Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial

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Summary

Background Patients with advanced non-squamous non-small-cell lung cancer (NSCLC) benefit from pemetrexed maintenance therapy after induction therapy with a platinum-containing, non-pemetrexed doublet. The PARAMOUNT trial investigated whether continuation maintenance with pemetrexed improved progression-free survival after induction therapy with pemetrexed plus cisplatin.

Methods In this double-blind, multicentre, phase 3, randomised placebo-controlled trial, patients with advanced non-squamous NSCLC aged 18 years or older, with no previous systemic chemotherapy for lung cancer, with at least one measurable lesion, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 participated. Before randomisation, patients entered an induction phase which consisted of four cycles of induction pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) on day 1 of a 21-day cycle. Patients who did not progress after completion of four cycles of induction and who had an ECOG performance status of 0 or 1 were stratified according to disease stage (IIIB or IV), ECOG performance status (0 or 1), and induction response (complete or partial response, or stable disease), and randomly assigned (2:1 ratio) to receive maintenance therapy with either pemetrexed (500 mg/m² every 21 days) plus best supportive care or placebo plus best supportive care until disease progression. Randomisation was done with the Pocock and Simon minimisation method. Patients and investigators were masked to treatment assignment. The primary endpoint was progression-free survival in the intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT00789373.

Findings Of the 1022 patients enrolled, 939 participated in the induction phase. Of these, 539 patients were randomly assigned to receive continuation maintenance with pemetrexed plus best supportive care (n=359) or with placebo plus best supportive care (n=180). Among the 359 patients randomised to continuation maintenance with pemetrexed, there was a significant reduction in the risk of disease progression over the placebo group (HR 0·62, 95% CI 0·49–0·79; p<0·0001). The median progression-free survival, measured from randomisation, was 4·1 months (95% CI 3·2–4·6) for pemetrexed and 2·8 months (2·6–3·1) for placebo. Possibly treatment-related laboratory grade 3–4 adverse events were more common in the pemetrexed group (33 [9%] of 359 patients) than in the placebo group (one [<1%] of 180 patients; p<0·0001), as were non-laboratory grade 3–5 adverse events (32 [9%] of 359 patients in the pemetrexed group; eight [4%] of 180 patients in the placebo group; p=0·080); one possibly treatment-related death was reported in each group. The most common adverse events of grade 3–4 in the pemetrexed group were anaemia (16 [4%] of 359 patients), neutropenia (13 [4%]), and fatigue (15 [4%]). In the placebo group, these adverse events were less common: anaemia (one [<1%] of 180 patients), neutropenia (none), and fatigue (one [<1%]). The most frequent serious adverse events were anaemia (eight [2%] of 359 patients in the pemetrexed group *vs* none in the placebo group) and febrile neutropenia (five [1%] *vs* none). Discontinuations due to drug-related adverse events occurred in 19 (5%) patients in the pemetrexed group and six (3%) patients in the placebo group.

Interpretation Continuation maintenance with pemetrexed is an effective and well tolerated treatment option for patients with advanced non-squamous NSCLC with good performance status who have not progressed after induction therapy with pemetrexed plus cisplatin.

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Introduction

Three-quarters of patients with non-small-cell lung cancer (NSCLC) have locally advanced (stage IIIB) or metastatic (stage IV) disease at the time of diagnosis.[1] Guidelines recommend platinum-based combinations as first-line treatment in suitable patients,[2,3] resulting in

response rates of 20–40% and median overall survival of 7–12 months.[3–5] Efforts to improve treatment outcome have identified a difference in survival depending on tumour histology; specifically, patients with non-squamous NSCLC, but not those with squamous NSCLC, had improved efficacy when treated with pemetrexed than when treated with gemcitabine (both in combination with cisplatin),[6] docetaxel (both as single-drug, second-line therapies),[7] and placebo (as maintenance therapy).[8]

Other efforts have focused on prolonging tumour response or stable disease by administering well tolerated maintenance treatment in patients who have not progressed during first-line or induction treatment.[8–13] Maintenance therapy is given until progressive disease or unacceptable toxic effects, with the specific goal of improving progression-free survival and overall survival with minimal side-effects.

Pemetrexed combined with cisplatin was efficacious in a first-line setting for non-squamous NSCLC,[6] and single-agent maintenance therapy with pemetrexed improved progression-free survival and overall survival after induction therapy with a non-pemetrexed platinum doublet.[8] However, pemetrexed has not been studied as a maintenance treatment after induction with pemetrexed plus cisplatin. Administration of a maintenance therapy that has been shown to be effective and well tolerated during the induction regimen combines the advantage of continuing a beneficial therapy with the improved safety of a single-agent treatment.

We therefore designed the PARAMOUNT double-blind, multicentre, phase 3, randomised placebo-controlled study to see whether continuation maintenance therapy with pemetrexed versus placebo would improve progression-free survival in patients with advanced non-squamous NSCLC whose disease had not progressed during four cycles of induction chemotherapy with pemetrexed plus cisplatin.[14]

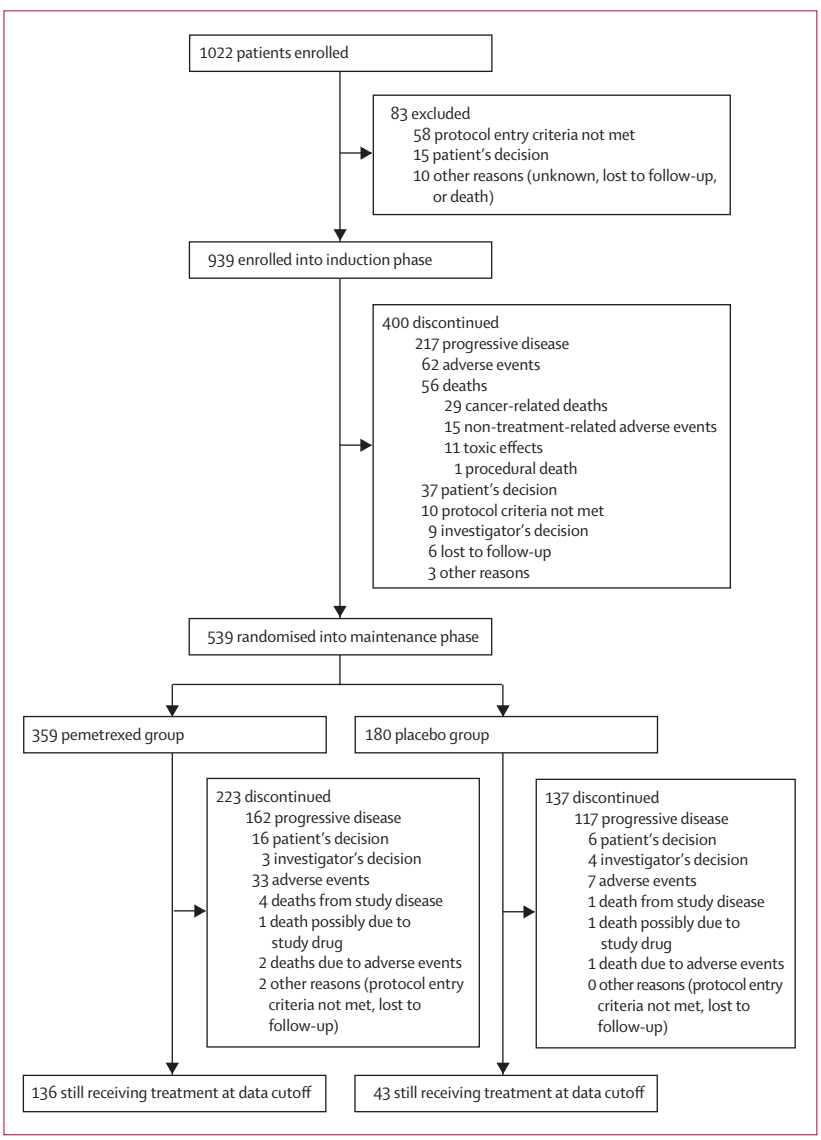

Figure 1: **Trial profile**

Methods

Study design and patients

This study had two phases: the non-randomised induction phase and the randomised maintenance phase. Patients were eligible for the induction phase of the study if they had: cytological or histological diagnosis of advanced non-squamous NSCLC (stage IIIB or IV); no previous systemic chemotherapy for lung cancer including adjuvant; age of 18 years or older; one or more measurable lesions per Response Evaluation Criteria In Solid Tumors (RECIST 1.0);[15] adequate organ function; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[16] Key exclusion criteria were concurrent administration of other antitumour therapy and tumour histology that was predominantly squamous cell, mixed small cell, or a combination of both histologies. Patients with CNS metastases were eligible if the metastases were stable and successfully treated with local therapy (that is, stable treated metastases), and the patient was off corticosteroids for at least 4 weeks.

Patients were eligible for the maintenance phase of the study if they had an ECOG performance status of 0 or 1 and had completed four cycles of induction therapy with pemetrexed plus cisplatin with documented radiographical evidence of a partial or complete tumour response or stable disease.

Institutional ethics review boards at each site approved the protocol. The study was done in accordance with good clinical practice and the ethics principles of the Declaration of Helsinki. Written informed consent was obtained from every patient before treatment initiation.

Randomisation and masking

After induction treatment, eligible patients were randomly assigned (2:1 ratio, block size of three) to receive maintenance treatment with pemetrexed plus best supportive care or with placebo plus best supportive care. This randomisation ratio was chosen to provide sufficient comparative data to show the superiority of pemetrexed plus best supportive care while reducing patient exposure to the potentially inferior treatment of placebo plus best supportive care. We used a stratified method of randomisation.[17] We did a separate and independent randomisation within each of the eight strata or subgroups, defined by all eight combinations of values of the following baseline and prognostic factors: ECOG performance status just before randomisation (0 *vs* 1); tumour response to induction chemotherapy (complete or partial response *vs* stable disease); and disease stage before administration of induction therapy (IIIB *vs* IV).

A centrally located, computerised, interactive, voice-activated response system (IVRS) controlled assignment of patient treatment. To maintain the double blind, investigators provided patient information to an unmasked third party, such as a pharmacist, who then called the IVRS and obtained the patient's treatment assignment. Masking was also maintained by the use of visually indistinguishable solutions of pemetrexed and placebo, and scheduling routine laboratory assessments immediately before the start of every cycle to minimise observation of haematological nadirs associated with treatment. Treatment group code and other variables that could link patients to study groups were masked in the database until the primary datalock; however, patients and physicians were unmasked to treatment group at the time of disease progression so that an informed decision on further treatment could be made.

Procedures

During the induction phase, patients were treated with intravenous pemetrexed (Alimta, Eli Lilly and Company, Indianapolis, IN, USA; 500 mg/m²) and intravenous cisplatin (75 mg/m²) on day 1 of a 21-day cycle, for four cycles. This phase was followed by a maintenance phase in which eligible patients were randomly assigned to receive intravenous pemetrexed (500 mg/m²) plus best supportive care or placebo (intravenous 0·9% sodium chloride) plus best supportive care, both on day 1 of a 21-day cycle. Maintenance treatment began 7 days or less from the date of randomisation and 21–42 days from day 1 of the fourth cycle of induction therapy. Maintenance therapy was continued until disease progression, unacceptable adverse events, or decision of the patient or physician. Patients were followed up until death or study closure.

During both phases of the study, all patients received folic acid, vitamin B_{12}, and prophylactic dexamethasone. Investigators followed current American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines for use of colony-stimulating factors and erythropoiesis-stimulating agents. Dose adjustments and cycle delays of 42 days or less were allowed as per label for resolution of toxic effects.

Baseline tumour measurements were done less than 4 weeks before the first dose of study drug of the induction phase. CT scans and MRIs were preferred for measurements; ultrasound and PET scans were not

	Pemetrexed (N=359)	Placebo (N=180)
Sex		
Male	201 (56%)	112 (62%)
Female	158 (44%)	68 (38%)
Age at randomisation (years)		
Median (range)	61 (32–79)	62 (35–83)
Age group		
<65 years	238 (66%)	112 (62%)
≥65 years	121 (34%)	68 (38%)
Ethnic origin		
Asian	16 (4%)	8 (4%)
African	4 (1%)	1 (<1%)
White	339 (94%)	171 (95%)
Smoking status		
Ever smoker	275 (77%)	144 (80%)
Never smoker	82 (23%)	34 (19%)
Unknown	2 (<1%)	2 (1%)
ECOG PS at randomisation		
0	115 (32%)	55 (31%)
1	243 (68%)	123 (68%)
2–3*	1 (<1%)	2 (1%)
Disease stage before maintenance therapy†		
Stage IIIB	31 (9%)	19 (11%)
Stage IV	328 (91%)	161 (89%)
Best tumour response to induction therapy		
Complete or partial response	166 (46%)	76 (42%)
Stable disease	186 (52%)	94 (52%)
Progressive disease*	1 (<1%)	3 (2%)
Unknown*	6 (2%)	7 (4%)
Time from start of induction therapy to randomisation (months)		
Median (range)	2·96 (2·14–4·14)	2·96 (2·53–3·71)
Histological classification‡§		
Bronchoalveolar	6 (2%)	2 (1%)
Adenocarcinoma	304 (85%)	158 (88%)
Large-cell carcinoma	24 (7%)	12 (7%)
Other or indeterminate¶	25 (7%)	8 (4%)

Data are number of patients (%) unless otherwise indicated. ECOG PS=Eastern Cooperative Oncology Group performance status. NSCLC=non-small-cell lung cancer. *Randomised patients with an ECOG PS of 2 or 3, or a best response to induction therapy of progressive disease or unknown were considered protocol violations. †Lung Cancer Staging Guidelines, Version 5.[22] ‡Grouped by WHO classification of lung tumours. §Patients with squamous-cell carcinoma were not eligible. ¶Represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma or large-cell carcinoma and includes NSCLC not otherwise specified, poorly differentiated, and adenocarcinoma, mucinous.

Table 1: **Patient and disease characteristics of all randomised patients**

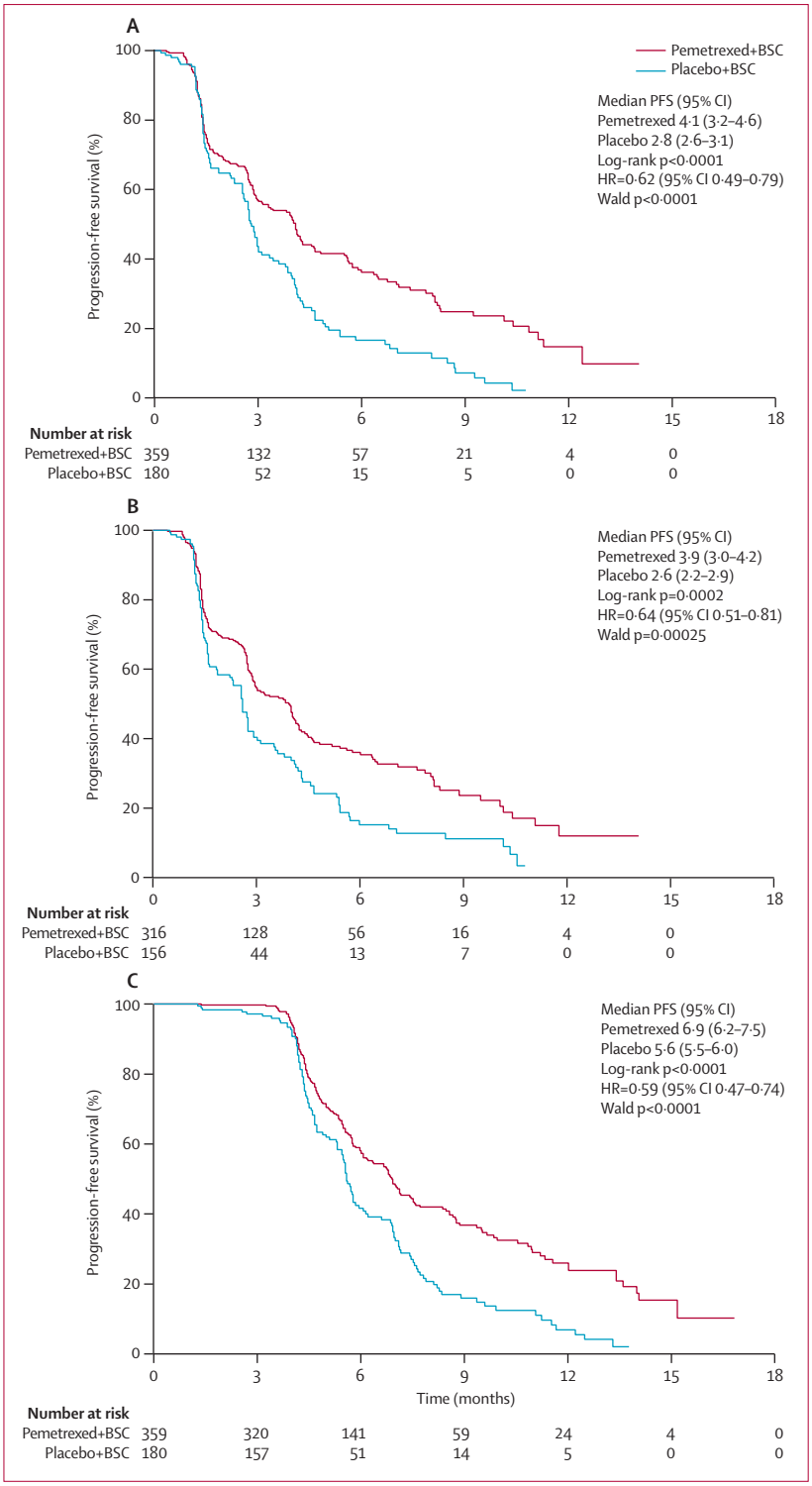

***Figure 2*: Progression-free survival in the randomised patient population**
BSC=best supportive care. PFS=progression-free survival. Kaplan-Meier curves of progression-free survival as measured from randomisation for maintenance treatment and determined by the investigator (A); as measured from randomisation for maintenance treatment and determined by independent review (B); and as measured from the start of induction treatment and determined by the investigator (C). Progression-free survival for maintenance treatment was calculated to the first date of objectively determined progressive disease or death. Patients who had not progressed or died as of the data cutoff date were censored at the date of the last tumour assessment.

allowed. The same method of tumour assessment used at baseline was used throughout the study and repeated every other cycle (6 weeks [±1]), including during cycle 4 to confirm eligibility before randomisation into the maintenance phase.

We assessed tumour response using RECIST 1.0 guidelines.[15] Response confirmation occurred 4 weeks or more after the initial measurement and every other cycle thereafter. Independent radiologists masked to treatment assignment did a central review of radiological data from all randomised patients with at least a baseline and one follow-up scan.

Patients rated their present health condition using the standardised EuroQol 5-dimensional scale (EQ-5D)[18] at baseline, on day 1 of every cycle of induction and maintenance therapy, and at the 30-day post-discontinuation visit. The EQ-5D consisted of two parts: five descriptive questions and a visual analogue scale (VAS) that allowed patients to rate their present health condition. We converted data into a weighted health-state index score using UK-based weights since most of the patients were enrolled at sites in Europe. Patients were assessed for adverse events before every cycle according to the Common Terminology Criteria for Adverse Events, version 3.0.[19] Resource use was assessed by recording the use of measures of best supportive care (eg, analgesics, antiemetic drugs, anti-infective drugs, colony-stimulating factors, erythropoiesis-stimulating agents, transfusions, palliative radiation to extrathoracic structures, and nutritional support) and treatment-related admissions to hospital.

Statistical analyses

The primary endpoint of the study was to compare progression-free survival of patients treated with pemetrexed continuation maintenance therapy versus placebo based on investigator assessed data. Secondary objectives were tumour response rate, patient-reported outcomes, resource use, adverse events, and overall survival.

For the maintenance phase, all randomised patients were eligible for efficacy and safety analyses (intention-to-treat analysis). The primary analysis of progression-free survival was based on the assumption that the true hazard ratio (HR) equals 0·65 (two-sided α=0·05), which provided 90% power to show a statistically significant difference between groups given a minimum of 238 events (52% censoring). The overall type-1 α error (0·05) was controlled for both progression-free survival and overall survival with a statistical gate-keeping scheme. We did a preliminary (interim) overall survival analysis, per protocol, at the time of the primary progression-free survival analysis, with a nominal two-sided α level of 0·0001. The final analysis of overall survival, based on the assumption that the true HR is 0·70 (two-sided α=0·05) and providing 93% power to show a statistically significant difference between groups

after a minimum of 390 events (30% censoring), will be based on a nominal α level of 0·0498 and will be reported separately when available.

We used the Kaplan-Meier method for analyses of progression-free survival and overall survival.[20] We used the Cox proportional hazards model to estimate HRs with assigned treatment as the only covariate.[21] We compared tumour response rates (complete or partial response) and disease control rates (complete or partial response, or stable disease) between groups using the Fisher's exact test. We used SAS version 9.1.3 for all statistical analyses.

This study is registered with ClinicalTrials.gov, NCT00789373.

Role of the funding source

The sponsor designed the study in collaboration with LP-A and CG. The sponsor supplied pemetrexed and did the statistical analyses of the data collected by the investigators. After datalock, the sponsor, physicians, statisticians, medical report writers, and investigators had full access to the data. All authors had final decision to submit for publication.

Results

Between Nov 19, 2008, and April 23, 2010, 939 patients at 83 investigational hospitals in 16 countries were enrolled in the induction phase of the study: 637 (68%) of them completed four cycles, 283 (30%) achieved a best response of complete or partial response, and 700 (75%) achieved a best response of disease control (complete or partial response or stable disease). Of the 939 patients who received induction therapy, 539 patients were randomly assigned to maintenance treatment with either pemetrexed and best supportive care (n=359) or placebo and best supportive care (n=180; (figure 1). Of the 400 patients not randomly assigned to maintenance therapy, nine were eligible for maintenance, but did not participate: eight because of patient's decision and one because of investigator's decision. Characteristics of randomised patients were well balanced between treatment groups (table 1).

As of June 30, 2010 (data cutoff date), 136 (38%) of 359 patients in the pemetrexed group and 43 (24%) of 180 patients in the placebo group were still receiving treatment, with 93% of the patients in each group (333 of 359 for pemetrexed, 167 of 180 for placebo) having received at least one cycle of maintenance treatment. A median of four cycles of pemetrexed (range 1–19, mean 4·9) and placebo (range 1–16, mean 4·2) was given, with 84 (23%) of 359 patients completing more than six cycles of pemetrexed versus 25 (14%) of 180 in the placebo group. Median patient follow-up, measured from time of randomisation, was 5·0 months (95% CI 4·5–5·5). More patients treated with pemetrexed required dose reductions than did those given placebo (11 [3%] of 359 patients in the pemetrexed group *vs* one [<1%] of 180 in the placebo group). Pemetrexed dose intensity was 94·8% of the planned mean dose.

A significant increase in investigator-assessed progression-free survival was noted for patients treated with pemetrexed (HR 0·62, 95% CI 0·49–0·79; log-rank p<0·0001). The median progression-free survival was 4·1 months (95% CI 3·2–4·6) for pemetrexed (175 of 359, 49% censored) and 2·8 months (95% CI 2·6–3·1) for placebo (62 of 180, 34% censored; figure 2A).

An independent and masked radiology board reviewed available scans from 472 (88%) of 539 patients (316 from the pemetrexed group, 156 from the placebo group) and reported similar results to the investigator-assessed outcome: median progression-free survival was 3·9 months (95% CI 3·0–4·2) for the pemetrexed group and 2·6 months (2·2–2·9) for the placebo group (HR 0·64, 95% CI 0·51–0·81; log-rank p=0·00020; figure 2B). The main reason patients were not included in the independent review was because they did not complete one full cycle of treatment before the data cutoff date (52 of 67 patients excluded).

An analysis of progression-free survival measured from the beginning of induction treatment (rather than from the time of randomisation) was consistent with the primary analysis: median progression-free survival was 6·9 months (95% CI 6·2–7·5) for the pemetrexed group and 5·6 months (5·5–6·0) for the placebo group (HR 0·59, 95% CI 0·47–0·74; log-rank p<0·0001; figure 2C).

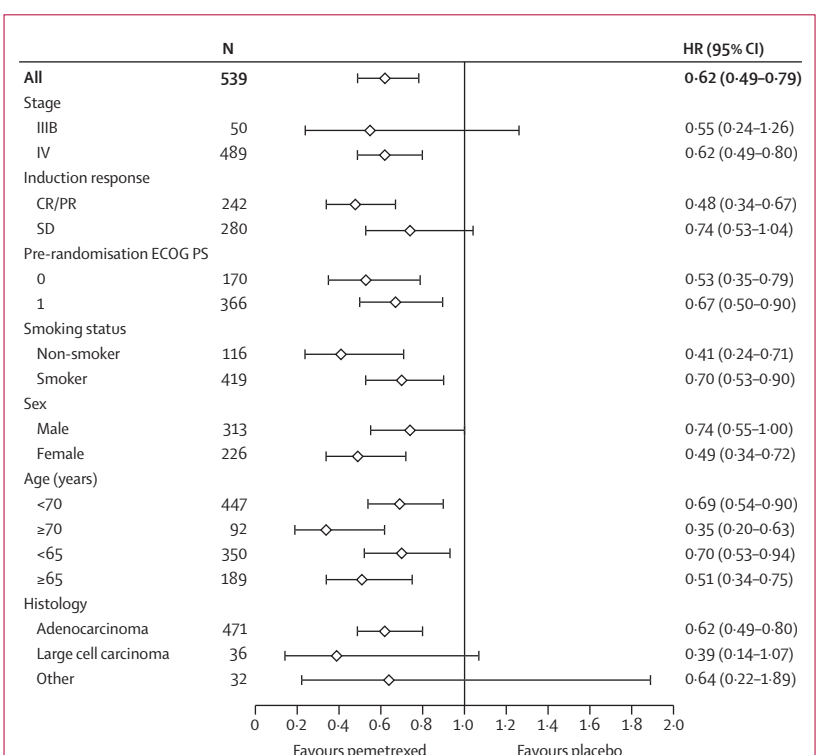

Figure 3: **Progression-free survival HRs (pemetrexed over placebo) in subgroups according to baseline characteristics as assessed by investigator**

HR=hazard ratio. CR=complete response. PR=partial response. SD=stable disease. ECOG PS=Eastern Cooperative Oncology Group performance status.

	Pemetrexed (N=316)		Placebo (N=156)		p value†
	n	% (95% CI)	n	% (95% CI)	
Complete response	0	0%	0	0%	NE
Partial response	9	3% (1·3–5·3)	1	0·6% (0·02–3·5)	0·18
Overall response rate (complete and partial response)	9	3% (1·3–5·3)	1	0·6% (0·02–3·5)	0·18
Stable disease	218	69% (63·6–74·1)	92	59% (50·8–66·8)	0·039
Disease control rate (complete response, partial response or stable disease lasting a minimum of 6 weeks)	227	72% (66·5–76·7)	93	60% (51·5–67·4)	0·009
Progressive disease	88	28% (23·0–33·1)	61	39% (31·4–47·2)	0·015
Unknown‡§	1	0·3% (0·01–1·8)	2	1% (0·2–4·6)	NE

NE=not estimable. *RECIST response criteria were used. Patients with complete or partial response during induction were not required to have response confirmation to be randomised into maintenance therapy. Assessment of tumour response during the maintenance phase used the radiological assessment before randomisation as the baseline measurement. Patients who discontinued study therapy before disease progression had imaging done around once every 6 weeks to determine the date of radiographical progression. †p value is from the Fisher's exact test. ‡Progression was not documented or one or more target or non-target sites were not assessed. §As of the data cutoff date (June 30, 2010), 179 patients were still receiving maintenance treatment. The best overall response is not known for all patients.

Table 2: **Best tumour responses* in randomised patients during maintenance treatment assessed by an independent reviewer**

	Pemetrexed (N=359)		Placebo (N=180)	
	All grades	Grades 3, 4, or 5*	All grades	Grades 3, 4, or 5*
Patients with ≥1 laboratory adverse event†	86 (24%)‡	33 (9%)‡	12 (7%)‡	1 (<1%)‡
Haematological adverse events				
Anaemia	50 (14%)‡	16 (4%)‡	8 (4%)‡	1 (<1%)‡
Neutropenia	30 (8%)‡	13 (4%)‡	1 (<1%)‡	0‡
Leucopenia	13 (4%)‡	6 (2%)	0‡	0
Thrombocytopenia	11 (3%)	4 (1%)	1 (<1%)	0
Non-haematological adverse events				
Alanine aminotransferase	9 (3%)	1 (<1%)	1 (<1%)	0
Patients with ≥1 non-laboratory adverse event†	146 (41%)‡	32 (9%)	49 (27%)‡	8 (4%)
Fatigue (asthenia, lethargy, malaise)	59 (16%)	15 (4%)‡	19 (11%)	1 (<1%)‡
Nausea	39 (11%)‡	1 (<1%)	4 (2%)‡	0
Vomiting	21 (6%)‡	0	3 (2%)‡	0
Mucositis or stomatitis	18 (5%)	1 (<1%)	4 (2%)	0
Oedema	17 (5%)	0	6 (3%)	0
Anorexia	14 (4%)	1 (<1%)	2 (1%)	0
Pain, any event	13 (4%)	3 (<1%)	3 (2%)	0
Infection	12 (3%)	4 (1%)	3 (2%)	2 (1%)
Diarrhoea	10 (3%)	0	3 (2%)	0
Neuropathy: sensory	10 (3%)	1 (<1%)	10 (6%)	1 (<1%)
Watery eye (epiphora, tearing)	9 (3%)	0	1 (<1%)	0
Constipation	8 (2%)	0	5 (3%)	0

Data are number of patients in the specified category (%). *Among possibly drug-related adverse events during the maintenance treatment period, no laboratory adverse events of grade 5 (deaths) and two non-laboratory adverse events of grade 5 (deaths) were recorded: one patient died in the pemetrexed group (pneumonia) and one died in the placebo group (sudden death—not otherwise specified). †Adverse events were reported using Common Terminology Criteria for Adverse Events version 3.0 (NCI 2006). ‡Difference between treatment groups was significant (Fisher's exact test p≤0·05).

Table 3: **Adverse events possibly related to study drug occurring in 3% or more of patients in either group during maintenance treatment**

The relative treatment effect of maintenance treatment with pemetrexed was consistent across all subgroups based on baseline characteristics (figure 3) and similar to that observed in the primary unadjusted analysis of progression-free survival.

A subgroup analysis of investigator progression-free survival data for all randomised patients with an induction response of complete or partial response yielded an unadjusted HR of 0·48 (95% CI 0·34–0·67) and a median progression-free survival of 4·1 months (95% CI 3·1–6·0) for the pemetrexed group (n=166) versus 2·6 months (1·6–2·9) for the placebo group (n=76). Patients with an induction response of stable disease had a median progression-free survival of 4·1 months (95% CI 3·0–4·6) for the pemetrexed group (n=186) while that for patients in the placebo group (n=94) was 3·0 months (2·8–4·1) and the unadjusted HR was 0·74 (0·53–1·04).

Overall response rate (complete and partial response) assessed by the independent reviewer showed tumour reductions during maintenance treatment beyond the baseline response to induction therapy (table 2). A greater proportion of patients receiving pemetrexed achieved disease control (complete or partial response, or stable disease lasting ≥6 weeks) than did those receiving placebo when assessed by the independent reviewer (table 2).

We did a prespecified interim analysis of overall survival after 123 deaths (77 of 359 patients in the pemetrexed group; 46 of 180 in the placebo group), with censoring rates of 79% (282 of 359 patients) in the pemetrexed group and 74% (134 of 180) in the placebo group. The results of the preliminary (interim) survival analysis did not meet the predefined level of statistical significance (p>0·0001). The final analysis of overall survival will be done after a minimum of 390 deaths.

Patients were given an EQ-5D questionnaire to assess their overall health status during the study. Treatment groups did not differ in compliance rates (>80%) during and after treatment (data not shown). The most commonly reported reason for not completing the questionnaire was failure to administer it to the patient. The baseline EQ-5D index scores were 0·77 in the pemetrexed group and 0·79 in the placebo group, and the baseline visual analogue scale (VAS) rating was 71·08 in the pemetrexed group and 71·02 in the placebo group. Based on the mixed-effects repeated measures analyses of the index scores and VAS ratings, no significant treatment-by-time interaction and no overall treatment differences were observed in the quality-of-life data during maintenance therapy. A full analysis of the health outcomes data will be presented separately.

Compared with placebo, patients in the pemetrexed group had a significantly higher incidence of drug-related grade 3–4 laboratory adverse events (p<0·0001), with more cases of neutropenia and anaemia in the pemetrexed group, and no possibly drug-related laboratory grade 5 (deaths) adverse events reported during maintenance

	Pemetrexed (N=200)	Placebo (N=122)	p value
Patients with post-discontinuation therapy	116 (58%)	78 (64%)	0·35
Drug name			
Erlotinib	62 (31%)	45 (37%)	0·33
Docetaxel	58 (29%)	43 (35%)	0·27
Gemcitabine	15 (8%)	4 (3%)	0·15
Investigational drug	10 (5%)	4 (3%)	0·58
Vinorelbine	8 (4%)	2 (2%)	0·33
Bevacizumab	3 (2%)	1 (<1%)	1·00
Cisplatin	3 (2%)	1 (<1%)	1·00
Other†	13 (7%)	6 (5%)	..

Data are number of patients (%). *Percentages are based on the population of patients who received post-discontinuation therapy, plus any other patients who were alive 30 days after discontinuation of study treatment (defined as post-discontinuation therapy-eligible patients). †Systemic therapies administered to 1% or fewer patients in both groups are summarised under "Other". These therapies included carboplatin, pemetrexed, BIBF 1120, paclitaxel, placebo, aspirin, aflibercept, cyclophosphamide, gefitinib, ifosfamide, vinflunine, and other antineoplastic drugs.

Table 4: **Summary of post-discontinuation anticancer systemic therapy for all eligible patients***

treatment (table 3). The proportion of patients with one or more non-laboratory grade 3–5 adverse events did not differ significantly between groups (table 3; p=0·080). Fatigue was the most common pemetrexed-associated toxic effect (table 3). The use of transfusions of red blood cells, colony-stimulating factors, and anti-infective drugs was higher in the pemetrexed group than in the placebo group (data not shown). Discontinuations due to possibly drug-related adverse events occurred in 19 patients (5%) in the pemetrexed group and six patients (3%) in the placebo group (p=0·39). The most frequently reported serious adverse events were anaemia (in eight [2%] of 359 patients in the pemetrexed group and none in the placebo group) and febrile neutropenia (five [1%] of 359 patients in the pemetrexed group and none in the placebo group).

Two possibly drug-related deaths occurred during maintenance treatment (pneumonia in the pemetrexed group; sudden death in the placebo group), and an additional possibly drug-related death occurred within 30 days of discontinuation of maintenance treatment (endocarditis in the pemetrexed group).

A preplanned analysis suggested that long exposure to maintenance pemetrexed (≤6 cycles *vs* >6 cycles) was not associated with an increase in the overall incidence of possibly drug-related grade 3–4 adverse events, with the exception of neutropenia (in seven [8%] of 84 patients receiving >6 cycles of pemetrexed *vs* six [2%] of 275 patients receiving ≤6 cycles of pemetrexed; p=0·015). Since this comparison was not randomised, we examined the baseline characteristics of patients who received either more than six cycles or six cycles or less. These baseline characteristics were similar between the two groups, but not identical (the group receiving more cycles had more patients with a performance status of 0 and more responders than the group receiving less cycles). Adverse events of grades 3, 4, or 5 analysed by age, sex, and ethnic origin were consistent with those reported in the overall study population (data not shown).

Post-discontinuation therapy was given at the discretion of the investigator. A similar proportion of patients in both groups received post-discontinuation therapy (table 4). 217 patients had not received post-discontinuation therapy at the time of this analysis; 179 (82%) of these patients were still receiving maintenance treatment at this time. The post-discontinuation therapy selections were well balanced between treatment groups.

Discussion

In this phase 3 study, patients with advanced non-squamous NSCLC who continued single-agent pemetrexed maintenance therapy after induction therapy with pemetrexed-cisplatin had a significant improvement in progression-free survival compared with those who received placebo maintenance therapy after the same induction therapy. This improvement was reported across all subgroups of patients. This study is the second fully powered phase 3 trial to show the efficacy of pemetrexed maintenance therapy,[8] and, to our knowledge, the first to demonstrate the efficacy of pemetrexed continuation maintenance therapy (panel).

Ciuleanu and colleagues[8] showed the benefit of pemetrexed switch maintenance therapy for advanced non-squamous NSCLC after induction with a non-pemetrexed-containing platinum doublet. The progression-free survival results of the pemetrexed maintenance group were similar to those of PARAMOUNT, with a median investigator-assessed progression-free survival of 4·5 months (95% CI 4·2–5·6) for the non-squamous population of the study. Progression-free survival was confirmed in both studies by independent assessments of tumour scans, as were response and disease control rates. Ciuleanu and colleagues[8] additionally showed a significant overall survival benefit at the final survival analysis, notably in the non-squamous NSCLC patient population. The overall survival results for PARAMOUNT will be analysed after the prespecified event number is reached.

Examination of progression-free survival data by induction response suggested that patients benefit from pemetrexed maintenance therapy irrespective of their response to induction therapy. The progression-free survival HR of the subgroup of complete or partial responses was numerically better than that of the subgroup of stable disease, but this numerical difference was possibly due to subgroup variation within the placebo group. These findings are consistent with those from the other pemetrexed maintenance study;[24] however, because this is a secondary analysis and previous response is a randomisation factor, these

Panel: **Research in context**

Systematic review

We know of no other phase 3 randomised trial exploring the same experimental group versus placebo in this patient population. We confirmed this by searching Scirus and Medline using the search terms "pemetrexed", "phase III", and "non-small cell lung cancer" in the title, and limiting the search to the years 2000–11, and by examination of a recent review article on the topic of maintenance therapy in advanced non-small-cell lung cancer (NSCLC).[23]

Interpretation

Results from this study show that pemetrexed continuation maintenance therapy, after induction with pemetrexed-cisplatin, extends progression-free survival relative to placebo and is well tolerated for patients with advanced non-squamous NSCLC with good performance status. Before this study, whether there would be clinical benefit when pemetrexed was continued as maintenance therapy after a pemetrexed-containing induction regimen was unknown. These data give doctors and patients a new option, showing that there are additional benefits to patients with the continuation of pemetrexed after four cycles of induction pemetrexed-cisplatin therapy in this setting.

results should be considered exploratory. Future analysis of the mature overall survival data will further our understanding of whether there is a differential benefit depending on response to induction treatment.

Similar to PARAMOUNT, other phase 3 studies in NSCLC have also shown the effectiveness of continuation maintenance therapy after a platinum-based induction doublet. In two studies,[9,13] maintenance therapy with gemcitabine after induction therapy with gemcitabine plus cisplatin led to improved progression-free survival compared with placebo as the maintenance therapy. Although both studies were underpowered for survival analysis, one[9] identified a significant improvement in overall survival for patients with good performance status at baseline. Another recent phase 3 study[25] examined continuation maintenance with gemcitabine in patients with disease control after four cycles of gemcitabine plus carboplatin. Results from this study showed no improvement in progression-free survival or overall survival in the maintenance group versus the placebo group. By contrast with other maintenance trials that were restricted to patients with good performance status (0 or 1), 64% of patients had a baseline performance status of 2 or more.[25] Additionally, few patients (<20%) received subsequent second-line treatment. Taken together, these results suggest that patients with poor performance status at baseline may not benefit from maintenance treatment following initial treatment for advanced NSCLC.

In advanced non-squamous NSCLC, bevacizumab is commonly used in combination with a platinum doublet in a first-line setting, with subsequent continuation maintenance with single-agent bevacizumab based on the results of ECOG 4599 and AVAiL.[26,27] PARAMOUNT did not include bevacizumab; however, a phase 3 trial, AVAPERL (MO22089),[28] recently reported that continuation maintenance with pemetrexed plus bevacizumab yielded superior progression-free survival results to that of continuation maintenance with bevacizumab after induction with pemetrexed plus cisplatin plus bevacizumab. Additionally, induction with pemetrexed plus bevacizumab plus carboplatin followed by continuation maintenance with pemetrexed plus bevacizumab is being studied in a phase 3 trial (POINTBREAK, NCT00614822).[29]

The safety results in the pemetrexed group of PARAMOUNT were consistent with the previously reported safety profile of pemetrexed.[6,8,30] In PARAMOUNT, pemetrexed was a relatively well tolerated maintenance treatment. The achieved dose intensity of pemetrexed was high, and the incidence of drug-related adverse events was low, with grade 3–4 neutropenia, anaemia, and fatigue each occurring in about 4% of patients. Furthermore, despite the slight increase in adverse events reported in the pemetrexed group, the similarity in EQ-5D scores between groups suggested that the quality of life was not adversely affected.

In this study, progression-free survival was selected as the primary endpoint because delaying progression is beneficial to patients. Furthermore, progression-free survival has been shown to be a valid and reliable measure of clinical benefit in another pemetrexed maintenance trial and has been associated with clinically meaningful improvement in overall survival.[8] Additionally, progression-free survival enables early assessment of benefit and is not influenced by additional lines of therapy.

A limitation of the trial was that its design only allowed patients with good performance status and disease control after pemetrexed-cisplatin induction to receive maintenance pemetrexed. It is unknown if patients with a performance status lower than 1 and who do not have disease control after four cycles of induction would benefit from continuation pemetrexed maintenance.

In conclusion, the results of PARAMOUNT support the safety and efficacy of pemetrexed as continuation maintenance therapy after induction with pemetrexed plus cisplatin for patients with advanced non-squamous NSCLC.

Contributors

NC, CG, WJ, SM, LP-A, and CV-G contributed to study design. PB, MD, CG, WJ, OM, LP-A, MR, SM, FdM, J-LP, JC, TPS, EL, and MT contributed to data collection. NC, CV-G, MD, CG, WJ, LP-A, MR, AHZ, SM, J-LP, EL, and MT contributed to data analysis and interpretation. All authors contributed to writing or review of the manuscript, and gave their approval of the final manuscript.

Conflicts of interest

MD, CG, OM, LP-A, J-LP, MR, and MT served as an adviser or consultant to Eli Lilly and were financially compensated for their contributions. MD has also acted as a consultant and advisory board

member for Sanofi-Aventis and Roche. MR has also served on advisory boards for Hoffmann-La Roche, BMS, Daiichi Sankyo, Pfizer, and AstraZeneca, and has received honoraria from Hoffmann-La Roche, Daiichi Sankyo, and AstraZeneca. NC, CV-G, WJ, SM, and AHZ are employees of Eli Lilly, with some owning Lilly stock. All other authors declare no conflicts of interest.

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