The novel multitargeted antimetabolite pemetrexed (Alimta), recently approved by the US Food and Drug Administration for the treatment of mesothelioma when combined with cisplatin, is also active in first- and second-line non–small-cell lung cancer (NSCLC). In a phase III trial comparing single-agent pemetrexed vs docetaxel (Taxotere) as secondline therapy in advanced NSCLC, survival was shown to be comparable between these agents, but side effects were significantly less frequent and severe for patients who received pemetrexed. In the frontline setting, phase II studies have shown significant activity and a very favorable toxicity profile of the combination of pemetrexed with a platinum agent. Pemetrexed has been well tolerated at systemic doses as a radiosensitizer when given as concurrent chest radiation, and a phase I study is under way to assess its tolerability in combination with carboplatin (Paraplatin) in this setting. Pemetrexed is an important addition to the armamentarium of medicines used to treat thoracic malignancies, and merits study in combination with other drugs having novel mechanisms of action.

Lung cancer is the leading cause of cancer death in both men and women in the United States, with an estimated 173,770 new cases and 160,440 deaths in 2004.[1] Eighty percent of lung cancers are non–small-cell lung cancer (NSCLC). More people die from lung cancer than from breast, prostate, and colon cancer combined, despite advances in the control of local disease. This is partly because one-third of patients with lung cancer present with metastatic disease, but also because most patients with stage III and as many as 50% with early-stage disease relapse after definitive therapy.[2] A large meta-analysis in 1995 showed a 10% increase in 1-year survival rate and an improvement of 1.5 months in median overall survival for cisplatin-containing regimens in advanced NSCLC.[3] In the late 1990s, third-generation agents including paclitaxel, docetaxel (Taxotere), gemcitabine (Gemzar), irinotecan (Camptosar), and vinorelbine (Navelbine) have been extensively studied. Combined with platinum agents, these form the standard of care for newly diagnosed advanced NSCLC. They produce response rates of 10% to 20% in previously untreated patients as single agents[4-7] and in combination with platinum, 20% to 40% response and median survival of 8 to 11 months in phase III trials.[ 8-13] However, these gains in survival have been rather modest. Moreover, there is no clearly demonstrated superiority of one of these modern platinum doublets over another.[ 14-18] Chemotherapy, in particular docetaxel, offers a survival advantage as second-line therapy as well.[19,20] Gefitinib (Iressa) is indicated for use in patients whose tumors have progressed after both platinum- and docetaxel- based chemotherapies[21,22] Pemetrexed (Alimta) has more recently been introduced into clinical study.[23] It has activity in multiple cancer types and is a novel antimetabolite.[ 24] On the basis of showing a survival advantage in combination with cisplatin as compared to singleagent cisplatin in mesothelioma, pemetrexed was approved for use in mesothelioma by the US Food and Drug Administration (FDA).[25] As a single agent in the treatment of second- line NSCLC, it showed equal efficacy with improved tolerability compared with docetaxel in a phase III study.[26] There are also data from phase II platinum/pemetrexed doublet studies showing efficacy comparable to best historical controls but with very promising toxicity profiles (Table 1). This article will focus on pemetrexed in the treatment of advanced NSCLC. **Pemetrexed.** Pemetrexed interferes with at least three enzymes in pyrimidine and purine biosynthesis, thymidylate synthase, dihydrofolate reductase, and glycaminide ribonucleotide formyltransferase (Figure 1).[27] A retrospective analysis of severe adverse events and their relationship to elevated plasma homocysteine (a surrogate for folate nutritional status) and methylmalonic acid (a surrogate for vitamin B12 status) levels was performed during the early clinical development of pemetrexed.[28] Elevated plasma homocysteine and methylmalonic acid levels, indicating folate and B12 deficiency, were associated with a statistically significantly greater risk of neutropenia, thrombocytopenia, nonhematologic toxicities such as infection, mucositis, and diarrhea,
In December 1999, all patients being treated with pemetrexed began receiving folic acid to reduce homocysteine and vitamin B\textsubscript{12} to reduce methylmelonic acid. This intervention has since been shown to reduce homocysteine and methylmelonic acid plasma levels, and patients who received supplementation in this way experienced significantly fewer toxicities.\textsuperscript{[33]} This was shown quite clearly through the phase III malignant pleural mesothelioma trial, where there was a clear improvement in the tolerability profile without a compromise in response or survival with the initiation of mandatory vitamin supplementation part of the way through the trial (Table 2).\textsuperscript{[25]}

**Clinical Trials Data** Single-Agent Pemetrexed With and Without Vitamin Supplementation: Phase I Trials
Multiple schedules of single agent pemetrexed have been evaluated in phase I trials, including a daily * 5 schedule every 3 weeks,[30] weekly for 4 weeks every 4 weeks,[31] and once every 3 weeks.[32] The schedule of pemetrexed administered once every 3 weeks as a 10-minute intravenous bolus has been studied most extensively. In one study, 37 patients received doses ranging from 50 to 700 mg/m² every 3 weeks.[32] However, neither folate nor vitamin B₁₂ supplementation was offered and side effects at the 700 mg/m² dose level were significant.

| Table 1: Common Toxicities in Phase III Trials in Advanced, Previously Untreated NSCLC* |
|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
| Grade 3/4 toxicities                   | Docetaxel/Carboplatin (n = 406) | Docetaxel/Carboplatin (n = 401) | Docetaxel/Carboplatin (n = 306) | Docetaxel/Carboplatin (n = 293) |
| Neutropenia                            | 75%                   | 74%                   | 79%                   | 57%                   |
| Neutropenia                            | 75%                   | 76%                   | 75%                   | 63%                   |
| Thrombocytopenia                       | 3%                    | 7%                    | 4%                    | 10%                   |
| Thrombocytopenia                       | 3%                    | 4%                    | 6%                    | 50%                   |
| Anemia                                 | 7%                    | 11%                   | 24%                   | 12%                   |
| Anemia                                 | 7%                    | 17%                   | 13%                   | 28%                   |
| Infection                              | 8%                    | 11%                   | 8%                    | 1%                    |
| Infection                              | 8%                    | 5%                    | 3%                    | 10%                   |
| Nausea/ vomiting                       | 10%                   | 6%                    | 16%                   | 7%                    |
| Nausea/ vomiting                       | 10%                   | 18%                   | 13%                   | 25%                   |
| Diarrhea                               | 7%                    | 5%                    | 3%                    | 7%                    |
| Diarrhea                               | 7%                    | 3%                    | 10%                   | 2%                    |
| Fatigue                                | 12%                   | 11%                   | 14%                   | 9%                    |
| Fatigue                                | 12%                   | 14%                   | 16%                   | 10%                   |
| Neurosensory                           | 4%                    | 0.7%                  | 4%                    | 13%                   |
| Neurosensory                           | 4%                    | 3%                    | 5%                    | 9%                    |
| Pruritis                               | 5%                    | 4%                    | 5%                    | 1%                    |
| Pruritis                               | 5%                    | 1%                    | 1%                    | 10%                   |
| Alopecia†                              | 74%                   | 68%                   | 41%                   | —                     |
| Alopecia†                              | 74%                   | 4%                    | 11%                   | —                     |

*Toxicity was graded using National Cancer Institute Common Toxicity Criteria.

†Data from Fossella [16]

‡Data from Kelly [17]

§Data from Schiller [18]

*Number includes grade 5 toxicity also.

†Grades 1–3.

NSCLC = non-small-cell lung cancer.
Neutropenia, thrombocytopenia, mucositis, fatigue, diarrhea, rash, and/or anorexia were dose-limiting. Side effects including grade 3 neutropenia, thrombocytopenia, and cumulative asthenia were experienced at the preceding dose level of 600 mg/m², and this dose was considered an acceptable one for further phase II trials. There was activity against advanced pancreatic cancer and colorectal cancer on this every-3-week schedule. Hammond[33] evaluated pemetrexed as a 10-minute intravenous bolus every 3 weeks at a starting dose of 600 mg/m² plus oral folic acid in patients who had had prior treatment in another phase I trial. Doses ranged from 600 to 1,400 mg/m² in 70 patients, all with prior chemotherapy. Neutropenia, anemia, and thrombocytopenia (more severe in the heavily pretreated patients), as well as nonhematologic side effects of rash, asthenia, pedal edema, and decline in creatinine clearance, have been observed. Less toxicity was observed with vitamin supplementation. More over, even at doses as high as 1,200 mg/m², none of these toxicities were dose-limiting. There was a partial response in one patient with metastatic colon cancer.

**Single-Agent Pemetrexed Without Vitamin Supplementation: Phase II Studies**

Two phase II single-agent studies of pemetrexed were conducted in previously untreated patients with NSCLC before the vitamin supplementation requirement: one in Canada and the other in Australia and South Africa. Prophylactic dexamethasone was not uniformly used in either study. The study done in Canada enrolled 33 patients.[34] The starting pemetrexed dose was reduced from 600 to 500 mg/m² once every 21 days after three patients had enrolled, because of excessive toxicities in these patients. Grade 3/4 hematologic toxicities were as follows: neutropenia, 39%; febrile neutropenia, 12%; anemia, 9%; and thrombocytopenia, 3%. Grade 3 nonhematologic toxicities (there were no grade 4 toxicities) were 39% for skin rash and 27% for fatigue. The incidences of anorexia, nausea, vomiting, diarrhea, and increased bilirubin or aspartate aminotransferase (AST) levels were all 9% to 12%. Grade 3 skin rash was seen in 47.5% of patients not treated with dexamethasone and 12% of patients who received dexamethasone prophylaxis. Response rate was 23.3%, median overall survival was 9.6 months, and the 1-year survival rate was 25.3%. The study authored by Clarke et al done in Australia and South Africa used 600 mg/m² of pemetrexed once
every 21 days throughout the study.[35] A total of 59 patients received therapy. Response rate was 15.8%, median time to progression was 4.4 months, median survival was 7.2 months, and the 1-year survival rate was 32%. Grade 3/4 hematologic toxicities included neutropenia (42%), anemia (10%), and thrombocytopenia (5%), and grade 3/4 nonhematologic toxicities were skin rash (31%) that improved after dexamethasone prophylaxis was introduced, fatigue (5%), nausea (14%), vomiting (9%), infection/fever (5%), diarrhea (3%), and stomatitis (5%). Grade 3/4 asymptomatic reversible hepatic enzyme elevation, which was seen in 24% of patients, did not require dose reduction or delay (see Tables 3 and 4).[25,26,34-42]

Single-Agent Pemetrexed in Previously Treated Patients With and Without Vitamin Supplementation: Phase II and III Studies

There have been two studies of single-agent pemetrexed for previously treated NSCLC: a phase II single-arm study by Smit et al.[43] and a phase III study comparing pemetrexed with docetaxel reported by Hanna et al.[26] In both studies pemetrexed was dosed at 500 mg/m$^2$ every 21 days. The phase II study did not include vitamin supplementation; the phase III study did. In both studies, all patients received premedication with dexamethasone to reduce rash. Of 81 advanced NSCLC patients who progressed within 3 months of their last chemotherapy in the phase II study, the response rate was 8.9%, median time to progression was 2 months, and median overall survival was 5.7 months. Grade 3/4 hematologic toxicities were neutropenia in 35% of patients, anemia in 13%, and thrombocytopenia in 15%; grade 3/4 nonhematologic toxicities were skin rash in 5%, lethargy in 5%, nausea in 1%, vomiting in 3%, aminotransferase level elevation in 6%, and alkaline phosphatase level elevation in 1%. There was greatly decreased skin toxicity with dexamethasone premedication even as compared with the studies mentioned earlier that did not routinely use dexamethasone. Four deaths on the study were possibly treatment related. In the study by Hanna et al.[26] patients were randomized to receive pemetrexed at 500 mg/m$^2$ (n = 283) or docetaxel at 75 mg/m$^2$ (n = 288) once every 21 days. There were nearly overlapping response rates, times to progression, and median survival times (Table 4). However, on the pemetrexed arm, there was significantly less grade 3/4 neutropenia, febrile neutropenia, hospitalization for febrile neutropenia, hospitalization for adverse events, and alopecia, but significantly more transient elevation of alanine aminotransferase levels.

Pemetrexed Plus Cisplatin Without Vitamin Supplementation

In a phase I trial by Thodtmann et al, pemetrexed at 500 mg/m$^2$ and cisplatin at 75 mg/m$^2$ were tolerated on a schedule of once every 21 days.[43] It was conducted without vitamin supplementation but was premedicated with dexamethasone incidental to premedication of cisplatin. Responses were seen in patients with NSCLC, mesothelioma, colorectal cancer, and head and neck cancers. Neutropenia was the dose-limiting toxicity. Pemetrexed and cisplatin had no observed pharmacokinetic interaction. Two phase II studies in chemonaive NSCLC were conducted using pemetrexed at 500 mg/m$^2$ plus cisplatin at 75 mg/m$^2$ without vitamin premedication but with dexamethasone prophylaxis. Shepherd et al accrued 31 patients, with treatment resulting in a 46% response rate, a median survival of 8.9 months, and a 1-year survival rate of 49%.[36] Hematologic toxicities (grade 3/4) were neutropenia in 35% of patients, febrile neutropenia in 3%, anemia in 19%, and thrombocytopenia in 3%. Nonhematologic toxicities (grade 3/4) were fatigue in 26%, nausea in 3%, vomiting in 3%, diarrhea in 10%, and stomatitis in 3%. The response rate was 39% with a median time to progression of 6.3 months and median overall survival of 10.9 months in the 36-patient study by Manegold et al.[37] Hematologic toxicities (grade 3/4) were neutropenia in 59% of patients, anemia in 14%, and thrombocytopenia in 17%. Grade 3/4 nonhematologic toxicities were fatigue in 6% of patients, nausea/vomiting in 6%, diarrhea in 3%, and grade 3 bilirubin and AST level elevations in 3% each. The Shepherd and Manegold studies showed activity comparable to that of the most active regimens available.
Plus Carboplatin With Vitamin Supplementation

Two phase II studies of pemetrexed plus carboplatin completed accrual with preliminary data reported: one by Zinner et al.[38] and the other by Scagliotti et al.[39] Encouraging activity seen in the Manegold and Shepherd studies, the prevalence of carboplatin-based therapy, together with preliminary data showing better tolerability of pemetrexed in lung cancer with vitamin use without loss of efficacy, encouraged an updated look at the efficacy and toxicity of pemetrexed/ platinum doublets in first-line advanced NSCLC. Patients were treated with pemetrexed at 500 mg/m² and carboplatin to an area under the concentration- time curve (AUC) of 6, with vitamin and dexamethasone prophylaxis in both studies. This regimen was based on data obtained from the phase I mesothelioma trial (no vitamin prophylaxis) by Hughes et al.[44]
In the study by Zinner et al, 50 patients were accrued with a response rate of 28.8% (49 patients evaluable for response). The median time to progression was 4.8 months, and with a minimum follow-up of 11 months, the median overall survival time is estimated at 13.5 months and the 1-year survival rate is estimated at 55.8%. Patients could elect to receive > 6 cycles if they had no disease progression, although at the start of the study, the intended number was 6 cycles. The median number of chemotherapy cycles administered was 6 (range: 1 to > 15 cycles). Fifteen patients (30%) received ≥ 8 cycles (8 cycles, n = 6, 10 cycles, n = 2; 12 cycles, n = 4; 14 cycles, n = 2; 15 cycles, n = 1). Greater than 277 cycles were administered. Nonhematologic toxicity of grade ≥ 3 was experienced by three patients (6%); grade 3 diarrhea, neutropenic infection, and grade 3 fatigue all first occurred during the first six courses. Five patients had deep-vein thromboses or pulmonary emboli. Given the low rate of clotting in the multiple other single-agent and doublet pemetrexed studies, these are presumed not to be caused by this regimen. The absence of alopecia or neurosensory toxicities of grade > 1 is notable. Four patients had grade 4 hematologic toxicities (grade 3 toxicities not yet tabulated) first occurring during the first 6 courses, including one with neutropenia and two with anemia. In this randomized phase II study in previously untreated patients with advanced NSCLC reported by Scagliotti et al,[39] patients were treated with either pemetrexed plus carboplatin exactly as in the study of Zinner et al[38] or pemetrexed at 500 mg/m² plus oxaliplatin (Eloxatin) at 120 mg/m² on day 1 of each 21-day cycle. Of 80 patients, 39 patients were randomized to pemetrexed/carboplatin and 41 to pemetrexed/oxaliplatin. The response rate, median time to progression, and estimated median overall survival on the pemetrexed/carboplatin arm were 31.6%, 4.5 months, and 9.9 months respectively. On the pemetrexed/oxaliplatin arm, response rate, median time to progression, and estimated median overall survival were 26.8%, 4.9 months, and 9.3 months, respectively. Patients treated with pemetrexed/carboplatin had grade 3/4 hematologic toxicities including neutropenia (26%), thrombocytopenia (18%), and anemia (8%). Grade 3/4 nonhematologic toxicities were fatigue (8%) and stomatitis (3%). On the pemetrexed/oxaliplatin arm grade 3/4 hematologic toxicities were neutropenia (7%) thrombocytopenia (2%), and anemia (2%) and grade 3/4 nonhematologic toxicities were vomiting (7%), neuropathy (2%), diarrhea (2%), and hypersensitivity reactions (2%). Both these studies showed activity comparable to standard platinum doublets but with impressive tolerability, especially with pemetrexed plus carboplatin. The longer-than-expected survival seen in the study by Zinner et al may be accounted for by the large number of patients receiving at least second-line therapy upon progressing (76%), as compared to historical controls. The large number of cycles in 15 of the patients, at the very least, demonstrate impressive tolerability, though it is not clear from this study whether it offered benefit. Randomized trials are indicated. **Pemetrexed Combinations With Nonplatinum Agents** There have been three phase II studies of pemetrexed-based nonplatinum regimens used to treat NSCLC reported. Two involved pemetrexed/gemcitabine and the other pemetrexed/vinorelbine. In one study by Monnerat et al, gemcitabine at 1,250 mg/m² was given on days 1 and 8 with pemetrexed at 500 mg/m² following gemcitabine on day 8 of a 21-day cycle.[40] The administration of vitamins was introduced after 3 patients had completed treatment and while 10 patients were undergoing treatment, and all 60 patients received dexamethasone. The response, median progression-free survival, median overall survival, and 1-year survival rate were 17%, 4.9 months,
11.3 months, and 44%, respectively. Grade 3/4 hematologic toxicities were neutropenia (63%), anemia (12%), and thrombocytopenia (5%). Febrile neutropenia occurred in 15% of patients. Grade 3 fatigue occurred in 23% of patients. There was an impressive survival, but a lower- than-expected response rate that may be ascribed to dose reductions and delays. To further explore this, a phase II by Adjei et al was done looking at alternative schedules of gemcitabine at 1,250 mg/m² and pemetrexed at 500 mg/m².[41] None of the following three schedules were the same as in the Monnerat study[40]: (A) pemetrexed followed by gemcitabine on day 1, gemcitabine on day 8; (B) gemcitabine followed by pemetrexed on day 1, gemcitabine on day 8; and (C) gemcitabine on day 1, pemetrexed followed by gemcitabine on day 8 (which was the schedule used in the earlier study). Schedule B was stopped early because of low response at interim analysis. Patients on arm A had less severe toxicity than patients on arm C with ≥ grade 3 events: 86% vs 93% (grade 4 events: 40% vs 50%). Response on arm A was 29%, thereby meeting the protocol-defined efficacy criteria, whereas arm C with partial response of 17% did not. The authors recommend schedule A (pemetrexed followed by gemcitabine on day 1 and gemcitabine on day 8) for further study. The second nonplatinum regimen used pemetrexed at 500 mg/m² on day 1 and vinorelbine at 30 mg/m² on days 1 and 8 of a 21-day cycle with vitamin supplementation.[42] Among the 34 patients, response was 35%. Survival data were not reported. Toxicities included grade 4 neutropenia (44%), febrile neutropenia (11%), and one treatment-related death. Twenty-one percent of patients had grade 3/4 fatigue. This regimen has an activity similar to standard platinum doublets, but it may be more toxic than the carboplatin-containing regimen. **Discussion** Pemetrexed is approved by the FDA for use in combination with cisplatin in the treatment of malignant pleural mesothelioma; it was the first agent to show improved survival in this disease.[25] In second-line NSCLC it was equally effective, but had superior tolerability compared to docetaxel in the largest second-line NSCLC phase III study yet reported.[26] In addition, it showed activity similar to historical controls formed by third-generation agents in multiple phase II studies of pemetrexed alone or in combination. The phase III mesothelioma trial showed that the addition of vitamin prophylaxis improved the tolerability without evident negative effects on activity. The combination of pemetrexed with carboplatin, cisplatin, or oxaliplatin is effective and safe, with activity comparable to any of the standard third-generation platinum doublet regimens. Phase II studies of pemetrexed/cisplatin with dexamethasone plus vitamins, in particular, showed powerful efficacy combined with a low incidence of grade 3/4 hematologic and nonhematologic toxicities. The excellent tolerability is apparent when compared to historical controls (Table 1). This suggests that this regimen may offer important improvements over standard regimens, a conclusion that would be consistent with the phase III single-agent second-line experience. This is reinforced by the observation that there was minimal toxicity of pemetrexed/cisplatin in multiple courses beyond 6 seen in the study by Zinner et al[38]; however, whether courses beyond 4 or 6 offer any anticancer benefit will require other studies to determine. Pemetrexed is also a convenient regimen, requiring administration once every 21 days. Building on an earlier study looking at single-agent pemetrexed with folic acid,[33] there are phase I studies under way evaluating pemetrexed at doses of > 500 mg/m² in combination with both folate and vitamin B₁₂, given the increased tolerability without decrease in efficacy observed with such prophylaxis in other studies. Combinations of nonplatinum agents with gemcitabine and vinorelbine in phase II studies have shown activity similar to that of standard platinum-containing doublets but without improvement in the toxicity profile. A recent presentation of results from a study of three dosing schemes showed best tolerability and activity with pemetrexed followed by gemcitabine on day 1, gemcitabine on day 8, a schedule that was both more active and less toxic than the pemetrexed plus gemcitabine schedule evaluated in an earlier study. Further study will be required to clarify the activity and tolerability. Given the efficacy and minimal severe and long-lasting toxicities (notably neurotoxicity) of pemetrexed in combination with platinum agents, these regimens should be studied as part of multimodality therapy in earlier-stage disease. In the case of surgery, such considerations are of increased relevance given data presented at the annual meetings of the American Society of Clinical Oncology in 2003 and 2004 showing clear and substantial reduction in the hazard ratio in those receiving standard platinum-containing doublets as adjuvant therapy.[47-49] Indeed, given its excellent tolerability, pemetrexed regimens may enable better compliance as postsurgical adjuvant therapy, a condition critical to providing a best chance at eradicating microscopic postsurgical disease. Pemetrexed is being studied in combination with radiation because there is preclinical evidence that it is a radiosensitizer. Full therapeutic doses of pemetrexed can be combined with therapeutic doses of chest radiation therapy as shown in a phase I dose-escalation study presented by Vokes et al.[50] Pemetrexed plus carboplatin is being dose-escalated concurrently with chest radiation in another study that is presently under way. It is
also an attractive candidate for combination with other new agents given excellent efficacy and tolerability. Thus, in addition to combining it with other modalities, pemetrexed-based treatment should be considered as a chemotherapy platform upon which to add novel therapy. Randomized trials comparing pemetrexed doublets to other doublets are also indicated.

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