Pemetrexed with or without Matuzumab as Second-Line Treatment for Patients with Stage IIIB/IV Non-small Cell Lung Cancer

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Introduction: This randomized phase II study investigated pemetrexed in combination with the epidermal growth factor receptor (EGFR)-targeting monoclonal antibody matuzumab compared with pemetrexed alone as second-line therapy for patients with advanced non-small cell lung cancer.

Methods: Patients received pemetrexed 500 mg/m^2 every 3 weeks either alone ($n = 50$) or in combination with matuzumab at either 800 mg weekly ($n = 51$) or 1600 mg every 3 weeks ($n = 47$). The primary end point was objective response, as assessed by an independent review committee.

Results: Tumor EGFR expression was detected in 87% of randomized patients. The objective response rate for the pooled matuzumab-treated arms was 11% compared with 5% for pemetrexed alone ($p = 0.332$). Apart from one patient in the pemetrexed alone group, all responses occurred in patients whose tumors expressed EGFR. The objective response rate for patients receiving weekly matuzumab was 16% compared with 2% for those receiving matuzumab every 3 weeks. There was also a trend for improved overall survival in patients receiving matuzumab weekly versus every 3 weeks (12.4 months versus 5.9 months, respectively, versus 7.9 months for pemetrexed alone). The combination of pemetrexed and matuzumab demonstrated an acceptable safety profile, with the most common grade 3/4 adverse event being neutropenia.

Conclusion: Although the analysis on the pooled matuzumab-treated arms did not demonstrate a statistically significant improvement in objective response for the addition of matuzumab to pemetrexed compared with pemetrexed alone, the trends for improvement in objective response and overall survival for pemetrexed plus weekly matuzumab compared with pemetrexed alone warrant confirmation in additional clinical trials.

Key Words: Matuzumab, Pemetrexed, EGFR, NSCLC, Second-line, Humanized monoclonal antibody.

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The majority of patients with non-small cell lung cancer (NSCLC) have locally advanced or metastatic disease at presentation.[1] First-line chemotherapy for patients with good performance status generally comprises a platinum-based chemotherapy doublet, with different doublets delivering similar levels of efficacy.[2–4] The addition of certain monoclonal antibodies to first-line regimens has been shown in randomized studies to improve overall survival in this setting. Compared with chemotherapy alone, bevacizumab, specific for vascular endothelial growth factor, improved survival when combined with paclitaxel and carboplatin in patients with nonsquamous cell carcinoma (hazard ratio [HR]: 0.79; $p = 0.003$)[5,6] and cetuximab, specific for the epidermal growth factor receptor (EGFR), improved survival when combined with cisplatin and vinorelbine in a broad patient population unselected according to NSCLC histology (HR: 0.871; $p = 0.044$).[7]

After the failure of first-line treatment, second-line chemotherapy options include single-agent treatment with

docetaxel or the antifolate antimetabolite, pemetrexed.[8–10] The EGFR tyrosine kinase inhibitors (TKIs), erlotinib and gefitinib, are also effective as single agents in this setting.[11–13] EGFR is expressed by the majority of NSCLCs, and some tumors have an increased *EGFR* gene copy number.[14,15] *EGFR* is also somatically mutated in a subset of NSCLCs, with the presence in the tumor of an *EGFR* kinase domain activating mutation being both a favorable prognostic indicator for patients receiving chemotherapy and also a predictive marker for clinical benefit in relationship to EGFR TKIs.[16–19] Nevertheless, *EGFR* mutation status is not predictive for the efficacy of cetuximab in the first-line treatment of NSCLC.[20]

Clinical studies have, therefore, validated EGFR as an effective anticancer target in both the first- and second-line treatment of patients with NSCLC. Matuzumab (EMD 72000)[21] is a recombinant, humanized, immunoglobulin G1 monoclonal antibody, which interacts with the ligand-binding domain of EGFR, sterically preventing domain rearrangement and the local conformational changes required for high-affinity ligand binding and receptor dimerization.[22] In addition to blocking EGFR-associated downstream signaling,[23] matuzumab also induces an antitumor antibody-dependent cell-mediated cytotoxicity response.[24] Matuzumab has demonstrated in vivo activity against human tumor xenografts, both as a single agent and in combination with conventional chemotherapeutic compounds.[25–27]

Phase I studies established that matuzumab monotherapy was active and well tolerated at weekly doses of up to 1600 mg[28] and when administered in combination with paclitaxel[29] or gemcitabine,[30] at weekly doses of 800 mg. When given in combination, matuzumab did not aggravate the typical side effects of the cytotoxic agents. Pemetrexed is approved for the second-line treatment of advanced NSCLC and has established activity and safety profiles. Thus, the risk-benefit relationship for the combination of matuzumab and pemetrexed was regarded as favorable. This phase II study was, therefore, designed to investigate the activity and tolerability of pemetrexed plus matuzumab compared with pemetrexed alone in previously treated patients with NSCLC. To define the most appropriate dose and schedule for future studies, two dose groups for matuzumab (800 mg every week and 1600 mg every 3 weeks) were evaluated. The study was to be discontinued if new findings arose that indicated a relevant deterioration of the risk-benefit relationship.

PATIENTS AND METHODS

Key Eligibility Criteria

Patients aged 18 years or older, with a life expectancy >12 weeks, an Eastern Cooperative Oncology Group performance status of 0 or 1, and histologically or cytologically confirmed NSCLC that had progressed on or after first-line platinum-based chemotherapy for stage IIIB/IV disease were eligible. Patients had to have at least one measurable lesion according to modified World Health Organization criteria, and those with stage IIIB disease were required to have no clinically significant pleural effusion, unless that pleural effusion could be effectively drained before admission into the study. A chemotherapy-free interval of at least 3 weeks between the end of first-line chemotherapy and start of the study treatment had to have elapsed. The availability of a tissue or cytology sample for the determination of EGFR expression was a requirement, as was adequate organ function at baseline, as determined by serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN; in the case of borderline values, clearance had to be ≥ 45 ml/min); total bilirubin $< 1.5 \times$ ULN; alanine aminotransferase/aspartate aminotransferase $\leq 2.5 \times$ ULN (patients with liver metastases required alanine aminotransferase/aspartate aminotransferase $< 5 \times$ ULN); absolute neutrophil count $\geq 1500/mm^3$; platelet count $\geq 100{,}000/mm^3$; and hemoglobin ≥ 10 g/dl.

Patients were not eligible if they had participated in another clinical study within 30 days before the start of study treatment or received radiotherapy or major surgery within 30 days before the start of study treatment, had received prior treatment with EGFR-directed therapy or pemetrexed, or if they had a weight loss >10% within 12 weeks before the start of study treatment. They were also excluded if they were pregnant/lactating or had documented or symptomatic brain metastases, leptomeningeal disease, a preexisting ≥grade 2 skin disorder (except for alopecia), and a concurrent malignancy or invasive carcinoma diagnosed within the past 5 years (except for adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix) or if the patient had any disease that, in the investigator's opinion, should exclude them from the study. Patients should not have a history of significant cardiovascular, neurologic or psychiatric disorder, or autoimmune disease with significant organ involvement.

Study Design

This was an open-labeled, multicenter, randomized, controlled, phase II study with three parallel treatment groups. Patients were randomized centrally to receive pemetrexed alone (500 mg/m^2 intravenous [IV] infusion over 10 minutes, day 1, every 3 weeks) or in combination with matuzumab (as either an 800 mg IV infusion over 1 hour, once every week or a 1600 mg IV infusion over 1 hour, once every 3 weeks). An observation period of at least 1 hour was specified between the end of the matuzumab infusion and the start of pemetrexed administration when these treatments were given on the same day. Pemetrexed was administered with dexamethasone, 4 mg twice daily, orally, the day before, the day of, and the day after infusion; vitamin B12 administered by intramuscular injection, as one injection of 1000 μg during the week preceding the first dose of pemetrexed and every 9 weeks thereafter; and folic acid, as daily oral doses of 350 to 1000 μg, with at least 5 daily doses taken during the 7-day period preceding the first dose of pemetrexed and continuing daily throughout treatment, up to 21 days after the last dose of pemetrexed.

Treatment was continued until disease progression or the occurrence of unacceptable toxicity. If one treatment was stopped due to agent-related toxicity, patients in the combination therapy groups could continue to receive the other treatment as monotherapy. The study protocol was approved by independent ethics committees at each center, and the study was conducted in accordance with the principles established in the Declaration of Helsinki. All patients provided written, informed consent before screening.

The safety/intention to treat (ITT) population was defined as all patients who were randomized and received at least one infusion of study treatment. The per protocol (PP) population was defined as all patients who were randomized and received at least two cycles of study treatment (except in the case of death or disease progression, as determined by an independent review committee [IRC], in the first two cycles of treatment); who had a baseline tumor assessment and at least one postbaseline tumor assessment; and who had no major protocol violation.

The primary study objective was to evaluate tumor response (as assessed by the IRC) for two different regimens of matuzumab in combination with pemetrexed (analysis of pooled arms) in comparison with pemetrexed alone in patients in the PP population with stage IIIB/IV NSCLC. Secondary objectives were to assess tumor response as determined by the investigators; overall survival; progression-free survival (PFS); duration of response; safety and tolerability; and quality of life (QoL).

Study Assessments

Tumor response was evaluated according to the modified World Health Organization criteria by radiologic assessment every 6 weeks (±3 days) during study treatment, regardless of any treatment delays, until disease progression. Patients who stopped treatment before disease progression remained in the study and continued to be assessed radiologically for tumor response every 6 weeks. The IRC conducted a blinded radiologic review of the images of all patients to determine best overall response and response duration using criteria based on a separate charter. All images were reviewed by two IRC radiologists. If the reviews were not in accordance, a third radiologist decided tumor status. Toxicity was assessed at each chemotherapy visit (every 3 weeks) and weekly in the group receiving weekly matuzumab. Complete blood counts (including platelets and absolute neutrophil count) were assessed weekly while the patient was on pemetrexed. The Lung Cancer Symptom Scale was used to measure QoL in relationship to six major symptoms. The questionnaire was completed at baseline, at 6, 12, 24, 36, and 48 weeks after the start of treatment, and at the end of treatment visit. After the end of study visit (≥6 weeks after the last study treatment), survival data were collected every 3 months. Information on subsequent anticancer treatments was also collected up to the first follow-up visit.

EGFR expression was assessed (DakoCytomation pharmDx immunohistochemistry kit) by a pathologist at a central facility. Tumors that stained with an intensity >0 were scored as EGFR detectable.

Statistical Methods and Considerations

The primary target variable was the objective tumor response as assessed by the IRC. Assuming a response rate of 10% with pemetrexed alone and 31% in the pooled matuzumab treatment arms, it was calculated that 40 patients per arm would give a 70% power to detect an increase in the response rate from 10 to 31% at a two-sided alpha level of 0.05. Allowing for dropout rate of 20%, randomization (1:1:1) of 150 patients was planned.

Analyses of efficacy were performed for both the PP and safety/ITT populations, with the PP population being the primary analysis set. Fisher's exact test was performed between the pooled matuzumab and pemetrexed arms for the difference in responders. All analyses of safety and QoL were performed using the safety/ITT population.

For time-to-event variables, Kaplan-Meier curves[31] were drawn by treatment group to visualize the effect of the treatment. The HRs between treatments and their 95% CIs and associated *p* values were computed using a Cox-proportional hazards model with treatment as a factor. HRs are presented in each case as experimental versus control arm. Safety and tolerability were summarized descriptively, with adverse events (AEs) and laboratory data classified according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (version 3.0).

RESULTS

Patient Demographics

The first patient was enrolled on August 16, 2005. The data cutoff for survival analyses was July 16, 2007, which

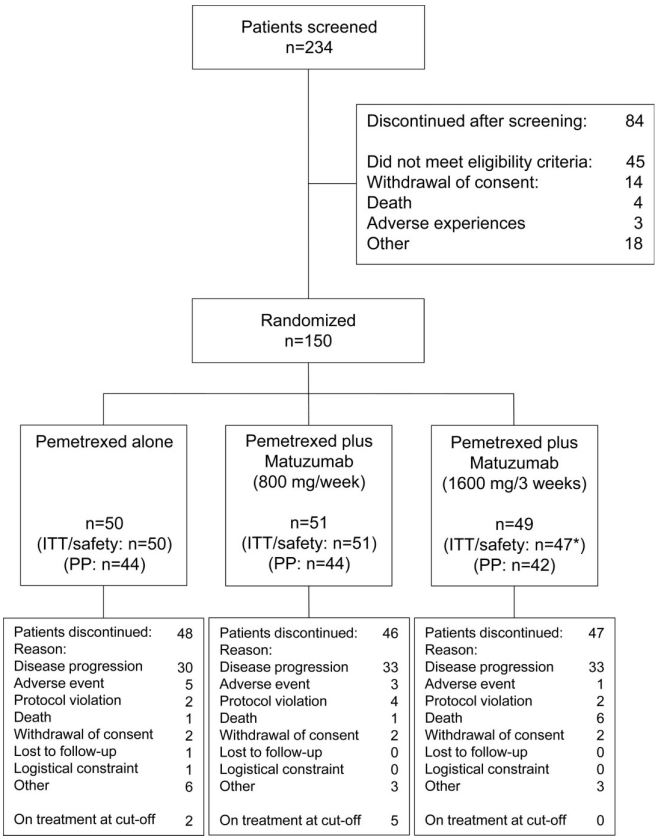

FIGURE 1. Consolidated Standards of Reporting Trials diagram: disposition of subjects at time of data cutoff (July 16, 2007). *Two patients did not receive any study treatment after randomization. One patient died after randomization and before first infusion, and one patient was withdrawn due to disease progression after randomization and before first infusion. ITT, intention to treat; PP, per protocol.

was 5 months after the last patient had entered the study. Of 234 patients from 46 centers who were initially screened, 150 were subsequently randomized to three treatment groups (Figure 1). After randomization, two patients in the pemetrexed plus matuzumab every 3 weeks group did not receive any study treatment and were, therefore, excluded from the safety/ITT population. The most frequent reason for treatment discontinuation during the study was disease progression (65% of patients). Baseline demographic and disease characteristics were broadly similar between the treatment groups, although a higher percentage of patients had adenocarcinoma and a lower percentage squamous cell carcinoma in the pemetrexed plus weekly matuzumab group compared with the other groups. EGFR expression was detected in the tumor tissue of 92% of patients who received pemetrexed alone, 92% of patients who received pemetrexed plus matuzumab weekly and 76% of patients who were randomized to receive pemetrexed plus matuzumab every 3 weeks (Table 1).

The PP population comprised a total of 130 patients, 44 who received pemetrexed alone, 44 who received pemetrexed plus matuzumab weekly, and 42 who received pemetrexed plus matuzumab every 3 weeks (Table 1).

TABLE 1. Patient and Disease Characteristics at Baseline in the Safety/ITT Population and Reasons for Exclusion from the Per Protocol Population

	Pemetrexed Alone, $n = 50$	Pemetrexed Plus Matuzumab (800 mg/wk), $n = 51$	Pemetrexed Plus Matuzumab (1600 mg/3 wk), $n = 47$
Ethnic origin, *n* (%)			
White	47 (94)	47 (92)	47 (100)
Black	3 (6)	4 (8)	0
Gender, *n* (%)			
Male	33 (66)	35 (69)	27 (57)
Female	17 (34)	16 (31)	20 (43)
Age (yr)			
Median	61	62	63
Range	37–83	48–81	46–78
Histology of primary, *n* (%)			
Adenocarcinoma	23 (46)	30 (59)	22 (47)
Squamous cell carcinoma	18 (36)	11 (22)	17 (36)
Undifferentiated carcinoma	3 (6)	3 (6)	0
Large cell carcinoma	1 (2)	2 (4)	2 (4)
Adenosquamous carcinoma	2 (4)	0	0
Other	3 (6)	5 (10)	6 (13)
Stage at study entry, *n* (%)			
IIIB	6 (12)	8 (16)	6 (13)
IV	44 (88)	42 (82)	41 (87)
Missing	0	1 (2)	0
EGFR expression status, *n* (%)[a,b]			
EGFR detectable	46 (92)	47 (92)	37 (76)
EGFR nondetectable	3 (6)	4 (8)	9 (18)
Not assessed	1 (2)	0	3 (6)
Prior therapy, *n* (%)			
First-line chemotherapy for advanced NSCLC	50 (100)	51 (100)	47 (100)
Prior best response = CR, PR, or SD	34 (68)	37 (73)	33 (70)
Prior nonresponse (PD)	16 (32)	14 (27)	14 (30)
Radiotherapy	19 (38)	25 (49)	29 (62)
Per protocol population, *n*			
No. of patients	44	44	42
Excluded ITT patients	6	7	5
Reasons for exclusion[c]			
Major protocol violation	1	2	3
<2 cycles of study treatment	6	6	2
No postbaseline assessment available[d]	4	4	1

[a] Randomized patients ($n = 49$ for group receiving pemetrexed and matuzumab every 3 wk).
[b] Each tumor sample that stained for EGFR with an intensity greater than zero, as evaluated by a pathologist at a central facility, was scored as EGFR detectable.
[c] More than one may apply.
[d] Except in the case of death or disease progression.
CR, complete response; EGFR, epidermal growth factor receptor; ITT, intention to treat; PD, progressive disease; PR, partial response; SD, stable disease.

Patients were excluded from the PP population (except in the case of death or PD) most frequently because they had received less than two cycles of study treatment (14 patients, 9%) and/or had not undergone any postbaseline assessment (nine patients, 6%). Six patients were excluded due to major protocol violations.

Treatment Exposure

Exposure to study treatment in the safety/ITT population is summarized in Table 2. More than 80% of patients in each of the study arms received two or more cycles of pemetrexed alone or pemetrexed in combination with matuzumab, with more than 20% of patients in each arm receiving six or more cycles of treatment. The median duration of pemetrexed treatment was 66.5 days for patients receiving pemetrexed alone and 42.0 and 46.0 days for patients receiving pemetrexed plus matuzumab administered weekly and every 3 weeks, respectively.

After the completion of study treatment, 19 patients (37%) in the pemetrexed plus weekly matuzumab group received further chemotherapy (any) and 10 patients (20%) continued with an anti-EGFR treatment comprising any EGFR TKI, compared with 10 (20%) and 15 patients (30%) in the pemetrexed alone group and 12 (26%) and five (11%) patients in the pemetrexed plus matuzumab every 3 weeks group, respectively (Table 2). There was, therefore, some degree of imbalance in poststudy therapy between the treatment groups.

Efficacy

In the primary IRC analysis on pooled matuzumab treatment arms, objective response rates for the PP population were higher in the combined group (weekly/every 3 weeks) of patients who received pemetrexed plus matuzumab compared with those who received pemetrexed alone ($n = 86$ versus $n = 44$; 11% versus 5%, respectively). Nevertheless, this difference was not statistically significant ($p = 0.332$). Rates of disease control were similar in the two groups (36% versus 41%, respectively). Considering the three individual treatment groups in the secondary analyses of the safety/ITT population (Table 3), objective response as assessed by the IRC was observed most frequently in patients receiving pemetrexed plus weekly matuzumab (16%) compared with those receiving pemetrexed alone (4%) or pemetrexed plus matuzumab administered every 3 weeks (2%). Rates of disease control were similar in the different treatment groups (33% versus 36% versus 34%, respectively). The same trend was observed for objective response based on investigator assessment.

Subgroup analyses revealed that tumor responses, all of which were partial, were confined to the group of patients who had responded to prior chemotherapy. Except for one patient in the pemetrexed alone group, all responses occurred in patients whose tumors were scored as EGFR detectable. Somatic *EGFR* coding sequence mutations were identified in the tumors of 4 of 69 patients (6%); none of these tumors had responded to treatment (data not shown, methods available on request).

TABLE 2. Exposure to Treatment in the Safety/ITT Population

	Pemetrexed Alone, $n = 50$	Pemetrexed Plus Matuzumab (800 mg/wk), $n = 51$	Pemetrexed Plus Matuzumab (1600 mg/3 wk), $n = 47$
Duration of pemetrexed treatment (d)			
Median	66.5	42.0	46.0
Range	21–385	21–260	21–253
Duration of matuzumab treatment (d)			
Median		43.0	46.0
Range		7–278	21–253
No. of entered pemetrexed cycles, *n* (%)			
≥1	50 (100)	51 (100)	47 (100)
≥2	41 (82)	42 (82)	40 (85)
≥4	24 (48)	20 (39)	19 (40)
≥6	12 (24)	14 (27)	10 (21)
≥8	7 (14)	6 (12)	2 (4)
No. of entered matuzumab cycles, *n* (%)			
≥1		51 (100)	47 (100)
≥2		42 (82)	40 (85)
≥4		21 (41)	18 (38)
≥6		15 (29)	12 (26)
≥8		9 (18)	3 (6)
Cumulative dose of pemetrexed, mg/m^2			
Median	1500.0	1000.0	1000.0
Range	500–9000	500–5500	500–6000
Cumulative dose of matuzumab (mg)			
Median		4800.0	3200.0
Range		800–30,400	1600–19,200
Poststudy anticancer therapy, *n* (%)			
Radiotherapy	2 (4)	3 (6)	1 (2)
Chemotherapy	10 (20)	19 (37)	12 (26)
EGFR TKI	15 (30)	10 (20)	5 (11)
Other	3 (6)	5 (10)	4 (9)

ITT, intention to treat; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

Median PFS time was similar for all three treatment groups (Figure 2*A*). Median overall survival time was 7.9 months (95% confidence interval [CI]: 7.2–9.9) for the pemetrexed alone group and 12.4 (95% CI: 8.8, not evaluable) and 5.9 (95% CI: 3.6–7.2) months for those receiving matuzumab weekly or every 3 weeks, respectively (Table 3, Figure 2*B*).

TABLE 3. Response Rate, Progression-Free Survival, and Overall Survival According to Treatment (Safety/ITT Population)

	Pemetrexed Alone, $n = 50$	Pemetrexed Plus Matuzumab (800 mg/wk), $n = 51$	Pemetrexed Plus Matuzumab (1600 mg/3 wk), $n = 47$
Best overall response,[a] *n* (%)			
Complete response	0	0	0
Partial response	2 (4)	8 (16)	1 (2)
Stable disease	16 (32)	9 (18)	15 (32)
Progressive disease	19 (38)	23 (45)	20 (43)
Not evaluable	13 (26)	11 (22)	11 (23)
Objective response rate,[b] *n* (%) [95% CI]	2 (4) [1–14]	8 (16) [7–29]	1 (2) [0–11]
Disease control rate,[c] *n* (%) [95% CI]	18 (36) [23–51]	17 (33) [21–48]	16 (34) [21–49]
Progression-free survival[a]			
No. of events	33	35	37
Hazard ratio[d] [95% CI]		0.96 [0.59–1.56]	1.46 [0.90–2.38]
Median (mo) [95% CI]	2.7 [1.6–4.4]	2.3 [1.5–3.8]	2.5 [1.4–2.9]
Overall survival			
No. of events	25	21	30
Hazard ratio[d] [95% CI]		0.67 [0.37–1.21]	1.66 [0.97–2.86]
Median (mo) [95% CI]	7.9 [7.2–9.9]	12.4 [8.8-NE]	5.9 [3.6–7.2]

[a] Independent review committee assessments.
[b] Complete responses + partial responses.
[c] Complete responses + partial responses + stable disease.
[d] Pemetrexed plus matuzumab versus pemetrexed alone.
CI, confidence interval; ITT, intention to treat; NE, not evaluable.

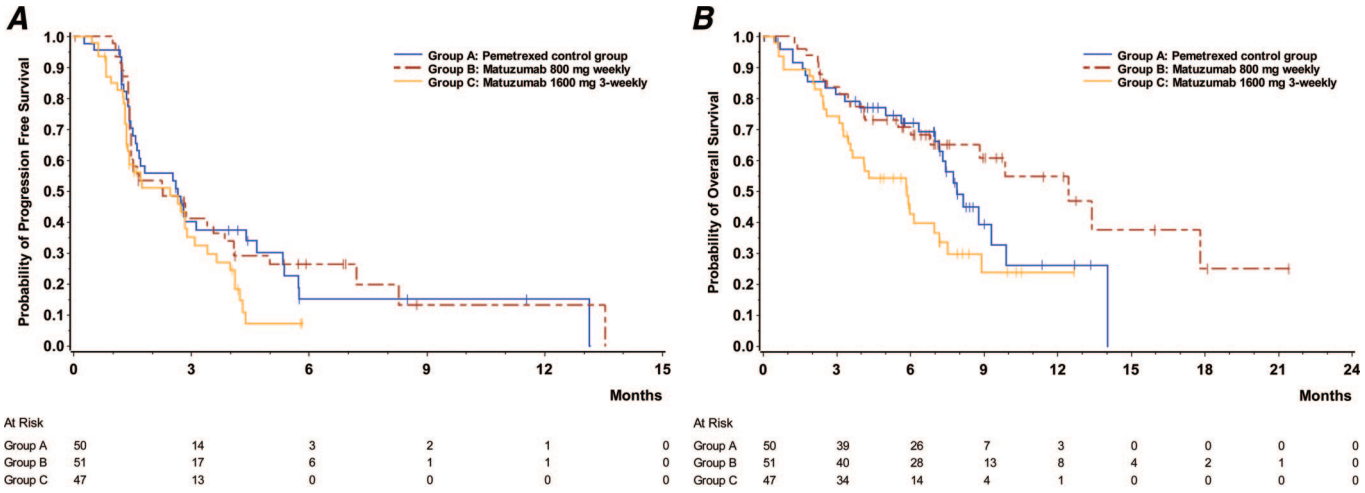

FIGURE 2. Survival analyses. Kaplan-Meier plots for progression-free survival (*A*) and overall survival (*B*) according to study arm. Group A received pemetrexed alone; group B, pemetrexed plus weekly matuzumab; and group C, pemetrexed plus matuzumab every 3 weeks.

Safety

Treatment-related rash (grade 1/2) was markedly more common in patients who received pemetrexed plus matuzumab weekly (37% of patients) or every 3 weeks (43% of patients; one patient grade 3) compared with those receiving pemetrexed alone (14% of patients). The incidence of grade 3/4 treatment-related AEs was broadly comparable between the three treatment groups (Table 4). The most common grade 3/4 treatment-related AE was neutropenia (16% of patients overall), reported for 22% of patients who received pemetrexed plus weekly matuzumab compared with 15% and 12% of those receiving pemetrexed plus matuzumab every 3 weeks or pemetrexed alone, respectively. Treatment-related fatigue and diarrhea were reported at grade 3/4, respectively, for one (2%) and no patients who received pemetrexed alone; four (8%) and one (2%) patient who received pemetrexed plus matuzumab weekly; and one (2%) and no patients who received pemetrexed plus matuzumab every 3 weeks. Nine patients discontinued treatment due to AEs. In four cases, these were deemed to be possibly related to matuzumab (or pemetrexed).

TABLE 4. Treatment-Related Grade 3/4 Adverse Events Experienced by ≥5% of Patients in Any Treatment Group According to Preferred Terms (Safety/ITT Population)

Preferred Term,[a] *n* (%)	Pemetrexed Alone, *n* = 50	Pemetrexed Plus Matuzumab (800 mg/wk), *n* = 51	Pemetrexed Plus Matuzumab (1600 mg/3 wk), *n* = 47
Any grade 3/4 adverse event	25 (50)	29 (57)	29 (62)
Any treatment-related grade 3/4 adverse event	17 (34)	20 (39)	18 (38)
Neutropenia	6 (12)	11 (22)	7 (15)
Lymphopenia	0	1 (2)	5 (11)
Fatigue	1 (2)	4 (8)	1 (2)
Leukopenia	1 (2)	3 (6)	3 (6)
Thrombocytopenia	0	1 (2)	3 (6)

[a] Events were coded according to the Medical Dictionary for Regulatory Activities version 9.0.
ITT, intention to treat.

Sixteen patients died within 30 days of the last administration of study treatment, with nine deaths linked to disease progression. Seven deaths were due to AEs: one patient in the pemetrexed alone group died due to sepsis, two patients in the pemetrexed plus weekly matuzumab group died due to respiratory failure and exsanguination, respectively, and four patients in the pemetrexed plus matuzumab every 3 weeks group died due to pneumonia and respiratory failure; renal failure; hemorrhage; and pulmonary embolism, respectively. None of these seven deaths were thought to be related to matuzumab, with two possibly related to pemetrexed (sepsis and pneumonia/respiratory failure).

Quality of Life

At baseline, weeks 6, 12, 24, 36, and at the end of treatment, 91%, 51%, 28%, 10%, 2% and 46%, respectively, of patients in the safety/ITT population completed QoL questionnaires. Changes in QoL parameters between baseline and cycle 2 were variable in pattern, and it was not clear whether they favored any of the treatment groups (Table 5). The data variability and the magnitude of changes between visits impeded a meaningful evaluation of QoL in relationship to the different regimens.

DISCUSSION

In the primary analysis of the PP population, this study failed to demonstrate a statistically significant increase in objective response rate for the addition of matuzumab to pemetrexed compared with pemetrexed alone (11% versus 5%, respectively, $p = 0.332$). Nevertheless, secondary analysis by treatment group in the safety/ITT population indicated that the majority of the responses in the matuzumab arms had occurred in patients receiving matuzumab at 800 mg weekly (objective response rate of 16% compared with 4% for the pemetrexed alone group). The risk of disease progression was similar for patients receiving pemetrexed plus weekly matuzumab compared with pemetrexed alone (HR: 0.96), but the risk of death at any given time point was notably lower (HR: 0.67, median overall survival 12.4 months [95% CI: 8.8-not evaluable] versus 7.9 months [95% CI: 7.2–9.9], respectively), suggesting an increase in overall survival for the pemetrexed plus matuzumab 800 mg weekly regimen over pemetrexed alone.

Although objective response rate was chosen as the primary end point for this study, it has been argued that alternative rapidly assessable end points may be more appropriate indicators of anticancer activity in phase II trials, particularly perhaps those investigating the newer targeted agents.[32–34] Indeed, despite the observation that overall survival seemed to be improved in the weekly pemetrexed compared with pemetrexed alone group, the possibility that this was related to imbalances in poststudy anticancer therapy cannot be discounted, especially because PFS was similar for all treatment groups. Recent analyses have also indicated that the survival benefit of pemetrexed is restricted to patients whose disease is of nonsquamous histology.[35] In considering the survival data in this study, it should, therefore, be noted that slightly fewer patients in the group receiving pemetrexed plus weekly matuzumab had squamous cell carcinomas (22%) compared with the other two groups (36%). Nevertheless, whether this factor contributed significantly to the improved survival in the pemetrexed plus weekly matuzumab group cannot be determined, as the number of patients is too small to permit meaningful subgroup analysis. In contrast to the data for weekly administration, there was no evidence from this study that the addition of matuzumab at 1600 mg every 3 weeks to pemetrexed provided any clinical benefit compared with pemetrexed alone.

The combination of pemetrexed and matuzumab was generally well tolerated, and the study provided no indication that the coadministration of both drugs aggravated the safety profile of the individual agents. The overall incidence of treatment-related grade 3/4 AEs was similar across the patient groups (34–39%). Previous studies have identified skin rash as a common side effect of matuzumab treatment, with such reactions typically reaching only grade 1 or 2.[23,28–30] Treatment-related grade 1/2 rash was also common in the matuzumab arms of this study (rash reported for 37% of patients receiving the weekly regimen and 43% of patients receiving the every 3 weeks regimen compared with 14% of patients receiving pemetrexed alone). Such skin reactions are a characteristic side effect of EGFR-targeted agents.[36]

The phase III FLEX study demonstrated that the addition of cetuximab to a standard first-line therapy for advanced NSCLC statistically significantly improved overall survival compared with chemotherapy alone.[7] This large randomized study, therefore, provided further data confirming EGFR as an effective molecular target in the treatment of advanced disease. The results of this study suggest that the EGFR-targeting monoclonal antibody matuzumab may prove to be most effective in this setting when administered weekly at 800 mg.

In conclusion, this study failed to demonstrate that the addition of matuzumab to pemetrexed as second-line therapy for NSCLC significantly improved objective response com-

TABLE 5. Subject Symptom, Activity, and Quality of Life Scales, Changes from Baseline to Cycle 2 (Safety/ITT Population)

	Pemetrexed Alone		Pemetrexed Plus Matuzumab (800 mg/wk)		Pemetrexed Plus Matuzumab (1600 mg/3 wk)	
	Baseline, $n = 45$	Change at Cycle 2, $n = 26$	Baseline, $n = 46$	Change at Cycle 2, $n = 25$	Baseline, $n = 44$	Change at Cycle 2, $n = 24$
Individual subject symptom scales						
Appetite						
Mean (SD)	30.8 (32.6)	−1.2 (31.3)	22.8 (22.1)	−2.4 (26.1)	29.9 (30.6)	5.6 (31.6)
Min, Max	0, 100	−100, 41	1, 83	−46, 60	0, 97	−92, 63
Fatigue						
Mean (SD)	41.7 (29.9)	14.9 (30.1)	37.0 (27.7)	−6.9 (24.2)	48.0 (30.8)	1.9 (41.7)
Min, Max	0, 98	−28, 79	0, 97	−67, 54	0, 100	−89, 67
Coughing						
Mean (SD)	33.0 (25.2)	0.5 (21.7)	29.1 (26.7)	−6.6 (19.0)	29.2 (28.8)	−5.1 (29.6)
Min, Max	0, 78	−41, 53	0, 97	−59, 45	0, 96	−95, 62
Dyspnea						
Mean (SD)	40.2 (29.5)	9.8 (35.0)	31.0 (30.3)	−1.9 (23.6)	33.2 (27.5)	11.5 (35.1)
Min, Max	0, 94	−40, 79	0, 98	−62, 48	0, 100	−77, 76
Hemoptysis						
Mean (SD)	4.5 (9.9)	−0.2 (9.1)	2.9 (6.6)	−1.4 (8.3)	4.1 (13.0)	−1.8 (16.3)
Min, Max	0, 50	−36, 19	0, 35	−35, 6	0, 76	−72, 24
Pain						
Mean (SD)	22.8 (29.3)	−1.7 (19.0)	23.4 (25.6)	−3.5 (15.0)	24.4 (31.0)	8.9 (37.2)
Min, Max	0, 100	−61, 46	0, 93	−33, 40	0, 100	−78, 85
Summary symptom scale						
Mean (SD)	30.5 (28.2)	3.2 (19.6)	21.8 (24.0)	−0.8 (16.6)	28.2 (32.5)	−7.7 (35.4)
Min, Max	0, 100	−42, 48	0, 100	−35, 47	0, 100	−96, 49
Subject activity scale						
Mean (SD)	42.6 (30.2)	2.7 (17.0)	35.6 (30.4)	−3.5 (16.8)	35.8 (27.1)	5.3 (27.2)
Min, Max	0, 100	−55, 28	0, 97	−43, 25	0, 91	−26, 83
Subject QoL scale						
Mean (SD)	35.9 (26.0)	3.5 (17.2)	31.1 (25.8)	0.8 (19.9)	35.8 (27.5)	15.7 (30.7)
Min, Max	0, 100	−48, 32	0, 94	−43, 43	0, 94	−41, 84

ITT, intention to treat; QoL, quality of life; max, maximum; min, minimum; SD, standard deviation.

pared with pemetrexed alone. Nevertheless, a preplanned subgroup efficacy analyses revealed some evidence of benefit for pemetrexed plus weekly matuzumab compared with pemetrexed alone or pemetrexed plus matuzumab given every 3 weeks. There were no marked differences between the treatment groups with respect to safety.

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