Approval Summary: Pemetrexed Maintenance Therapy of Advanced/Metastatic Nonsquamous, Non-Small Cell Lung Cancer (NSCLC)

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Consider tumor histology when making treatment decisions for patients with NSCLC.
2. Identify patients with NSCLC who may be appropriate candidates for maintenance therapy with pemetrexed.

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ABSTRACT

On July 2, 2009, the U.S. Food and Drug Administration approved pemetrexed injection (Alimta® Injection; Eli Lilly and Company, Indianapolis, IN) for maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based doublet induction chemotherapy.

A double-blind study of pemetrexed plus best supportive care versus placebo plus best supportive care was conducted. Pemetrexed, 500 mg/m² i.v., was administered every 21 days until disease progression. Folic acid, vitamin B₁₂, and a corticosteroid were given to all study patients.

There were 663 randomized patients (pemetrexed,

441; placebo, 222). Treatments were well balanced with respect to baseline disease characteristics and stratification factors.

The median overall survival (OS) time for intent-to-treat (ITT) patients was 13.4 months for patients receiving pemetrexed and 10.6 months for those receiving placebo (hazard ratio [HR] 0.79; 95% confidence interval [CI], 0.65–0.95; $p = .012$). Median OS times were 15.5 months versus 10.3 months for patients with nonsquamous histologies receiving pemetrexed and placebo, respectively (HR, 0.70; 95% CI, 0.56–0.88). The median OS time in patients with squamous histology receiving pemetrexed was 9.9

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months, versus 10.8 months for those receiving placebo (HR, 1.07; 95% CI, 0.77–1.50). A significantly longer progression-free survival interval for both the ITT and nonsquamous patient populations receiving pemetrexed maintenance therapy was also observed.

The most common (>5%) adverse reactions in patients receiving pemetrexed were hematologic toxicity, an increase in hepatic enzymes, fatigue, gastrointestinal toxicity, sensory neuropathy, and skin rash. *The Oncologist* 2010;15:1352–1358

INTRODUCTION

Pemetrexed received its first non-small cell lung cancer (NSCLC) accelerated approval on August 19, 2004 as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy [1, 2]. Because of evidence that there might be a greater benefit of pemetrexed therapy among nonsquamous NSCLC patients than among squamous cell patients [3–7], a retrospective analysis of a histology effect on efficacy outcomes was performed. That analysis demonstrated that pemetrexed was more effective in patients with adenocarcinoma and large cell lung cancer than in patients with squamous cell carcinoma.

As a result of this observation, the statistical analysis plan for a proposed phase III study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin for the initial treatment of patients with locally advanced or metastatic nonsquamous NSCLC included a pemetrexed treatment-by-histology interaction analysis. Again, pemetrexed was more effective in patients with adenocarcinoma and large cell lung cancer than in patients with squamous cell carcinoma. This second, accelerated approval occurred on September 26, 2008 [8, 9].

Based on these results and preliminary data from the study currently reported, the pemetrexed labeled indication states that therapy should be administered only to patients with locally advanced or metastatic nonsquamous NSCLC. Pemetrexed is not indicated for treatment of patients with squamous cell NSCLC.

The current submitted study sought a third nonsquamous NSCLC pemetrexed indication, as maintenance therapy for patients who had not progressed after four cycles of platinum-based first-line doublet chemotherapy.

PATIENTS AND METHODS

The pivotal study was a global, multicenter, randomized, double-blind, placebo-controlled trial that entered 741 patients at 83 sites in 20 countries. Eligible patients had stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or stage IV NSCLC and had a complete response (CR), partial response (PR), or stable disease (SD) following four cycles of a first-line platinum-containing doublet chemotherapy regimen. Acceptable regimens included gemcitabine plus carboplatin or cisplatin, paclitaxel

plus carboplatin or cisplatin, and docetaxel plus carboplatin or cisplatin. Maintenance treatment had to begin ≥ 21 days and ≤ 42 days from the last dose of induction therapy.

Randomization, following induction therapy, was in a 2:1 ratio to pemetrexed plus best supportive care (BSC) or placebo plus BSC. Pemetrexed (500 mg/m²) was administered as an i.v. infusion over 10 minutes on day 1 of each 21-day cycle. The placebo consisted of normal saline (0.9% sodium chloride), which also served as the diluent for pemetrexed. BSC included, but was not limited to, antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, and nutritional support (enteral or parenteral). All study patients received folic acid (350–1,000 μ g) daily orally beginning approximately 1–2 weeks before the first dose of study therapy and continuing daily until 3 weeks after the last dose of study therapy, vitamin B₁₂ (1,000 μ g) i.m. injection beginning approximately 1–2 weeks before the first dose of study therapy and approximately every 9 weeks until 3 weeks after the last dose of study therapy, and dexamethasone (or equivalent), 4 mg, orally twice per day (or equivalent) to be taken on the day before, the day of, and the day after each dose of study therapy. Higher or additional dexamethasone doses were permitted for reasons other than routine rash prophylaxis (e.g., antiemetic prophylaxis).

To achieve a balance between study arms, patients were stratified by disease stage prior to administration of induction therapy (stage IIIB versus stage IV), Eastern Cooperative Oncology Group (ECOG) performance status score just prior to randomization (0 versus 1), best tumor response to induction chemotherapy (CR/PR versus SD), gender (male versus female), previously treated brain metastases (yes versus no), and nonplatinum component of induction chemotherapy (gemcitabine versus paclitaxel versus docetaxel).

Each patient underwent a treatment and follow-up period. Treatment was continued until objective disease progression. All patients were followed until death or study closure.

The sponsor's primary objective was to compare maintenance therapy using pemetrexed plus BSC with maintenance therapy using placebo plus BSC in terms of the objective progression-free survival (PFS) time. PFS was determined by the individual investigator. In addition, available scans were reviewed by an independent review

Figure 1. Progression-free survival.
Abbreviation: BSC, best supportive care.

committee (IRC). The IRC charter required a minimum of three board-certified radiologists assigned to the study. Two primary radiologists independently read each case (double read) in a blinded fashion, with a third radiologist serving as adjudicator when necessary. If both primary readers did not agree on all overall tumor responses at every time point, then adjudication was required. The adjudicator did not provide an independent assessment but provided an assessment of the two primary reviews and determined which review was final.

Secondary objectives of the study were to compare the randomized study arms for overall survival (OS) time, time to objective progressive disease (TTP), measured from the date of randomization to the first date of objective progression of disease, objective tumor response rate, changes in individual symptom scores, quality of life using the Lung Cancer Symptom Scale (LCSS), and adverse events (AEs). An additional secondary objective was the consideration of efficacy with respect to histology, including an assessment of the treatment-by-histology interaction.

Prespecified tests for a histology-by-treatment interaction were performed using Cox models that included cofactors potentially prognostic for PFS and OS, including the nonplatinum component of induction therapy (gemcitabine versus paclitaxel/docetaxel), and included terms for treatment (pemetrexed versus placebo), squamous histology (no versus yes), treatment-by-squamous interaction (nonsquamous pemetrexed versus all other patients), ECOG performance status score (0 versus 1), induction response (CR/PR versus SD), East Asian ethnicity (yes versus no), smoking status (never versus ever), gender (female versus male), and age (<65 versus ≥65).

Patients were eligible to be included in the study if they had a histologic or cytologic diagnosis of stage IIIB NSCLC (with pleural effusion and/or positive supraclavicular lymph nodes) or stage IV disease, four 21-day cycles of platinum-containing doublet chemotherapy, documented evidence of tumor response (CR or PR) or SD, an ECOG

performance status score 0 or 1, adequate organ function, prior radiation therapy to ≤25% of the bone marrow, adequate contraception, and signed informed consent. Patients with clinically detectable (by physical exam) third-space fluid collections, for example, ascites or pleural effusions that could not be controlled by drainage or other procedures prior to study entry, were excluded.

RESULTS

In total, 663 patients were enrolled, 441 receiving pemetrexed plus BSC and 222 receiving placebo plus BSC. The two arms were balanced with regard to demographic characteristics: the median age was 60.6 years, 73% of patients were male, 64% of patients were white, 23% of patients were East Asian, and 27% of patients were never-smokers.

Approximately 20% of study patients had stage IIIB disease and approximately 8% had previously treated brain metastases. Approximately 50% of patients had a PR and 50% had SD as their best response to induction chemotherapy. About 14% of patients had prior radiation therapy and 11% had prior surgery.

About 72% of patients had nonsquamous histology, based on their local pathology report. Adenocarcinoma, including bronchioloalveolar carcinoma, was diagnosed in approximately 50% of patients, large cell carcinoma was diagnosed in about 3% of patients, other or indeterminate (including poorly differentiated and mixed cell) NSCLC was diagnosed in about 20% of patients, and squamous cell NSCLC was diagnosed in about 26% of patients.

PFS

The median PFS interval was 4.0 months in the pemetrexed arm and 2.0 months in the placebo arm (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.49–0.73; $p < 0.00001$) (Fig. 1). Results for TTP were consistent with results for PFS. Several sensitivity analyses, including a covariate-adjusted analysis and an independent review of available scans from 581 of the 663 randomized patients

Figure 2. Overall survival.

Abbreviation: BSC, best supportive care.

Table 1. PFS and OS by histology

Histologic subgroup	Final PFS ^a		Overall survival	
	Pemetrexed (n = 441), median mos	Placebo (n = 222), median mos	Pemetrexed (n = 441), median mos	Placebo (n = 222), median mos
	HR ^b (95% CI) p-value		HR (95% CI) p-value	
Nonsquamous ^c (n = 481)	4.4 0.47 (0.37–0.60)	1.8	15.5 0.70 (0.56–0.88)	10.3
Adenocarcinoma (n = 328)	4.6 0.51 (0.38–0.68)	2.7	16.8 0.73 (0.56–0.96)	11.5
Large cell (n = 20)	4.5 0.40 (0.12–1.29)	1.5	8.4 0.98 (0.36–2.65)	7.9
Other/indeterminate ^d (n = 133)	4.1 0.44 (0.28–0.68)	1.6	11.3 0.61 (0.40–0.94)	7.7
Squamous (n = 181)	2.4 1.03 (0.71–1.49) 0.039	2.5	9.9 1.07 (0.77–1.50)	10.8

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

^aValues for PFS are given based on independent review (pemetrexed, n = 387; placebo, n = 194).

^bUnadjusted HRs are provided. An HR <1.0 indicates that the result is better in the pemetrexed arm than in the placebo arm. An HR >1.0 indicates that the result is better in the placebo arm than in the pemetrexed arm.

^cIncludes patients with adenocarcinoma, large cell carcinoma, and other histology.

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

Abbreviations: CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

(87.6%), were also performed. These analyses confirmed the initial PFS results. Other sensitivity analyses also supported the robustness of the primary analysis by demonstrating that postdiscontinuation therapy and delayed radiologic assessments also did not bias the primary analysis in favor of pemetrexed.

OS

For the final OS datalock, the median follow-up time was 12.0 months for patients receiving pemetrexed and 10.1 months for patients receiving placebo. There were 303

events in the pemetrexed arm (68.7%) and 174 in the BSC arm (78.4%). The median OS time was 13.4 months for patients receiving pemetrexed and 10.6 months for patients receiving placebo (HR, 0.79; 95% CI, 0.65–0.95; $p = .012$). The 1-year survival rate was estimated at 55% for the pemetrexed arm and 43% for the placebo arm (Fig. 2).

The objective response rate to maintenance therapy, as determined by investigators, was higher for patients in the pemetrexed arm (6.8%; 95% CI, 0.05%–0.10%) than for those in the placebo arm (1.8%; 95% CI, 0.00%–0.05%). The inde-

Table 2. Postdiscontinuation systemic anticancer therapy

Therapy	Pemetrexed (n = 441), n (%)	Placebo (n = 222), n (%)
Any systemic therapy (%)	226 (51)	149 (67)
Pemetrexed	4 (1)	41 (19)
Docetaxel	99 (22)	65 (29)
Erlotinib	95 (21)	46 (21)
Gefitinib	58 (13)	22 (10)
Vinorelbine	56 (12)	37 (17)
Gemcitabine	40 (9)	30 (14)
Carboplatin	32 (7)	21 (10)
Cisplatin	23 (5)	13 (6%)

pendently reviewed tumor response rate (CR + PR) was 3.4% in the pemetrexed arm and 0.5% in the placebo arm.

Tests for Histology-by-Treatment Interaction in PFS and OS

Comparison of baseline characteristics for all randomized patients with nonsquamous versus squamous histology indicated that patients were similar with respect to most characteristics; although the percentages of females (31% versus about 16%), East Asians (27% versus 14%), and never-smokers (30% versus about 16%) were higher for the nonsquamous population.

There were statistically significant interactions for PFS (interaction HR, 0.65; $p = .036$) and for OS (interaction HR, 0.52; $p = .011$) (Table 1). Patients with a nonsquamous histology in the pemetrexed arm had longer PFS and OS times than patients with squamous cell histology.

Postdiscontinuation systemic anticancer therapy was received by 51% of pemetrexed-treated patients and by 67% of placebo-treated patients. Postdiscontinuation pemetrexed was received by 19% of placebo-treated patients (Table 2).

Time without symptoms and delays in worsening of pain and hemoptysis were longer for patients receiving pemetrexed than for patients receiving placebo. No other differences in LCSS scores were noted.

The safety results in the pemetrexed arm were consistent with the known safety profile of single-agent pemetrexed. Pemetrexed-treated patients received a median of five cycles of treatment whereas placebo-treated patients received a median of 3.5 cycles. The dose intensity for pemetrexed was 96.1%.

A larger percentage of dose delays related to AEs occurred in the pemetrexed arm (71 patients, 16.1%) than in

the placebo arm (13 patients, 5.9%). In total, 100 cycles of pemetrexed (0.6% of total cycles administered) and 18 cycles of placebo (0.5% of total cycles administered) were delayed as a result of AEs, regardless of causality. Taken together, AEs related to decreased renal function (creatinine clearance decreased, glomerular filtration rate decreased, blood creatinine increased, renal function test abnormal, and renal failure) accounted for the largest number of dose delays in the pemetrexed arm. Other commonly reported AEs causing dose delays in the pemetrexed arm included fatigue, asthenia, and bronchitis.

All dose reductions in both study arms were caused by AEs. Of the 18 patients (4.1%) with dose reductions in the pemetrexed arm, fatigue was the most common reason, followed by anemia, febrile neutropenia, general physical health deterioration, and mucosal inflammation.

No study drug-related deaths were reported for either study arm. No patients in the placebo arm experienced any possibly study drug-related serious adverse events (SAEs), compared with 4.3% ($p = .001$) of patients in the pemetrexed arm; only one patient receiving pemetrexed discontinued study treatment because of an SAE (thrombocytopenia) considered to be possibly related to study drug.

The percentage of patients with at least one grade 3 or 4 drug-related laboratory toxicity was significantly higher for patients in the pemetrexed arm (5.9%) than for patients in the placebo arm (2.3%; $p = .049$). The only statistically significant difference in the incidence of individual drug-related grade 3 or 4 Common Terminology Criteria for Adverse Events (CTCAE) laboratory toxicities was for neutropenia (2.7% versus 0%, respectively; $p = .011$).

Overall, there were no statistically significant differences in the hospitalization rate between study arms, except for hospitalizations resulting from drug-related AEs; no patients receiving placebo were admitted for hospitalization, compared with 19 patients (4.3%) receiving pemetrexed. Compared with patients receiving placebo, patients in the pemetrexed arm had significantly more transfusions of any type (9.5% versus 3.2%; $p = .003$) and RBC transfusions (8.6% versus 2.7%; $p = .003$), as well as a statistically significantly greater use of erythropoiesis-stimulating agents (5.9% versus 1.8%; $p = .011$). No statistically significant differences were observed for other supportive care medications, including antiemetics, anti-infectives, and G-CSF.

The percentage of patients with at least one grade 3 or 4 drug-related nonlaboratory toxicity was also significantly higher for patients in the pemetrexed arm (10.7%) than for patients in the placebo arm (1.4%; $p < .001$). The only sta-

tistically significant difference in the incidence of individual drug-related grade 3 or 4 CTCAE nonlaboratory toxicities was for fatigue.

A greater number of patients in the pemetrexed arm than in the placebo arm experienced AEs associated with decreased renal function. Thirty-three patients in the pemetrexed arm (7.5%) were reported to have an AE associated with decreased renal function. Of these 33 patients, 10 (2.3%) were discontinued from pemetrexed because of their drug-related renal event, and one of these patients was reported to have an SAE of renal failure (grade 3) that required hospitalization. No patients in the placebo arm were reported to have any grade 3 or 4 AE signifying decreased renal function possibly related to study treatment.

Safety was also evaluated by histologic subgroup (nonsquamous versus squamous). The safety profile for each of these subgroups was consistent with the safety profile of pemetrexed observed in the entire patient population.

DISCUSSION

The submitted study demonstrated significantly longer PFS and OS times for the overall population of NSCLC patients treated with pemetrexed, and more specifically for patients with nonsquamous NSCLC. This was the third pemetrexed study submitted to the U.S. Food and Drug Administration (FDA) that demonstrated this treatment-by-histology interaction. A possible explanation for this finding is that thymidine synthetase (TS) expression is significantly higher in squamous cell carcinoma than in adenocarcinoma ($p < .0001$) [5], and preclinical data have indicated that overexpression of TS correlates with lower sensitivity to pemetrexed [6, 7]. Other possible explanations for the observed treatment-by-histology interaction might involve the presence or absence of other molecular markers [10, 11].

One issue arising from this review is the appropriate clinical endpoint for a maintenance study. Currently, three to six cycles of platinum-based chemotherapy are administered to patients with advanced/metastatic NSCLC [12–15]. Patients are then followed until disease progression, whereupon those with a satisfactory performance status and organ function may receive additional therapy.

In a maintenance therapy scenario, patients who complete a specified number of cycles of frontline therapy and who do not have progressive disease are offered immediate treatment with a new regimen. This is continued until disease progression. The rationale for such treatment is the Goldie–Coleman hypothesis that early use of noncrossresistant chemotherapy results in greater tumor cell death [16, 17].

If the new regimen has antitumor activity, it might be ex-

pected that the PFS duration will be longer than in patients who do not receive such therapy. If patients who do not receive maintenance therapy receive second-line therapy (docetaxel, pemetrexed, and erlotinib are FDA approved for such use) at the time of progression, however, they may live as long as patients who receive maintenance therapy with or without additional therapy at the time of progression.

Thus, OS is likely the superior endpoint for maintenance treatment trials. Demonstration of a survival benefit would lead to regular approval and would not require phase IV commitments.

Based on the above, it is necessary to demonstrate that an adequate percentage of patients who did not receive maintenance therapy did subsequently receive postprogression therapy with active NSCLC drugs. As described in recent first-line and maintenance studies, approximately 30%–60% of patients with advanced NSCLC go on to receive second-line therapy after disease progression [18–20]. Factors increasing the likelihood that second-line therapy is administered include younger age, a performance status score of 0–1, female gender, nonsquamous histology, and having received two or more cycles of frontline therapy [21]. In the submitted trial, postdiscontinuation second-line anticancer therapy was given to 67% of placebo-treated patients and to 51% of pemetrexed-treated patients. Postdiscontinuation pemetrexed was received by 19% of placebo-treated patients. These figures seem reasonable, compared with historical data.

Although OS remains the “gold standard” clinical benefit endpoint, health-related quality of life (HRQoL) might also provide evidence of clinical benefit. HRQoL represents a summation of how patients feel or function relative to their disease and its treatment. There are numerous challenges with respect to this endpoint, including the need for randomized studies, for patient and health professional blinding, for the management of missing data, and for a statistical analysis plan that permits testing of multiple hypotheses and provides for consistency of endpoint results [22, 23]. The U.S. FDA welcomes discussion with sponsors regarding specific HRQoL claims.

In conclusion, the submitted pemetrexed maintenance trial demonstrated significantly longer PFS and OS times for the overall population of patients treated with maintenance pemetrexed and, more specifically, for patients with nonsquamous NSCLC. The significant treatment-by-histology interaction observed in this study was also observed in another previously submitted phase III advanced NSCLC study [9]. The safety results in the pemetrexed arm were consistent with the known safety profile of single-agent pemetrexed. In addition, safety analyses for histologic sub-

groups were consistent with the safety profile of pemetrexed observed in the entire patient population.

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AUTHOR CONTRIBUTIONS

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REFERENCES

- Cohen MH, Johnson JR, Wang YC et al. FDA drug approval summary: Pemetrexed for injection (Alimta) for the treatment of non-small cell lung cancer. *The Oncologist* 2005;10:363–368.
- Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589–1597.
- Peterson P, Park K, Fossella F et al. Is pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2007;2(suppl 4):s316–s317.
- Scagliotti G, Hanna N, Fossella F et al. The differential efficacy of pemetrexed according to NSCLC histology: A review of two phase III studies. *The Oncologist* 2009;14:253–263.
- Cepi P, Volante M, Saviozzi S et al. Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. *Cancer* 2006;107:1589–1596.
- Sigmond J, Backus HH, Wouters D et al. Induction of resistance to the multitargeted antifolate pemetrexed (ALIMTA) in WiDr human colon cancer cells is associated with thymidylate synthase overexpression. *Biochem Pharmacol* 2003;66:431–438.
- Hashimoto H, Ozeki Y, Sato M et al. Significance of thymidylate synthase gene expression level in patients with adenocarcinoma of the lung. *Cancer* 2006;106:1595–1601.
- Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.
- Cohen MH, Justice R, Pazdur R. Approval summary: Pemetrexed in the initial treatment of advanced/metastatic non-small cell lung cancer. *The Oncologist* 2009;14:930–935.
- Selvaggi G, Scagliotti GV. Histologic subtype in NSCLC: Does it matter? *Oncology (Williston Park)* 2009;23:1133–1140.
- Neal JW. Histology matters: Individualizing treatment in non-small cell lung cancer. *The Oncologist* 2010;15:3–5.
- Rinaldi M, Belvedere O, Cauchi C et al. Maintenance chemotherapy in non-small cell lung cancer. *Ann Oncol* 2006;17(suppl 2):ii67–ii70.
- Smith IE, O'Brien ME, Talbot DC et al. Duration of chemotherapy in advanced non-small-cell lung cancer: A randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. *J Clin Oncol* 2001;19:1336–1343.
- Socinski MA, Scell MJ, Peterman A et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small cell lung cancer. *J Clin Oncol* 2002; 20:1335–1343.
- Pfister DG, Johnson DH, Azzoli CG et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: Update 2003. *J Clin Oncol* 2004;22:330–353.
- Goldie JH, Coldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treat Rep* 1982;66:439–449.
- Grossi F, Aita M, Follador A et al. Sequential, alternating, and maintenance/consolidation chemotherapy in advanced non-small cell lung cancer: A review of the literature. *The Oncologist* 2007;12:451–464.
- Scagliotti GV, De Marinis F, Rinaldi M et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002;20:4285–4291.
- Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
- Brodowicz T, Krzakowski M, Zwitter M et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: A phase III trial. *Lung Cancer* 2006;52:155–163.
- Hensing TA, Schell MJ, Lee JH et al. Factors associated with the likelihood of receiving second line therapy for advanced non-small cell lung cancer. *Lung Cancer* 2005;47:253–259.
- Rock EP, Scott JA, Kennedy DL et al. Challenges to use of health-related quality of life for Food and Drug Administration approval of anticancer products. *J Natl Cancer Inst Monogr* 2007;(37):27–30.
- Lipscomb J, Reeve BB, Clauser SB et al. Patient-reported outcomes assessment in cancer trials: Taking stock, moving forward. *J Clin Oncol* 2007;25: 5133–5140.