Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study

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See Comment page 1398

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Summary

Background Several studies have shown the efficacy, tolerability, and ease of administration of pemetrexed—an antifolate antineoplastic agent—in patients with advanced non-small-cell lung cancer. We assessed pemetrexed as maintenance therapy in patients with this disease.

Methods This randomised double-blind study was undertaken in 83 centres in 20 countries. 663 patients with stage IIIB or IV disease who had not progressed on four cycles of platinum-based chemotherapy were randomly assigned (2:1 ratio) to receive pemetrexed (500 mg/m², day 1) plus best supportive care (n=441) or placebo plus best supportive care (n=222) in 21-day cycles until disease progression. Treatment was randomised with the Simon and Pocock minimisation method. Patients and investigators were masked to treatment. All patients received vitamin B_{12}, folic acid, and dexamethasone. The primary endpoint of progression-free survival and the secondary endpoint of overall survival were analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00102804.

Findings All randomly assigned participants were analysed. Pemetrexed significantly improved progression-free survival (4·3 months [95% CI 4·1–4·7] *vs* 2·6 months [1·7–2·8]; hazard ratio [HR] 0·50, 95% CI 0·42–0·61, p<0·0001) and overall survival (13·4 months [11·9–15·9] *vs* 10·6 months [8·7–12·0]; HR 0·79, 0·65–0·95, p=0·012) compared with placebo. Treatment discontinuations due to drug-related toxic effects were higher in the pemetrexed group than in the placebo group (21 [5%] *vs* three [1%]). Drug-related grade three or higher toxic effects were higher with pemetrexed than with placebo (70 [16%] *vs* nine [4%]; p<0·0001), specifically fatigue (22 [5%] *vs* one [1%], p=0·001) and neutropenia (13 [3%] *vs* 0, p=0·006). No pemetrexed-related deaths occurred. Relatively fewer patients in the pemetrexed group than in the placebo group received systemic post-discontinuation therapy (227 [51%] *vs* 149 [67%]; p=0·0001).

Interpretation Maintenance therapy with pemetrexed is well tolerated and offers improved progression-free and overall survival compared with placebo in patients with advanced non-small-cell lung cancer.

Funding Eli Lilly.

Introduction

More than 1 million people worldwide die every year from lung cancer.[1] More than 87% of the cases are non-small-cell lung cancer.[2] About 40% of patients have either stage IIIB disease with malignant effusion or stage IV disease at presentation.[3] Historically, standard first-line platinum-based chemotherapy has provided modest improvements in overall survival.[4–8] However, less than 40% of patients show significant tumour reduction. Clearly, opportunities exist to improve the clinical benefit of first-line treatment for patients before disease progression. In two large, randomised, phase 3 trials, the addition of cetuximab[9] and bevacizumab[10] (antibodies to epidermal growth factor receptor and vascular endothelial growth factor, respectively) to chemotherapy has shown improved survival in specific patient populations; however, the separate benefit of continuing these agents in the maintenance setting has not been proven.

Although present guidelines recommend four to six cycles of platinum-based chemotherapy for stage IIIB and IV non-small-cell lung cancer,[6] response typically occurs within the first two to four cycles,[11] and many patients cannot tolerate long-term treatment.[12,13] Consequently, treatment guidelines recommend waiting until disease progression to administer second-line and third-line anticancer systemic therapy.[6,7] Patients who go on to receive second-line therapy (<50%) represent a select subgroup with an improved overall prognosis.[14]

Continued chemotherapeutic treatment before progression with single-agent docetaxel[15] and gemcitabine[16] has improved progression-free survival, but in some cases, was limited by toxic effects. Studies examining maintenance therapy with carboxyaminoimidazole[17] and vinorelbine[18] did not show a significant survival benefit, nor did investigations of targeted agents gefitinib[19] or erlotinib[20] when these agents were combined with an

induction platinum regimen and continued until disease progression. A meta-analysis[21] of 13 randomised trials also showed that third-generation chemotherapy beyond three or four cycles significantly increased progression-free survival but not overall survival.

Pemetrexed is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolism.[22] Pemetrexed is approved in combination with cisplatin for first-line treatment of malignant pleural mesothelioma,[23] as a single agent for second-line treatment of advanced non-squamous non-small-cell lung cancer,[24] and in combination with cisplatin for first-line therapy of advanced non-squamous non-small-cell lung cancer.[25] Several studies[25–27] have now consistently shown the differential effects of pemetrexed according to disease histology.

On the basis of its efficacy in non-small-cell lung cancer and favourable toxicity profile, we assessed maintenance therapy with pemetrexed in patients with advanced stage IIIB and IV non-small-cell lung cancer. The primary objective of this study was to compare the progression-free survival of maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care in patients who had not progressed after completion of four cycles of platinum-based induction therapy.

Methods

Study design and patients

This multicentre, randomised, double-blind, placebo-controlled study was undertaken in 83 centres in 20 countries. Patients were enrolled immediately after completing induction therapy, no earlier than 21 days and no later than 42 days from their last cycle (day 1) of induction therapy. The first patient visit occurred on March 4, 2005; the datalock for the primary analysis of progression-free survival occurred on Nov 21, 2007; and the final datalock for analysis of overall survival occurred on Dec 18, 2008.

Inclusion criteria included age 18 years or older, estimated life expectancy of 12 weeks or more, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, histological or cytological diagnosis of stage IIIB (with pleural effusion or positive supraclavicular lymph nodes, or both) or stage IV non-small-cell lung cancer before induction therapy, and adequate organ function. Patients must not have progressed during four 21-day cycles of one of the following six initial doublet chemotherapy regimens: gemcitabine-carboplatin, gemcitabine-cisplatin, paclitaxel-carboplatin, paclitaxel-cisplatin, docetaxel-carboplatin, or docetaxel-cisplatin. Induction regimens did not include pemetrexed. Previous radiotherapy was completed 4 weeks or more before study enrolment.

Exclusion criteria included a previous malignancy other than non-small-cell lung cancer; inability to take corticosteroid drugs, folic acid, or vitamin B_{12}; uncontrolled cardiac disease; progressive brain metastases; uncontrolled third-space fluid collections; and pregnancy or breastfeeding.

The protocol was approved by the Institutional Review Board of each participating institution. We obtained written informed consent from all patients before study enrolment. The study was undertaken in accordance with the ethics principles of the Declaration of Helsinki and was consistent with good clinical practices and applicable laws and regulations.

Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to receive either pemetrexed (500 mg/m²; Alimta, Eli Lilly, Indianapolis, IN, USA) intravenously on day 1 or placebo (0·9% sodium chloride) intravenously on day 1. Both groups received best supportive care in 21-day cycles. We anticipated that patients would benefit from maintenance therapy with pemetrexed, thus the study was designed with a 2:1 randomisation ratio to provide

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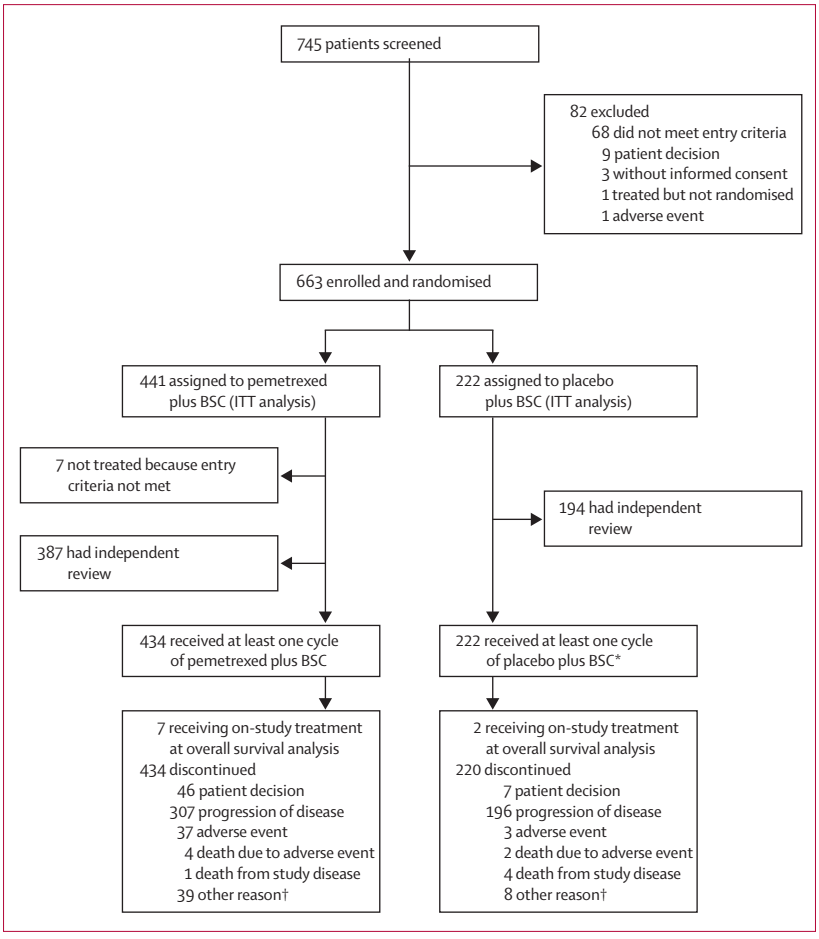

Figure 1: **Trial profile**
BSC=best supportive care. ITT=intention to treat. *Three patients were assigned to placebo but received pemetrexed. These three patients were analysed on an intention-to-treat basis according to their randomised assignment (placebo). †Includes protocol violation, entry criteria not met, satisfactory response, loss to follow-up, and physician or sponsor decision.

sufficient comparative data to show the superiority of pemetrexed while reducing patient exposure to the potentially inferior treatment with placebo.

A computerised, interactive, voice-activated response system (IVRS) at a central location controlled random assignment for all study sites. To preserve the masking of the patient and the personnel involved in patient assessments or data collection, an unmasked third party, such as a pharmacist, was designated. The investigator provided the necessary information to the unmasked pharmacist or designee who called the IVRS to obtain the patient's treatment assignment. Patients and the study team were all masked to the treatment assigned. We used Pocock and Simon method, which minimises imbalance between groups for each selected factor, for random assignment[28] to randomly assign patients to treatment according to the following factors: disease stage (IIIB *vs* IV), ECOG performance status (0 *vs* 1), sex (men *vs* women), best response to induction therapy (complete or partial response *vs* stable disease), non-platinum component of induction therapy (gemcitabine *vs* paclitaxel *vs* docetaxel), and history of brain metastases (yes *vs* no). All patients received vitamin B_{12} and folic acid supplementation and dexamethasone prophylaxis during study treatment.

	Pemetrexed (n=441)	Placebo (n=222)
Age (years)	60·6 (54·3–67·5)	60·4 (53·8–67·0)
Sex		
Men	322 (73%)	161 (73%)
Women	119 (27%)	61 (27%)
Ethnic origin		
White	279 (63%)	149 (67%)
East/west Asian	143 (32%)	66 (30%)
Other*	19 (4%)	7 (3%)
Disease stage		
IIIB	79 (18%)	47 (21%)
IV	361 (82%)	175 (79%)
Smoking status		
Smoker	324 (73%)	158 (71%)
Never-smoker	113 (26%)	63 (28%)
ECOG performance status†		
0	176 (40%)	85 (38%)
1	263 (60%)	137 (62%)
Histology		
Non-squamous	325 (74%)	156 (70%)
Adenocarcinoma	222 (50%)	106 (48%)
Large cell	10 (2%)	10 (5%)
Other or indeterminate	93 (21%)	40 (18%)
Squamous	116 (26%)	66 (30%)
Best response to induction treatment		
CR+PR	207 (47%)	115 (52%)
Stable disease	230 (52%)‡	107 (48%)
Induction regimen		
Docetaxel-carboplatin	21 (5%)	7 (3%)
Docetaxel-cisplatin	7 (2%)	4 (2%)
Paclitaxel-carboplatin	132 (30%)	59 (27%)
Paclitaxel-cisplatin	27 (6%)	20 (9%)
Gemcitabine-carboplatin	107 (24%)	48 (22%)
Gemcitabine-cisplatin	146 (33%)	84 (38%)

Data are median (IQR) or number (%). ECOG=Eastern Cooperative Oncology Group. CR=complete response. PR=partial response. *Other includes Hispanic, African, and Aboriginal. †Two patients had unknown performance status. ‡Three patients had progressive disease after induction (protocol violation), one unknown.

Table 1: **Patient characteristics**

Procedures

Patients continued treatment until disease progression. Patients who required a dose reduction continued to receive a reduced dose for the remainder of the study. Any patient who could not be given the study drug for 42 days or who had toxic effects that would cause a third dose reduction was discontinued from treatment. Other reasons for discontinuation included necessity of treatment with another therapeutic agent, physician or patient decision, and non-compliance.

Investigator-reported histology of non-small-cell lung cancer was grouped for statistical analysis into four main categories: adenocarcinoma, large-cell carcinoma, squamous-cell carcinoma, and other non-small-cell lung cancer not otherwise specified, consistent with published guidelines.[29] A data safety monitoring board was not used in this study since no interim analyses were undertaken.

Within 4 weeks of study entry, baseline tumour measurements were done by imaging (CT scans or MRI), and response was assessed every two cycles with Response Evaluation Criteria In Solid Tumors (RECIST).[30] An independent central review of scans was undertaken for all patients who had a baseline and at least one follow-up scan.

Progression-free survival, the primary endpoint, was measured from the date of randomisation, after completion of induction therapy, to the first date of objective progression of disease or of death from any cause. Progression-free survival was censored at the date of the patient's last tumour assessment before datalock. Secondary objectives included overall survival, objective tumour response rate, safety, and patient-reported outcomes (to be reported elsewhere). Overall survival time was measured from the date of randomisation to the date of death from any cause. Overall survival was censored at the date of last previous contact before the data-inclusion cut-off date for the analysis. The final analysis of overall survival included 477 events. Additional analyses of progression-free and overall survival were calculated from the date of the first dose of induction chemotherapy.

Tumour response was assessed from the date of randomisation, after completion of induction therapy, and represented a further tumour reduction from the baseline response of complete or partial response or

stable disease to induction therapy. For a tumour response of complete or partial response, best response was confirmed according to RECIST, with a second assessment that was undertaken 28 days or later but no longer than 42 days after the first documentation of response. Best response of stable disease was defined as disease that did not meet the criteria for complete or partial response or progressive disease and had been assessed at least once, a minimum of 6 weeks after the start of treatment. Best response was calculated from the sequence of assessed responses. According to the protocol, imaging for response and progression was done every two cycles in both study groups, with baseline scans done after the completion of induction treatment, before randomisation.

Tumour response rates were calculated per treatment group as the proportion of randomly assigned patients having a confirmed tumour response of partial or complete response, as defined by RECIST. Additionally, we calculated the disease control rate (complete and partial response plus stable disease). Rates of tumour response and disease control were compared between treatment groups with Fisher's exact test.

Efficacy and safety analyses, including progression-free survival, incorporated all randomly assigned patients on an intention-to-treat basis. An independent central review was undertaken to ensure that there was no systematic bias in investigator assessments of progressive disease that would favour one study group with respect to the primary endpoint of progression-free survival. All patients were assessed for toxicity before each cycle with common terminology criteria for adverse events (version 3.0).

We measured time to worsening of patient-reported symptoms from the date of randomisation to the first date of worsening for each of the six symptoms and three summary items of the lung cancer symptom scale.[31,32] Worsening was defined by a 15-mm increase from the baseline lung cancer symptom score on a 100-mm scale. Patients completed the lung cancer symptom scale once per cycle during study treatment and once within 30 days of discontinuation. Detailed results will be presented in a separate publication.

Patients were unmasked to study treatment at the time of disease progression, and subsequent treatment, including pemetrexed, was allowed at the discretion of the investigator. For patients who discontinued study treatment for reasons other than disease progression, lesion assessments continued every 6 weeks. After disease progression, patients were unmasked to study treatment and were followed up every 90 days until death. Subsequent treatment was allowed at the discretion of the investigator.

Statistical analysis

This trial was designed to test for the superiority of pemetrexed over placebo for progression-free survival.

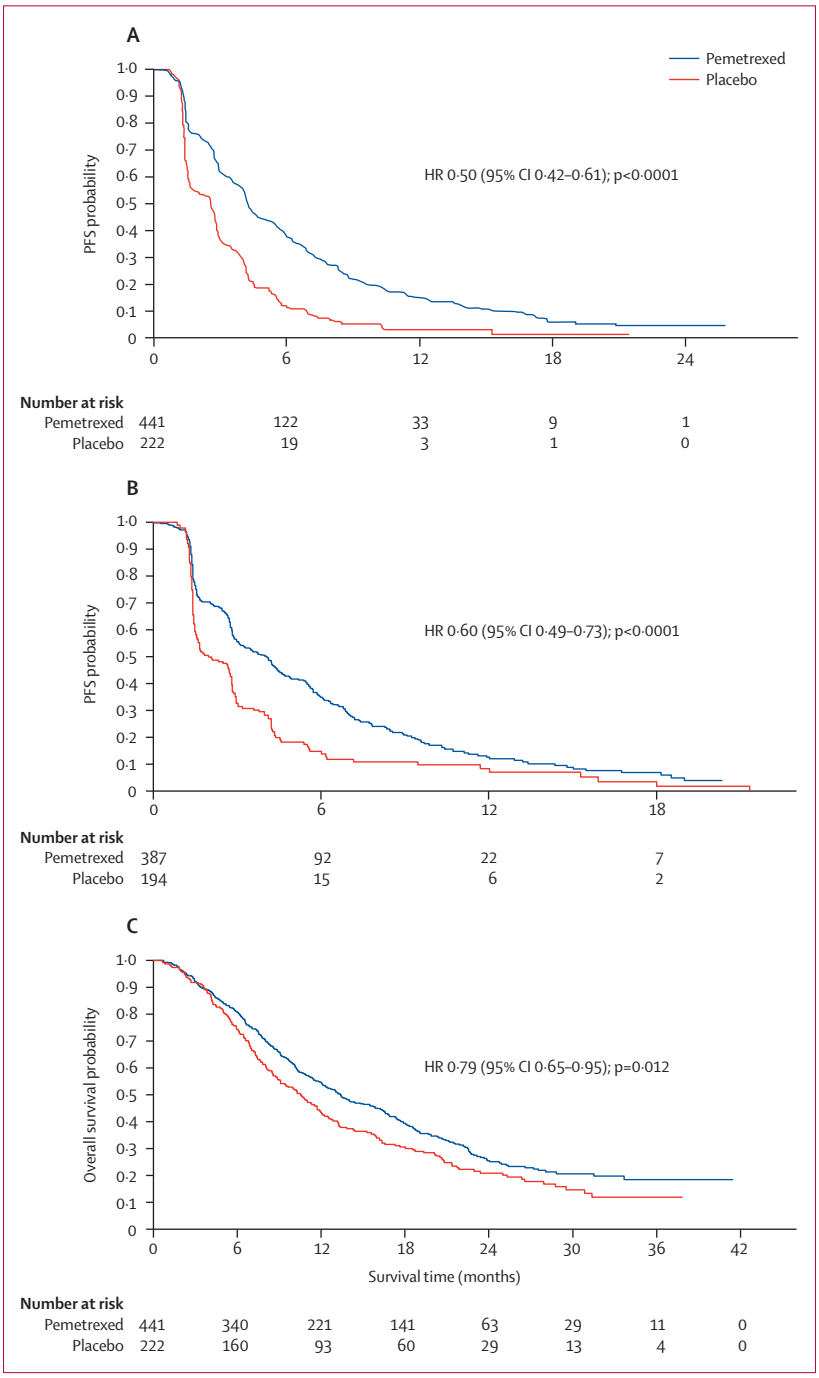

Figure 2: **Progression-free survival (investigator assessed data [A] and independent review [B]) and overall survival (C)**

(A) Progression-free survival (PFS), as assessed by the investigators, in the intention-to-treat population of 663 randomly assigned patients. (B) PFS data from independent, central review of scans available from 581 randomly assigned patients. (C) Overall survival in the intention-to-treat population of 663 randomly assigned patients.

According to a prespecified statistical plan, the primary endpoint of progression-free survival, and the secondary endpoints of tumour response and preliminary overall survival, were analysed roughly 1 year before the final

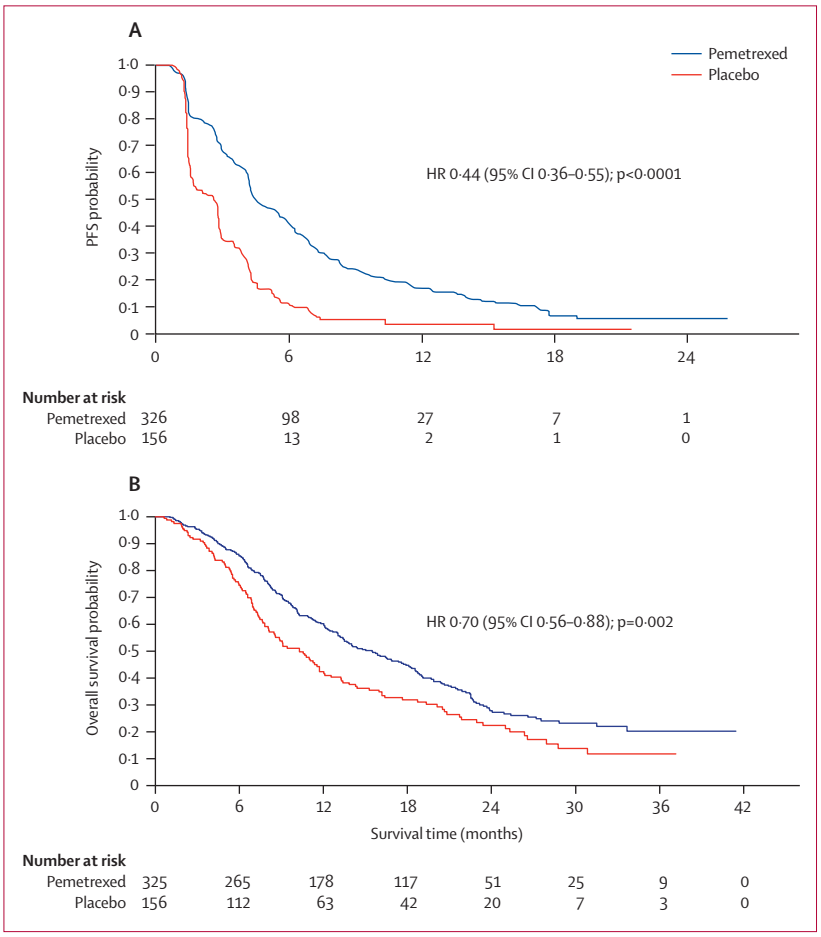

Figure 3: **Progression-free survival ([PFS] investigator assessed data, A) and overall survival (B) in non-squamous population**

analysis of overall survival. We used statistical analysis software versions 8.02 and 9.1.3 for statistical analyses.

The overall type-1 α error was controlled for the primary endpoint of progression-free survival and secondary endpoint of overall survival to guarantee an overall α level no greater than 0·05. If progression-free survival was significant at a nominal α level of 0·05, then a preliminary analysis of overall survival was to be done with a nominal α level of 0·00002, followed by a final analysis of overall survival with a nominal α level of 0·04998; if progression-free survival was not significant, then no formal hypothesis tests of overall survival were to be done. Under this scheme, a type-1 error could only occur if there was no progression-free survival benefit in this population from pemetrexed (in which case, there was a 0·05 probability of mistakenly finding progression-free survival significant), or there was a benefit in terms of progression-free survival but not in overall survival (in which case, there was, at most, a 0·05 probability of mistakenly finding overall survival significant). Prespecified analyses for survival with respect to histology were included on the basis of results from previous studies.[25,27]

For the α-controlled analyses, Cox models[33] with treatment group as the only cofactor were used to estimate and test hazard ratios (HRs) for overall and progression-free survival. Additional secondary analyses of overall and progression-free survival used Cox models to test the significance of prognostic cofactors and treatment-by-cofactor interactions. A sample size of 660 patients allocated in a 2:1 ratio was planned, assuming the true HR for progression-free survival was 0·75 (85% power at 462 events of progression-free survival) and the true HR for overall survival was 0·767 (80% power at 475 events of overall survival).

This study is registered with ClinicalTrials.gov, number NCT00102804.

Role of the funding source

The sponsor designed the study in collaboration with CPB, TB, and CZ, and reviewed all study reports with TB. The sponsor provided pemetrexed and did the statistical analyses. After datalock, the sponsor's study team (including sponsor physicians, statisticians, and medical study report writers) had full access to the data, which were also discussed in detail with the principal and other investigators. All authors contributed to the decision to submit for publication.

Results

745 patients were enrolled (figure 1) and 663 patients were randomly assigned from March, 2005, to July, 2007. The study groups were well balanced in terms of prognostic factors and other baseline characteristics (table 1). Most patients were white, and three-fifths had an ECOG performance status of 1 (table 1). A third of patients were 65 years or older. Most patients had a history of smoking (table 1). Although histology was not a randomisation factor, study groups were well balanced for histological subtypes; nearly three-quarters of patients had non-squamous histology (table 1).

434 (98%) patients in the pemetrexed group and 222 (100%) in the placebo group received at least one cycle of study treatment. The median number of maintenance cycles delivered was 5·0 (range 1–55) in the pemetrexed group and 3·5 (1–46) in the placebo group. 213 (48%) patients in the pemetrexed group and 61 (27%) in the placebo group remained on study treatment for six or more cycles, and 103 (23%) and 19 (9%), respectively, continued treatment for ten or more cycles. The mean weekly dose intensity of pemetrexed was 159·60 mg (SD 11·3; 95·76%, 478·8 mg per 3-week cycle).

Treatment discontinuations due to drug-related toxic effects were higher in the pemetrexed group (21 patients [5%]) than in the placebo group (three patients [1%]). Only a few patients needed dose reductions (22 patients [5%] for pemetrexed and two [1%] for placebo), and dose delays were mainly due to scheduling conflicts.

The median follow-up time for progression-free and overall survival, measured from the time of randomisa-

	Median PFS* (months [95% CI; investigator assessed])		HR (95% CI); p value	Median PFS† (months [95% CI; independent])		HR (95% CI); p value	Median OS (months; 95% CI)		HR (95% CI); p value	Patients with CR+PR+SD (%)‡		p value
	Pemetrexed	Placebo		Pemetrexed	Placebo		Pemetrexed	Placebo		Pemetrexed	Placebo	
Overall population	4·3 (4·1–4·7)	2·6 (1·7–2·8)	0·50 (0·42–0·61); <0·0001	4·0 (3·1–4·4)	2·0 (1·5–2·8)	0·60 (0·49–0·73); <0·0001	13·4 (11·9–15·9)	10·6 (8·7–12·0)	0·79 (0·65–0·95); 0·012	228 (52%)	74 (33%)	<0·0001
Non–squamous§ (n=481)	4·5 (4·2–5·6)	2·6 (1·6–2·8)	0·44 (0·36–0·55); <0·0001	4·4 (4·0–5·6)	1·8 (1·5–2·8)	0·47 (0·37–0·60); <0·0001	15·5 (13·2–18·1)	10·3 (8·1–12·0)	0·70 (0·56–0·88); 0·002	188 (58%)	51 (33%)	<0·0001
Adenocarcinoma (n=328)	4·7 (4·2–6·1)	2·6 (1·6–2·8)	0·45 (0·35–0·59); <0·0001	4·6 (4·0–6·0)	2·7 (1·6–2·8)	0·51 (0·38–0·68); <0·0001	16·8 (14·0–19·7)	11·5 (9·1–15·3)	0·73 (0·56–0·96); 0·026	136 (61%)	35 (33%)	<0·0001
Large cell (n=20)	3·5 (1·6–6·9)	2·1 (1·4–2·9)	0·40 (0·13–1·22); 0·109	4·5 (1·4–15·5)	1·5 (1·4–3·0)	0·40 (0·12–1·29); 0·125	8·4 (6·4–10·3)	7·9 (4·1–13·2)	0·98 (0·36–2·65); 0·964	5 (46%)	3 (33%)	0·670
Other (n=133)	4·2 (3·1–5·6)	2·8 (1·5–3·6)	0·43 (0·28–0·68); 0·0002	4·1 (3·0–4·7)	1·6 (1·4–2·9)	0·44 (0·28–0·68); 0·0003	11·3 (9·5–18·3)	7·7 (6·6–11·0)	0·61 (0·40–0·94); 0·025	47 (51%)	13 (32%)	0·041
Squamous (n=182)	2·8 (2·4–4·0)	2·6 (1·6–3·2)	0·69 (0·49–0·98); 0·039	2·4 (1·6–2·8)	2·5 (1·5–3·2)	1·03 (0·71–1·49); 0·896	9·9 (7·5–11·5)	10·8 (8·5–13·2)	1·07 (0·77–1·50); 0·678	40 (35%)	23 (35%)	>0·999

PFS=progression-free survival. HR=hazard ratio. OS=overall survival. CR=complete response. PR=partial response. SD=stable disease. *Investigator-assessed PFS in intention-to-treat population. †PFS based on independently reviewed population (N=581: pemetrexed=387, placebo=194). The most common reason for omission of patients from independent review was availability of only baseline scans. Other reasons included poor imaging quality and missing baseline data or other scans. ‡Percentage values based on number of patients in each histology group. §Non-squamous histology included patients with adenocarcinoma, large-cell carcinoma, and other or unknown histology (ie, all patients without a diagnosis of predominantly squamous-cell carcinoma).

Table 2: **Efficacy by histology**

tion, was 11·2 months (range 6·1–19·4; 12·0 months [6·4–19·7] for patients receiving pemetrexed and 10·1 months [5·5–18·5] for those receiving placebo). The maximum length of survivor follow-up was 41·5 months (41·5 months for pemetrexed and 37·8 months for placebo).

In the intention-to-treat population of 663 randomly assigned patients, assessed by the investigators, the median progression-free survival was significantly higher with pemetrexed (4·3 months, 95% CI 4·1–4·7) than with placebo (2·6 months, 1·7–2·8; HR 0·50, 95% CI 0·42–0·61; p<0·0001; figure 2A). These results were confirmed by analysis of progression-free survival with independently reviewed data. In the 581 patients with independent review of scans, median progression-free survival was 4·0 months (95% CI 3·1–4·4) with pemetrexed compared with 2·0 months (1·5–2·8) with placebo (HR 0·60, 95% CI 0·49–0·73, p<0·0001; figure 2B). Median overall survival in the intention-to-treat population also improved significantly with pemetrexed treatment: 13·4 months (95% CI 11·9–15·9) versus 10·6 months (8·7–12·0) for placebo (HR 0·79, 0·65–0·95, p=0·012; figure 2C).

The investigator-assessed response rate was significantly higher in the pemetrexed group than in the placebo group (6·8% [n=30] *vs* 1·8% [n=4]; p=0·005). These results were confirmed by an independent review of scans, which reported response rates of 3·4% (n=13) in the pemetrexed group and 0·5% (n=1) in the placebo group (p=0·042). The disease control rate was significantly higher for pemetrexed than for placebo, according to both investigator assessment (51·7% [n=228] *vs* 33·3% [n=74]; p<0·0001) and independent review (49·1% [n=190] *vs* 28·9% [n=56]; p<0·0001).

Assessment from the start of induction therapy did not change the HRs or the p values (data not shown). Median progression-free survival measured from the start of induction treatment was 7·7 months (95% CI 7·2–8·2) in the pemetrexed group and 5·9 months (5·3–6·1) in the placebo group, and median overall survival was 16·5 months (15·1–19·1) and 13·9 months (12·2–15·4), respectively.

The improvements in progression-free and overall survival were recorded mainly in patients with non-squamous histology (progression-free survival HR 0·44, 95% CI 0·36–0·55; and overall survival HR 0·70, 0·56–0·88; figure 3), compared with squamous histology (progression-free survival HR 0·69, 0·49–0·98; and overall survival HR 1·07, 0·77–1·50). Table 2 summarises results by histology. In patients with non-squamous disease (from intention-to-treat population), the improvement in both progression-free and overall survival was significant for pemetrexed in the adenocarcinoma and other non-small-cell lung cancer subgroups (table 2). We noted a significant treatment-by-histology interaction with both progression-free survival (p=0·036) and overall survival (p=0·033).

A small, masked, central pathology review was undertaken for 14% (93/663) of patients who had specimens submitted for the purpose of a companion biomarker study. A retrospective analysis of this review determined that there was 89% agreement between the investigator assessment and independent review of histological diagnosis in the differentiation of non-squamous and squamous non-small-cell lung cancer tumours.

22 patients (3%) died on-study or within 30 days of last dose: 12 patients (3%) in the pemetrexed group and ten (5%) in the placebo group. None of the deaths was drug-related. The overall rate of drug-related grade three or four toxic effects was significantly higher for pemetrexed than for placebo (16% [n=70] *vs* 4% [n=9];

	Pemetrexed		Placebo	
	All grades	Grades 3 or 4	All grades	Grades 3 or 4
Haematological toxicities				
Neutropenia*	26 (6%)	13 (3%)	0	0
Anaemia	67 (15%)	12 (3%)	12 (5%)	1 (<1%)
Leukopenia	27 (6%)	7 (2%)	3 (1%)	1 (<1%)
Non-haematological toxicities				
ALT	42 (10%)	1 (<1%)	8 (4%)	0
AST	36 (8%)	0	8 (4%)	0
Fatigue*	108 (24%)	22 (5%)	23 (10%)	1 (<1%)
Anorexia	82 (19%)	8 (2%)	11 (5%)	0
Infection	23 (5%)	7 (2%)	4 (2%)	0
Diarrhoea	23 (5%)	2 (<1%)	6 (3%)	0
Nausea	83 (19%)	4 (<1%)	12 (5%)	1 (<1%)
Vomiting	38 (9%)	1 (<1%)	3 (1%)	0
Sensory neuropathy	39 (9%)	3 (<1%)	9 (4%)	0
Mucositis/stomatitis	31 (7%)	3 (<1%)	4 (2%)	0
Rash	9 (2%)	1 (<1%)	2 (<1%)	0

ALT=alanine aminotransferase. AST=aspartate aminotransferase. *p<0·05 for grade 3 or 4 rates of neutropenia and fatigue between study groups. †Updated safety analysis done 6 months after initial analysis of progression-free survival. For the purpose of this table, a cut-off of 5% was used for inclusion of all events for which the investigator considered a possible link with pemetrexed.

Table 3: **Drug-related toxic effects†**

	Pemetrexed (n=441)	Placebo (n=222)
Any anticancer systemic therapy	227 (51%)	149 (67%)
Pemetrexed	4 (<1%)	41 (18%)
Docetaxel	99 (22%)	65 (29%)
Erlotinib	95 (22%)	46 (21%)
Gefitinib	59 (13%)	22 (10%)
Vinorelbine	57 (13%)	37 (17%)
Gemcitabine	41 (9%)	30 (14%)
Carboplatin	32 (7%)	21 (9%)
Cisplatin	23 (5%)	13 (6%)
Paclitaxel	18 (4%)	14 (6%)

Data are number (%) of patients who received post-discontinuation therapy. Patients could have received more than one additional line of therapy.

Table 4: **Post-discontinuation anticancer systemic therapy**

p<0·0001), including fatigue (p=0·001) and neutropenia (p=0·006; table 3); three patients in the pemetrexed group (<1%) had febrile neutropenia. Although sensory neuropathy (all grades) was more frequently reported in the pemetrexed group than in the placebo group (table 3), three patients (<1%) had grade three or four sensory neuropathy (all in pemetrexed group). The safety profile of pemetrexed recorded within histological subgroups was consistent with the safety profile noted for the overall study population (data not shown). Although we recorded some increases in toxic effects (all grades) with longer exposures to pemetrexed, we noted no significant differences in the incidences of drug-related grade three or four toxic effects for patients who received more than six cycles or ten or more cycles of pemetrexed compared with those who received six or fewer cycles (data not shown).

The overall rates of transfusions and growth-factor use were low. Significantly more patients in the pemetrexed group than in the placebo group received transfusions (42 [10%] *vs* seven [3%]; p=0·003) and erythropoiesis-stimulating agents (26 [6%] *vs* four [2%]; p=0·017); however, we noted no difference in the use of colony-stimulating factors between groups (13 [3%] *vs* eight [4%]). The incidence of admissions to hospital due to drug-related toxic effects was higher in the pemetrexed group (19 patients [4%]) than in the placebo group (no patients).

The overall on-study compliance for completion of assessment on the lung cancer symptom scale was 87·0% for the pemetrexed group (2976 of 3421 cumulative assessments completed) and 81·3% for the placebo group (1083 of 1332). For patients who had post-discontinuation visits in the pemetrexed (n=343) and placebo (n=191) groups, compliance decreased to 48·1% (n=165) and 54·5% (n=104), respectively. We recorded significant delays in symptom worsening in favour of pemetrexed for pain (median 6·1 months [95% CI 4·6–9·6] *vs* 4·6 months [3·3–6·0]; HR 0·76 [0·59–0·99], p=0·041) and haemoptysis (HR 0·58 [0·34–0·97], p=0·038); because of a high rate of censoring for haemoptysis, medians could not be estimated. None of the other time-to-worsening comparisons differed significantly between groups.

Table 4 provides a summary of post-discontinuation systemic anticancer therapies. 227 patients (51%) in the pemetrexed group and 149 (67%) in the placebo group received systemic post-discontinuation therapy (p=0·0001). Docetaxel was the most commonly selected agent (table 4). The rate of crossover to post-discontinuation pemetrexed was 18% (n=41) for the placebo group. Apart from pemetrexed, the selection of other agents did not differ significantly between groups. We noted no significant difference between groups in the use of erlotinib or gefitinib (table 4).

Discussion

Findings from this randomised, double-blind, placebo-controlled study have shown a significant progression-free survival and overall survival benefit for the maintenance treatment of patients with advanced non-small-cell lung cancer. Pemetrexed treatment resulted in a 50% reduction in the risk of disease progression or death. Moreover, we noted a 21% reduction in the risk of death, and long-term exposures were well tolerated.

The significant improvements in the primary endpoint of progression-free survival, and the secondary endpoint of overall survival, were recorded mainly in patients with non-squamous histology. Three randomised phase 3 trials[25–27] have shown the differential treatment effect (for progression-free and overall survival) for pemetrexed

according to histology of non-small-cell lung cancer. A possible mechanism for this effect could be the differential expression of thymidylate synthase, which has been shown in vitro to correlate with sensitivity to pemetrexed.[34] The improvement that we noted in overall survival with maintenance pemetrexed for patients with non-squamous histology was significant, unlike previous maintenance trials with other agents. Previously, Brodowicz and colleagues[16] reported that time to progression was significantly improved with gemcitabine maintenance therapy after response to gemcitabine and cisplatin induction therapy. However, the study was underpowered to show definitive effects on overall survival. In another randomised study with either immediate or delayed docetaxel after gemcitabine and carboplatin induction therapy,[15] progression-free survival was significantly improved with immediate docetaxel, but without a significant improvement in overall survival. A significant improvement in progression-free survival was also recorded in two recently reported phase 3, placebo-controlled trials of maintenance treatment with erlotinib[35] and with erlotinib plus bevacizumab[36] in patients with advanced non-small-cell lung cancer; however, data for overall survival from these trials are not yet available.

In this study, the survival results were probably not affected by post-study therapy in view of the higher rate of follow-up treatment in the placebo group than in the pemetrexed group, low rate of crossover, and the balanced selection of therapies between groups. The rates of post-discontinuation therapy use in both groups in this study were consistent with rates reported in previous first-line and maintenance trials in advanced non-small-cell lung cancer.[10,14–16] Patients who received immediate maintenance treatment with pemetrexed had a significant survival benefit compared with those in the placebo group, in which only two-thirds of all patients received additional therapy after progression. A delay in subsequent treatment seems to increase the risk that some patients might never receive additional therapy, thus negatively affecting survival.

The present study did not include pemetrexed induction regimens, mainly because it was started before the completion of the pivotal first-line study of pemetrexed-cisplatin versus gemcitabine-cisplatin.[25] Recently, pemetrexed was approved for the maintenance treatment of patients with advanced non-squamous non-small-cell lung cancer who have not progressed after platinum treatment.[26] We cannot make definitive conclusions from our study about the safety and efficacy of pemetrexed maintenance after initial treatment with pemetrexed-containing regimens. Since pemetrexed-cisplatin is approved for first-line treatment of advanced non-small-cell lung cancer, a phase 3, double-blind, placebo-controlled study has been started and is in progress, to assess the safety and efficacy of maintenance pemetrexed after induction treatment with pemetrexed-cisplatin in patients with advanced non-squamous non-small-cell lung cancer (registered with ClinicalTrials.gov, number NCT00789373).

In conclusion, pemetrexed maintenance therapy is well tolerated and offers significantly improved progression-free and overall survival compared with placebo, making it a new treatment option for patients with advanced non-squamous non-small-cell lung cancer who do not progress after initial induction therapy.

Contributors

CPB, TB, CZ, EL, KK, WJJ, and PP were involved in the conception and design of the trial. TB, CZ, and EL also provided administrative support. CPB, TC, TB, CZ, JHK, MK, EL, IB, SB, VT, BC, JRP, SHY, and JM provided study materials or patients. TC, TB, CZ, JHK, MK, EL, Y-LW, IB, VT, and BC collected and assembled data. CPB, TC, TB, CZ, EL, KK, WJJ, PP, and KPS interpreted or analysed data. CPB, TC, TB, CZ, EL, SB, MK, KK, WJJ, and PP were involved in writing of this report, and all authors approved the final version.

Conflicts of interest

TC is a member of an advisory board for Eli Lilly. TB is a consultant for Amgen, Bayer, Novartis, and PharmaMar. CZ has received honoraria from Eli Lilly. Y-LW is a consultant for AstraZeneca, Roche, and Eli Lilly; and has received honoraria from AstraZeneca, Roche, and Eli Lilly. KPS, PP, WJJ, and KK are employees of Eli Lilly and have stock in that company. CPB is a consultant for Eli Lilly. JHK, MK, EL, IB, SB, VT, BC, JRP, SHY, and JM declare that they have no conflicts of interest.

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