

Pemetrexed plus Cetuximab in Patients with Recurrent Non-small Cell Lung Cancer (NSCLC)

A Phase I/II Study from the Hoosier Oncology Group

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Purpose: Pemetrexed is a standard treatment against recurrent non-small cell lung cancer (NSCLC), and cetuximab has single-agent activity against NSCLC. This study evaluates the safety and efficacy of the combination of these agents in patients with advanced NSCLC.

Patients and Methods: Patients with recurrent NSCLC and an Eastern Cooperative Oncology Group performance status of 0 to 1 were entered. Patients on the phase I portion of the study received cetuximab 400 mg/m² intravenously (IV) on day -7 followed by weekly doses of cetuximab at 250 mg/m² IV with escalating doses of pemetrexed every 3 weeks (dose levels: 500, 600, 750, 900 mg/m²) in a standard 3 + 3 design. Once the maximum tolerated dose (MTD) of the combination was determined, patients were enrolled on the phase II portion. The primary end point was to determine the median time to disease progression (TTP) (null hypothesis 12 weeks, alternative hypothesis 24 weeks).

Results: Thirty-six patients were enrolled (phase I: $n = 13$, phase II: $n = 23$). Patient characteristics included 60.6% men, median age 64 years (range, 37–80 years), 57.6% had performance status 0 and 54.6% had adenocarcinoma histology. The median number of previous regimens was 2 (range, 1–6). The maximum tolerated dose of pemetrexed in combination with cetuximab was determined to be 750 mg/m². The median TTP was 14.6 weeks. The median survival time was 42 weeks and 1-year survival was 38.5%.

Conclusion: The combination of pemetrexed at 750 mg/m² every 21 days with weekly cetuximab at 250 mg/m² was feasible; however, in this unselected patient population, the combination regimen does not seem to improve TTP compared with historical controls of either single agent.

Key Words: Recurrent non-small cell, Pemetrexed, Cetuximab.

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The treatment of patients with metastatic non-small cell lung cancer (NSCLC) remains challenging. Although a majority of patients with a good performance status (PS) achieve temporary disease control with initial therapy, cancer progression is universal. The success of achieving subsequent disease control is diminished possibly because chemotherapy-resistant clones become a more dominant cell population within the tumor. There are only three agents approved by the Food and Drug Administration for treating patients beyond first-line therapy. Pemetrexed,¹ docetaxel,² and erlotinib³ are each approved in the second-line setting, and erlotinib is also approved in the third-line setting. Each has modest single-agent activity (response rate, <10%) and results in an improvement in median survival of only 2 to 3 months.

The initial phase I and II studies of pemetrexed were conducted without vitamin B₁₂ and folate supplementation and identified the maximum tolerated dose (MTD) to be 500 to 600 mg/m².^{4,5} The addition of these vitamins results in significantly reduced toxicity without apparent loss of efficacy.^{6,7} Subsequent trials have identified the MTD of pemetrexed when given with vitamin supplementations to be 900 to 1000 mg/m².^{8,9} At the time of this study, the efficacy of escalated doses of pemetrexed against NSCLC was unknown.

Cetuximab (C225, Erbitux, BMS) is a chimeric monoclonal antibody that targets the epidermal growth factor receptor (EGFR),¹⁰ which is overexpressed in most patients with NSCLC.¹¹ Through blocking ligand binding to EGFR, cetuximab leads to a decrease in receptor dimerization, autophosphorylation, and activation of signaling pathways.¹² In a phase II trial, evaluating cetuximab in patients with relapsed NSCLC, the

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response rate was 4.5%, stable disease was seen in 30.3% of patients, and median survival time (MST) was 8.9 months.¹³

Therefore, we conducted this trial to evaluate the feasibility of combining higher doses of pemetrexed with cetuximab in patients with recurrent NSCLC. Once a MTD was identified, additional patients were enrolled to estimate whether the combination may be superior to the activity of each agent individually in this therapeutically challenging patient population.

PATIENTS AND METHODS

Eligibility criteria included age more than or equal to 18 years, histologic or cytologic diagnosis of NSCLC (any histology), previous therapy with at least one platinum-containing regimen for either locally advanced or metastatic disease, Eastern Cooperative Oncology Group PS of 0 to 1, and measurable disease by RECIST group response criteria. Adequate hematologic (absolute neutrophil count $\geq 1500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$), renal (creatinine clearance ≥ 45 ml/min), and liver function at baseline (bilirubin \leq upper limit of normal, aspartate transaminase $\leq 1.5 \times$ upper limit of normal, alkaline phosphatase $\leq 5 \times$ upper limit of normal) were required. Patients with previous brain metastases were allowed if they had been adequately treated for their brain metastases and were asymptomatic and off steroids. Patients must not have received radiation or chemotherapy within 3 weeks of registration or any investigational drugs within 30 days of registration. Patients were excluded if they had serious concomitant systemic disorders or history of uncontrolled cardiac disease. They were also excluded if they had received previous therapy with pemetrexed or cetuximab, were pregnant, or breast-feeding. All patients provided written informed consent before enrolling on the study.

Pretreatment evaluation included history and physical examination, assessment of Eastern Cooperative Oncology Group PS, complete blood count with differential, and chemistry panel obtained within 14 days of registration, and a computed tomography scan of chest and upper abdomen obtained within 28 days of registration. Brain and bone imaging was obtained only if clinically indicated. Women of childbearing age must have a negative pregnancy test within 7 days of registration. Laboratory tests were repeated weekly (days 1, 8, and 15), and disease evaluation by computed tomography was repeated every other cycle.

Treatment Plan

All patients received a loading dose of cetuximab of 400 mg/m² intravenously (IV) over 120 minutes on day -7 followed by weekly doses of 250 mg/m² IV over 60 minutes. Patients were premedicated with 50 mg IV of diphenhydramine hydrochloride (or an equivalent antihistamine) 30 to 60 minutes before the first dose of cetuximab. All patients received folic acid, vitamin B₁₂, and dexamethasone per the label of pemetrexed. Pemetrexed was given starting day 1 of each 21 day cycle following cetuximab. Patients were treated with up to six cycles of pemetrexed and cetuximab and in the absence of disease progression were allowed to remain on weekly cetuximab until the time of progressive disease or toxicity.

Up to four dose levels of pemetrexed were to be evaluated (500, 600, 750, and 900 mg/m²) in a standard 3 +

3 design. Three patients were initially enrolled at dose level 1. If no patients experienced dose limiting toxicities (DLTs), three patients were enrolled at the next dose level. If one of three patients at any dose level experienced a DLT, three additional patients were enrolled at that dose level. If only one of six patients experienced a DLT, dose escalation was permitted. If two or more patients at any dose level experienced a DLT, then the previous dose was considered the MTD. The DLTs for the phase I trial would include any toxicity that required dose modifications or delays based on \geq grade 3 toxicities including hematologic toxicity, mucositis, diarrhea, and rash.

Once the MTD of pemetrexed in combination with cetuximab was determined, patients were subsequently entered onto the phase II portion of the trial and treated at the recommended dose.

Statistical Analysis

The primary objective of the phase I portion was to determine the MTD of the combination of pemetrexed and cetuximab in this patient population. Secondary objectives were to characterize the DLTs.

The primary end point of the phase II portion was to estimate the time to disease progression (TTP) of the combination. The secondary end points included estimation of clinical benefit rate (complete response plus partial response plus stable disease lasting at least 90 days), MST and to further characterize the toxicity profile of this regimen.

All phase I patients that were treated at the MTD were rolled over to the phase II portion when determining the efficacy analysis. The median TTP using historical controls is approximately 12 weeks. With a total number of 22 patients, 91% power, and $\alpha = 5\%$, this design could detect a doubling of the median TTP to 24 weeks. Anticipating a 10% lost-to-follow-up rate, the sample size for the phase II portion would be approximately 25 patients.

RESULTS

Between May 15, 2005 and May 22, 2006, 36 patients were enrolled onto the study (phase I: $n = 13$, phase II: $n = 23$). Baseline characteristics of phase I and phase II patients are summarized in Table 1.

In the phase I portion of the study, the DLTs identified included acneform rash, alanine aminotransferase elevation, febrile neutropenia, dizziness, and dyspnea. The MTD for pemetrexed was determined to be 750 mg/m² IV every 21 days when combined with cetuximab at 250 mg/m² administered IV on a weekly basis.

Treatment Administered

The median number of cycles administered on the phase I portion was 3 (range, 1–6). Nine patients tolerated treatment without dose modifications or delays of either pemetrexed or cetuximab. Three patients required dose modifications or delays of either pemetrexed or cetuximab (two of pemetrexed and one of cetuximab) because of toxicity.

Median number of cycles administered on the phase II portion was 4 (range, 1–34). Ten and 15 patients tolerated treatment with pemetrexed and cetuximab, respectively, with-

TABLE 1. Baseline Characteristics for Phase I/II Patients

Characteristics	Phase I Patients (n = 12)	Phase II Patients (n = 21)
Age, yr		
Median	63	66
Range	37–68	46–80
Sex		
Male	7 (58)	13 (62)
Female	5 (42)	8 (38)
ECOG PS		
0	8 (67)	11 (52.4)
1	4 (33)	10 (47.6)
Stage of disease		
III	0 (0)	2 (9.5)
IV	12 (100)	19 (90.5)
Tumor histology		
Adenocarcinoma	6 (50)	12 (57.1)
Squamous cell carcinoma	1 (8)	7 (33.3)
Large cell carcinoma	2 (17)	0 (0)
Non-small cell carcinoma (NOS)	3 (25)	2 (9.5)
Smoking history		
Current	2 (17)	4 (19.1)
Former	9 (75)	15 (71.4)
Never	1 (8)	2 (9.5)
Previous treatments		
1 Chemotherapy	9 (75)	17 (81)
2 Chemotherapy	2 (17)	3 (14.2)
>2 Chemotherapy	1 (8)	1 (4.8)
Previous targeted therapy	3 (25)	3 (14.2)
Previous radiotherapy	4 (33)	10 (47.6)
Median time since prior regimen, d	133	96
Median time since initial diagnosis to registration, d	387.5	282

Values in parenthesis are in percent.
ECOG PS, Eastern Cooperative Oncology Group performance status.

out dose modifications or delays. A total of nine patients required dose modifications (five of pemetrexed and four of cetuximab) because of toxicity. Three patients required dose modifications of pemetrexed because of intercurrent illness.

Three patients received maintenance cetuximab for 8, 9, and 34 cycles, respectively, after 6 cycles of the combination as allowed per study schema.

Efficacy

Efficacy data is based on 27 patients including six treated at the MTD of the phase I portion of the trial, and 21 patients treated on the phase II portion (two additional patients enrolled on the phase II portion were not considered in this evaluation as they withdrew consent before receiving any treatment). The median TTP was 14.6 weeks and 6 month TTP rate was 38.7% (Figure 1). The MST was 42 weeks, and 1-year survival rate was 38.5% (Figure 2). One complete response was observed in addition to two partial responses for an overall response rate of 11.1%. Fifteen additional patients achieved stable disease (57.7%). The clinical benefit rate (defined as complete responses, partial responses and stable disease lasting >90 days) was 69.2%.

Safety/Toxicity

Phase I and II toxicities occurring in 10% or more of patients are outlined in Table 2, respectively. No anaphylactic or infusion reactions were reported with either agent. Of note, hematologic toxicities were minimal. The most common toxicities were acne-like rash, fatigue, mucositis, and nausea.

DISCUSSION

The current study demonstrated the feasibility of combining pemetrexed up to 750 mg/m² IV every 3 weeks with cetuximab 250 mg/m² IV weekly in patients with recurrent NSCLC. Nevertheless, although the combination was generally well tolerated, efficacy outcomes were disappointing and failed to demonstrate improved TTP over historical controls with each single agent. To our knowledge, only one other study has evaluated the combination of cetuximab with chemother-

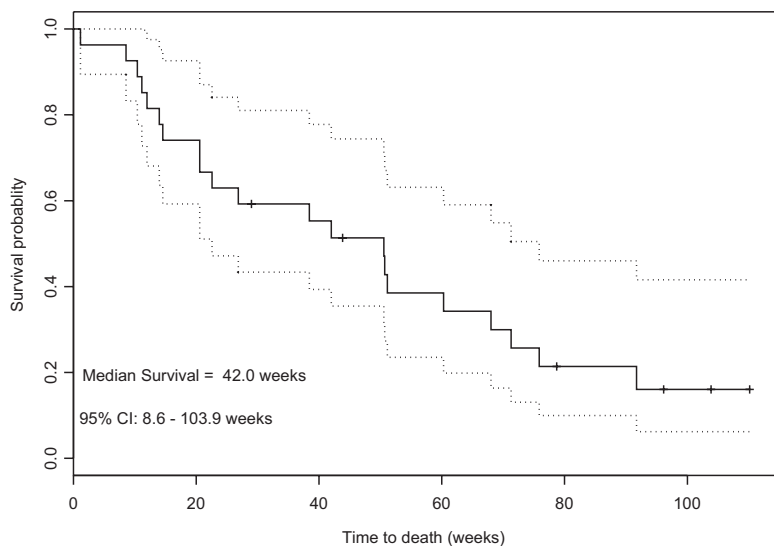


FIGURE 1. Kaplan-Meier curve for median survival in weeks (n = 27).

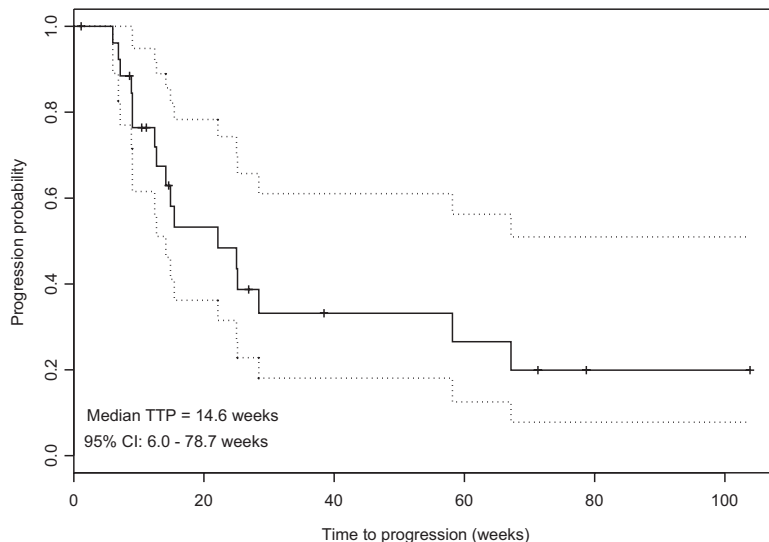


FIGURE 2. Kaplan-Meier curve for median time to disease progression (TTP) in weeks (n = 27).

TABLE 2. Phase I/II Toxicity

Toxicity	Phase I	Phase I	Phase II	Phase II
	(n = 12) Any Grade (%)	(n = 12) Grade 3/4 (%)	(n = 21) Any Grade (%)	(n = 21) Grade 3/4 (%)
Acne-like rash	58.3	16.7	57	23.8
ALT elevation	33.3	16.7	0	0
Hematologic				
Anemia	0	0	14.3	0
Thrombocytopenia	8.3	0	14.3	0
Neutropenia	8.3	0	4.8	4.8
Febrile neutropenia	8.3	8.3	0	0
Dizziness	8.3	8.3	19	4.8
Dyspnea	25	8.3	33.3	0
Cough	25	0	28.6	0
Fatigue	33.3	0	76	4.8
Anorexia	33.3	0	19	4.8
Mucositis	41.7	0	38	4.8
Nausea	33.3	0	28.6	0
Diarrhea	33.3	0	33.3	9.5
Constipation	16.7	0	23.8	4.8
Fever (no neutropenia)	8.3	0	19	4.8
Headache	50	0	23.8	0
Hypomagnesemia	0	0	19	4.8
Vomiting	16.7	0	23.8	4.8

ALT, alanine aminotransferase.

apy in patients with previously treated patients with NSCLC. Kim et al.¹⁴ combined cetuximab with docetaxel in 54 patients with advanced NSCLC who progressed or recurred within 3 months of first-line chemotherapy. Median TTP was 104 days and median overall survival was 7.5 months. The modest efficacy outcomes of these trials suggest that the addition of cetuximab in an unselected patient population in this setting is unlikely to result in significantly superior outcomes to single-agent therapy alone.

Because the completion of this trial additional information has emerged regarding the use of pemetrexed. Pemetrexed is now approved for use only in patients with nonsquamous histology based on both prospective and retrospective analyses from separate trials demonstrating significant superiority of pemetrexed in patients with nonsquamous histology.¹⁵⁻¹⁷ Second, two randomized trials have compared giving a standard dose of pemetrexed at 500 mg/m² versus a higher dose (900 or 1000 mg/m²) in the second-line setting.^{18,19} Neither of these trials demonstrated any therapeutic advantage to dose escalation of pemetrexed.

Similarly, additional information has been reported on cetuximab in the treatment of NSCLC. A phase III trial randomized untreated patients with EGFR detectable NSCLC to cisplatin and vinorelbine with or without cetuximab.²⁰ Response rates were modestly improved with the addition of cetuximab and median survival improved 1.2 months (HR, 0.87; *p* = 0.04). Similar benefits were seen in patients with squamous cell and adenocarcinoma. A smaller phase III trial compared carboplatin with a taxane (docetaxel or paclitaxel) with and without cetuximab.²¹ Response rates were slightly improved with cetuximab, but there was no difference in overall survival.

Recently Hirsch et al.²² reported that increased EGFR gene copy number detected by fluorescence in situ hybridization analysis may be predictive of improved disease control rate (81% versus 55%, *p* = 0.02) and median survival (*p* = 0.04) in patients with NSCLC treated with cetuximab and chemotherapy. Future studies will be evaluating cetuximab-based regimens in an enriched patient population evaluating for differential effects on EGFR FISH-positive and -negative patient populations. In addition, patients with metastatic colorectal cancer were more likely to benefit from cetuximab combined with chemotherapy if their tumors expressed kirsten rat sarcoma viral oncogene wild type compared with those with mutant type.²³ Similar efforts are underway to evaluate kirsten rat sarcoma viral oncogene as a molecular marker of cetuximab in NSCLC.

In conclusion, our study failed to demonstrate improved efficacy outcomes with the combination of pemetrexed and cetuximab in previously treated patients with advanced NSCLC. Future studies will involve enriched patient populations who are most likely to benefit from these agents.

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