Randomized Phase 2b Study of Pralatrexate Versus Erlotinib in Patients With Stage IIIB/IV Non–Small-Cell Lung Cancer (NSCLC) After Failure of Prior Platinum-Based Therapy

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Introduction: Pralatrexate, a folate analogue targeting dihydrofolate reductase, has antitumor activity in non–small-cell lung cancer (NSCLC). This randomized phase 2b trial was designed to further evaluate pralatrexate activity in NSCLC by estimating overall survival (OS) relative to erlotinib in patients with relapsed/refractory disease.

Methods: In 43 centers across 6 countries, patients were randomized 1:1 to receive intravenous pralatrexate 190 mg/m² on days 1 and 15 of a 28-day cycle, or oral erlotinib 150 mg/day. The primary objective was to estimate OS in all patients and prespecified subgroups using relative comparisons of hazard ratios (HRs). Secondary endpoints included progression-free survival, response rate, and safety. Key eligibility criteria included: (1) ≥1 prior platinum-based therapy, (2) Eastern Cooperative Oncology Group performance status of 0 to 1, and 3) a smoking history of 100 cigarettes or more.

Results: A total of 201 patients were randomized. A trend toward improvement in OS favoring pralatrexate was observed with an HR of 0.84 (95% confidence interval: 0.61–1.14) in the intent-to-treat population. This favorable survival result was seen in most prespecified subgroups for pralatrexate. The largest reduction in the risk of death was observed in patients with nonsquamous cell carcinoma (n = 107; HR = 0.65; 95% confidence interval: 0.42–1.0). The most common grade 3 to 4 adverse event in the pralatrexate arm was mucositis (23%). Discontinuation of pralatrexate for any grade of mucositis was 21%.

Conclusions: Pralatrexate demonstrated a trend toward improved survival relative to erlotinib in patients with advanced NSCLC. Future studies should include a mucositis management plan to improve tolerability and maximize treatment benefit.

Key Words: antifolate, non–small-cell lung cancer, pralatrexate, survival.

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The efficacy of first-line systemic therapy for advanced non–small-cell lung cancer (NSCLC) has improved during the past decade, with median overall survival (OS) ranging from 7 to 11 months in unselected patients, and 30 months for patients with epidermal growth factor receptor (EGFR) mutations; however, all patients will experience tumor progression.[1,2] In the United States, three agents are approved to treat patients after failure of first-line therapy: erlotinib, which may be administered as either second-line or third-line treatment, and docetaxel and pemetrexed, which are both indicated in second-line treatment.[3–5] Recently, the landscape for subsequent therapies has changed because of the broader indications for pemetrexed and erlotinib for use in the first-line setting. Pemetrexed is now frequently used in combination with platinum-based regimens as first-line treatment in patients with nonsquamous cell carcinoma, and erlotinib is the treatment of choice for patients with EGFR mutations.[6,7] Both pemetrexed and erlotinib may also be administered as maintenance therapy.[8,9] Thus, there is an urgent need for new active therapies in second-line treatment of patients with NSCLC.

Pralatrexate is a novel folate analogue that impedes folate metabolism by inhibiting dihydrofolate reductase.[10] In cell lines and animal models, pralatrexate demonstrated greater antitumor effects than pemetrexed or methotrexate.[11–14] This increased potency is caused by preferential uptake and internalization of pralatrexate by the reduced folate carrier-1 oncoprotein and increased accumulation in tumor cells through formation of polyglutamylated metabolites.[10] Pralatrexate has been granted accelerated approval in the United States for the treatment of relapsed or refractory peripheral T-cell lymphoma.

Initial studies of pralatrexate in NSCLC were performed without vitamin B_{12} and folic acid supplementation. The first phase 1 study, conducted in 33 previously treated patients, recommended a pralatrexate 150 mg/m^2 intravenous push every 2 weeks for future studies.[15] Mucositis was the dose-limiting toxicity. No significant myelosuppression was observed. Two patients had an objective response, and 6 patients had durable stable disease. In a phase 2 study in relapsed patients, 4 of 38 evaluable patients (11%) had a response and 12 patients (31%) had stable disease.[16] The median time to progression was 3 months, and median OS was 13.5 months. Grade 3 to 4 mucositis occurred in 20% of the patients. To minimize toxicity and evaluate dose escalation, a phase 1 study with vitamin supplementation was launched. Reversible mucositis was the most common and most severe adverse event (AE) but was manageable with proper oral care and dose modifications. Importantly, hematologic toxicity was infrequent, and the addition of vitamin supplementation allowed for the administration of higher doses. The recommended dose for future phase 2 studies was 190 mg/m^2 every 2 weeks. Four of 39 relapsed patients (10%) achieved an objective response, including 2 patients with a complete response lasting more than 2 years. The resulting disease control rate (complete response + partial response + stable disease for >2 months) was 51%. The consistent antitumor activity of pralatrexate in these studies warranted additional investigation of the drug in NSCLC.

Erlotinib is the first targeted therapy to prolong survival in patients with NSCLC. A randomized, controlled, phase 3 study conducted by the National Cancer Institute of Canada Clinical Trials Group (study BR.21) confirmed the benefit of erlotinib in all NSCLC histologic subtypes.[3] Though it is noted that there is still a chance (13%) of having EGFR mutation in patients with a smoking history, patients in BR.21 who were current or former smokers derived less of a benefit than lifetime nonsmokers, presumably because of an increase in activating EGFR mutations in the tumors of nonsmokers.[17] Thus, there is a need to develop more effective therapies for patients whose tumors harbor wild-type EGFR gene expression. Using smoking history as a surrogate for patients with wild-type EGFR tumors, this randomized phase 2b study (PDX-012) estimated OS in patients receiving pralatrexate relative to a known active agent, erlotinib.

MATERIALS AND METHODS

Eligibility

Eligible patients were 18 years of age or more with histologically or cytologically proven stage IIIB/IV NSCLC, and relapsed disease after 1 to 2 prior chemotherapy regimens. Patients must have previously received a platinum-based regimen and may have received pemetrexed. Only patients with a lifetime smoking history of 100 cigarettes or more were eligible. Additional criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, adequate hematologic, hepatic, and renal function, and no significant cardiac history or other active, uncontrolled diseases. Patients received 1 to 1.25 mg daily of folic acid for 7 days or more before randomization and 1 mg of vitamin B_{12} intramuscularly within 10 weeks of randomization. The study was approved by the institutional review boards of participating institutions and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to study entry.

Treatment Plan

Patients were randomized 1:1 to receive pralatrexate (FOLOTYN; Allos Therapeutics, Inc., Westminster, CO) or erlotinib (Tarceva; Genentech USA, Inc., South San Francisco, CA). All patients received folic acid daily and a vitamin B_{12} injection every 8 to 10 weeks. The original starting dose of pralatrexate was a 230 mg/m^2 intravenous push on days 1 and 15 of a 28-day cycle, based on interim results from the phase 1 study with vitamins. Because of the emergence of additional safety data at the biweekly dose of 230 mg/m^2, an amendment was made reducing the starting dose of pralatrexate to 190 mg/m^2 with the aim of improving tolerability and maintaining patients on treatment. Erlotinib 150 mg was administered by mouth daily for 28-day cycles. Patients were treated until progressive disease, unmanageable toxicities, or withdrawal of consent.

Dose Modifications

AEs were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. For patients receiving pralatrexate at a starting dose of 190 mg/m^2, 1 dose reduction to 150 mg/m^2 was allowed for any grade 3/4 AE; no further dose reduction was allowed. For patients who developed mucositis, it must have been completely resolved by the day of treatment; if not, treatment was delayed. For mucositis of grade 2 or higher, the patient was to have 1 dose reduction but to discontinue treatment upon recurrence. A maximum delay of 4 weeks for any AE of grade 2 or higher could elapse between treatments; if 4 weeks or more had passed, the patient was discontinued from treatment. For patients receiving the starting pralatrexate dose of 190 mg/m^2, the dose could be escalated to 230 mg/m^2 if, after 2 doses, no hematologic toxicity or mucositis of grade 1 or higher occurred, or if no treatment-related nonhematologic AEs of grade 2 or higher were observed. Dose modifications for patients on erlotinib adhered to the local erlotinib (Tarceva) package insert.[18]

Evaluations

All patients had a pretreatment history and physical examination including ECOG performance status and smoking history, complete blood work, and computed tomography or positron-emission tomography/computed tomography at baseline. All patients underwent a physical examination, safety assessment, and complete blood work on days 1 and 15 of every cycle (± 2 days for the erlotinib arm). Tumor response by

the Response Evaluation Criteria in Solid Tumors was assessed at fixed intervals for both arms every 2 cycles (8 weeks) using the same radiographic means as those used at baseline.

Statistical Considerations

OS was selected as the primary efficacy endpoint of this study because it is a relevant endpoint for patients with advanced-stage NSCLC suffering from progressing disease. Our objective was to estimate OS using the hazard ratio (HR) for pralatrexate in relation to an active control arm treated with erlotinib. Secondary endpoints included progression-free survival (PFS) and objective response rate by investigator assessment, and safety. Degree of smoking was the one stratification factor included in the study. Light smokers were defined as patients having smoked 100 cigarettes or more in a lifetime or 15 pack-years or less, and heavy smokers were defined as having 15 pack-years or more of smoking. Analysis populations included the intent-to-treat (ITT) population, which included all randomized patients, the primary efficacy population (all patients randomized after amendment of the pralatrexate starting dose to 190 mg/m^2), and prespecified subgroups. The overall population, including the prespecified subgroups, was not powered to detect a statistically significant difference in OS. The stratified Cox model was used to estimate the HR for the treatment effect with respect to OS (using the randomization stratification factors) and to produce a 95% confidence interval (CI) for the HR.

The relationship of several prespecified covariates, such as smoking status, smoking history, sex, histology, ECOG performance status, response to prior therapy, use of prior pemetrexed, number of previous lines of therapy, stage of disease at time of enrollment, weight loss in the previous 6 months before randomization (<5% versus ≥5%), and age at study enrollment (<65 years versus ≥65 years), to OS time, PFS time, and response rate was explored using a logistic regression model for tumor response rate and Cox proportional hazards regression models for time-to-event endpoints.[19]

This phase 2b study was designed to determine if a larger phase 3 study should be conducted. A desirable, clinically meaningful outcome in this disease setting would be a 31% reduction in the risk of death, which is equivalent to an HR of 0.69. Approximately 450 deaths would allow for a 95% CI that would discriminate between an HR of 1 and an HR of 0.69, and would therefore be a reasonably sized phase 3 study. The sample size of 160 patients (or 120 deaths) was based on the Fleming and Richardson methodology that randomized phase 2b studies with time-to-event endpoints should target one-quarter to one-third of the number of events that would be planned for a phase 3 study.[20] To analyze 160 patients at the amended pralatrexate starting dose of 190 mg/m^2, an additional 40 patients were randomized.

RESULTS

From January 2008 to July 2009, a total of 201 patients were randomized to receive treatment with pralatrexate (n = 100) or erlotinib (n = 101). Patient characteristics are displayed in Table 1. Baseline demographics were similar between the 2 arms with the exception of histology; more patients with nonsquamous histology were randomized to the pralatrexate arm (61% pralatrexate versus 46% erlotinib), and more patients with squamous histology were randomized to the erlotinib arm (29% pralatrexate versus 47% erlotinib). More patients receiving pralatrexate had an ECOG performance status of 0, and the median time from initial diagnosis to randomization was longer in the pralatrexate arm. The majority of patients in both arms were white males in their mid-sixties with a history of former, heavy smoking. Prior pemetrexed use was low in both arms. All patients, except three in the pralatrexate arm, received study treatment. The median number of 28-day cycles delivered was two (range, 1–22) for pralatrexate and three (range, 1–23) for erlotinib.

TABLE 1. Baseline Patient Characteristics

Parameter (n)	Pralatrexate (N = 100)	Erlotinib (N = 101)
Median age (y)	63	62
Range	40–85	35–82
Male/female	69/31	68/33
White/other	74/26	78/23
Nonsquamous histology	61	46
Squamous histology	29	47
Other/NOS histology	10	8
ECOG PS 0	32	22
Stage IV disease	87	84
Prior NSCLC regimens (½)	65/32	64/35
Prior pemetrexed use	18	12
Median time from initial diagnosis to randomization (mo)	12	10
Current/former smoker[a]	24/76	26/75
Light/heavy smoker[b]	20/80	17/84

[a]Former smoker defined as a patient who quit smoking any time before study start.
[b]Light smoker defined as having 100 lifetime cigarettes or more or 15 pack-years or less; heavy smoker defined as having 15 pack-years or more of smoking.
ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PS, performance status.

Efficacy

OS in the ITT population (N = 201) favored the pralatrexate arm, with an HR of 0.84 (95% CI: 0.61–1.14; Fig. 1*A*). The 1-year survival estimate was 28% for pralatrexate compared with 18% for erlotinib, whereas the median OS was 6.7 months for pralatrexate and 7 months for erlotinib. OS for the primary efficacy population (N = 166) mirrored the ITT survival curve with a favorable survival for pralatrexate (HR = 0.87; 95% CI: 0.62–1.23; Fig. 1*B*). As with the ITT population, the 1-year survival estimate was higher at 27% for pralatrexate compared with 17% for erlotinib. Median survivals for pralatrexate and erlotinib were 6.7 and 7.2 months, respectively. Median PFS in the ITT population was numerically longer for patients receiving pralatrexate (3.4 months) than for those receiving erlotinib (2.8 months). The HR for PFS was 0.91 (95% CI: 0.63–1.32) for the ITT population and 0.93 (95% CI: 0.61–1.40) for the primary efficacy population. The objective response rate for all treated patients was 2% for pralatrexate and 7% for erlotinib. The disease control rate for

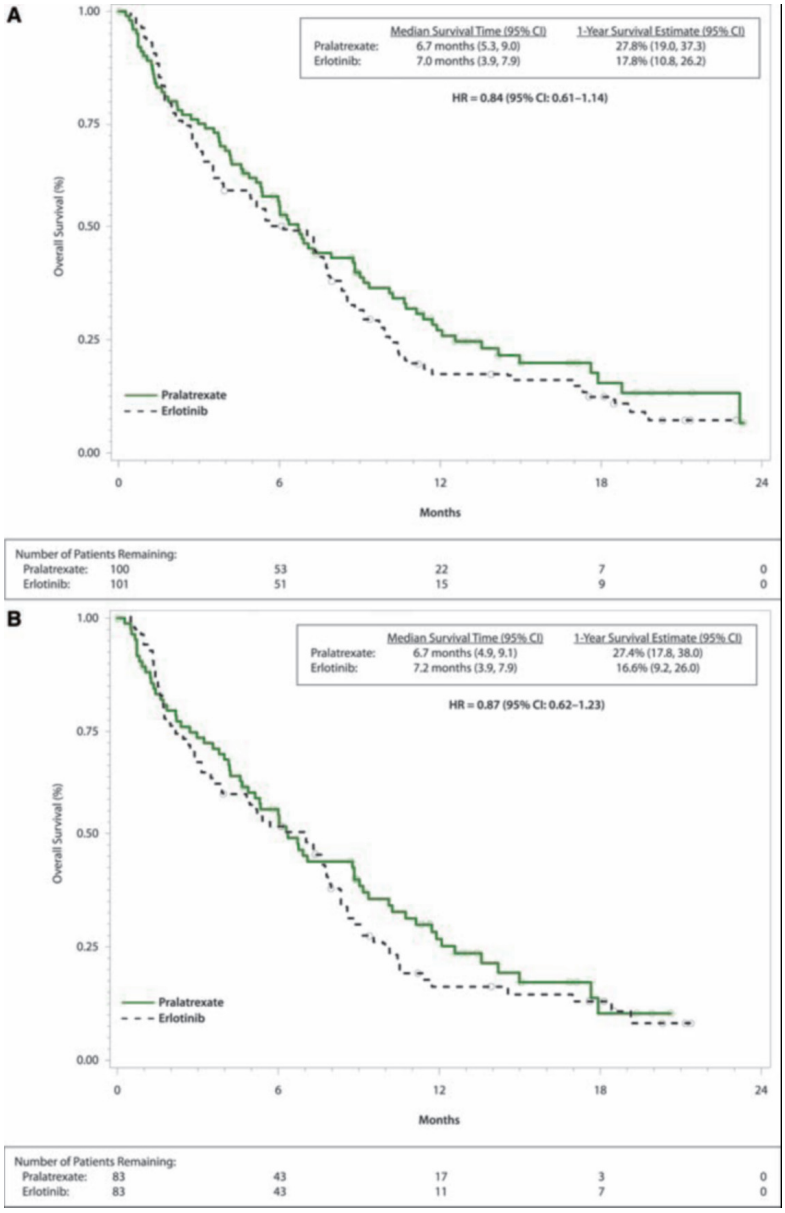

FIGURE 1. Kaplan-Meier estimate of overall survival based on (*A*) the intent-to-treat population of 100 patients randomized to the pralatrexate arm and 101 patients randomized to the erlotinib arm and (*B*) the primary efficacy population of 166 patients (n = 83 in each arm). CI, confidence interval; HR, hazard ratio.

the pralatrexate and erlotinib arms in all patients with baseline measurable disease was 36% and 43%, respectively. Patients with measurable disease and on-study response assessment(s) had a disease control rate of 53% and 54%, respectively.

In the exploratory analysis of prespecified subgroups, OS favored pralatrexate (Fig. 2). The largest benefit was seen in the patients with nonsquamous cell carcinoma (n = 107), with an HR of 0.65 (95% CI: 0.42–1.00). In this subset of patients, the median OS and 1-year survival estimates were 6.9 months and 30% for the pralatrexate arm and 6.3 months and 8% for the erlotinib arm, respectively (Fig. 3*A*). Median PFS for patients with nonsquamous cell carcinoma was 3.5 months for patients receiving pralatrexate and 2.1 months for patients receiving erlotinib, with an HR of 0.58 (95% CI: 0.35–0.96; Fig. 3*B*). Of note, 25% of patients with nonsquamous cell carcinoma in the pralatrexate arm had received prior pemetrexed. Patients with squamous cell histology had an HR of 1.06 (95% CI: 0.64–1.77), suggesting comparable efficacy between pralatrexate and erlotinib.

Subsequent systemic therapy was administered in 41 patients (41%) receiving pralatrexate, with 28 patients (28%) receiving erlotinib and 10 patients (10%) receiving another single-agent chemotherapy. A total of 32 patients (32%) receiving erlotinib went on to receive systemic therapy, with 30 patients (30%) receiving single-agent or combination chemotherapy. In the patients with nonsquamous NSCLC, the arms were balanced with respect to subsequent systemic therapy (pralatrexate, 36%; erlotinib, 35%). In this subgroup,

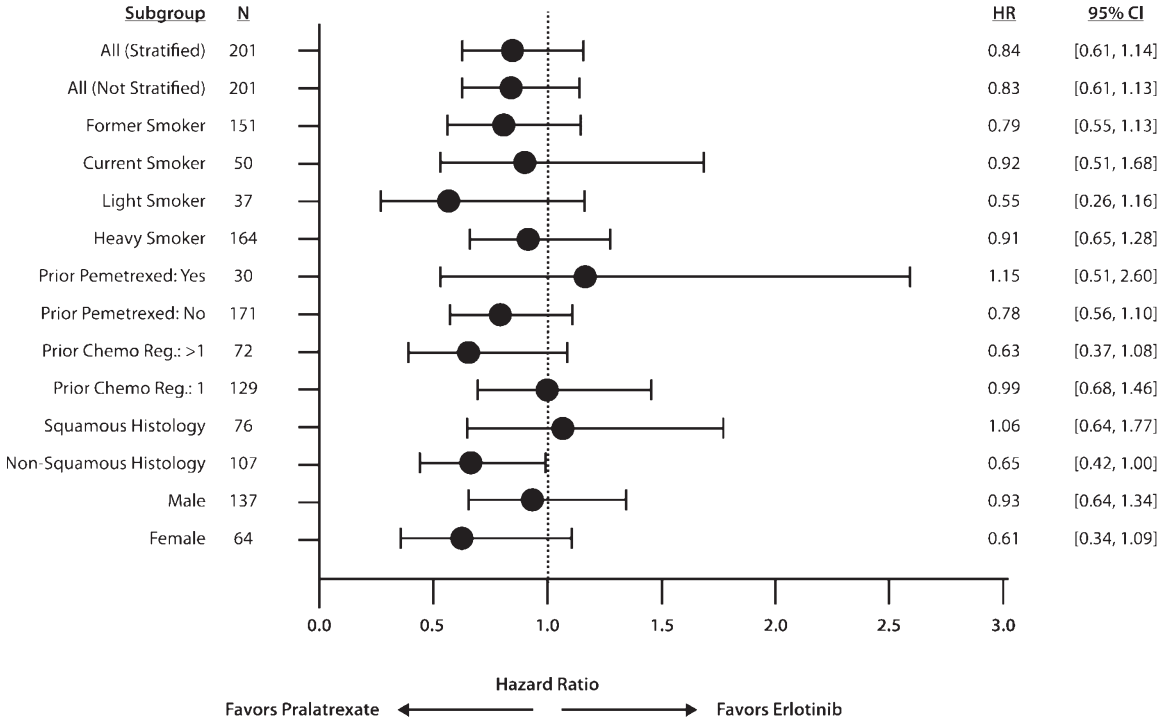

FIGURE 2. Forest plot of the treatment effect on overall survival by subgroups in the intent-to-treat population of 100 patients randomized to the pralatrexate arm and 101 patients randomized to the erlotinib arm. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; Reg, regimen.

25% of patients in the pralatrexate arm received subsequent erlotinib and 20% of patients in the erlotinib arm received pemetrexed.

Toxicity

Among the 97 patients who received treatment in the pralatrexate arm, mucositis (particularly stomatitis) was the most frequent and most serious AE, with fatigue as the next most common (Table 2). Of note, 6 patients in the pralatrexate arm had their dose increased, per protocol, to 230 mg/m^2 in cycle 2 (from an initial dose of 190 mg/m^2); four of these patients experienced either grade 1 or 2 oral mucositis (grade 1, n = 3; grade 2, n = 1). As expected, rash and diarrhea were the most common AEs in the erlotinib arm. Hematologic AEs were modest in both groups, and AEs of grade 3 or higher were infrequent. AEs resulted in a 33% discontinuation rate for patients receiving pralatrexate compared with 10% for patients treated with erlotinib. Of the patients who discontinued because of AEs in the pralatrexate arm, 63% were because of mucositis, with many patients discontinuing pralatrexate before their first scheduled response assessment. Overall, 40% of patients receiving pralatrexate and 16% of those receiving erlotinib discontinued treatment in the first 30 days. The rate of discontinuation for progressive disease within the first 30 days was similar between treatment groups (pralatrexate, 13%; erlotinib, 11%). Treatment-related serious AEs were also higher in the pralatrexate arm at 14% compared with 2% for erlotinib. Three treatment-related deaths (3%) occurred in the pralatrexate arm; two deaths were associated with complications from myelosuppression thought to be related to pralatrexate, and one patient died because of respiratory complications thought to be caused by underlying disease but conservatively coded as possibly related to pralatrexate.

DISCUSSION

Treatment options for patients with relapsed or refractory NSCLC have diminished in recent years, mostly because of the increasing use of pemetrexed and erlotinib in the first-line setting. Moreover, research efforts focusing on combination regimens in the second-line setting have also been unsuccessful. This presents an ideal opportunity to evaluate novel agents for second-line therapy. Pralatrexate is a novel antifolate selected for further evaluation in NSCLC. Unlike pemetrexed, which is thought to primarily target thymidylate synthase, pralatrexate has been shown to target dihydrofolate reductase.[13] Furthermore, pralatrexate has documented consistent antitumor activity and a manageable toxicity profile in multiple phase 1 to 2 studies, including NSCLC.[15,16]

This randomized phase 2b study was designed to estimate OS in second-line treatment of NSCLC relative to erlotinib, an EGFR inhibitor approved for use in this setting. Although not statistically significant given the sample size, the primary endpoint of estimating OS showed a trend favoring patients who received pralatrexate, with a 16% reduction in

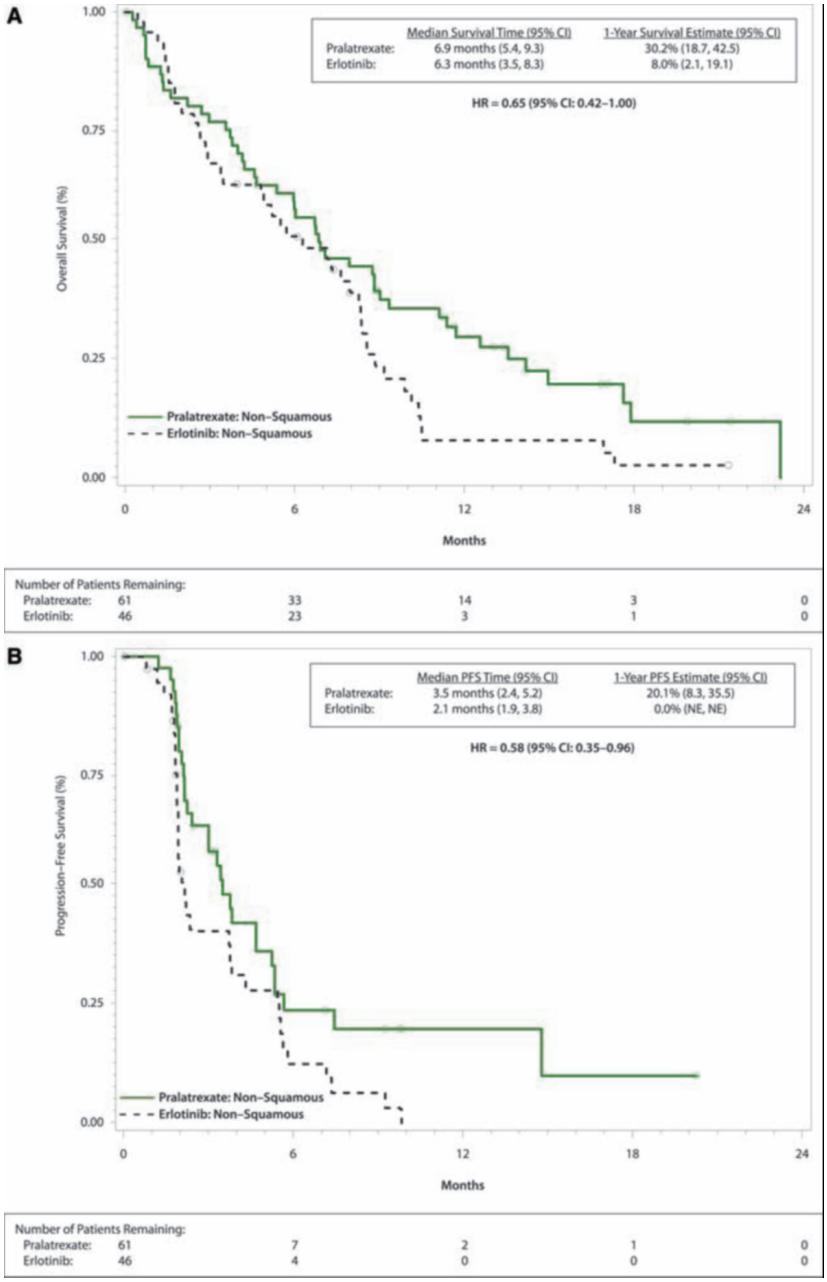

FIGURE 3. Kaplan-Meier estimate of (*A*) overall survival based on the patients with nonsquamous histology (pralatrexate arm, n = 61; erlotinib arm, n = 46) and (*B*) progression-free survival (PFS) based on the patients with nonsquamous histology (pralatrexate arm, n = 61; erlotinib arm, n = 46). CI, confidence interval; HR, hazard ratio; NE, not estimable.

the risk of death. There was also a trend toward prolonged survival in most prespecified subgroups. The greatest reduction in the risk of death was observed in the nonsquamous cell subset, where pralatrexate-treated patients had an HR of 0.65 (95% CI: 0.42–1.00) for death and an HR of 0.58 (95% CI: 0.35–0.96) for progression.

To assess the robustness of the OS results, a prespecified univariate survival analysis adjusting for histology and a prespecified multivariate survival analysis adjusting for 12 prespecified covariates were conducted, which resulted in HRs of 0.82 (95% CI: 0.58–1.14) and 0.73 (95% CI: 0.51–1.04), respectively, in favor of pralatrexate. Patients in the erlotinib arm performed in a similar manner to those in BR.21, a randomized study of erlotinib versus placebo.[3] In a subset analysis of BR.21, current and former smokers receiving erlotinib had a median OS of 5.5 months and a 1-year survival rate of approximately 25%. Post-study systemic therapy was not felt to have biased the survival data because less than one-half of the patients in either arm received erlotinib. In addition, the arms were well balanced for subsequent therapy in the patients with nonsquamous NSCLC, where the performance of pralatrexate relative to erlotinib was most clearly demonstrated.

The favorable survival data in the nonsquamous cell subset analysis raises the question of the role of EGFR

TABLE 2. Most Common (≥5% of Patients) Adverse Events

	Pralatrexate (N = 97)			Erlotinib (N = 101)		
Adverse Event, n (%)	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Nonhematologic adverse events						
Stomatitis	66 (68)	19 (20)	3 (3)	5 (5)	0 (0)	0 (0)
Fatigue	39 (40)	7 (7)	2 (2)	24 (24)	5 (5)	0 (0)
Dyspnea	12 (12)	4 (4)	2 (2)	23 (23)	8 (8)	0 (0)
Rash	16 (16)	1 (1)	0 (0)	64 (63)	8 (8)	0 (0)
Diarrhea	15 (15)	1 (1)	0 (0)	33 (33)	3 (3)	0 (0)
Hematologic adverse events						
Anemia	34 (35)	5 (5)	0 (0)	33 (33)	6 (6)	2 (2)
Thrombocytopenia	22 (23)	3 (3)	2 (2)	11 (11)	0 (0)	1 (1)
Neutropenia	18 (19)	4 (4)	2 (2)	5 (5)	1 (1)	1 (1)

mutational status. This study did not mandate tissue submission for EGFR mutation testing, and the number of voluntary samples acquired was too low to provide meaningful analyses. Although EGFR mutations can occur in patients with a smoking history, it is a relatively small percentage; therefore, it is unlikely that a significant imbalance in patients with EGFR mutations would have occurred between the arms. The similar survival rates for pralatrexate and erlotinib in patients with squamous cell carcinoma provide a potential rationale for further evaluation, as erlotinib is one of the few agents with previously demonstrated activity in this population, including smokers.[21] Only 30 of these patients had previously received pemetrexed, limiting the ability to draw conclusions regarding the activity of pralatrexate in this setting. However, 25% of patients with nonsquamous cell carcinoma receiving pralatrexate had received prior pemetrexed, and tumor reductions were observed in some of these patients, suggesting retention of activity in this patient group. With regard to the secondary efficacy endpoints, median PFS was numerically higher in the pralatrexate arm, but the response rate was lower than projected from earlier studies. One possible explanation for the lower-than-expected response rate in the pralatrexate arm was the high rate of early dropouts, mainly associated with mucositis, coupled with the conservative dose management plan employed.

Mucositis is the most common and most severe pralatrexate-associated toxicity. Mucositis-related treatment discontinuation was unexpectedly high in the pralatrexate arm, with a majority of patients stopping because of mucositis of grade 2 or higher. Several factors likely contributed to this high dropout rate, including a lack of familiarity with management of this specific toxicity in the NSCLC setting and limited ability allowed by the study protocol to adapt to the mucositis occurrence through use of dose delays and reductions, along with challenges administering pralatrexate on an every other week schedule because of the timing of onset and improvement or resolution of treatment-related toxicities. Mucositis is often a reversible and manageable toxicity, though we recognize that mucositis represents a significant barrier to the future development of pralatrexate in light of the well-tolerated toxicity profile of erlotinib. Physician and patient education, along with a management guideline and more liberal dose modifications, should significantly decrease the rate of discontinuation in future studies. Exploring the use of leucovorin along with pralatrexate administration and evaluation of alternative dosages and schedules should also be considered. Based on post-hoc analysis, patients who continued pralatrexate beyond 30 days had improved survival with an HR of 0.61 (95% CI: 0.42–0.90) and a median OS of 9.7 months compared with 6.8 months for patients treated with erlotinib. This suggests that there is potential for a greater efficacy result if pralatrexate dose exposure can be improved. Other toxicities associated with pralatrexate were infrequent. Noteworthy was the low rate of hematologic toxicity, which suggests that pralatrexate could be partnered with other cytotoxic and targeted agents.

In conclusion, this study confirmed the clinical activity of pralatrexate in the overall population and in prespecified subgroups by showing a trend towards improved OS in the pralatrexate group. Although mucositis was problematic in this study, efforts to improve tolerability and maintain efficacy are being developed, such as the use of leucovorin and evaluation of alternative dosages and schedules. The findings of this study demonstrate the need for larger randomized studies to validate the role of pralatrexate in NSCLC.

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