic epidermal necrolysis can occur with ALIMTA. Permanently discontinue ALIMTA for severe and life-threatening bullous, blistering or exfoliating skin toxicity.

5.4 Interstitial Pneumonitis

Serious interstitial pneumonitis, including fatal cases, can occur with ALIMTA treatment. Withhold ALIMTA for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, or fever pending diagnostic evaluation. If pneumonitis is confirmed, permanently discontinue ALIMTA.

5.5 Radiation Recall

Radiation recall can occur with ALIMTA in patients who have received radiation weeks to years previously. Monitor patients for inflammation or blistering in areas of previous radiation treatment. Permanently discontinue ALIMTA for signs of radiation recall.

5.6 Increased Risk of Toxicity with Ibuprofen in Patients with Renal Impairment

Exposure to ALIMTA is increased in patients with mild to moderate renal impairment who take concomitant ibuprofen, increasing the risks of adverse reactions of ALIMTA. In patients with creatinine clearances between 45 mL/min and 79 mL/min, avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA. If concomitant ibuprofen use cannot be avoided, monitor patients more frequently for ALIMTA adverse reactions, including myelosuppression, renal, and gastrointestinal toxicity *[see Dosage and Administration (2.5), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and increased malformations at doses lower than the recommended human dose of 500 mg/m^2. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ALIMTA and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALIMTA and for 3 months after the final dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Renal failure *[see Warnings and Precautions (5.2)]*
- Bullous and exfoliative skin toxicity *[see Warning and Precautions (5.3)]*
- Interstitial pneumonitis *[see Warnings and Precautions (5.4)]*
- Radiation recall *[see Warnings and Precautions (5.5)]*

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 ≥20%) of ALIMTA, when administered as a single agent, are fatigue, nausea, and anorexia. The most common adverse reactions (incidence ≥20%) of ALIMTA, when administered in combination with cisplatin are vomiting, neutropenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Non-Squamous NSCLC

Initial Treatment in Combination with Cisplatin
The safety of ALIMTA was evaluated in Study JMDB, a randomized (1:1), open-label, multicenter trial conducted in chemotherapy-naive patients with locally advanced or metastatic NSCLC. Patients received either ALIMTA 500 mg/m^2 intravenously and cisplatin 75 mg/m^2 intravenously on Day 1 of each 21-day cycle (n=839) or gemcitabine 1250 mg/m^2 intravenously on Days 1 and 8 and cisplatin 75 mg/m^2 intravenously on Day 1 of each 21-day cycle (n=830). All patients were fully supplemented with folic acid and vitamin B_{12}.

Study JMDB excluded patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS of 2 or greater), uncontrolled third-space fluid retention, inadequate bone marrow reserve and organ function, or a calculated creatinine clearance less than 45 mL/min. Patients unable to stop using aspirin or other non-steroidal anti-inflammatory drugs or unable to take folic acid, vitamin B_{12} or corticosteroids were also excluded from the study.

The data described below reflect exposure to ALIMTA plus cisplatin in 839 patients in Study JMDB. Median age was 61 years (range 26-83 years); 70% of patients were men; 78% were White,16% were Asian, 2.9% were Hispanic or Latino, 2.1% were Black or African American, and <1% were other ethnicities; 36% had an ECOG PS 0. Patients received a median of 5 cycles of ALIMTA.

Table 2 provides the frequency and severity of adverse reactions that occurred in ≥5% of 839 patients receiving ALIMTA in combination with cisplatin in Study JMDB. Study JMDB was not designed to demonstrate a statistically significant reduction in adverse reaction rates for ALIMTA, as compared to the control arm, for any specified adverse reaction listed in Table 2.

Table 2: Adverse Reactions Occurring in ≥5% of Fully Vitamin-Supplemented Patients Receiving ALIMTA in Combination with Cisplatin Chemotherapy in Study JMDB

Adverse Reaction[a]	ALIMTA/Cisplatin (N=839)		Gemcitabine/Cisplatin (N=830)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
All adverse reactions	90	37	91	53
Laboratory				
Hematologic				
Anemia	33	6	46	10
Neutropenia	29	15	38	27
Thrombocytopenia	10	4	27	13
Renal				
Elevated creatinine	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				
Sensory neuropathy	9	0	12	1
Taste disturbance	8	0	9	0
Dermatology/Skin				
Alopecia	12	0	21	1
Rash/Desquamation	7	0	8	1

[a] NCI CTCAE version 2.0.

The following additional adverse reactions of ALIMTA were observed.

Incidence 1% to <5%
Body as a Whole — febrile neutropenia, infection, pyrexia
General Disorders — dehydration
Metabolism and Nutrition — increased AST, increased ALT
Renal —renal failure
Eye Disorder — conjunctivitis

Incidence <1%
Cardiovascular — arrhythmia
General Disorders — chest pain
Metabolism and Nutrition — increased GGT
Neurology — motor neuropathy

Maintenance Treatment Following First-line Non-ALIMTA Containing Platinum-Based Chemotherapy
In Study JMEN, the safety of ALIMTA was evaluated in a randomized (2:1), placebo-controlled, multicenter trial conducted in patients with non-progressive locally advanced or metastatic NSCLC following four cycles of a first-line, platinum-based chemotherapy regimen. Patients received either ALIMTA 500 mg/m^2 or matching placebo intravenously every 21 days until disease progression or unacceptable toxicity. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.

Study JMEN excluded patients with an ECOG PS of 2 or greater, uncontrolled third-space fluid retention, inadequate bone marrow reserve and organ function, or a calculated creatinine clearance less than 45 mL/min. Patients unable to stop using aspirin or other non-steroidal anti-inflammatory drugs or unable to take folic acid, vitamin B_{12} or corticosteroids were also excluded from the study.

The data described below reflect exposure to ALIMTA in 438 patients in Study JMEN. Median age was 61 years (range 26-83 years), 73% of patients were men; 65% were White, 31% were Asian, 2.9% were Hispanic or Latino, and <2% were other ethnicities; 39% had an ECOG PS 0. Patients received a median of 5 cycles of ALIMTA and a relative dose intensity of ALIMTA of 96%. Approximately half the patients (48%) completed at least six, 21-day cycles and 23% completed ten or more 21-day cycles of ALIMTA.

Table 3 provides the frequency and severity of adverse reactions reported in ≥5% of the 438 ALIMTA-treated patients in Study JMEN.

Table 3: Adverse Reactions Occurring in ≥5% of Patients Receiving ALIMTA in Study JMEN

Adverse Reaction[a]	ALIMTA (N=438)		Placebo (N=218)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
All adverse reactions	66	16	37	4
Laboratory				
Hematologic				
Anemia	15	3	6	1
Neutropenia	6	3	0	0
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				
Sensory neuropathy	9	1	4	0
Dermatology/Skin				
Rash/desquamation	10	0	3	0

[a] NCI CTCAE version 3.0.

The requirement for transfusions (9.5% versus 3.2%), primarily red blood cell transfusions, and for erythropoiesis stimulating agents (5.9% versus 1.8%) were higher in the ALIMTA arm compared to the placebo arm.

The following additional adverse reactions were observed in patients who received ALIMTA.

Incidence 1% to<5%
Dermatology/Skin — alopecia, pruritus/itching
Gastrointestinal — constipation
General Disorders — edema, fever
Hematologic — thrombocytopenia
Eye Disorder — ocular surface disease (including conjunctivitis), increased lacrimation

Incidence <1%
Cardiovascular — supraventricular arrhythmia
Dermatology/Skin — erythema multiforme
General Disorders — febrile neutropenia, allergic reaction/hypersensitivity
Neurology — motor neuropathy
Renal — renal failure

Maintenance Treatment Following First-line ALIMTA Plus Platinum Chemotherapy
The safety of ALIMTA was evaluated in PARAMOUNT, a randomized (2:1), placebo-controlled study conducted in patients with non-squamous NSCLC with non-progressive (stable or responding disease) locally advanced or metastatic NSCLC following four cycles of ALIMTA in combination with cisplatin as first-line therapy for NSCLC. Patients were randomized to receive ALIMTA 500 mg/m^2 or matching placebo intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity. Patients in both study arms received folic acid and vitamin B_{12} supplementation.

PARAMOUNT excluded patients with an ECOG PS of 2 or greater, uncontrolled third-space fluid retention, inadequate bone marrow reserve and organ function, or a calculated creatinine clearance less than 45 mL/min. Patients unable to stop using aspirin or other non-steroidal anti-inflammatory drugs or unable to take folic acid, vitamin B_{12} or corticosteroids were also excluded from the study.

The data described below reflect exposure to ALIMTA in 333 patients in PARAMOUNT. Median age was 61 years (range 32 to 83 years); 58% of patients were men; 94% were White, 4.8% were Asian, and <1% were Black or African American; 36% had an ECOG PS 0. The median number of maintenance cycles was 4 for ALIMTA and placebo arms. Dose reductions for adverse reactions occurred in 3.3% of patients in the ALIMTA arm and 0.6% in the placebo arm. Dose delays for adverse reactions occurred in 22% of patients in the ALIMTA arm and 16% in the placebo arm.

Table 4 provides the frequency and severity of adverse reactions reported in ≥5% of the 333 ALIMTA-treated patients in PARAMOUNT.

Table 4: Adverse Reactions Occurring in ≥5% of Patients Receiving ALIMTA in PARAMOUNT

Adverse Reaction[a]	ALIMTA (N=333)		Placebo (N=167)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grades 3-4 (%)
All adverse reactions	53	17	34	4.8
Laboratory				
Hematologic				
Anemia	15	4.8	4.8	0.6
Neutropenia	9	3.9	0.6	0
Clinical				
Constitutional symptoms				
Fatigue	18	4.5	11	0.6
Gastrointestinal				
Nausea	12	0.3	2.4	0
Vomiting	6	0	1.8	0
Mucositis/stomatitis	5	0.3	2.4	0
General disorders				
Edema	5	0	3.6	0

[a] NCI CTCAE version 3.0.

The requirement for red blood cell (13% versus 4.8%) and platelet (1.5% versus 0.6%) transfusions, erythropoiesis stimulating agents (12% versus 7%), and granulocyte colony stimulating factors (6% versus 0%) were higher in the ALIMTA arm compared to the placebo arm.

The following additional Grade 3 or 4 adverse reactions were observed more frequently in the ALIMTA arm.

Incidence 1% to <5%
Blood/Bone Marrow — thrombocytopenia
General Disorders — febrile neutropenia

Incidence <1%
Cardiovascular — ventricular tachycardia, syncope
General Disorders — pain
Gastrointestinal — gastrointestinal obstruction
Neurologic — depression
Renal — renal failure
Vascular — pulmonary embolism

Treatment of Recurrent Disease After Prior Chemotherapy
The safety of ALIMTA was evaluated in Study JMEI, a randomized (1:1), open-label, active-controlled trial conducted in patients who had progressed following platinum-based chemotherapy. Patients received ALIMTA 500 mg/m^2 intravenously or docetaxel 75 mg/m^2 intravenously on Day 1 of each 21-day cycle. All patients on the ALIMTA arm received folic acid and vitamin B_{12} supplementation.

Study JMEI excluded patients with an ECOG PS of 3 or greater, uncontrolled third-space fluid retention, inadequate bone marrow reserve and organ function, or a calculated creatinine clearance less than 45 mL/min. Patients unable to discontinue aspirin or other non-steroidal anti-inflammatory drugs or unable to take folic acid, vitamin B_{12} or corticosteroids were also excluded from the study.

The data described below reflect exposure to ALIMTA in 265 patients in Study JMEI. Median age was 58 years (range 22 to 87 years); 73% of patients were men; 70% were White, 24% were Asian, 2.6% were Black or African American, 1.8% were Hispanic or Latino, and <2% were other ethnicities; 19% had an ECOG PS 0.

Table 5 provides the frequency and severity of adverse reactions reported in ≥5% of the 265 ALIMTA-treated patients in Study JMEI. Study JMEI is not designed to demonstrate a statistically significant reduction in adverse reaction rates for ALIMTA, as compared to the control arm, for any specified adverse reaction listed in the Table 5 below.

Table 5: Adverse Reactions Occurring in ≥5% of Fully Supplemented Patients Receiving ALIMTA in Study JMEI

Adverse Reaction[a]	ALIMTA (N=265)		Docetaxel (N=276)	
	All Grades (%)	Grades 3-4 (%)	All Grade (%)	Grades 3-4 (%)
Laboratory				
Hematologic				
Anemia	19	4	22	4
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
Pruritus	7	0	2	0
Alopecia	6	1	38	2

[a] NCI CTCAE version 2.0.

The following additional adverse reactions were observed in patients 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

Incidence <1%
Cardiovascular — supraventricular arrhythmias
Renal — renal failure

First-line Treatment of Non-squamous NSCLC, with Carboplatin and Pembrolizumab
The safety of ALIMTA administered with carboplatin and pembrolizumab was investigated in a randomized (1:1) open-label cohort in Study KEYNOTE-021. Patients with previously untreated, metastatic non-squamous NSCLC received ALIMTA with carboplatin and pembrolizumab (n=59) or ALIMTA with carboplatin alone (n=62). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible *[see Clinical Studies (14.1)]*.

The median number of cycles of ALIMTA was 11 (range, 1-24). The study population characteristics were: median age of 64 years (range: 37 to 80), 48% age 65 years or older, 39% Male, 87% White and 8% Asian, 97% with metastatic disease, and 12% with brain metastases.

ALIMTA was discontinued for adverse reactions in 9% of patients. The most common adverse reaction resulting in discontinuation of ALIMTA (≥2%) was acute kidney injury (3.4%). Adverse reactions leading to interruption of ALIMTA occurred in 36% of patients; the most common (≥2%) were fatigue (9%), neutrophil count decreased (9%), anemia (7%), dyspnea (3.4%), and pneumonitis (3.4%).

Table 6 summarizes the adverse reactions that occurred in at least 20% of patients in KEYNOTE-021. KEYNOTE-021 was not designed to demonstrate a statistically significant difference in adverse reactions between study arms for any specified reaction listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-021

	ALIMTA Carboplatin Pembrolizumab n=59		ALIMTA Carboplatin n=62	
Adverse Reaction	**All Grades[a] Toxicity (%)**	**Grade 3-4[a] Toxicity (%)**	**All Grades[a] Toxicity (%)**	**Grades 3-4[a] Toxicity (%)**
General Disorders and Administration Site Conditions				
Fatigue	71	3.4	50	0
Peripheral Edema	22	0	18	0
Gastrointestinal Disorders				
Nausea	68	1.7	56	0
Constipation	51	0	37	1.6
Vomiting	39	1.7	27	0
Diarrhea	37	1.7	23	1.6
Skin and Subcutaneous Tissue Disorders				
Rash[b]	42	1.7	21	1.6
Pruritus	24	0	4.8	0
Alopecia	20	0	3.2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	39	3.4	21	0
Cough	24	0	18	0
Metabolism and Nutrition Disorders				
Decreased Appetite	31	0	23	0
Nervous System Disorders				
Headache	31	0	16	1.6
Dizziness	24	0	16	0
Dysgeusia	20	0	11	0
Psychiatric Disorders				
Insomnia	24	0	15	0
Infections and Infestations				
Upper respiratory tract infection	20	0	3.2	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	15	0	24	1.6

[a] Graded per NCI CTCAE v4.0.

[b] Includes rash, rash generalized, rash macular, rash maculo-papular, and rash pruritic.

Table 7: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients in KEYNOTE-021

	ALIMTA Carboplatin Pembrolizumab		ALIMTA Carboplatin	
Laboratory Test[a]	**All Grades[b] Toxicity (%)**	**Grade 3-4[b] Toxicity (%)**	**All Grades[b] Toxicity (%)**	**Grades 3-4[b] Toxicity (%)**
Chemistry				
Hyperglycemia	74	9	61	5
Lymphocytes decreased	53	23	60	28
Aspartate aminotransferase increased	51	3.5	46	1.7
Hypertriglyceridemia	50	0	43	0
Alanine aminotransferase increased	40	3.5	32	1.7
Creatinine increased	34	3.4	19	1.7
Hyponatremia	33	5	35	3.5
Hypoalbuminemia	32	0	31	0
Hypocalcemia	30	5	19	1.7
Hypokalemia	29	5	22	1.7
Hypophosphatemia	29	5	24	11
Alkaline phosphatase increased	28	0	9	0
Hematology				
Hemoglobin decreased	83	17	84	19
Neutrophils decreased	47	14	43	8
Platelets decreased	24	9	36	10

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: ALIMTA carboplatin pembrolizumab (range: 56 to 58 patients) and ALIMTA carboplatin (range: 55 to 61 patients).

[b] Graded per NCI CTCAE v 4.0.

Mesothelioma

The safety of ALIMTA was evaluated in Study JMCH, a randomized (1:1), single-blind study conducted in patients with MPM who had received no prior chemotherapy for MPM. Patients received ALIMTA 500 mg/m^2 intravenously in combination with cisplatin 75 mg/m^2 intravenously on Day 1 of each 21-day cycle or cisplatin 75 mg/m^2 intravenously on Day 1 of each 21-day cycle administered until disease progression or unacceptable toxicity. Safety was assessed in 226 patients who received at least one dose of ALIMTA in combination with cisplatin and 222 patients who received at least one dose of cisplatin alone. Among 226 patients who received ALIMTA in combination with cisplatin, 74% (n=168) received full supplementation with folic acid and vitamin B_{12} during study therapy, 14% (n=32) were never supplemented, and 12% (n=26) were partially supplemented.

Study JMCH excluded patients with Karnofsky Performance Scale (KPS) of less than 70, inadequate bone marrow reserve and organ function, or a calculated creatinine clearance less than 45 mL/min. Patients unable to stop using aspirin or other non-steroidal anti-inflammatory drugs were also excluded from the study.

The data described below reflect exposure to ALIMTA in 168 patients that were fully supplemented with folic acid and vitamin B_{12}. Median age was 60 years (range 19 to 85 years); 82% were men; 92% were White, 5% were Hispanic or Latino, 3.0% were Asian, and <1% were other ethnicities; 54% had KPS of 90-100. The median number of treatment cycles administered was 6 in the ALIMTA/cisplatin fully supplemented group and 2 in the ALIMTA/cisplatin never supplemented group. Patients receiving ALIMTA in the fully supplemented group had a relative dose intensity of 93% of the protocol-specified ALIMTA dose intensity. The most common adverse reaction resulting in dose delay was neutropenia.

Table 8 provides the frequency and severity of adverse reactions ≥5% in the subgroup of ALIMTA-treated patients who were fully vitamin supplemented in Study JMCH. Study JMCH was not designed to demonstrate a statistically significant reduction in adverse reaction rates for ALIMTA, as compared to the control arm, for any specified adverse reaction listed in the table below.

Table 8: Adverse Reactions Occurring in ≥5% of Fully Supplemented Subgroup of Patients Receiving ALIMTA/Cisplatin in Study JMCH[a]

Adverse Reaction[b]	ALIMTA/cisplatin (N=168)		Cisplatin (N=163)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Laboratory				
Hematologic				
Neutropenia	56	23	13	3
Anemia	26	4	10	0
Thrombocytopenia	23	5	9	0
Renal				
Elevated creatinine	11	1	10	1
Decreased creatinine clearance	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				
Sensory neuropathy	10	0	10	1
Taste disturbance	8	0	6	0
Dermatology/Skin				
Rash	16	1	5	0
Alopecia	11	0	6	0

[a] In Study JMCH, 226 patients received at least one dose of ALIMTA in combination with cisplatin and 222 patients received at least one dose of cisplatin. Table 8 provides the ADRs for subgroup of patients treated with ALIMTA in combination with cisplatin (168 patients) or cisplatin alone (163 patients) who received full supplementation with folic acid and vitamin B_{12} during study therapy.

[b] NCI CTCAE version 2.0.

The following additional adverse reactions were observed in patients receiving 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 <1%
Cardiovascular — arrhythmia
Neurology — motor neuropathy

Exploratory Subgroup Analyses based on Vitamin Supplementation
Table 9 provides the results of exploratory analyses of the frequency and severity of NCI CTCAE Grade 3 or 4 adverse reactions reported in more ALIMTA-treated patients who did not receive vitamin supplementation (never supplemented) as compared with those who received vitamin supplementation with daily folic acid and vitamin B_{12} from the time of enrollment in Study JMCH (fully-supplemented).

Table 9: Exploratory Subgroup Analysis of Selected Grade 3/4 Adverse Reactions Occurring in Patients Receiving ALIMTA in Combination with Cisplatin with or without Full Vitamin Supplementation in Study JMCH[a]

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

[a] NCI CTCAE version 2.0.

The following adverse reactions occurred more frequently in patients who were fully vitamin supplemented than in patients who were never supplemented:

- hypertension (11% versus 3%),
- chest pain (8% versus 6%),
- thrombosis/embolism (6% versus 3%).

Additional Experience Across Clinical Trials

Sepsis, with or without neutropenia, including fatal cases: 1%
Severe esophagitis, resulting in hospitalization: <1%

6.2 Postmarketing 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.

Blood and Lymphatic System — immune-mediated hemolytic anemia
Gastrointestinal — colitis, pancreatitis
General Disorders and Administration Site Conditions — edema
Injury, poisoning, and procedural complications — radiation recall
Respiratory — interstitial pneumonitis
Skin — Serious and fatal bullous skin conditions, Stevens-Johnson syndrome, and toxic epidermal necrolysis

7 DRUG INTERACTIONS

Effects of Ibuprofen on Pemetrexed

Ibuprofen increases exposure (AUC) of pemetrexed *[see Clinical Pharmacology (12.3)]*. In patients with creatinine clearance between 45 mL/min and 79 mL/min:

- Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA *[see Dosage and Administration (2.5)]*.
- Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on ALIMTA use in pregnant women. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and malformations at doses lower than the recommended human dose of 500 mg/m^2 *[see Data]*. Advise pregnant women of the potential risk to a fetus *[see Use in Special Populations (8.3)]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Pemetrexed was teratogenic in mice. Daily dosing of pemetrexed by intravenous injection to pregnant mice during the period of organogenesis increased the incidence of fetal malformations (cleft palate; protruding tongue; enlarged or misshaped kidney; and fused lumbar vertebra) at doses (based on BSA) 0.03 times the human dose of 500 mg/m^2. At doses, based on BSA, greater than or equal to 0.0012 times the 500 mg/m^2 human dose, pemetrexed administration resulted in dose-dependent increases in developmental delays (incomplete ossification of talus and skull bone; and decreased fetal weight).

8.2 Lactation

Risk Summary

There is no information regarding the presence of pemetrexed or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from ALIMTA, advise women not to breastfeed during treatment with ALIMTA and for one week after last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ALIMTA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with ALIMTA for at least 6 months after the final dose of ALIMTA.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALIMTA and for 3 months after the final dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

ALIMTA may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ALIMTA in pediatric patients have not been established. The safety and pharmacokinetics of ALIMTA were evaluated in two clinical studies conducted in pediatric patients with recurrent solid tumors. ALIMTA was administered at doses ranging from 400 to 2480 mg/m^2 intravenously over 10 minutes on Day 1 of a 21-day cycle to 32 pediatric patients with recurrent solid tumors in a dose-finding study. The maximum tolerated dose (MTD) was determined to be 1910 mg/m^2 (60 mg/kg for patients <12 months old). ALIMTA was administered at the MTD every 21 days in an activity-estimating study enrolling 72 patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral primitive neural ectodermal tumor (PNET), rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high grade glioma. Patients in both studies received concomitant vitamin B_{12} and folic acid supplementation and dexamethasone.

No tumor responses were observed. Adverse reactions observed in pediatric patients were similar to those observed in adults.

Single-dose pharmacokinetics of ALIMTA administered at doses ranging from 400 to 2480 mg/m^2 were evaluated in 22 patients (13 males and 9 females) age 4 to 18 years (average age 12 years). Pemetrexed exposure (AUC and C_{max}) appeared to increase proportionally with dose. Average clearance (2.30 L/h/m^2) and half-life (2.3 hours) were similar in pediatric patients compared to adults.

8.5 Geriatric Use

Of the 3,946 patients enrolled in clinical studies of ALIMTA, 34% were 65 and over and 4% were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. The incidences of Grade 3-4 anemia, fatigue, thrombocytopenia, hypertension, and neutropenia were higher in patients 65 years of age and older as compared to younger patients: in at least one of five randomized clinical trials *[see Adverse Reactions (6.1) and Clinical Studies (14.1, 14.2)].*

8.6 Patients with Renal Impairment

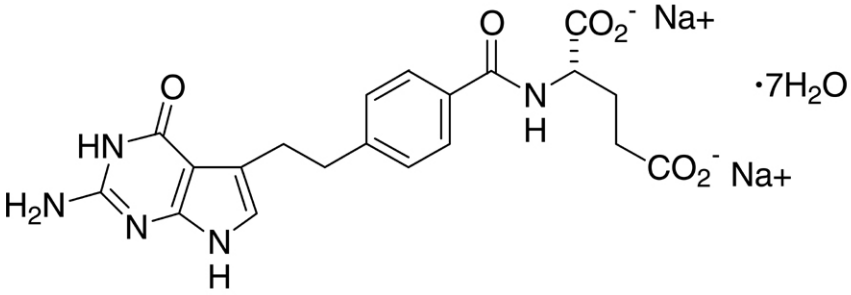
ALIMTA is primarily excreted by the kidneys. Decreased renal function results in reduced clearance and greater exposure (AUC) to ALIMTA compared with patients with normal renal function *[Warnings and Precautions (5.2, 5.6) and Clinical Pharmacology (12.3)]*. No dose is recommended for patients with creatinine clearance less than 45 mL/min *[see Dosage and Administration (2.3)]*.

10 OVERDOSAGE

No drugs are approved for the treatment of ALIMTA overdose. Based on animal studies, administration of leucovorin may mitigate the toxicities of ALIMTA overdosage. It is not known whether pemetrexed is dialyzable.

11 DESCRIPTION

ALIMTA (pemetrexed for injection) is a folate analog metabolic inhibitor. The drug substance, pemetrexed disodium heptahydrate, has the chemical name L-glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate with a molecular formula of $C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$ and a molecular weight of 597.49. The structural formula is as follows:



ALIMTA is a sterile white-to-light yellow or green-yellow lyophilized powder in single-dose vials to be reconstituted for intravenous infusion. Each 100-mg vial of ALIMTA contains 100 mg pemetrexed (equivalent to 139.8 mg pemetrexed disodium heptahydrate) and 106 mg mannitol. Each 500-mg vial of ALIMTA contains 500 mg pemetrexed (equivalent to 699 mg pemetrexed disodium heptahydrate) and 500 mg mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ALIMTA is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. In vitro studies show that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT.

12.2 Pharmacodynamics

Pemetrexed inhibited the in vitro growth of mesothelioma cell lines (MSTO-211H, NCI-H2052) and showed synergistic effects when combined with cisplatin.

Based on population pharmacodynamic analyses, the depth of the absolute neutrophil counts (ANC) nadir correlates with the systemic exposure to pemetrexed and supplementation with folic acid and vitamin B_{12}. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of pemetrexed when ALIMTA was administered as a single agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increased proportionally with increase of dose. The pharmacokinetics of pemetrexed did not change over multiple treatment cycles.

Distribution
Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicated that pemetrexed is 81% bound to plasma proteins.

Elimination
The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). As renal function decreases, the clearance of pemetrexed decreases and exposure (AUC) of pemetrexed increases.

Metabolism
Pemetrexed is not metabolized to an appreciable extent.

Excretion
Pemetrexed is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. In vitro studies indicated that pemetrexed is a substrate of OAT3 (organic anion transporter 3), a transporter that is involved in the active secretion of pemetrexed.

Specific Populations
Age (26 to 80 years) and sex had no clinically meaningful effect on the systemic exposure of pemetrexed based on population pharmacokinetic analyses.

Racial Groups
The pharmacokinetics of pemetrexed were similar in Whites and Blacks or African Americans. Insufficient data are available for other ethnic groups.

Patients with Hepatic Impairment
Pemetrexed has not been formally studied in patients with hepatic impairment. No effect of elevated AST, ALT, or total bilirubin on the PK of pemetrexed was observed in clinical studies.

Patients with Renal Impairment
Pharmacokinetic analyses of pemetrexed included 127 patients with impaired renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.

Third-Space Fluid
The pemetrexed plasma concentrations in patients with various solid tumors with stable, mild to moderate third-space fluid were comparable to those observed in patients without third space fluid collections. The effect of severe third space fluid on pharmacokinetics is not known.

Drug Interaction Studies

Drugs Inhibiting OAT3 Transporter
Ibuprofen, an OAT3 inhibitor, administered at 400 mg four times a day decreased the clearance of pemetrexed and increased its exposure (AUC) by approximately 20% in patients with normal renal function (creatinine clearance >80 mL/min).

In Vitro Studies
Pemetrexed is a substrate for OAT3. Ibuprofen, an OAT3 inhibitor inhibited the uptake of pemetrexed in OAT3-expressing cell cultures with an average $[I_u]/IC_{50}$ ratio of 0.38. In vitro data predict that at clinically relevant concentrations, other NSAIDs (naproxen, diclofenac, celocoxib) would not inhibit the uptake of pemetrexed by OAT3 and would not increase the AUC of pemetrexed to a clinically significant extent. *[see Drug Interactions (7)]*.

Pemetrexed is a substrate for OAT4. In vitro, ibuprofen and other NSAIDs (naproxen, diclofenac, celocoxib) are not inhibitors of OAT4 at clinically relevant concentrations.

Aspirin
Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed.

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

Vitamins
Neither folic acid nor vitamin B_{12} affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes
In vitro studies suggest that pemetrexed does not inhibit the 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 an in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, Chinese Hamster Ovary cell assay).

Pemetrexed administered intraperitoneally at doses of ≥0.1 mg/kg/day to male mice (approximately 0.006 times the recommended human dose based on BSA) resulted in reduced fertility, hypospermia, and testicular atrophy.

14 CLINICAL STUDIES

14.1 Non-Squamous NSCLC

Initial Treatment in Combination with Cisplatin
The efficacy of ALIMTA was evaluated in Study JMDB (NCT00087711), a multi-center, randomized (1:1), open-label study conducted in 1725 chemotherapy-naive patients with Stage IIIb/IV NSCLC. Patients were randomized to receive ALIMTA with cisplatin or gemcitabine with cisplatin. Randomization was stratified by Eastern Cooperative Oncology Group Performance Status (ECOG PS 0 versus 1), gender, disease stage, basis for pathological diagnosis (histopathological/cytopathological), history of brain metastases, and investigative center. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 on Day 1 of each 21-day cycle. Cisplatin was administered intravenously at a dose of 75 mg/m^2 approximately 30 minutes after ALIMTA administration on Day 1 of each cycle, gemcitabine was administered at a dose of 1250 mg/m^2 on Day 1 and Day 8, and cisplatin was administered intravenously at a dose of 75 mg/m^2 approximately 30 minutes after administration of gemcitabine, on Day 1 of each 21-day cycle. Treatment was administered up to a total of 6 cycles; patients in both arms received folic acid, vitamin B_{12}, and dexamethasone *[see Dosage and Administration (2.4)]*. The primary efficacy outcome measure was overall survival.

A total of 1725 patients were enrolled with 862 patients randomized to ALIMTA in combination with cisplatin and 863 patients to gemcitabine in combination with cisplatin. The median age was 61 years (range 26-83 years), 70% were male, 78% were White, 17% were Asian, 2.9% were Hispanic or Latino, and 2.1% were Black or African American, and <1% were other ethnicities. Among patients for whom ECOG PS (n=1722) and smoking history (n=1516) were collected, 65% had an ECOG PS of 1, 36% had an ECOG PS of 0, and 84% were smokers. For tumor characteristics, 73% had non-squamous NSCLC and 27% had squamous NSCLC; 76% had Stage IV disease. Among 1252 patients with non-squamous NSCLC histology, 68% had a diagnosis of adenocarcinoma, 12% had large cell histology and 20% had other histologic subtypes.

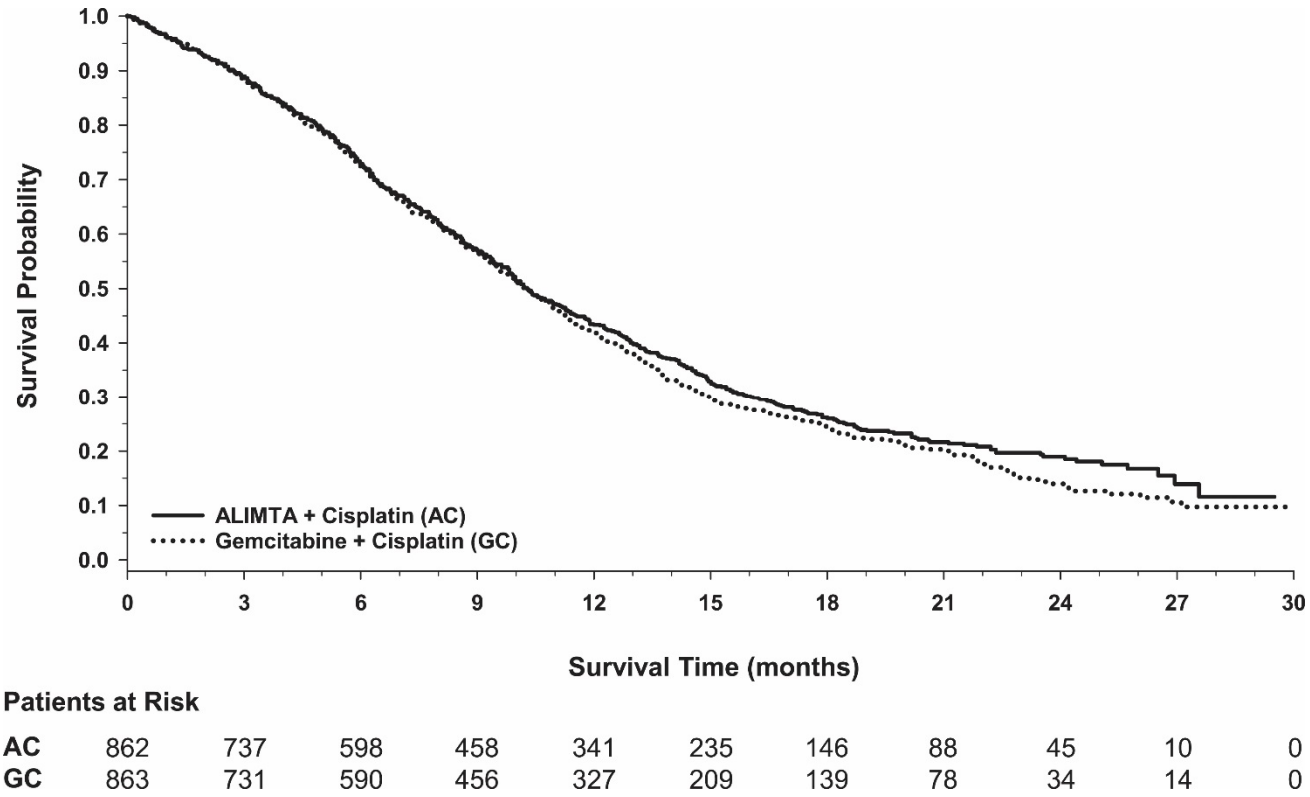
Efficacy results in Study JMDB are presented in Table 10 and Figure 1.

Table 10: Efficacy Results in Study JMDB

Efficacy Parameter	ALIMTA plus Cisplatin (N=862)	Gemcitabine plus Cisplatin (N=863)
Overall Survival		
Median (months) (95% CI)	10.3 (9.8-11.2)	10.3 (9.6-10.9)
Hazard ratio (HR)[a,b] (95% CI)	0.94 (0.84-1.05)	
Progression-Free Survival		
Median (months) (95% CI)	4.8 (4.6-5.3)	5.1 (4.6-5.5)
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] Unadjusted for multiple comparisons.

[b] Adjusted for gender, stage, basis of diagnosis, and performance status.



Patients at Risk

AC	862	737	598	458	341	235	146	88	45	10	0
GC	863	731	590	456	327	209	139	78	34	14	0

Figure 1: Kaplan-Meier Curves for Overall Survival in Study JMDB

In pre-specified analyses assessing the impact of NSCLC histology on overall survival, clinically relevant differences in survival according to histology were observed. These subgroup analyses are shown in Table 11 and Figures 2 and 3. This difference in treatment effect for ALIMTA based on histology demonstrating a lack of efficacy in squamous cell histology was also observed in Studies JMEN and JMEI.

Table 11: Overall Survival in NSCLC Histologic Subgroups in Study JMDB

Histologic Subgroups	ALIMTA plus Cisplatin (N=862)	Gemcitabine plus Cisplatin (N=863)
Non-squamous NSCLC (N=1252)		
Median (months) (95% CI)	11.0 (10.1-12.5)	10.1 (9.3-10.9)
HR[a,b] (95% CI)	0.84 (0.74-0.96)	
Adenocarcinoma (N=847)		
Median (months) (95% CI)	12.6 (10.7-13.6)	10.9 (10.2-11.9)
HR[a,b] (95% CI)	0.84 (0.71-0.99)	
Large Cell (N=153)		
Median (months) (95% CI)	10.4 (8.6-14.1)	6.7 (5.5-9.0)
HR[a,b] (95% CI)	0.67 (0.48-0.96)	
Other[c] (N=252)		
Median (months) (95% CI)	8.6 (6.8-10.2)	9.2 (8.1-10.6)
HR[a,b] (95% CI)	1.08 (0.81-1.45)	
Squamous Cell[c] (N=473)		
Median (months) (95% CI)	9.4 (8.4-10.2)	10.8 (9.5-12.1)
HR[a,b] (95% CI)	1.23 (1.00-1.51)	

[a] Unadjusted for multiple comparisons.

[b] Adjusted for ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

[c] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

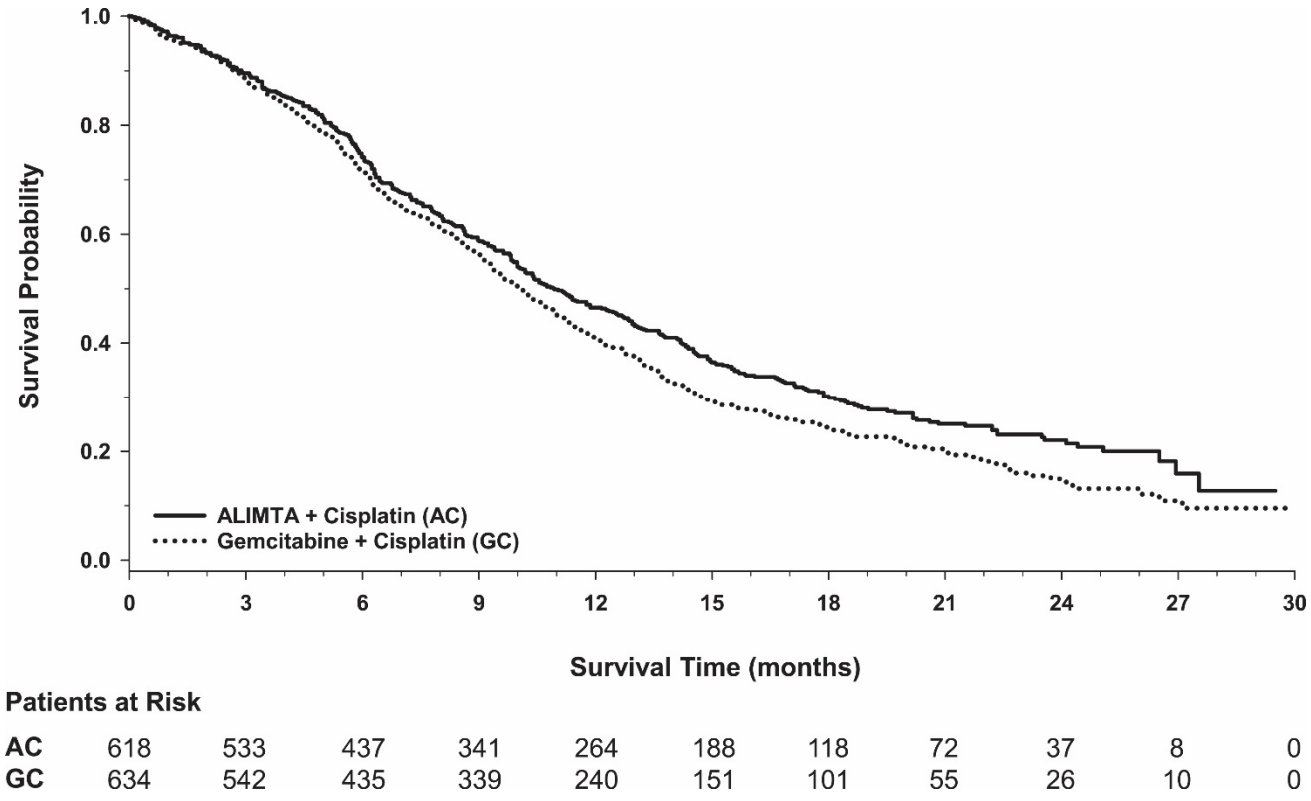
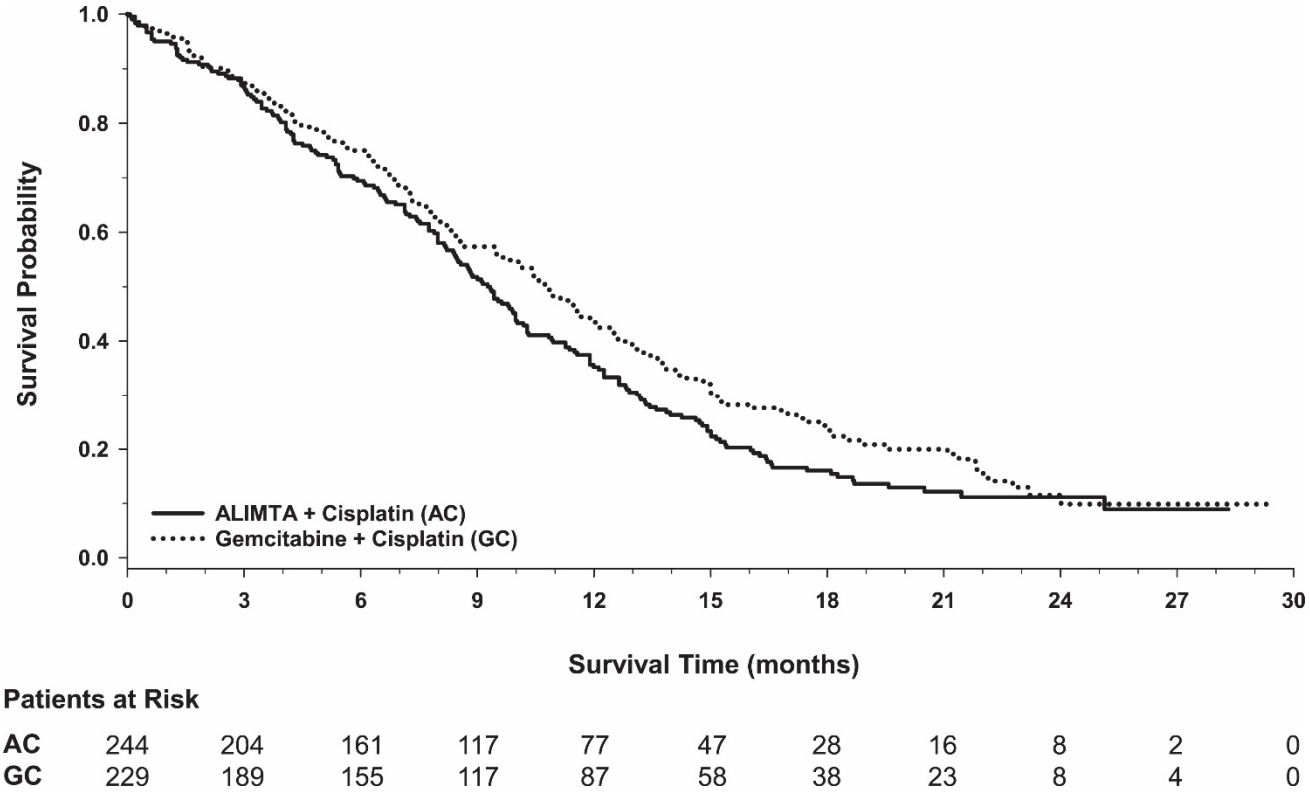


Figure 2: Kaplan-Meier Curves for Overall Survival in Non-squamous NSCLC in Study JMDB



Patients at Risk

AC	244	204	161	117	77	47	28	16	8	2	0
GC	229	189	155	117	87	58	38	23	8	4	0

Figure 3: Kaplan-Meier Curves for Overall Survival in Squamous NSCLC in Study JMDB

First-Line Treatment of Metastatic Non-Squamous NSCLC with Carboplatin and Pembrolizumab

The efficacy of ALIMTA administered with carboplatin and pembrolizumab was investigated in patients enrolled in an open-label, multicenter, multi-cohort study, Study KEYNOTE-021 (NCT02039674); the efficacy data are limited to patients with metastatic non-squamous NSCLC randomized within a single cohort (Cohort G1). The key eligibility criteria for this cohort were locally advanced or metastatic non-squamous NSCLC, regardless of tumor PD-L1 expression status, and no prior systemic treatment for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by PD-L1 tumor expression (TPS <1% versus TPS ≥1%). Patients were randomized (1:1) to one of the following treatment arms:

- Pembrolizumab 200 mg, ALIMTA 500 mg/m^2, and carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles followed by pembrolizumab 200 mg intravenously every 3 weeks. Pembrolizumab was administered prior to chemotherapy on Day 1.
- ALIMTA 500 mg/m^2 and carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles.

At the investigator's discretion, maintenance ALIMTA 500 mg/m^2 every 3 weeks was permitted in both treatment arms and continued until RECIST1.1-defined progression of disease or unacceptable toxicity.

Pembrolizumab was continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (BICR), unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab in the pembrolizumab-containing arm was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Patients on ALIMTA with carboplatin were offered pembrolizumab as a single agent at the time of disease progression.

Assessment of tumor status was performed every 6 weeks through Week 18 and every 9 weeks thereafter. The major efficacy outcome measure was objective response rate (ORR) as assessed by BICR using RECIST 1.1. Additional efficacy outcome measures were progression-free survival (PFS) as assessed by BICR using RECIST 1.1, duration of response, and overall survival (OS).

A total of 123 patients were randomized: 60 patients to the ALIMTA with carboplatin and pembrolizumab arm and 63 to the ALIMTA with carboplatin arm. The study population characteristics were: median age of 64 years (range 37 to 80 years); 48% age 65 or older; 39% male; 87% White and 8% Asian; ECOG performance status of 0 (41%) and 1 (56%); 97% had metastatic disease; and 12% had brain metastases. Thirty-six percent had tumor PD-L1 expression TPS <1%; no patients had sensitizing EGFR or ALK genomic aberrations. A total of 20 (32%) patients in the ALIMTA with carboplatin arm received pembrolizumab at the time of disease progression and 12 (19%) additional patients received a checkpoint inhibitor as subsequent therapy.

In Cohort G1 of KEYNOTE-021, there was a statistically significant improvement in ORR in patients randomized to ALIMTA with carboplatin and pembrolizumab compared to ALIMTA with carboplatin alone (see Table 12).

Table 12: Efficacy Results in Cohort G1 of KEYNOTE-021

Endpoint	ALIMTA Carboplatin Pembrolizumab n=60	ALIMTA Carboplatin n=63
Overall Response Rate		
Overall Response Rate	55%	29%
(95% CI)	(42, 68)	(18, 41)
Complete Response	0%	0%
Partial Response	55%	29%
p-value[a]	0.0032	
Duration of Response		
% with duration ≥6 months[b]	93%	81%
Range (months)	1.4+ to 13.0+	1.4+ to 15.2+
PFS		
Number of events (%)	23 (38%)	33 (52%)
Progressive Disease	15 (25%)	27 (43%)
Death	8 (13%)	6 (10%)
Median in months (95% CI)	13 (8.3, NE)	8.9 (4.4, 10.3)
Hazard ratio[c] (95% CI)	0.53 (0.31, 0.91)	
p-value[d]	0.020	

[a] Based on Miettinen-Nurminen method stratified by PD-L1 status (TPS <1% versus TPS ≥1%).
[b] Based on Kaplan-Meier estimation.
[c] Based on the Cox proportional hazard model stratified by PD-L1 status (TPS <1% versus TPS ≥1%).
[d] Based on the log-rank test stratified by PD-L1 status (TPS <1% versus TPS ≥1%).
NE = not estimable.

Exploratory analyses for ORR were conducted in subgroups defined by the stratification variable, PD-L1 tumor expression (TPS <1% and TPS ≥1%). In the TPS <1% subgroup, the ORR was 57% in the ALIMTA with carboplatin and pembrolizumab arm and 13% in the ALIMTA with carboplatin arm. In the TPS ≥1% subgroup, the ORR was 54% in the ALIMTA with carboplatin and pembrolizumab arm and 38% in the ALIMTA with carboplatin arm.

Maintenance Treatment Following First-line Non-ALIMTA Containing Platinum-Based Chemotherapy

The efficacy of ALIMTA as maintenance therapy following first-line platinum-based chemotherapy was evaluated in Study JMEN (NCT00102804), a multicenter, randomized (2:1), double-blind, placebo-controlled study conducted in 663 patients with Stage IIIb/IV NSCLC who did not progress after four cycles of platinum-based chemotherapy. Patients were randomized to receive ALIMTA 500 mg/m^2 intravenously every 21 days or placebo until disease progression or intolerable toxicity. Patients in both study arms received folic acid, vitamin B_{12}, and dexamethasone *[see Dosage and Administration (2.4)].* Randomization was carried out using a minimization approach [Pocock and Simon (1975)] using the following factors: gender, ECOG PS (0 versus 1), response to prior chemotherapy (complete or partial response versus stable disease), history of brain metastases (yes versus no), non-platinum component of induction therapy (docetaxel versus gemcitabine versus paclitaxel), and disease stage (IIIb versus IV). The major efficacy outcome measures were progression-free survival based on assessment by independent review and overall survival; both were measured from the date of randomization in Study JMEN.

A total of 663 patients were enrolled with 441 patients randomized to ALIMTA and 222 patients randomized to placebo. The median age was 61 years (range 26-83 years); 73% were male; 65% were White, 32% were Asian, 2.9% were Hispanic or Latino, and <2% were other ethnicities; 60% had an ECOG PS of 1; and 73% were current or former smokers. Median time from initiation of platinum-based chemotherapy to randomization was 3.3 months (range 1.6 to 5.1 months)

and 49% of the population achieved a partial or complete response to first-line, platinum-based chemotherapy. With regard to tumor characteristics, 81% had Stage IV disease, 73% had non-squamous NSCLC and 27% had squamous NSCLC. Among the 481 patients with non-squamous NSCLC, 68% had adenocarcinoma, 4% had large cell, and 28% had other histologies.

Efficacy results are presented in Table 13 and Figure 4.

Table 13: Efficacy Results in Study JMEN

Efficacy Parameter	ALIMTA	Placebo
Overall survival	N=441	N=222
Median (months) (95% CI)	13.4 (11.9-15.9)	10.6 (8.7-12.0)
Hazard ratio[a] (95% CI)	0.79 (0.65-0.95)	
p-value	p=0.012	
Progression-free survival per independent review	N=387	N=194
Median (months) (95% CI)	4.0 (3.1-4.4)	2.0 (1.5-2.8)
Hazard ratio[a] (95% CI)	0.60 (0.49-0.73)	
p-value	p<0.00001	

[a] Hazard ratios are adjusted for multiplicity but not for stratification variables.

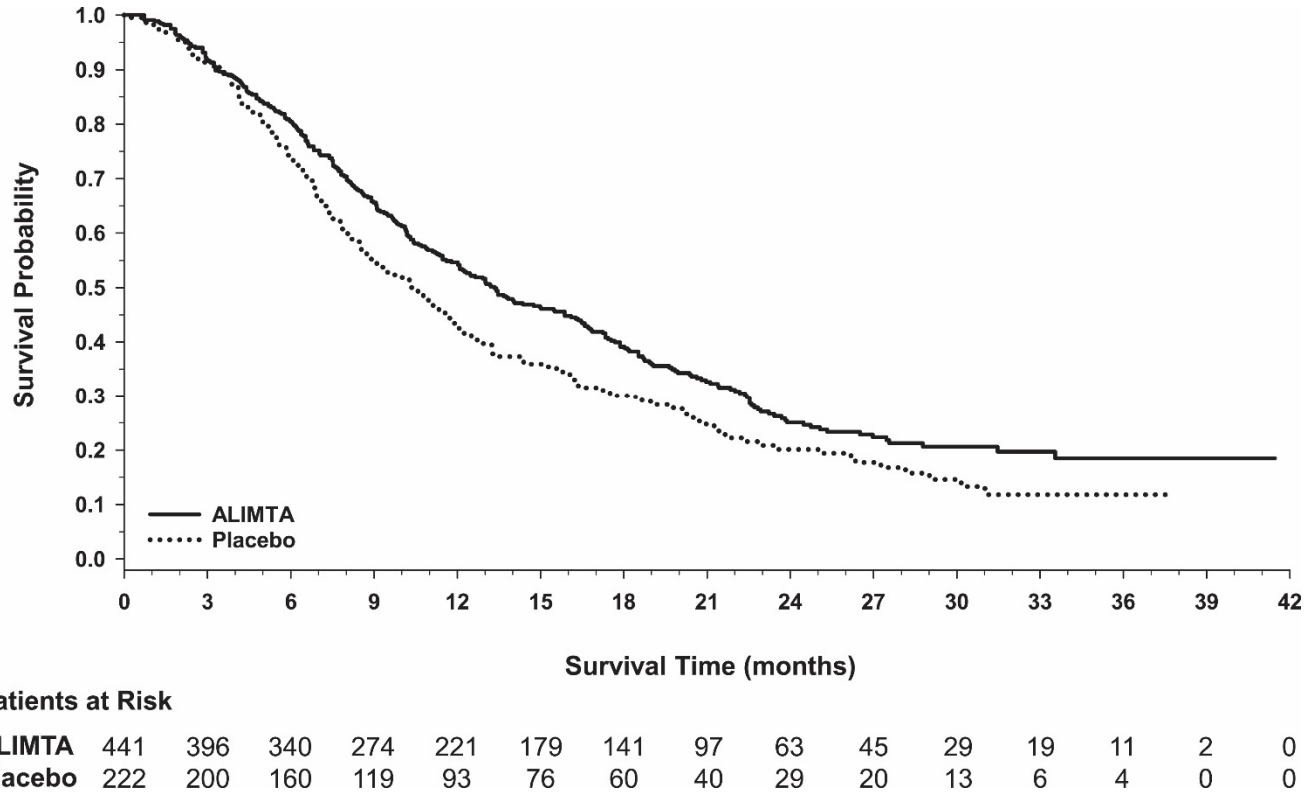


Figure 4: Kaplan-Meier Curves for Overall Survival in Study JMEN

The results of pre-specified subgroup analyses by NSCLC histology are presented in Table 14 and Figures 5 and 6.

Table 14: Efficacy Results in Study JMEN by Histologic Subgroup

Efficacy Parameter	Overall Survival		Progression-Free Survival Per Independent Review	
	ALIMTA (N=441)	Placebo (N=222)	ALIMTA (N=387)	Placebo (N=194)
Non-squamous NSCLC (n=481)				
Median (months)	15.5	10.3	4.4	1.8
HR[a] (95% CI)	0.70 (0.56-0.88)		0.47 (0.37-0.60)	
Adenocarcinoma (n=328)				
Median (months	16.8	11.5	4.6	2.7
HR[a] (95% CI)	0.73 (0.56-0.96)		0.51 (0.38-0.68)	
Large cell carcinoma (n=20)				
Median (months)	8.4	7.9	4.5	1.5
HR[a] (95% CI)	0.98 (0.36-2.65)		0.40 (0.12-1.29)	
Other[b] (n=133)				
Median (months)	11.3	7.7	4.1	1.6
HR[a] (95% CI)	0.61 (0.40-0.94)		0.44 (0.28-0.68)	
Squamous cell NSCLC (n=182)				
Median (months)	9.9	10.8	2.4	2.5
HR[a] (95% CI)	1.07 (0.77-1.50)		1.03 (0.71-1.49)	

[a] Hazard ratios are not adjusted for multiplicity.

[b] Primary diagnosis of NSCLC not specified as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

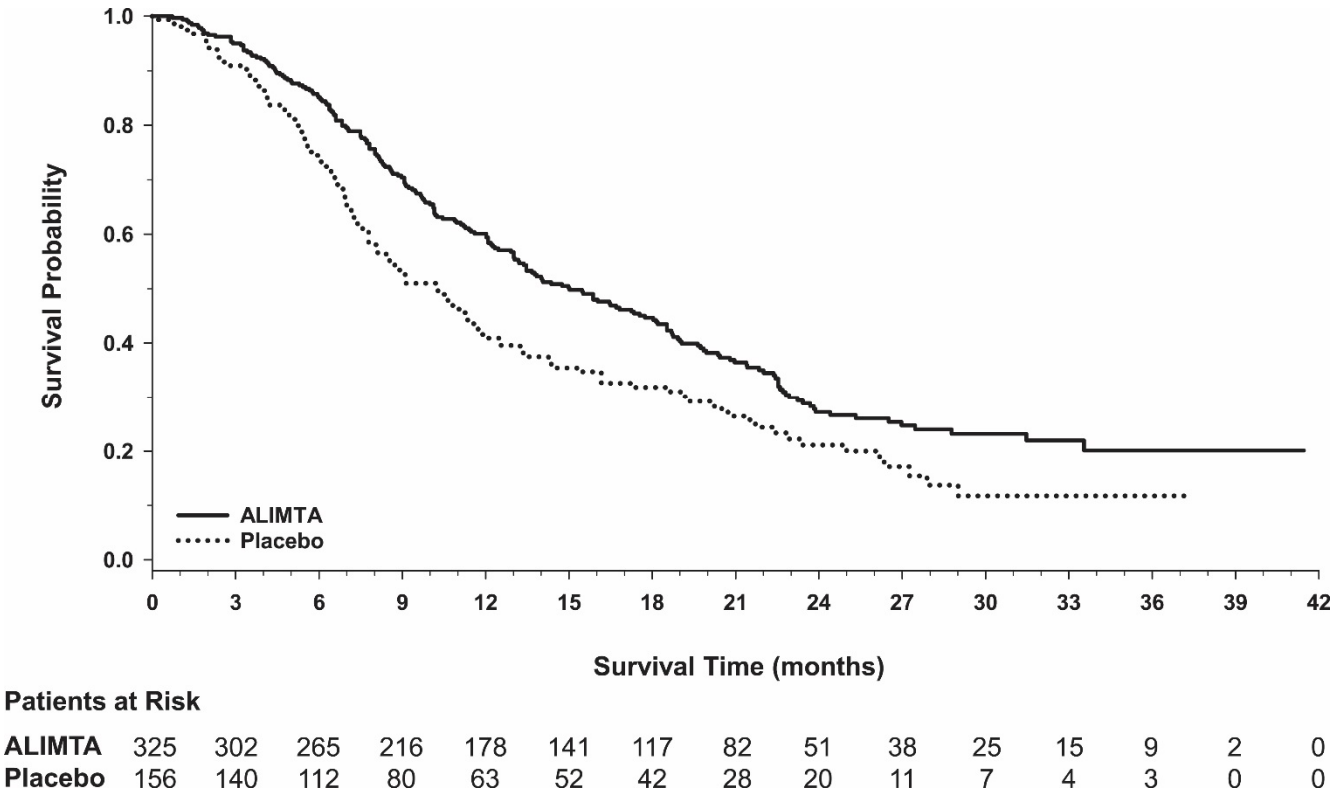
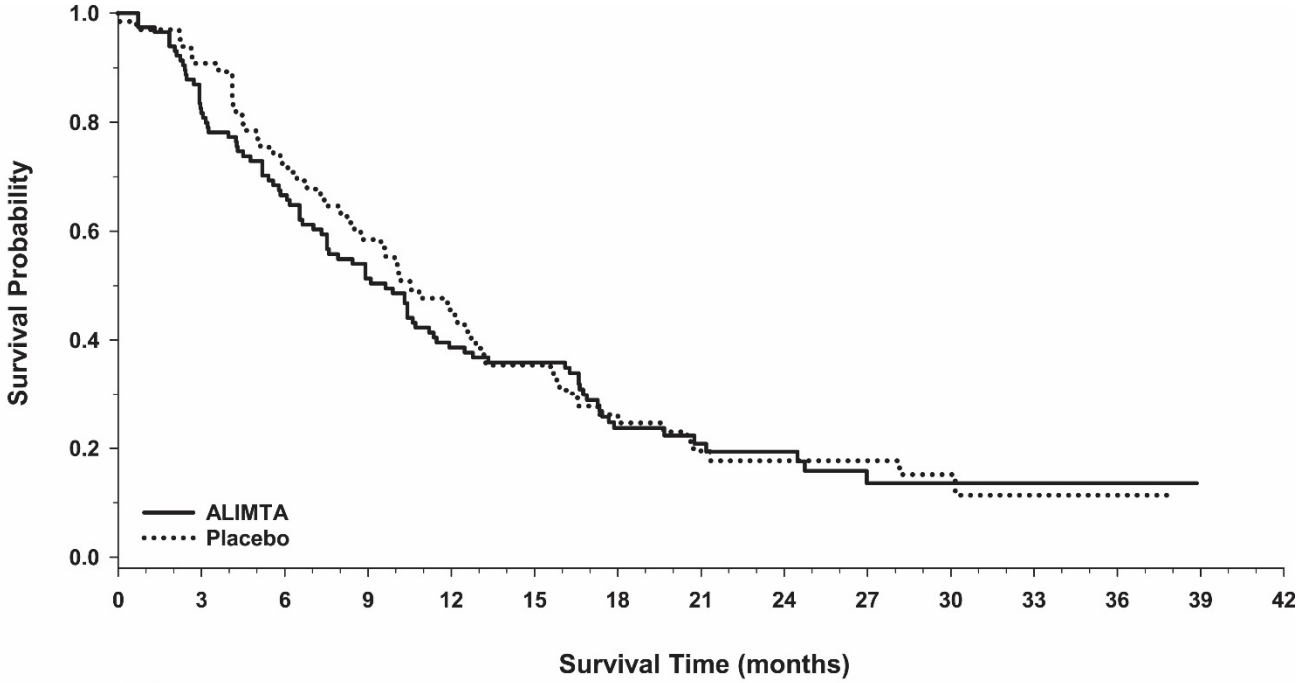


Figure 5: Kaplan-Meier Curves for Overall Survival in Non-squamous NSCLC in Study JMEN



Patients at Risk

ALIMTA	116	94	75	58	43	38	24	15	12	7	4	4	2	0	0
Placebo	66	60	48	39	30	24	18	12	9	9	6	2	1	0	0

Figure 6: Kaplan-Meier Curves for Overall Survival in Squamous NSCLC in Study JMEN

Maintenance Treatment Following First-line ALIMTA Plus Platinum Chemotherapy

The efficacy of ALIMTA as maintenance therapy following first-line platinum-based chemotherapy was also evaluated in PARAMOUNT (NCT00789373), a multi-center, randomized (2:1), double-blind, placebo-controlled study conducted in patients with Stage IIIb/IV non-squamous NSCLC who had completed four cycles of ALIMTA in combination with cisplatin and achieved a complete response (CR) or partial response (PR) or stable disease (SD). Patients were required to have an ECOG PS of 0 or 1. Patients were randomized to receive ALIMTA 500 mg/m^2 intravenously every 21 days or placebo until disease progression. Randomization was stratified by response to ALIMTA in combination with cisplatin induction therapy (CR or PR versus SD), disease stage (IIIb versus IV), and ECOG PS (0 versus 1). Patients in both arms received folic acid, vitamin B_{12}, and dexamethasone. The main efficacy outcome measure was investigator-assessed progression-free survival (PFS) and an additional efficacy outcome measure was overall survival (OS); PFS and OS were measured from the time of randomization.

A total of 539 patients were enrolled with 359 patients randomized to ALIMTA and 180 patients randomized to placebo. The median age was 61 years (range 32 to 83 years); 58% were male; 95% were White, 4.5% were Asian, and <1% were Black or African American; 67% had an ECOG PS of 1; 78% were current or former smokers; and 43% of the population achieved a partial or complete response to first-line, platinum-based chemotherapy. With regard to tumor characteristics, 91% had Stage IV disease, 87% had adenocarcinoma, 7% had large cell, and 6% had other histologies.

Efficacy results for PARAMOUNT are presented in Table 15 and Figure 7.

Table 15: Efficacy Results in PARAMOUNT

Efficacy Parameter	ALIMTA (N=359)	Placebo (N=180)
Overall survival		
Median (months) (95% CI)	13.9 (12.8-16.0)	11.0 (10.0-12.5)
Hazard ratio (HR)[a] (95% CI)	0.78 (0.64-0.96)	
p-value	p=0.02	
Progression-free survival[b]		
Median (months) (95% CI)	4.1 (3.2-4.6)	2.8 (2.6-3.1)
Hazard ratio (HR)[a] (95% CI)	0.62 (0.49-0.79)	
p-value	p<0.0001	

[a] Hazard ratios are adjusted for multiplicity but not for stratification variables.
[b] Based on investigator's assessment.

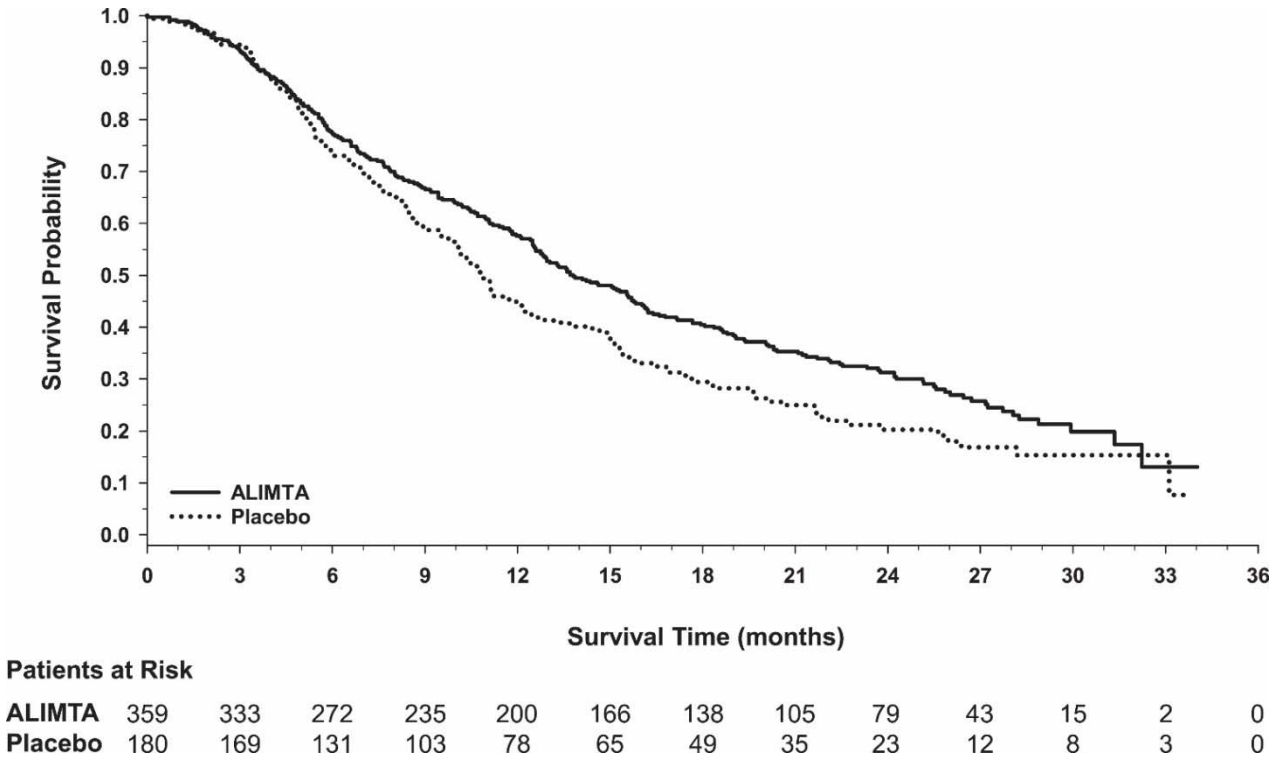


Figure 7: Kaplan-Meier Curves for Overall Survival in PARAMOUNT

Treatment of Recurrent Disease After Prior Chemotherapy

The efficacy of ALIMTA was evaluated in Study JMEI (NCT00004881), a multicenter, randomized (1:1), open-label study conducted in patients with Stage III or IV NSCLC that had recurred or progressed following one prior chemotherapy regimen for advanced disease. Patients were randomized to receive ALIMTA 500 mg/m^2 intravenously or docetaxel 75 mg/m^2 as a 1-hour intravenous infusion once every 21 days. Patients randomized to ALIMTA also received folic acid and vitamin B_{12}. The study was designed to show that overall survival with ALIMTA was non-inferior to docetaxel, as the major efficacy outcome measure, and that overall survival was superior for patients randomized to ALIMTA compared to docetaxel, as a secondary outcome measure.

A total of 571 patients were enrolled with 283 patients randomized to ALIMTA and 288 patients randomized to docetaxel. The median age was 58 years (range 22 to 87 years); 72% were male; 71% were White, 24% were Asian, 2.8% were Black or African American, 1.8% were Hispanic or Latino, and <2% were other ethnicities; 88% had an ECOG PS of 0 or 1. With regard to tumor characteristics, 75% had Stage IV disease; 53% had adenocarcinoma, 30% had squamous histology; 8% large cell; and 9% had other histologic subtypes of NSCLC.

The efficacy results in the overall population and in subgroup analyses based on histologic subtype are provided in Tables 16 and 17, respectively. Study JMEI did not show an improvement in overall survival in the intent-to-treat population. In subgroup analyses, there was no evidence of a treatment effect on survival in patients with squamous NSCLC; the absence of a treatment effect in patients with NSCLC of squamous histology was also observed Studies JMDB and JMEN *[see Clinical Studies (14.1)]*.

Table 16: Efficacy Results in Study JMEI

Efficacy Parameter	**ALIMTA (N=283)**	**Docetaxel (N=288)**
Overall survival		
Median (months) (95% CI)	8.3 (7.0-9.4)	7.9 (6.3-9.2)
Hazard ratio[a] (95% CI)	0.99 (0.82-1.20)	
Progression-free survival		
Median (months) (95% CI)	2.9 (2.4-3.1)	2.9 (2.7-3.4)
Hazard ratio[a] (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] Hazard ratios are not adjusted for multiplicity or for stratification variables.

Table 17: Exploratory Efficacy Analyses by Histologic Subgroup in Study JMEI

Histologic Subgroups	**ALIMTA (N=283)**	**Docetaxel (N=288)**
Non-squamous NSCLC (N=399)		
Median (months) (95% CI)	9.3 (7.8-9.7)	8.0 (6.3-9.3)
HR[a] (95% CI)	0.89 (0.71-1.13)	
Adenocarcinoma (N=301)		
Median (months) (95% CI)	9.0 (7.6-9.6)	9.2 (7.5-11.3)
HR[a] (95% CI)	1.09 (0.83-1.44)	
Large Cell (N=47)		
Median (months) (95% CI)	12.8 (5.8-14.0)	4.5 (2.3-9.1)
HR[a] (95% CI)	0.38 (0.18-0.78)	
Other[b] (N=51)		
Median (months) (95% CI)	9.4 (6.0-10.1)	7.9 (4.0-8.9)
HR[a] (95% CI)	0.62 (0.32-1.23)	
Squamous NSCLC (N=172)		
Median (months) (95% CI)	6.2 (4.9-8.0)	7.4 (5.6-9.5)
HR[a] (95% CI)	1.32 (0.93-1.86)	

[a] Hazard ratio unadjusted for multiple comparisons.

[b] Primary diagnosis of NSCLC not specified as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

14.2 Mesothelioma

The efficacy of ALIMTA was evaluated in Study JMCH (NCT00005636), a multicenter, randomized (1:1), single-blind study conducted in patients with MPM who had received no prior chemotherapy. Patients were randomized (n=456) to receive ALIMTA 500 mg/m^2 intravenously over 10 minutes followed 30 minutes later by cisplatin 75 mg/m^2 intravenously over two hours on Day 1 of each 21-day cycle or to receive cisplatin 75 mg/m^2 intravenously over 2 hours on Day 1 of each 21-day cycle; treatment continued until disease progression or intolerable toxicity. The study was modified after randomization and treatment of 117 patients to require that all patients receive folic acid 350 mcg to 1000 mcg daily beginning 1 to 3 weeks prior to the first dose of ALIMTA and continuing until 1 to 3 weeks after the last dose, vitamin B_{12} 1000 mcg intramuscularly 1 to 3 weeks prior to first dose of ALIMTA and every 9 weeks thereafter, and dexamethasone 4 mg orally, twice daily, for 3 days starting the day prior to each ALIMTA dose. Randomization was stratified by multiple baseline variables including KPS, histologic subtype (epithelial, mixed, sarcomatoid, other), and gender. The major efficacy outcome measure was overall survival and additional efficacy outcome measures were time to disease progression, overall response rate, and response duration.

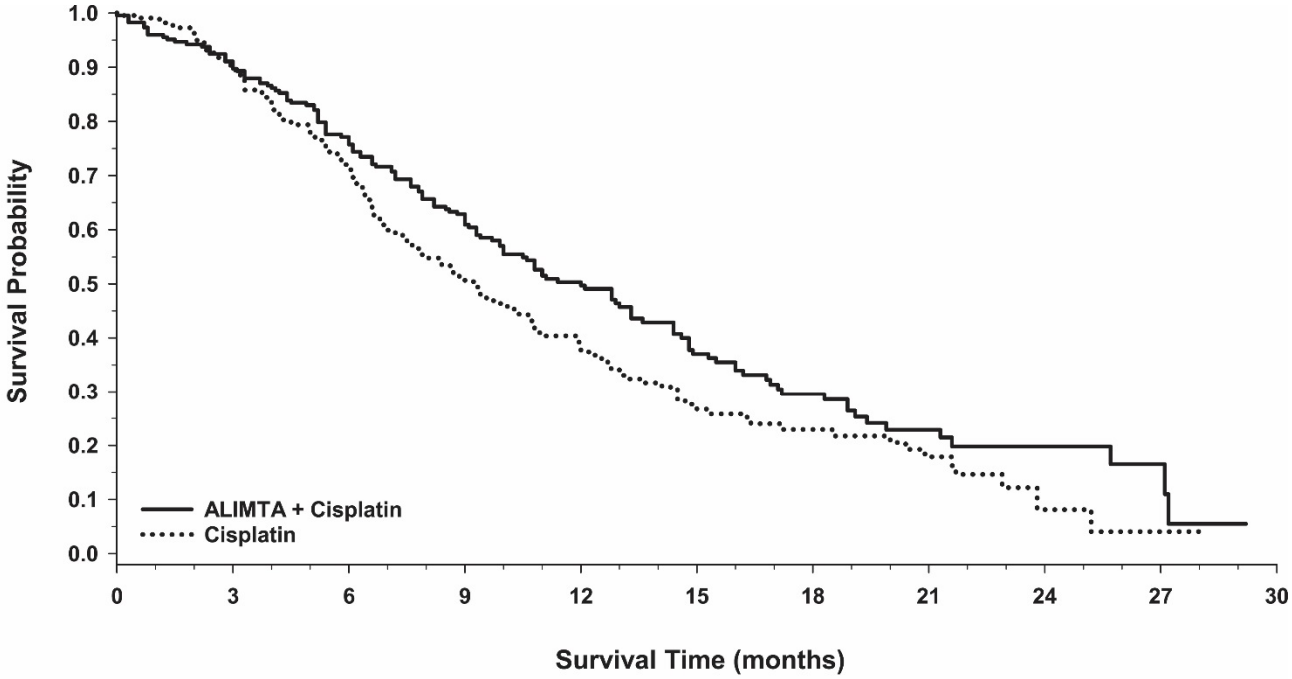
A total of 448 patients received at least one dose of protocol-specified therapy; 226 patients were randomized to and received at least one dose of ALIMTA plus cisplatin, and 222 patients were randomized to and received cisplatin. Among the 226 patients who received cisplatin with ALIMTA, 74% received full supplementation with folic acid and vitamin B_{12} during study therapy, 14% were never supplemented, and 12% were partially supplemented. Across the study population, the median age was 61 years (range: 20 to 86 years); 81% were male; 92% were White, 5% were Hispanic or Latino, 3.1% were Asian, and <1% were other ethnicities; and 54% had a baseline KPS score of 90-100% and 46% had a KPS score of 70-80%. With regard to tumor characteristics, 46% had Stage IV disease, 31% Stage III, 15% Stage II, and 7% Stage I disease at baseline; the histologic subtype of mesothelioma was epithelial in 68% of patients, mixed in 16%, sarcomatoid in 10% and other histologic subtypes in 6%. The baseline demographics and tumor characteristics of the subgroup of fully supplemented patients was similar to the overall study population.

The efficacy results from Study JMCH are summarized in Table 18 and Figure 8.

Table 18: Efficacy Results in Study JMCH

Efficacy Parameter	All Randomized and Treated Patients (N=448)		Fully Supplemented Patients (N=331)	
	ALIMTA/Cisplatin (N=226)	Cisplatin (N=222)	ALIMTA/Cisplatin (N=168)	Cisplatin (N=163)
Median overall survival (months)	12.1	9.3	13.3	10.0
(95% CI)	(10.0-14.4)	(7.8-10.7)	(11.4-14.9)	(8.4-11.9)
Hazard ratio[a]	0.77		0.75	
Log rank p-value	0.020		NA[b]	

[a] Hazard ratios are not adjusted for stratification variables.
[b] Not a pre-specified analysis.



Patients at Risk

ALIMTA + Cisplatin	226	201	166	128	84	50	32	17	8	4	0
Cisplatin	222	195	153	104	63	31	21	14	3	1	0

Figure 8: Kaplan-Meier Curves for Overall Survival in Study JMCH

Based upon prospectively defined criteria (modified Southwest Oncology Group methodology) 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.

15 REFERENCES

1. "OSHA Hazardous Drugs." *OSHA*. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
ALIMTA, pemetrexed for injection, is a white-to-light yellow or green-yellow lyophilized powder supplied in single-dose vials for reconstitution for intravenous infusion.

NDC 0002-7640-01 (VL7640): Carton containing one (1) single-dose vial of 100 mg pemetrexed.

NDC 0002-7623-01 (VL7623): Carton containing one (1) single-dose vial of 500 mg pemetrexed.

Storage and Handling
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
ALIMTA is a cytotoxic drug. Follow applicable special handling and disposal procedures *[see References (15)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Premedication and Concomitant Medication: Instruct patients to take folic acid as directed and to keep appointments for vitamin B_{12} injections to reduce the risk of treatment-related toxicity. Instruct patients of the requirement to take corticosteroids to reduce the risks of treatment-related toxicity *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1)*].

Myelosuppression: Inform patients of the risk of low blood cell counts and instruct them to immediately contact their physician for signs of infection, fever, bleeding, or symptoms of anemia *[see Warnings and Precautions (5.1)]*.

Renal Failure: Inform patients of the risks of renal failure, which may be exacerbated in patients with dehydration arising from severe vomiting or diarrhea. Instruct patients to immediately contact their healthcare provider for a decrease in urine output *[see Warnings and Precautions (5.2)]*.

Bullous and Exfoliative Skin Disorders: Inform patients of the risks of severe and exfoliative skin disorders. Instruct patients to immediately contact their healthcare provider for development of bullous lesions or exfoliation in the skin or mucous membranes *[see Warnings and Precautions (5.3)]*.

Interstitial Pneumonitis: Inform patients of the risks of pneumonitis. Instruct patients to immediately contact their healthcare provider for development of dyspnea or persistent cough *[see Warnings and Precautions (5.4)]*.

Radiation Recall: Inform patients who have received prior radiation of the risks of radiation recall. Instruct patients to immediately contact their healthcare provider for development of inflammation or blisters in an area that was previously irradiated *[see Warnings and Precautions (5.5)]*.

Increased Risk of Toxicity with Ibuprofen in Patients with Renal Impairment: Advise patients with mild to moderate renal impairment of the risks associated with concomitant ibuprofen use and instruct them to avoid use of all ibuprofen containing products for 2 days before, the day of, and 2 days following administration of ALIMTA *[see Dosage and Administration (2.5), Warnings and Precautions (5.6), and Drug Interactions (7)]*.

Embryo-Fetal Toxicity: Advise females of reproductive potential and males with female partners of reproductive potential of the potential risk to a fetus *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ALIMTA and for 6 months after the final dose. Advise females to inform their prescriber of a known or suspected pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALIMTA and for 3 months after the final dose *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.3)]*.

Lactation: Advise women not to breastfeed during treatment with ALIMTA and for 1 week after the final dose *[see Use in Specific Populations (8.2)]*.

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

B6-ALM-0001-USPI-YYYYMMDD

PATIENT INFORMATION
ALIMTA® (uh-LIM-tuh)
(pemetrexed for injection)

What is ALIMTA?

ALIMTA is a prescription medicine used to treat:

- **a kind of lung cancer called non-squamous non-small cell lung cancer (NSCLC).** ALIMTA is used:
  - as the first treatment in combination with cisplatin when your lung cancer has spread (advanced NSCLC).
  - as the first treatment in combination with carboplatin and pembrolizumab of your advanced NSCLC.
  - alone as maintenance treatment after you have received 4 cycles of chemotherapy that contains platinum for first treatment of your advanced NSCLC and your cancer has not progressed.
  - alone when your lung cancer has returned or spread after prior chemotherapy.
- **a kind of cancer called malignant pleural mesothelioma.** This cancer affects the lining of the lungs and chest wall. ALIMTA is used in combination with cisplatin as the first treatment for malignant pleural mesothelioma that cannot be removed by surgery or you are not able to have surgery.

It is not known if ALIMTA is safe and effective in children.

Do not take ALIMTA:

if you have had a severe allergic reaction to any medicine that contains pemetrexed.

Before taking ALIMTA, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems.
- have had radiation therapy.
- are pregnant or plan to become pregnant**.** ALIMTA can harm your unborn baby.
  - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with ALIMTA and for 6 months after the final dose. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with ALIMTA.
  - **Males** with female partners who are able to become pregnant should use effective birth control (contraception) during treatment with ALIMTA and for 3 months after the final dose.
- are breastfeeding or plan to breastfeed**.** It is not known if ALIMTA passes into breast milk. Do not breastfeed during treatment with ALIMTA and for 1 week after the final dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Tell your healthcare provider if you have kidney problems and take a medicine that contains ibuprofen. You should avoid taking ibuprofen for 2 days before, the day of, and 2 days after receiving treatment with ALIMTA.

How is ALIMTA given?

- **It is very important to take folic acid and vitamin B_{12} during your treatment with ALIMTA to lower your risk of harmful side effects.**
  - Take folic acid exactly as prescribed by your healthcare provider 1 time a day, beginning 7 days (1 week) before your first dose of ALIMTA and continue taking folic acid until 21 days (3 weeks) after your last dose of ALIMTA.
  - Your healthcare provider will give you vitamin B_{12} injections during treatment with ALIMTA. You will get your first vitamin B_{12} injection 7 days (1 week) before your first dose of ALIMTA, and then every 3 cycles.
- Your healthcare provider will prescribe a medicine called corticosteroid for you to take 2 times a day for 3 days, beginning the day before each treatment with ALIMTA.
- ALIMTA is given to you by intravenous (IV) infusion into your vein. The infusion is given over 10 minutes.
- ALIMTA is usually given once every 21 days (3 weeks).

What are the possible side effects of ALIMTA?

ALIMTA can cause serious side effects, including:

- **Low blood cell counts.** Low blood cell counts can be severe, including low white blood cell counts (neutropenia), low platelet counts (thrombocytopenia), and low red blood cell counts (anemia). Your healthcare provider will do a blood test to check your blood cell counts regularly during your treatment with ALIMTA. **Tell your healthcare provider right away if you have any signs of infection, fever, bleeding, or severe tiredness during your treatment with ALIMTA.**

- **Kidney problems, including kidney failure.** ALIMTA can cause severe kidney problems that can lead to death. Severe vomiting or diarrhea can lead to loss of fluids (dehydration) which may cause kidney problems to become worse. Tell your healthcare provider right away if you have a decrease in amount of urine.
- **Severe skin reactions.** Severe skin reactions that may lead to death can happen with ALTIMA. Tell your healthcare provider right away if you develop blisters, skin sores, skin peeling, or painful sores, or ulcers in your mouth, nose, throat or genital area.
- **Lung problems (pneumonitis).** ALIMTA can cause serious lung problems that can lead to death. Tell your healthcare provider right away if you get any new or worsening symptoms of shortness of breath, cough, or fever.
- **Radiation recall.** Radiation recall is a skin reaction that can happen in people who have received radiation treatment in the past and are treated with ALTIMA. Tell your healthcare provider if you get swelling, blistering, or a rash that looks like a sunburn in an area that was previously treated with radiation.

The most common side effects of ALIMTA when given alone are:

- tiredness
- nausea
- loss of appetite

The most common side effects of ALIMTA when given with cisplatin are:

- vomiting
- swelling or sores in your mouth or sore throat
- constipation
- low white blood cell counts (neutropenia)
- low platelet counts (thrombocytopenia)
- low red blood cell counts (anemia)

The most common side effects of ALIMTA when given with carboplatin and pembrolizumab are:

- tiredness
- constipation
- vomiting
- diarrhea
- loss of appetite
- nausea
- rash
- shortness of breath
- headache

ALIMTA may cause fertility problems in males. This may affect your ability to father a child. It is not known if these effects are reversible. Talk to your healthcare provider if this is a concern for you.

Your healthcare provider will do blood test to check for side effects during treatment with ALIMTA. Your healthcare provider may change your dose of ALIMTA, delay treatment, or stop treatment if you have certain side effects.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the side effects of ALIMTA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ALIMTA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

You can ask your pharmacist or healthcare provider for information about ALIMTA that is written for health professionals.

What are the ingredients in ALIMTA?

Active ingredient: pemetrexed

Inactive ingredients: mannitol, hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

For more information, go to www.ALIMTA.com or call 1-800-LILLY-RX (1-800-545-5979).

This Patient Information has been approved by the U.S. Food and Drug Administration.

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