Welcome to today’s presentation titled *In Advanced Non–Small Cell Lung Cancer: The Evidence-Based Rationale for ALIMTA on Clinical Pathways.*

This presentation features topics designed to raise awareness about the importance of histology when making coverage decisions for members with NSCLC and the need for more personalized lung cancer care.

The clinical data presented provides information to help payers make formulary decisions that may include open access for ALIMTA.

**Next slide: Presentation Overview**
Today's presentation focuses on topics that include:

- Clinical pathways
- NSCLC histology
- Why histology matters in developing NSCLC pathways
- Histology matters with ALIMTA® (pemetrexed for injection)
  - 1st-line phase III study
  - 2nd-line phase III study
  - Maintenance phase III study
- Dosing and administration for ALIMTA
- Important Safety Information for ALIMTA

We will also review the dosing and administration for ALIMTA and Important Safety Information for ALIMTA.

Next slide: Clinical Pathways: An Emerging Trend in Oncology
Clinical pathways are an emerging trend in oncology.\textsuperscript{1-4} Although there is some variation among actual pathways, there are many common characteristics:

- Defined as a path or steps that network physicians in managed care organizations (MCOs) and other healthcare providers take in managing a disease\textsuperscript{1-3}
- Developed by oncologists to encourage the consistent delivery of value-driven, evidence-based treatment\textsuperscript{1}
- Based on clinical guidelines or other commonly used clinical parameters\textsuperscript{2}
- Designed to increase the predictability of care\textsuperscript{2}

The results of a 2008 Web-based survey found that 95% of providers (n=50) and 64% of payers (n=50) agreed that guidelines and pathways played a “somewhat significant” or “very significant” role in their organization.\textsuperscript{4}

Next slide: Clinical Pathway Parameters

References
Clinical pathways utilize a variety of inputs. When developing or adding a pathway, oncologists make a systematic evaluation of a drug’s:

- Efficacy
- Tolerability
- Costs

Clinical pathways must be supported by scientific evidence and national guidelines from:

- National Comprehensive Cancer Network (NCCN)
- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)

In a recently published study, by definition, patients treated with chemotherapy beyond third line were considered “off pathway”.

Clinical pathways must be supported by scientific evidence and national guidelines from:

- National Comprehensive Cancer Network (NCCN)
- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)

In a recently published study, by definition, patients treated with chemotherapy beyond third line were considered “off pathway”.

Therefore, more than one treatment option was available when making treatment decisions for patients with advanced NSCLC

Next Slide: All Pathways Are Not Created Equal

References

All pathways are not created equal and payers can benefit from having a clear understanding of these factors during the evaluation and decision making process.\textsuperscript{1,2}

Consequently, oncology groups and payers must ask critical questions when examining pathways, such as:\textsuperscript{1}:

- Who developed the pathways?
- How were they developed?
- Do the pathways define one best treatment for each state and stage of disease?
- Are the pathways detailed and comprehensive?
- Are clinical trials supported by the pathways?
- Are the pathways regularly updated?
- Are the pathways available and accessible in real time at the point of care?
- Has the decision support solution been road tested by real oncologists?

References
There are a number of reasons why multiple treatment options should be considered on clinical pathways.

Cancer care is complicated by vast differences in:
- Diagnosis
- Staging
- Physician training
- Available therapies

Important differences also exist among patients with regard to:
- Medical history
- Genetics
- Desired treatments

Therefore, clinical guidelines cannot be applied uniformly in every case, and their application to actual treatment decisions require a degree of flexibility.

Next Slide: Why Histology Matters in Developing NSCLC Clinical Pathways

Reference
In this section we will provide an overview of
• NSCLC histology
• Incidence and prevalence of NSCLC histologic subgroups
• Histology as a predictor of survival

Taken together, this data will illustrate why there is a need for NSCLC clinical pathways to offer multiple options.

Next slide: Overview of NSCLC Histologies
Adenocarcinoma is a malignant epithelial tumor with glandular differentiation or mucin production, showing acinar, papillary, bronchoalveolar, or solid with mucin growth patterns or a mixture of these patterns.

Large cell carcinoma is an undifferentiated non–small cell carcinoma that lacks the cytologic and architectural features of small cell carcinoma and glandular or squamous differentiation.

Squamous cell carcinoma is a malignant epithelial tumor showing keratinization and/or intercellular bridges that arise from bronchial epithelium. These features vary with degree of differentiation, being prominent in well-differentiated tumors and focal in poorly differentiated tumors.

Next slide: Approximately 55% of Patients With Lung Cancer Have Nonsquamous NSCLC

Reference
The graphic clearly illustrates that there is variation within the NSCLC universe.

- This slide focuses on 2003 incidence rates discussed on the previous slide; however, these figures have been rounded\(^1\) [Wahbah p93/col1/¶1/ 7-10/col2/¶1/ 21-3]
- Histologic subtype data from the American Cancer Society in 2010 are similar to the findings of Wahbah and colleagues
- Squamous cell carcinoma accounts for about 25% to 30% of all lung cancers
- Adenocarcinoma accounts for about 40% of lung cancers
- Large cell (undifferentiated) carcinoma constitutes about 10% to 15% of lung cancers
- These data suggest that the incidence of nonsquamous cell carcinoma, which represents 55% of all lung cancers, has held steady since 2003\(^2\) [American Cancer Society (ACS) p3, bullets 3-5]

Next slide: Histology Is One Prognostic Factor of NSCLC Survival

References
Point out that histology and histologic grade affect disease prognosis.

Examples of negative prognostic factors include:
- More advanced disease
- Poor performance status
- Substantial recent weight loss

Examples of positive prognostic factors include:
- Female sex
- Adenocarcinoma
- Asian ethnicity

References:
This quote sets the stage for ALIMTA study data that are featured in the next section.

Point out that NCCN recognizes the importance of histology as an important criteria when choosing the right course of treatment for patients with NSCLC.¹

**Next slide: Histology Matters With ALIMTA**

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**Reference**

This section discusses 3 randomized phase III studies—1st-line study, 2nd-line study, and maintenance study—which demonstrate why histology matters with ALIMTA. Because clinical and safety considerations are important aspects of the pathway development process, it's important that all stakeholders have access to all available data.

These study results show that ALIMTA can help payers achieve the goal of ensuring that the right patients are receiving appropriate therapy in the management of NSCLC.

Next slide: ALIMTA® (pemetrexed for injection) and GEMZAR® (gemcitabine HCl for injection) NSCLC Indications
Read all indications as defined in this slide.

Reinforce that the FDA has approved ALIMTA for 1st-line treatment, 2nd-line treatment, and maintenance therapy in patients with nonsquamous NSCLC—and that ALIMTA is not appropriate for patients with squamous NSCLC.

[ALIMTA PI/p2/col1/sections 1.1, 1.2,1.3,1.5]

Next slide: ALIMTA Is Recognized by National Drug Compendia
Important Safety Information
Important Safety Information for ALIMTA

Myelosuppression is usually the dose-limiting toxicity with ALIMTA therapy.

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

Warnings and Precautions
Patients must be instructed to take folic acid and vitamin B₁₂ with ALIMTA as a prophylaxis to reduce treatment-related hematologic and GI toxicities.

Pretreatment with dexamethasone or its equivalent has been reported to reduce the incidence and severity of skin rash.

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia). Reduce doses for subsequent cycles based on hematologic and nonhematologic toxicities.

ALIMTA should not be administered to patients with a creatinine clearance <45 mL/min. 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.
Important Safety Information for ALIMTA (cont)

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). 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 toxicities.

Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm³, the platelet count is ≥100,000 cells/mm³, and creatinine clearance is ≥45 mL/min.

Pregnancy Category D—ALIMTA may cause fetal harm when administered to a pregnant woman. Women should be apprised of the potential hazard to the fetus and should be advised to use effective contraceptive measures to prevent pregnancy during treatment with ALIMTA.

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.
Important Safety Information for ALIMTA (cont)

Drug Interactions
Concomitant administration of nephrotoxic drugs or substances that are tubularly secreted could result in delayed clearance of ALIMTA.
See Warnings and Precautions for specific information regarding ibuprofen administration.

Use in Specific Patient Populations
It is recommended that nursing be discontinued if the mother is being treated with ALIMTA or discontinue the drug, taking into account the importance of the drug for the mother.
The safety and effectiveness of ALIMTA in pediatric patients have not been established.
Dose adjustments may be necessary in patients with hepatic insufficiency.

Dosage and Administration Guidelines
Complete blood cell counts, including platelet counts and periodic chemistry tests, should be performed on all patients receiving ALIMTA.
Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Modify or suspend therapy according to the Dosage Reduction Guidelines in the full Prescribing Information.
Important Safety Information for ALIMTA (cont)

Abbreviated Adverse Reactions (% incidence) for NSCLC 1st-line

The most severe adverse reactions (Grades 3/4) with ALIMTA in combination with cisplatin versus gemcitabine in combination with cisplatin, respectively, for the 1st-line treatment of patients with advanced non-small cell lung cancer (NSCLC) were neutropenia (15 vs 8); leukopenia (5 vs 8); thrombocytopenia (4 vs 13); anemia (6 vs 10); fatigue (7 vs 5); nausea (7 vs 4); vomiting (6 vs 6); anorexia (2 vs 1); and creatinine elevation (1 vs 1). Common adverse reactions (all grades) with ALIMTA in combination with cisplatin versus gemcitabine in combination with cisplatin, respectively, were nausea (56 vs 53); fatigue (43 vs 45); vomiting (40 vs 36); anemia (33 vs 46); neutropenia (29 vs 38); anorexia (27 vs 24); constipation (21 vs 20); leukopenia (18 vs 21); stomatitis/pharyngitis (14 vs 12); alopecia (12 vs 21); diarrhea (12 vs 13); thrombocytopenia (10 vs 27); neuropathy/sensory (9 vs 12); taste disturbance (8 vs 9); rash/desquamation (7 vs 8); and dyspepsia/heartburn (5 vs 6).

Abbreviated Adverse Reactions (% incidence) for NSCLC Maintenance

The most severe adverse reactions (Grades 3/4) with ALIMTA as a single agent versus placebo, respectively, for the maintenance treatment of patients with locally advanced nonsquamous non–small cell lung cancer (NSCLC) were anemia (3 vs 1); neutropenia (3 vs 0); leukopenia (2 vs 1); fatigue (5 vs 1); nausea (1 vs 1); anorexia (2 vs 0); mucositis/stomatitis (1 vs 0); diarrhea (1 vs 0); infection (2 vs 0); and neuropathy-sensory (1 vs 0). Common adverse reactions (all grades) with ALIMTA as a single agent versus placebo, respectively, were anemia (15 vs 6); neutropenia (6 vs 0); leukopenia (6 vs 1); increased ALT (10 vs 4); increased AST (8 vs 4); fatigue (25 vs 11); nausea (19 vs 6); anorexia (19 vs 5); vomiting (9 vs 1); mucositis/stomatitis (7 vs 2); diarrhea (5 vs 3); infection (5 vs 2); neuropathy-sensory (9 vs 4); and rash/desquamation (10 vs 3).
Important Safety Information for ALIMTA (cont)

Abbreviated Adverse Reactions (\% incidence) for NSCLC 2nd-line

The most severe adverse reactions (Grades 3-4) with ALIMTA as a single agent versus docetaxel, respectively, for the 2nd-line treatment of patients with advanced non-small cell lung cancer (NSCLC) were neutropenia (5 vs 40); leukopenia (4 vs 27); thrombocytopenia (2 vs 0); anemia (4 vs 4); fatigue (6 vs 5); nausea (3 vs 2); anorexia (2 vs 3); vomiting (2 vs 1); increased ALT (2 vs 0); increased AST (1 vs 0); and stomatitis/pharyngitis (1 vs 1). Common adverse reactions (all grades) with ALIMTA as a single agent versus docetaxel, respectively, were fatigue (34 vs 36); nausea (31 vs 17); anorexia (22 vs 24); anemia (19 vs 22); vomiting (16 vs 12); stomatitis/pharyngitis (15 vs 17); rash (14 vs 6); diarrhea (13 vs 24); leukopenia (12 vs 34); and neutropenia (11 vs 45).

For safety and dosing guidelines, see complete Warnings and Precautions, Adverse Reactions, and Dosage and Administration sections in the accompanying full Prescribing Information.
Important Safety Information for GEMZAR

Important Safety Information
Myelosuppression is usually the dose-limiting toxicity with GEMZAR therapy.

Contraindication
Known hypersensitivity to GEMZAR.

Warnings and Precautions
Patients receiving therapy with GEMZAR should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents.
Infusions of GEMZAR longer than 60 minutes or dosing more frequently than once weekly have been shown to increase toxicity.
GEMZAR can suppress bone marrow function, as manifested by leukopenia, thrombocytopenia, and anemia. Patients should be monitored for myelosuppression during therapy including a complete blood count with differential prior to each dose.
Pulmonary toxicity has been reported. In cases of severe lung toxicity, GEMZAR therapy should be discontinued immediately and appropriate supportive care measures instituted.
Monitor renal and hepatic function prior to initiation of GEMZAR therapy and periodically thereafter. Use GEMZAR with caution in patients with renal impairment or hepatic impairment. Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of GEMZAR.
Important Safety Information for GEMZAR (cont)

Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been reported. The majority of the cases of renal failure leading to death were due to HUS. Serious hepatotoxicity, including liver failure and death, has been reported in patients receiving GEMZAR alone or in combination with other potentially hepatotoxic drugs. Discontinue GEMZAR for HUS, or severe renal or hepatic toxicity.

GEMZAR can cause fetal harm. Advise women of potential risk to the fetus.

GEMZAR has radiosensitizing activity, and radiation recall reactions have been reported. The optimum regimen for safe administration of GEMZAR with therapeutic doses of radiation has not yet been determined in all tumor types.

**Abbreviated Adverse Reactions (% incidence)**

The most severe adverse reactions (grades 3/4, with incidence of 5% or greater) with GEMZAR plus cisplatin for the first-line treatment of patients with NSCLC in comparative trials of a 28-day regimen (GEMZAR plus cisplatin versus cisplatin alone) and a 21-day regimen (GEMZAR plus cisplatin versus etoposide plus cisplatin), respectively, were neutropenia (57 vs 4, 64 vs 76); thrombocytopenia (50 vs 4, 55 vs 13); leukopenia (46 vs 3, 29 vs 43); lymphocytopenia 28d (43 vs 17); anemia (25 vs 7, 22 vs 15); nausea/vomiting 21d (39 vs 26); nausea 28d (27 vs 21); vomiting 28d (23 vs 19); alopecia 21d (13 vs 31); neuromotor 28d (12 vs 3); dyspnea (7 vs 5, 1 vs 0); hypomagnesemia 28d (7 vs 2); neurohearing 28d (6 vs 6); creatinine elevation 28d (5 vs 3); and infection (5 vs 1, 4 vs 8).
Important Safety Information for GEMZAR

The most common adverse reactions (all grades, with incidence of 20% or greater) of the 28-day regimen (GEMZAR plus cisplatin versus cisplatin alone) and the 21-day regimen (GEMZAR plus cisplatin versus etoposide plus cisplatin), respectively, were anemia (89 vs 67, 88 vs 77); neutropenia (79 vs 20, 88 vs 87); leukopenia (82 vs 25, 86 vs 87); thrombocytopenia (85 vs 13, 81 vs 45); lymphocytopenia 28d (75 vs 51); RBC transfusion (39 vs 13, 29 vs 21); platelet transfusions (21 vs 1, 3 vs 8); nausea 28d (93 vs 87); vomiting 28d (78 vs 71); nausea and vomiting 21d (96 vs 86); alopecia (53 vs 33, 77 vs 92); creatinine elevation (36 vs 31, 2 vs 2); paresthesias 21d (38 vs 16); neuroromatic 28d (35 vs 15); hyperglycemia 28d (30 vs 23); hypomagnesemia 28d (30 vs 17); infection (16 vs 12, 29 vs 21); neurohearing 28d (25 vs 21); diarrhea (24 vs 13, 14 vs 13); proteinuria (23 vs 18, 12 vs 5); neurosensory 28d (23 vs 18); hematuria (12 vs 13, 22 vs 10); hepatic transaminase 28d (22 vs 10); and stomatitis (14 vs 5, 20 vs 18).

Use in Specific Populations

GEMZAR is Pregnancy Category D. GEMZAR can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, GEMZAR is expected to result in adverse reproductive effects. It is not known whether GEMZAR is excreted in human milk.

The safety and efficacy of GEMZAR in pediatric patients has not been established.

Use caution in patients with preexisting renal impairment or hepatic insufficiency. Administration of GEMZAR may exacerbate underlying hepatic insufficiency.

GEMZAR clearance is affected by age as well as gender.
Important Safety Information for GEMZAR (cont)

Dose Modifications and Administration Guidelines

GEMZAR is for intravenous use only. Dosage adjustments for hematologic toxicity may be required. Dose modifications may be considered for severe nonhematologic toxicity. Modify or suspend therapy according to the Dosage and Administration guidelines in the full Prescribing Information.

Serum creatinine, potassium, calcium, and magnesium should be monitored during combination therapy with cisplatin. See the manufacturers’ prescribing information for more information on any drug indicated in combination with GEMZAR.

Please see the full Prescribing Information for Patient Counseling Information on low blood cell counts and the use of GEMZAR in pregnant and nursing women.

For safety and dosing guidelines, see complete Warnings and Precautions, Adverse Reactions, and Dosage and Administration sections in the accompanying full Prescribing Information.
ALIMTA is recognized by national drug compendia which are important inputs of the pathway development process.\textsuperscript{1,2}

ALIMTA in combination with cisplatin is recognized as an appropriate therapy for 1st-line treatment of advanced or metastatic nonsquamous NSCLC by
- NCCN Drugs and Biologics Compendium
  - Category 2A
- Thomson Micromedex\textsuperscript{®} and DRUGDEX\textsuperscript{®}
  - Class IIb

ALIMTA is also recognized as an appropriate therapy for the maintenance treatment of patients with advanced or metastatic nonsquamous NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy by
- NCCN Drugs and Biologics Compendium
- Thomson Micromedex and DRUGDEX
- Gold Standard Clinical Pharmacology

Next slide: ALIMTA Delivered Consistent Histology-Based Survival

References
When used as a 1st-line treatment, 2nd-line treatment, and maintenance therapy, ALIMTA demonstrated statistically significant improvements in overall survival in patients with nonsquamous NSCLC.¹,²

References
In this section, we will discuss ALIMTA/cisplatin in 1st-line advanced NSCLC.

Next slide: ALIMTA/Cisplatin Versus GEMZAR/Cisplatin Is the Largest Trial in 1st-line Advanced NSCLC (N=1725)
Highlight the following important first-line study design features:

• With 1725 patients randomized, this was the largest multicenter, randomized, phase III trial conducted to date in 1st-line advanced NSCLC\(^1\) [Scagliotti2008/p3544/col1/¶6]

• Eligible patients were randomized to receive either gemcitabine HCl plus cisplatin or ALIMTA plus cisplatin for a maximum of 6 cycles of therapy\(^1\) [Scagliotti2008/p3544/col1/¶6/¶4]

• Patients in both arms received folic acid, vitamin B\(_{12}\), and dexamethasone\(^1\) [Scagliotti2008/p3544/col1/¶7]

• ALIMTA is highly sensitive to the level of natural folate vitamins in cells. When the folate level in cancer cells is high, the antitumor effect of ALIMTA is suppressed. When the folate level is low, the antitumor effect of ALIMTA is enhanced. This has important ramifications with respect to how folic acid is used in conjunction with ALIMTA to reduce toxicity to patients

• ALIMTA toxicity is decreased when patients are supplemented with folic acid\(^2\) [ALIMTA PI/p6/col1/section 14.1]

• Folic acid and vitamin B\(_{12}\) supplementation is mandatory to maximize ALIMTA efficacy and help reduce hematological and GI toxicities\(^2\) [ALIMTA PI/p2/col2/section 5.5]

• Randomization factors included performance status, disease stage, and tumor histotype [Scagliotti2008/p3544/col1/¶6]

• Gemcitabine HCl/cisplatin was selected as the standard treatment arm based on the consistently proven survival and safety benefits of gemcitabine HCl-based therapy in 1st-line advanced NSCLC\(^3\) [Gemzar PI/p2/sec1.3]

References
2. ALIMTA\(^\text{®}\) (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
Point out the following key eligibility criteria, which included:\footnote{Scagliotti2008/p3544/col1/¶3}

- Histologically or cytologically confirmed Stage IIIB or IV advanced NSCLC with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST)
- An ECOG PS score of 0 or 1
- Adequate bone marrow reserve and organ function
- Prior radiation therapy was permitted if it had occurred at least 4 weeks prior to study enrollment and patients had recovered fully from its acute effects

Exclusion criteria included:

- National Cancer Institute Common Toxicity Criteria (CTC) Grade ≥1 peripheral neuropathy \footnote{Scagliotti2008/p3544/col1/¶4}
- Progressive brain metastases \footnote{Scagliotti2008/p3544/col1/¶4}
- Uncontrolled third-space fluid retention before study entry \footnote{Scagliotti2008/p3544/col1/¶4}
- An inability to interrupt aspirin other nonsteroidal anti-inflammatory drugs, or to take folic acid, vitamin B\textsubscript{12}, and corticosteroids \footnote{Scagliotti2008/p3544/col1/¶4}
- Highlight the fact that nearly half of all of the patients who participated in the trial (49.1%) were classified as adenocarcinoma \footnote{Scagliotti2008/p3549/col2/¶2/Scagliotti2008/p3546/col2/¶4 847/1725=49.1%}

\textbf{Next slide: Noninferiority Study Design Endpoints}
Overall survival was the primary endpoint of the noninferiority study of ALIMTA plus cisplatin in 1st-line advanced NSCLC.\(^1\)

The secondary endpoints for this study included

- Progression-free survival (PFS)
- Time to progressive disease (TTP)
- Objective tumor response
- Toxicity

Next slide: ALIMTA/Cisplatin Demonstrated Clinically Relevant Survival Advantage in Nonsquamous\(^a\) Histologies

Reference
For each histologic subgroup, the Kaplan-Meier method was used to estimate unadjusted within-arm medians (with 95% confidence intervals [CIs]), and Cox models were used to estimate covariate-adjusted between-arm HRs with 95% CIs.\(^1\)

A significant treatment-by-histology interaction indicated a differential treatment effect according to histology.\(^1\)

Shown are data comparing ALIMTA/cisplatin with gemcitabine HCl/cisplatin in patients with nonsquamous histologies (ie, adenocarcinoma, large cell carcinoma, and those that were otherwise not specified).\(^1\)

Nonsquamous patients had a longer overall survival time on ALIMTA/cisplatin than on gemcitabine HCl/cisplatin (adjusted HR, 0.84; 95% CI, 0.74-0.96).\(^2\)

Conversely, squamous patients had a shorter overall all survival time on ALIMTA/cisplatin than on gemcitabine HCl/cisplatin (adjusted HR, 1.23; 95% CI, 1.00-1.51).\(^1\)

Next slide: Clinically Relevant Survival Advantage for Patients With Adenocarcinoma

References
2. ALIMTA\(^®\) (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
Overall survival was significantly longer with ALIMTA/cisplatin versus gemcitabine HCl/cisplatin when limiting the analysis to patients with adenocarcinoma: 12.6 vs 10.9 months (HR, 0.84; 95% CI, 0.71-0.99).\(^1,2\) Myelosuppression is usually the dose-limiting toxicity with ALIMTA and gemcitabine HCl therapies. For safety and dosing guidelines, see complete Warnings and Precautions, Adverse Reactions, and Dosage and Administration sections in the accompanying full Prescribing Information. See Important Safety Information on slides 50-59.

References
2. ALIMTA\(^\circledast\) (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
Overall survival was also significantly longer with ALIMTA plus cisplatin versus gemcitabine HCl plus cisplatin when limiting the analysis to patients with large cell carcinoma: 10.4 versus 6.7 months (HR, 0.67; 95% CI, 0.48-0.96).1,2

The adjusted HR of 0.67 is <1.0 and favors patients with large cell carcinoma treated with ALIMTA plus cisplatin.1,2

References
1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
The Kaplan-Meier curves are shown here for patients with squamous cell carcinoma, by treatment arm.

As shown, ALIMTA plus cisplatin was associated with shorter survival time than gemcitabine HCl plus cisplatin in patients with squamous cell carcinoma.\(^1\)

These data show that ALIMTA is targeted therapy for patients with nonsquamous NSCLC.

Additionally, histology serves an important biomarker in making an appropriate treatment selection for patients with NSCLC.

Next slide: ALIMTA /Cisplatin Provided Select Hematologic Safety Advantages over GEMZAR Plus Cisplatin

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Reference

1. ALIMTA\(^\circledR\) (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
Key hematologic Grade 3 or 4 drug-related toxicities were lower for ALIMTA plus cisplatin compared with gemcitabine HCl plus cisplatin: anemia, 6% versus 10%; neutropenia, 15% versus 27%; and thrombocytopenia, 4% versus 13%, respectively.¹

For ALIMTA plus cisplatin versus gemcitabine HCl plus cisplatin, drug-related Grade 3 or 4 febrile neutropenia (1% versus 4%, respectively) was also lower.¹

Next slide: Fewer Supportive Care Interventions Were Required in Patients Receiving ALIMTA/Cisplatin

Reference
Patients treated with ALIMTA plus cisplatin required fewer transfusions (16.4% vs 28.9%), including red blood cell transfusions (16.1% vs 27.3%) and platelet transfusions (1.8% vs 4.5%) compared with gemcitabine HCl/cisplatin.1

The administration of erythropoietic (10.4% vs 18.1%) and granulocyte colony-stimulating factors (3.1% vs 6.1%) was lower with ALIMTA plus cisplatin.1

Reference
• This table shows a detailed analysis of adverse reactions in each treatment arm

• There were generally similar incidences of treatment-emergent events between treatment arms [ALIMTA PI/p3/col1/Table4]

• For the purpose of this table, a cutoff of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA [ALIMTA PI/p3/col1/Table4 footnote a]

**Reference**
1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
This table provides a detailed analysis of the rest of the adverse reactions in each treatment arm.

There were generally similar incidences of treatment-emergent events between treatment arms\(^1\) [ALIMTA PI/p3/ col2/Table4]

For the purpose of this table, a cutoff of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA\(^1\) [ALIMTA PI/p3/ col2/Table4/footnote a]

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**1st-line Advanced NSCLC**

**Comparison of Treatment-Related Adverse Reactions\(^a,1\) (cont)**

<table>
<thead>
<tr>
<th>Reaction(^b)</th>
<th>ALIMTA/Cisplatin (N=839)</th>
<th>Gemcitabine HCl/Cisplatin (N=836)</th>
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<tbody>
<tr>
<td></td>
<td>All grades toxicity (%)</td>
<td>Grades 3/4 toxicity (%)</td>
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<td><strong>Clinical</strong></td>
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<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

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

\(^b\) Refer to NCI CTC criteria version 2.0 for each grade of toxicity.

\(^1\) According to NCI CTC criteria version 2.0, this adverse event term should be reported only as Grade 1 or 2.

---

**Reference**

1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
In this section, we will discuss ALIMTA in 2nd-line advanced NSCLC.
In the phase III trial of ALIMTA versus docetaxel, patients with locally advanced or metastatic NSCLC previously treated with chemotherapy were randomized to receive ALIMTA\(^*\) 500 mg/m\(^2\) as a 10-minute intravenous infusion on day 1 of a 21-day cycle, folic acid 350-1000 µg daily, vitamin B\(_{12}\) 1000 µg every 9 weeks until after discontinuation, plus dexamethasone 4 mg orally twice daily the day before, the day of, and the day after pemetrexed\(^1,2\) or Docetaxel\(^*\) 75 mg/m\(^2\) as a 1-hour intravenous infusion on day 1 of a 21-day cycle plus dexamethasone 8 mg twice daily the day before, the day of, and the day after docetaxel\(^1,2\). 

\(^*\)Treatment was continued until disease progression or unacceptable toxicity. This was a noninferiority trial design.

References
1. ALIMTA\(^\circledR\) (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
This table shows the baseline characteristics of eligible patients who participated in the trial.

The two arms were well balanced for all demographic and stratification factors.\(^1\)

As you can see, slightly more than half of these patients were classified with adenocarcinoma histology.\(^2\)

References
1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
Patients treated with pemetrexed demonstrated clinically equivalent efficacy compared with patients treated with docetaxel.

There were no significant differences in progression-free survival, time to progressive disease, and time to treatment failure.¹,²

Additionally, there was also no significant difference in median time to response, median duration of response, and median duration of clinical benefit.¹,²

On an intent-to-treat basis, the median survival time for pemetrexed was 8.3 months versus 7.9 for docetaxel (HR, 0.99; 95% CI, 0.82 to 1.2), which shows noninferiority.¹,²
In this study, treatment with pemetrexed demonstrated a significantly improved safety profile compared with those receiving docetaxel in the 2nd-line setting for advanced NSCLC.\(^1\)\(^2\)

References
1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
This table shows the safety profile of ALIMTA with regard to nonhematologic toxicities.¹,²

References
1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
In this section, we will review the phase III, multicenter, randomized, double-blind, placebo-controlled study of ALIMTA in the maintenance of advanced NSCLC.1 [ALIMTA PI/p7/ col1/sec14.2/col1/¶1]

This study was designed to demonstrate superior progression-free survival and overall survival of ALIMTA maintenance therapy over placebo immediately following 4 cycles of platinum-based chemotherapy, prior to disease progression.1 [ALIMTA PI/p7/ col1/sec14.2/col1/¶1,2]
The study of ALIMTA in the maintenance of advanced NSCLC was a randomized, placebo-controlled, multicenter phase III registration trial.\textsuperscript{1,2}

The main objective of this study was to assess whether ALIMTA plus best supportive care as a maintenance therapy can improve the progression-free survival of patients with Stage IIIB/IV advanced NSCLC.\textsuperscript{1,2}

Patients who had a primary diagnosis of Stage IIIB or IV advanced NSCLC were enrolled.\textsuperscript{2}

Randomization occurred immediately following completion of 4 cycles of induction chemotherapy (which did not include ALIMTA vs cisplatin) for those patients who did not have disease progression during induction therapy.\textsuperscript{2}

Induction therapy choices\textsuperscript{2}:
- Gemcitabine + platinum
- Paclitaxel + platinum
- Docetaxel + platinum

663 patients were randomly assigned at a 2:1 ratio between the 2 treatment arms\textsuperscript{2}:
- ALIMTA 500 mg/m\textsuperscript{2} plus best supportive care administered until disease progression
- Placebo plus BSC until disease progression

References
1. ALIMTA\textsuperscript{®} (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
The study was designed to demonstrate superior progression-free survival and overall survival after completion of 4 cycles of platinum-containing induction therapy.\(^1\) [ALIMTA PI/p7/col1/sec14.2/¶1,2/col2/¶3/Table13-14/w/footnotes]

The study included a prespecified analysis for all efficacy endpoints by advanced NSCLC histology.\(^1\) [ALIMTA PI/p7/col2/¶3]

- The primary endpoint was progression-free survival (PFS)\(^2\)
- Overall survival (OS) was a secondary endpoint (study was powered for full OS analysis)\(^2\) [Ciuleanu/p1435/col2¶1/p1436/col1/¶1-2]
- The assessment of PFS included a full independent review\(^1\) [ALIMTA PI/p7/col2/Table13/footnote b]

References
1. ALIMTA\(^®\) (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
Enrollment and randomization occurred immediately following the completion of induction therapy.\textsuperscript{1,2} [Ciuleanu/p1433/col1/¶4] [ALIMTA PI/p7/col1/sec14.2/¶2]

Patients were required to receive maintenance therapy no earlier than 21 days and no later than 42 days from Day 1 of their last cycle of induction therapy.\textsuperscript{2} [Ciuleanu/p1433/col1/¶4]

Patient characteristics upon randomization were well balanced between treatment arms.\textsuperscript{1} [ALIMTA PI/p7/col1/sec14.2/¶2]

Adenocarcinoma was the predominant subtype, followed by squamous cell carcinoma.\textsuperscript{1}

A total of 72.7\% of patients in the study population had nonsquamous histology (adenocarcinoma, large cell carcinoma, or “other” histology).\textsuperscript{1} [ALIMTA PI/p7/col1/Table12]

Non-squamous (73.7\% and 70.3\%) and squamous (26.3\% and 29.7\%) populations were well balanced between the ALIMTA plus best supportive care and placebo plus best supportive care arms, respectively.\textsuperscript{1,2} [Ciuleanu/p1436/col2/¶3/p1434/Table1] [ALIMTA PI/p7/col1/Table12]

References
1. ALIMTA\textsuperscript{®} (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
In patients with nonsquamous advanced NSCLC, ALIMTA plus best supportive care administered as maintenance therapy demonstrated improvement in overall survival over placebo plus best supportive care.\textsuperscript{1,2}

\textbf{ALIMTA plus best supportive care showed a median overall survival of 15.5 months versus 10.3 months for placebo plus best supportive care.\textsuperscript{1,2} The hazard ratio was 0.70 (95% CI: 0.56-0.88). For nonsquamous patients receiving ALIMTA plus best supportive care, this represents an increase in overall survival.\textsuperscript{1,2}}

Nonsquamous includes patients with adenocarcinoma, large cell carcinoma, and other histology.\textsuperscript{1,2}

\textbf{References}

1. ALIMTA\textsuperscript{\textregistered} (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
This table represents an overview of the progression-free survival (based on independent review) and overall survival by histologic subgroups.

As you can see, ALIMTA plus best supportive care as a maintenance therapy improved overall survival in patients with adenocarcinoma by nearly 5 months.¹

References
1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
According to both investigator assessment and independent review, the disease control rate was significantly higher for patients treated with ALIMTA plus best supportive care compared with placebo and best supportive care.\(^1\)

In the overall population, more than half the patients receiving ALIMTA (52%) achieved disease control, which was defined as complete and partial response plus stable disease.\(^2\)

As we look at the outcomes for nonsquamous histology, we find that the percentage of patients who achieve disease control increases to 58%.

This figure climbs even higher and reaches 61% for patients with adenocarcinoma who achieve stable disease.

These findings further highlight the role of histology in treatment selection for patients with NSCLC.

References
The table represents the summary of all Grades and Grades 3/4 laboratory toxicities per treatment arm possibly related to study therapy for the overall population.¹ [ALIMTA PI/p3/ col2/Table5]

Increases in adverse reactions (all Grades) were observed with longer exposure to ALIMTA; however, no clinically relevant differences in Grades 3/4 adverse reactions were seen.¹ [ALIMTA PI/p3/ ¶6,7]

**References**

1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
This table summarizes nonhematologic toxicities per treatment arm that may be related to study therapy.¹

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>ALIMTA + BSC (N=438)</th>
<th>Placebo + BSC (N=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades (%)</td>
<td>Grades 3/4 (%)</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Mucositis/Stomatitis</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy–sensory</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Dermatology/Skin</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Rash/Desquamation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ For the purpose of this table, a cutoff of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

References

1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
This schematic of the current paradigm for the treatment of advanced NSCLC is based on ASCO and NCCN guidelines.1,2

In 2003, the ASCO guidelines recommended that first-line chemotherapy should be “stopped at four cycles in patients who are not responding” and “administered for no more than six cycles.”1 [Soon/p1/col2/¶1] [Pfister/p345/Table 1]

It is important to note that ASCO also held a position that “NSCLC histology is not an important prognostic factor in patients with advanced, unresectable disease.” [Pfister p334/col2/¶10]

This statement is challenged by the clinical data we just presented for 3 ALIMTA studies that show histology does, in fact, matter and is a prognostic indicator of overall survival.

In the current paradigm, the NCCN guidelines state that “patients with responsive or stable disease can continue to receive a total of four to six cycles (preferred) of chemotherapy or until the disease progresses.”1 [Soon/p1/col2/¶1/p2/col1¶2]

However, this paradigm is shifting based on findings of a meta-analysis from Soon and colleagues, which concluded that extending chemotherapy beyond a standard number of cycles delays disease progression substantially, but has only modest effects on overall survival in patients with advanced NSCLC.1

The authors recommend that future trials should test extending treatment with more effective and/or better tolerated agents.1 [Soon/p6/col2/¶4,5]

As we presented earlier, treatment with ALIMTA demonstrated select hematologic safety advantages that reduced the need for costly supportive care interventions.

References
In this section we will discuss ALIMTA dosing and administration.
This table shows the dosing and administration for ALIMTA in combination with cisplatin or as a single agent.¹

[ALIMTA PI/p1/col1/Dosage and Administration/bullets 1,2/p2/col1/sec2.1]

[ALIMTA PI/p2/col1/sec2.2]

References
1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
Shown are patient monitoring and dosing modifications for ALIMTA as a single agent or in combination with cisplatin.

[ALIMTA PI/p2/col1/sec2.3/¶1]
Shown are the dosing modifications for ALIMTA as a single agent or in combination with cisplatin.

References
1. ALIMTA® (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
In summary, ALIMTA is a targeted therapy and is efficacious in a specific subpopulation of patients with nonsquamous histology. More importantly, ALIMTA is not a treatment option for patients with squamous histology. Therefore, appropriate utilization based on histology supports open access for ALIMTA.

The key points in this slide provide more reasons why ALIMTA should be included on NSCLC clinical pathways.

- ALIMTA demonstrated a differential effect on survival based on histology
- ALIMTA/cisplatin shows select hematologic safety advantages over GEMZAR/cisplatin
  - Reduces resource utilization (transfusions, medications, and hospitalizations)
- Appropriate utilization of ALIMTA/cisplatin in nonsquamous NSCLC can lead to improved clinical and economic outcomes compared with GEMZAR/cisplatin
  - Can provide benefits to payers, providers, and patients
References


References (cont)


