VOLUME 31 · NUMBER 23 · AUGUST 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

PARAMOUNT: Final Overall Survival Results of the Phase III Study of Maintenance Pemetrexed Versus Placebo Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non–Small-Cell Lung Cancer

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Published online ahead of print at www.jco.org on July 8, 2013.

Supported by Eli Lilly.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00789373.

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0732-183X/13/3123w-2895w/$20.00

DOI: 10.1200/JCO.2012.47.1102

ABSTRACT

Purpose
In the phase III PARAMOUNT trial, pemetrexed continuation maintenance therapy reduced the risk of disease progression versus placebo (hazard ratio [HR], 0.62; 95% CI, 0.49 to 0.79; $P < .001$). Here we report final overall survival (OS) and updated safety data.

Patients and Methods
In all, 939 patients with advanced nonsquamous non–small-cell lung cancer (NSCLC) received four cycles of pemetrexed-cisplatin induction therapy; then, 539 patients with no disease progression and Eastern Cooperative Oncology Group performance status 0 or 1 were randomly assigned (2:1) to maintenance pemetrexed (500 mg/m^2 on day 1 of 21-day cycles; n = 359) or placebo (n = 180). Log-rank test compared OS between arms as measured from random assignment ($\alpha = .0498$).

Results
The mean number of maintenance cycles was 7.9 (range, one to 44) for pemetrexed and 5.0 (range, one to 38) for placebo. After 397 deaths (pemetrexed, 71%; placebo, 78%) and a median follow-up of 24.3 months for alive patients (95% CI, 23.2 to 25.1 months), pemetrexed therapy resulted in a statistically significant 22% reduction in the risk of death (HR, 0.78; 95% CI, 0.64 to 0.96; $P = .0195$; median OS: pemetrexed, 13.9 months; placebo, 11.0 months). Survival on pemetrexed was consistently improved for all patient subgroups, including induction response: complete/partial responders (n = 234) OS HR, 0.81; 95% CI, 0.59 to 1.11 and stable disease (n = 285) OS HR, 0.76; 95% CI, 0.57 to 1.01). Postdiscontinuation therapy use was similar: pemetrexed, 64%; placebo, 72%. No new safety findings emerged. Drug-related grade 3 to 4 anemia, fatigue, and neutropenia were significantly higher in pemetrexed-treated patients.

Conclusion
Pemetrexed continuation maintenance therapy is well-tolerated and offers superior OS compared with placebo, further demonstrating that it is an efficacious treatment strategy for patients with advanced nonsquamous NSCLC and good performance status who did not progress during pemetrexed-cisplatin induction therapy.

J Clin Oncol 31:2895-2902. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Recent phase III trials have explored the efficacy of maintenance therapy following a platinum-based first-line doublet as treatment for locally advanced or metastatic (stage IIIB to IV) non–small-cell lung cancer (NSCLC).[1-6] Maintenance therapy is started immediately after first-line (induction) therapy and aims to prolong tumor response or stable disease (SD), thus improving progression-free survival (PFS) and overall survival (OS), while maintaining or improving quality of life and minimizing toxicity. Maintenance therapy is usually administered until disease progression or unacceptable toxicity.

Some NSCLC maintenance therapy studies use a different drug for maintenance therapy than that used for induction (switch maintenance) to expose patients to an agent with a different mechanism of action.[1,3,4] Other studies use a drug effective during the induction regimen for maintenance therapy

(continuation maintenance) while discontinuing the more toxic compound, reasoning that a treatment already demonstrated to be effective and tolerable would combine the advantage of an ongoing beneficial therapy with the improved safety of a single-agent treatment.[2,5]

Pemetrexed maintenance therapy improved PFS and OS following a non-pemetrexed–containing platinum doublet.[1] However, pemetrexed had not been studied as maintenance treatment following induction with pemetrexed-cisplatin, a known efficacious first-line treatment.[7] The PARAMOUNT phase III study examined the efficacy of pemetrexed continuation maintenance therapy versus placebo in patients with advanced nonsquamous NSCLC whose disease had not progressed during four cycles of pemetrexed-cisplatin induction chemotherapy.[8] Only patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS)[9] of 0 or 1 received maintenance therapy in this trial because results from other maintenance studies suggested patients with poor PS would not benefit.[2,10]

Current treatment guidelines for patients with advanced NSCLC recommend four to six cycles of a platinum-based doublet as first-line or induction treatment.[11,12] PARAMOUNT specified four cycles of induction therapy, modeled after other recent maintenance trials[1,3-5] and because evidence suggested this was an acceptable duration.[13-15] Indeed, 90% (160 of 177) of the maximum responses observed in a recent study of first-line pemetrexed-cisplatin occurred in the first four cycles.[16]

The primary end point of the PARAMOUNT study was to compare PFS of the maintenance arms. The study was also fully powered for analysis of OS, a secondary objective. Primary and some secondary outcomes have been reported.[17,18] This article reports the final OS data and provides a safety update of pemetrexed continuation maintenance therapy.

PATIENTS AND METHODS

Study Design and Patients

Previous reports have described trial methodology.[8,17] Briefly, this phase III study had two treatment phases: an induction phase in which all patients were administered four cycles of pemetrexed (500 mg/m^2 intravenously [IV]; Alimta, Eli Lilly, Indianapolis, IN) and cisplatin (75 mg/m^2 IV) on day 1 of 21-day cycles and a double-blind maintenance phase in which eligible patients were randomly assigned (2:1) to either continuation pemetrexed (500 mg/m^2 IV) plus best supportive care or placebo (0.9% sodium chloride IV) plus best supportive care, both on day 1 of 21-day cycles.

Key induction phase eligibility criteria included advanced nonsquamous NSCLC (stage IIIB to IV),[19] at least one measureable lesion per Response Evaluation Criteria in Solid Tumors (RECIST 1.0),[20] no prior systemic chemotherapy for lung cancer, and an ECOG PS of 0 to 1.[9] Maintenance phase eligibility requirements included PS 0 to 1 and completion of four cycles of pemetrexed-cisplatin induction therapy with radiographic evidence of a partial response (PR) or complete tumor response (CR) or SD.[20]

Random assignment to the maintenance phase and associated masking proceeded as described previously.[17,21] Maintenance treatment began within 7 days of random assignment, 21 to 42 days from day 1 of induction cycle 4, and continued until disease progression, patient-physician decision, or unacceptable toxicity. All patients were observed until study closure or death.

During both phases of the study, patients received folic acid and vitamin B_{12} supplementation and prophylactic dexamethasone according to the pemetrexed label. Cycle delays ($\leq$ 42 days) and dose adjustments as specified by the label were permitted for resolution of toxicities.

Tumor measurement and patient-reported health outcome methodology have been reported.[8,17,18] Toxicity was assessed before each cycle by using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.[22]

The protocol was approved by site-specific ethics review boards. Study conduct was guided by principles of good clinical practice and the Declaration of Helsinki. Patients provided written informed consent before treatment initiation.

Statistical Analyses

All patients randomly assigned to the maintenance phase were eligible for efficacy and safety analyses (intent-to-treat). OS was analyzed by using the unadjusted Cox proportional hazards regression model[23] to estimate hazard ratios (HRs) and 95% CIs. Kaplan-Meier curves were used to estimate survival.[24] Differences in survival estimates between pemetrexed and placebo arms were assessed by using a two-sided log-rank test. Planned subgroup analyses of OS were performed by using stratification and predefined prognostic variables. SAS version 9.1.3 was used for all statistical analyses. Fisher's exact test was used for between-arm comparisons of toxicities.

A sample size of 558 randomly assigned patients was derived, assuming the true OS HR was 0.70 and assuming 30% censoring (that is, 93% power with 390 deaths).[25] Under the assumption that the true PFS HR was 0.65, the primary unadjusted log-rank test of PFS had 90% power to show a statistically significant difference between arms if $\geq$ 238 events were included in the analysis.[25] Approximately 900 patients were planned for the induction phase in order to randomly assigned $\geq$ 558 patients. The type I alpha error ($\alpha = .05$) was controlled for the analyses of PFS and OS by using a statistical gatekeeping and alpha-spending scheme to maintain the statistical power for assessment of OS at the time of survival maturity.

A planned interim OS analysis was performed and reported at the time of the primary PFS analysis (two-sided $\alpha = .0001$).[17] A regulatory request necessitated an additional preliminary OS analysis (two-sided $\alpha = .0001$), leaving .0498 to be spent for the final analysis of OS. As expected, the results of the preliminary (interim) survival analyses did not meet the predefined level of statistical significance ($P > .001$).

RESULTS

Patients and Treatment

Of the 939 patients enrolled in the induction phase (November 2008-April 2010) at the 83 primarily European investigational sites, 700 patients (75%) achieved disease control (tumor response or SD), and 637 (68%) completed four cycles of pemetrexed-cisplatin. Of these patients, 539 were randomly assigned to maintenance treatment: 359 to pemetrexed and 180 to placebo (Fig 1), from February 2009 to July 2010. The median time from the end of induction (day 21 of cycle 4) to the first maintenance dose was 3 days (range, −2 to 30 days), with the majority of the patients (68%) initiating maintenance therapy within 7 days.

As reported previously,[17] characteristics of randomly assigned patients were well balanced between treatment arms: median age of 61 years, 59% male, 94% white, 32% ECOG PS 0, 91% stage IV NSCLC, 86% adenocarcinoma, and 43% CR/PR induction response (Appendix Table A1, online only.)

At the OS data cutoff date (March 5, 2012), with a median follow-up of 12.5 months (95% CI, 11.1 to 13.7 months) for all patients and 24.3 months (95% CI, 23.2 to 25.1 months) for alive patients, 97% of the patients in the pemetrexed arm and 99% in the placebo arm had discontinued maintenance treatment (Fig 1). Among those discontinuing, 12.0% of the patients receiving pemetrexed and 4.4% of those receiving placebo had discontinued because of a possibly treatment-related adverse event. A total of 397 deaths were reported: 256 (71.3%) in the pemetrexed arm and 141 (78.3%) in the placebo arm. Most patients received at least one maintenance cycle

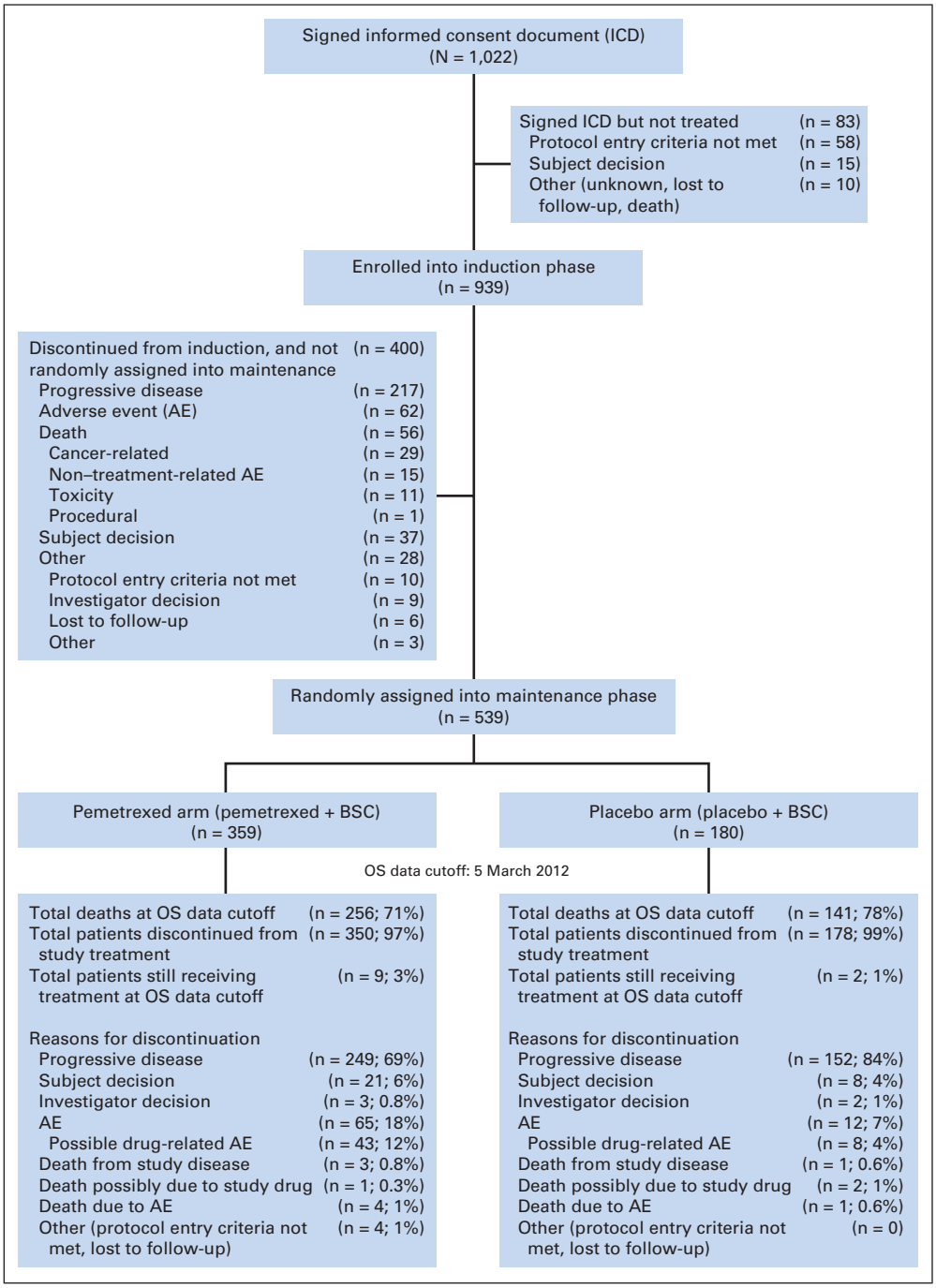

Fig 1. CONSORT diagram. BSC, best supportive care; OS, overall survival.

before treatment discontinuation: 99.4% (357 of 359) in the pemetrexed arm and 98.9% (178 of 180) in the placebo arm. Both arms reported a median of four maintenance cycles (range, one to 44 for pemetrexed and one to 38 for placebo); the mean number of cycles was 7.9 (standard deviation, 8.3) for pemetrexed and 5.0 (standard deviation, 5.2) for placebo. More than twice the number of patients given pemetrexed (37.0%) received more than six maintenance cycles than those given placebo (18.3%). This represents a minimum of 10 total cycles of pemetrexed treatment: four cycles of induction plus six cycles of maintenance. Likewise, more patients given pemetrexed (27.6%) than placebo (11.7%) received $\geq$ 10 cycles of maintenance therapy. The mean weekly dose of pemetrexed was 156.11 mg (standard deviation, 15.80), 93.7% of the planned mean dose and equivalent to 468.3 mg per 3-week cycle.

Efficacy

As shown in Figure 2A and Table 1, patients treated with continuation maintenance pemetrexed experienced statistically significantly longer OS (unadjusted HR, 0.78; 95% CI, 0.64 to 0.96; log-rank $P = .0195$) compared with those treated with placebo. Median OS was 13.9 months (95% CI, 12.8 to 16.0 months) pemetrexed and 11.0 months (95% CI, 10.0 to 12.5 months) placebo. Likewise, 1-year and

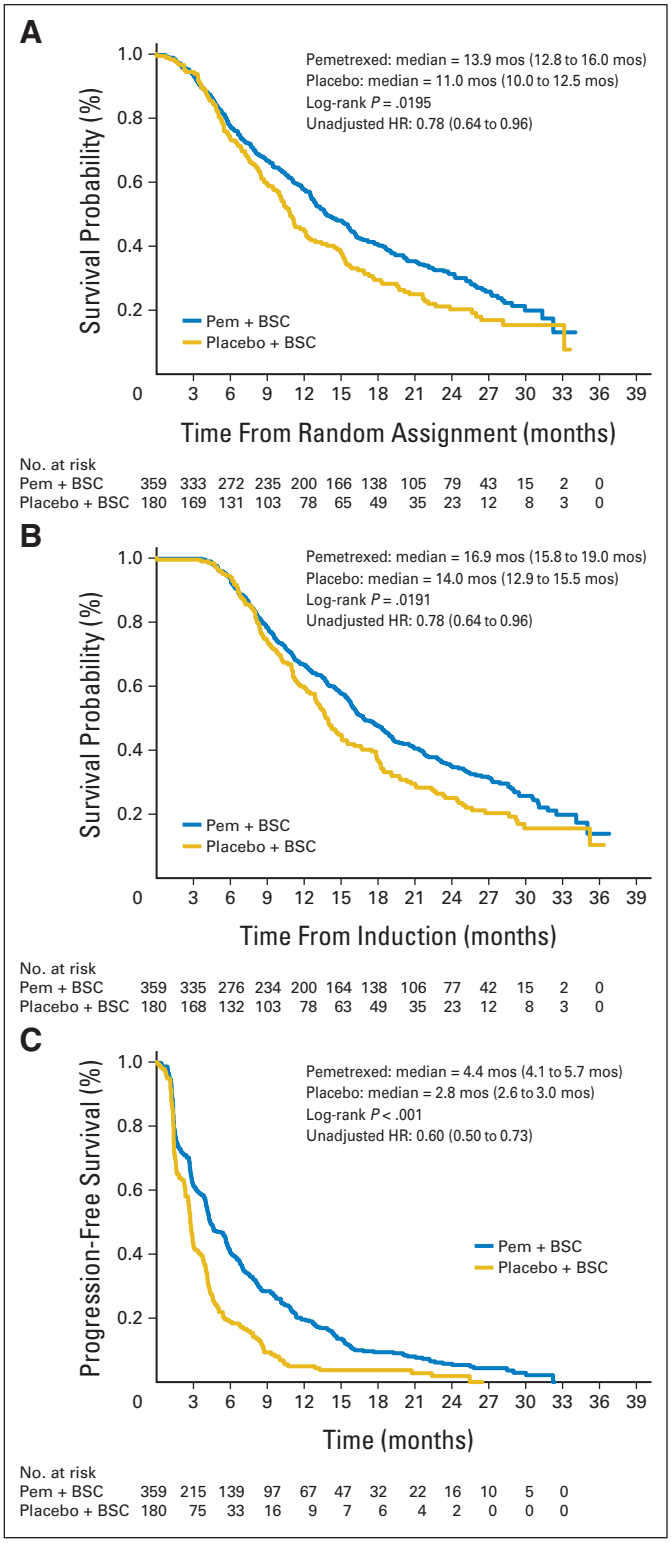

Fig 2. Kaplan-Meier plots of overall survival (OS) and progression-free survival (PFS) from randomly assigned patients. (A) OS as measured from random assignment for maintenance treatment. (B) OS as measured from the start of induction treatment, excluding patients who were not randomly assigned to maintenance because of disease progression or other reasons for discontinuing during induction treatment. (C) PFS reassessed at the time of OS data cutoff. PFS 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 tumor assessment. BSC, best supportive care; HR, hazard ratio; mos, months; Pem, pemetrexed.

2-year survival rates were significantly longer for patients given pemetrexed (58% and 32%, respectively) than for those given placebo (45% and 21%; Table 1).

Assessment of OS from the start of induction therapy (rather than from random assignment to maintenance) was consistent with the primary analysis, with no change in the HR (Fig 2B). The median OS measured from induction was 16.9 months (95% CI, 15.8 to 19.0 months) for pemetrexed and 14.0 months (95% CI, 12.9 to 15.5 months) for placebo.

Although prior publications reported PFS, the primary efficacy end point, measured from the time of random assignment,[17] Figure 2C demonstrates reassessment of investigator-assessed PFS by using data from the current (OS) datalock 20 months later. The unadjusted HR of 0.60 (95% CI, 0.50 to 0.73; $P < .001$) was similar to the HR originally reported: 0.62 (95% CI, 0.49 to 0.79; $P < .001$).[17]

Additional prespecified analyses examined OS in subgroups based on baseline characteristics. The impact of pemetrexed maintenance treatment on OS was consistent for all subgroups (Fig 3) and similar to that observed for subgroups in the primary analysis of PFS.[17] Figures 4A and 4B show a clear separation between the curves for both CR/PR and SD induction response subgroups, respectively, that numerically favors the pemetrexed arm. However, the study was not adequately powered for these two subgroups, and the differences were not statistically significant. Survival for all randomly assigned patients with CR/PR induction response yielded an unadjusted HR of 0.81 (95% CI, 0.59 to 1.11) and median OS of 15.5 months (95% CI, 12.5 to 18.8 months) for pemetrexed (n = 159) versus 11.2 months (95% CI, 8.4 to 15.8 months) for placebo (n = 75). Patients with an induction response of SD had an unadjusted HR of 0.76 (95% CI, 0.57 to 1.01) and median OS of 13.7 months (95% CI, 12.5 to 15.8 months) for pemetrexed (n = 190) versus 11.1 months (95% CI, 9.8 to 13.8 months) for placebo (n = 95). There was not a significant interaction term of response by treatment (CR/PR *v* SD; $P = .731$) by using the Cox model of response, treatment, and response by treatment interaction.

Postdiscontinuation Therapy

Postdiscontinuation therapy use after maintenance was at the discretion of the investigator. The fraction of randomly assigned patients receiving additional therapy was similar in both arms: 64.3% (n = 231) for pemetrexed and 71.7% (n = 129) for placebo (Appendix Table A2, online only). Postdiscontinuation selections were well balanced between treatment groups, with the exception of docetaxel (32.3% in the pemetrexed arm and 43.3% in the placebo arm), and the majority of patients received an approved second-line treatment (docetaxel or erlotinib). As expected with pemetrexed induction treatment, the use of second-line pemetrexed was low on both treatment arms: 1.9% for pemetrexed versus 3.9% for placebo.

Updated Safety Analysis

To detect any new safety findings, an updated safety analysis was performed that included data collected for 7 months (July 1, 2010, to February 7, 2011) after the primary end point analysis.[17] At the time of the data cutoff, 44 patients (8.2% of the study population) remained on study treatment: 41 (11.4%) receiving pemetrexed and three (1.7%) receiving placebo.[17]

Table 1. Summary of OS As Measured From Randomization

Variable	Pemetrexed (n = 359) No.	%	95% CI	HR	95% CI	*P*	Placebo (n = 180) No.	%	95% CI	*P*
Patient deaths	256	71					141	78		
Patients censored	103	29					39	22		
OS				0.78	0.64 to 0.96	.0199*				
Median, months	13.9		12.8 to 16.0				11.0		10.0 to 12.5	.0195†
Survival rate, years										
1		58	53 to 63					45	38 to 53	.0062
2		32	27 to 37					21	15 to 28	.0103

Abbreviations: HR, hazard ratio; OS, overall survival.
*Wald test.
†Log-rank test.

Compared with placebo, patients receiving pemetrexed had significantly greater incidence of drug-related grade 3 to 4 anemia, neutropenia, and fatigue; however, in each case, fewer than 7% of patients were affected (Table 2). Patients given pemetrexed also had statistically higher rates of some low-grade (grade 1 to 2) adverse events including anemia and neutropenia, as well as fatigue, nausea, vomiting, mucositis/stomatitis, anorexia, and watery eye. A notable percentage of patients given placebo (11%) also experienced grade 1 to 2 fatigue. There were no grade 5 (death) drug-related laboratory toxicities and three grade 5 drug-related nonlaboratory toxicities during maintenance treatment: one patient given pemetrexed (pneumonia) and two patients given placebo (sudden death, not otherwise specified and respiratory arrest, occurring during the safety update period).

Comparison of the patients with longer (more than six cycles) versus shorter exposure (six or fewer cycles) to pemetrexed maintenance therapy revealed no significant differences in all grades of toxicity, all grade 3 to 4 drug-related laboratory toxicities, and individual grade 3 to 4 drug-related laboratory toxicities. However, longer exposure to pemetrexed (more than six cycles) was associated with a numeric increase in grade 3 to 4 neutropenia (9% *v* 4%; $P = .062$). Notably the rate of grade 3 to 4 infections was similar ($P = .334$) in those receiving six or fewer cycles (3.5%) and in those receiving more than six cycles of pemetrexed (1.5%). Consistent with the primary analysis,[17] drug-related all-grade nonlaboratory toxicities were more frequent with longer pemetrexed exposure, but differences were not significant.

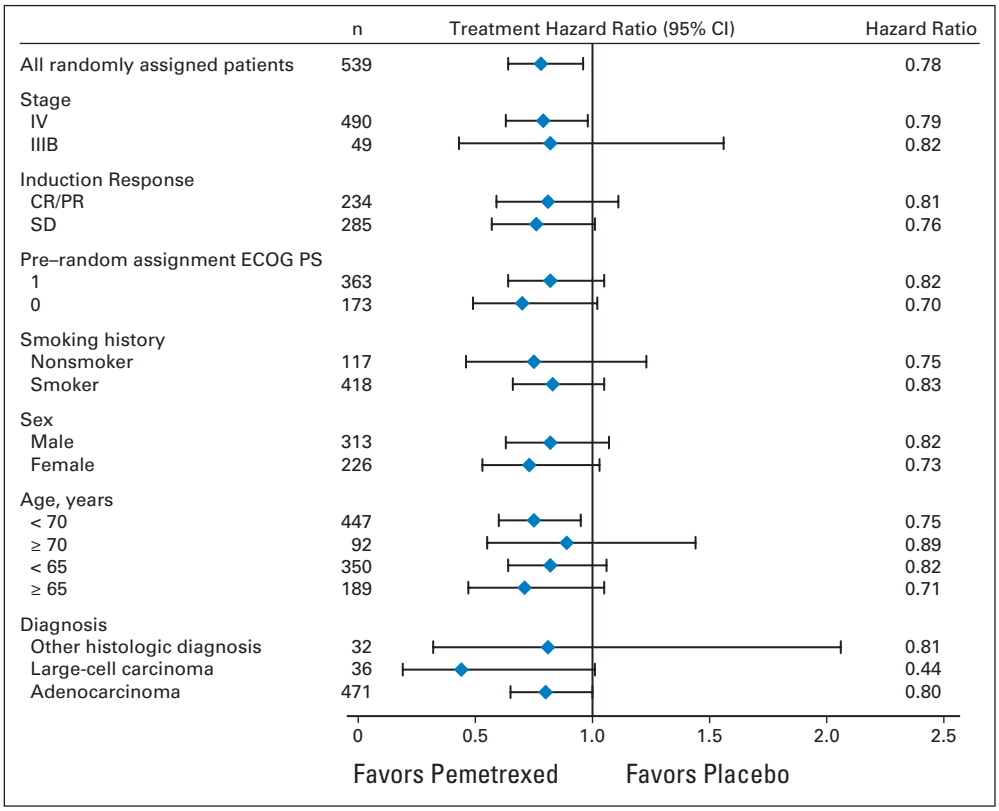

Fig 3. Overall survival hazard ratios (pemetrexed over placebo) in subgroups according to baseline characteristics. CR/PR, complete tumor response/partial tumor response; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, stable disease.

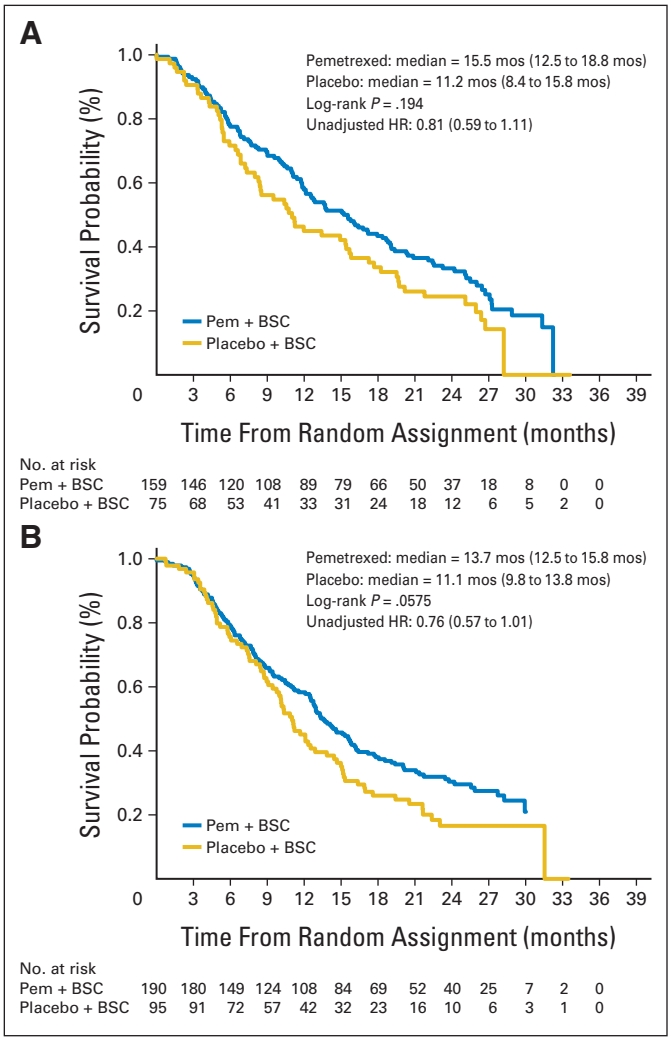

Fig 4. Kaplan-Meier plots of overall survival from induction response subgroups. Overall survival by (A) complete tumor response/partial tumor response induction response and (B) stable disease induction response. BSC, best supportive care; HR, hazard ratio; mos, months; Pem, pemetrexed.

Table 2. Possible Drug-Related Adverse Events During Maintenance Therapy*

Adverse Event	Pemetrexed (n = 359) Grade 1 to 2 (%)	Pemetrexed (n = 359) Grade 3 to 4 (%)†	Placebo (n = 180) Grade 1 to 2 (%)	Placebo (n = 180) Grade 3 to 4 (%)†
Laboratory toxicities				
Anemia	11.7‡	6.4‡	4.4‡	0.6‡
Neutropenia	5.0‡	5.8‡	0.6‡	0‡
Leukopenia	2.8‡	2.2	0‡	0
Thrombocytopenia	2.2	1.9	0	0
Creatinine	2.8	0	1.1	0
ALT	2.5	0.3	0.6	0
AST	2.5‡	0	0‡	0
Nonlaboratory toxicities				
Fatigue	17.5‡	4.7‡	10.6‡	1.1‡
Nausea	13.4‡	0.6	2.2‡	0
Vomiting	7.5‡	0.3	1.1‡	0
Edema, limb	6.7	0	3.3	0
Neuropathy, sensory	5.3	0.3	6.1	0.6
Mucositis/stomatitis, oral cavity	4.5‡	0.6	1.1‡	0
Anorexia	4.5‡	0.3	1.1‡	0
Diarrhea	4.2	0.3	2.2	0
Glomerular filtration rate	4.2	0	1.7	0
Watery eye (epiphora, tearing)	4.2‡	0	0.6‡	0
Pain, any event§	4.2	1.1	2.2	0
Fever, without neutropenia	2.8‡	0	0‡	0
Constipation	2.5	0	2.8	0
Dry eye syndrome	2.2	0	0	0
Rash, desquamation	1.4	0	0	0
Febrile neutropenia	0	1.9	0	0

*Data derived from the February 2011 safety update. Toxicities of any grade occurring in ≥ 2% of patients in either arm are listed, along with some select toxicities. Toxicities were reported using Common Terminology Criteria for Adverse Events version 3.0.[22]

†In addition to grade 3 to 4 possibly drug-related toxicities, there were three grade 5 drug-related nonlaboratory toxicities (deaths) during the maintenance treatment period: one in the pemetrexed arm (pneumonia) and two in the placebo arm (respiratory arrest and sudden death, not otherwise specified). There were no grade 5 drug-related laboratory toxicities (deaths).

‡Difference between treatment groups was significant (Fisher's exact test $P \leq .05$).

§Combined term.

DISCUSSION

The final PARAMOUNT results show that pemetrexed continuation maintenance therapy produces an OS benefit for patients with advanced nonsquamous NSCLC, with a 22% reduction in the risk of death (HR, 0.78; 95% CI, 0.64 to 0.96; $P = .0195$) and an improvement of almost 3 months in median OS. The OS benefit is particularly evident several months from random assignment and improves with time until approximately 12 months. These results coincide with the previously reported approximately 40% reduction in the risk of progression or death,[17] which was confirmed in this updated analysis of PFS (HR, 0.60). This is the first randomized phase III trial to demonstrate a significant OS benefit for continuation maintenance therapy.

Previous studies have demonstrated that switch maintenance affects OS.[12,26] Indeed, a recent meta-analysis that included 4,286 patients found superior efficacy of the switch maintenance strategy.[27] Although PFS was statistically significant for both switch maintenance (HR, 0.62) and continuation maintenance (HR, 0.90), OS was significantly improved in the switch analysis only (HR, 0.84; $P = .00026$ *v* HR, 0.92; $P = .33$). Another recent phase III study by Pérol et al[5] also found that gemcitabine continuation maintenance delivered a PFS benefit but not improvement in OS. However, that study was not powered to assess a difference in OS. Interestingly, in the adenocarcinoma subgroup of the Pérol study, there was no advantage in favor of gemcitabine continuation maintenance (HR, 0.98; 95% CI, 0.72 to 01.35). Until PARAMOUNT, no trial evaluating continuation maintenance therapy reported an OS improvement. This result may be because PARAMOUNT was sufficiently powered to detect a difference in OS, only enrolled patients with good PS, and denoted the favorable efficacy/toxicity ratio of pemetrexed in this setting.

PARAMOUNT is the second phase III randomized study to demonstrate that maintenance pemetrexed yields a PFS and OS benefit. A previous study investigated maintenance pemetrexed following induction with a non-pemetrexed–containing platinum doublet.[1]

These two pemetrexed maintenance studies differ in the induction regimens used and patient ethnicities enrolled. A recent retrospective exploratory analysis that sought to control for tumor subtype and ethnicity found that nonsquamous, non–East Asian patients in the Ciuleanu et al[1] study exhibited a 55% improvement in the risk of progression and a 13.2-month survival benefit versus 8.5 months for placebo,[28] results that are comparable to those of PARAMOUNT.

The survival results were not likely confounded by poststudy therapy given the higher rate of poststudy treatment for placebo versus pemetrexed (71.7% *v* 64.3%) and the relatively balanced selection of therapies between arms. The percentage of patients who received second-line therapy after progressing on maintenance treatment is consistent with current clinical practice in Europe and with rates reported in other first-line and maintenance trials.[1,3,4] The cross-over rate of patients given placebo therapy to pemetrexed therapy after discontinuing from the maintenance regimen was low, likely because all patients had received four cycles of pemetrexed-cisplatin first-line (induction) therapy.

All subgroups of patients analyzed demonstrated positive survival results, including both response to induction therapy subgroups (CR/PR and SD). OS and PFS in this[17] and the other pemetrexed maintenance trial[29] were not affected by response to induction. In the maintenance erlotinib trial, survival was improved only in patients with an induction response of SD.[30] With the PARAMOUNT PFS analysis, there was a difference in the PFS HRs between the CR/PR and SD groups; however, this was primarily caused by differences in the placebo arm, with patients in the pemetrexed arm deriving similar median benefits in both subgroups. Likewise in the final OS analysis reported here, the SD placebo subgroup did better than expected, with a median OS identical with that of the CR/PR placebo subgroup.

This report also included updated PARAMOUNT safety results, collected for an additional 7 months. The toxicity profile was consistent with the known safety profile of single-agent pemetrexed,[31] the primary safety analysis of PARAMOUNT,[17,18] and the previous phase III pemetrexed maintenance study.[1] No new safety findings emerged. Overall, the pemetrexed dose-intensity achieved in this study was high (93.7%), and maintenance pemetrexed was well tolerated. Statistically significant differences in grade 3 to 4 drug-related toxicities were noted for anemia, fatigue, and neutropenia. Although numerically higher grade 3 to 4 neutropenia occurred with longer pemetrexed exposure (more than six cycles), longer exposure did not result in increased infection or in significant differences in drug-related grade 3 to 4 toxicities, underscoring the relative safety of maintenance pemetrexed. Likewise, previous reports of PARAMOUNT safety results detailed low resource use, positive patient-reported outcome results (EQ-5D [health questionnaire] scores),[18] and two thirds of the patients receiving poststudy treatment.[17] These findings confirm that patients tolerated continuation maintenance pemetrexed, maintained quality of life, and received additional therapy after disease progression.[17,18]

In summary, this study shows that pemetrexed continuation maintenance therapy extends OS, in addition to PFS, and is well tolerated in patients with advanced nonsquamous NSCLC and good PS who did not progress after induction with pemetrexed-cisplatin. Survival findings from this trial were consistent across subgroups, including tumor response to induction. Continuation maintenance pemetrexed is a means of achieving maximal benefit from an effective agent among patients with disease control following pemetrexed-cisplatin induction. Once a patient progresses, there are limited data recommending re-treatment with the same agent and limited treatment options. Because not all patients require maintenance therapy, as evidenced by patients receiving placebo for multiple cycles without progressing, additional studies are necessary to further identify patients who benefit most from treatment. An additional question to address is the benefit of reinitiation of second-line pemetrexed among patients who did not progress on induction therapy with pemetrexed, but who had a break in therapy because of patient or physician preference. Certainly, our understanding of optimal use of maintenance therapy will be furthered when several ongoing clinical trials are completed over the next few years. Then and now, the decision to use maintenance therapy should be based on an individualized approach that includes patient-specific factors and wishes. The results of the PARAMOUNT study provide evidence to direct those choices by providing new data on the benefits/risks of maintenance pemetrexed, supporting the use of continuation maintenance pemetrexed for patients with advanced nonsquamous NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Symantha Melemed, Eli Lilly (C); William John, Eli Lilly (C); Nadia Chouaki, Eli Lilly (C); Annamaria H. Zimmermann, Eli Lilly (C); Carla Visseren-Grul, Eli Lilly (C) **Consultant or Advisory Role:** Mircea Dediu, Roche (C), Eli Lilly (C); Michael Thomas, Eli Lilly (C), Pfizer (C), Boehringer Ingelheim (C), Roche (C), Novartis (C); Jean-Louis Pujol, Eli Lilly (C); Olivier Molinier, Eli Lilly (C); Martin Reck, Hoffmann-La Roche (C), Eli Lilly (C), AstraZeneca (C), Daiichi Sankyo (C), Bristol-Myers Squibb (C); Cesare Gridelli, Eli Lilly (C), Roche (C) **Stock Ownership:** Symantha Melemed, Eli Lilly; William John, Eli Lilly; Nadia Chouaki, Eli Lilly; Annamaria H. Zimmermann, Eli Lilly; Carla Visseren-Grul, Eli Lilly **Honoraria:** Luis G. Paz-Ares, Eli Lilly; Mircea Dediu, Roche, Eli Lilly; Michael Thomas, Eli Lilly, Roche, Pfizer; Paolo Bidoli, Pierre Fabre, Amgen, Boehringer Ingelheim; Martin Reck, Hoffmann-La Roche, Eli Lilly, Daiichi Sankyo, AstraZeneca; Cesare Gridelli, Eli Lilly, Roche **Research Funding:** Michael Thomas, Eli Lilly **Expert Testimony:** None **Patents:** None **Other Remuneration:** None

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Manuscript writing: All authors

Final approval of manuscript: All authors

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Acknowledgment

Presented as an oral presentation at the 48th Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, June 1-5, 2012, the 47th Annual Meeting of ASCO, Chicago, IL, June 3-7, 2011, and the 14th World Conference on Lung Cancer, Amsterdam, the Netherlands, July 3-7, 2011.

We thank the patients, investigators, and institutions involved in this study. We also thank Mary Dugan Wood, who provided medical writing services on behalf of Eli Lilly and Noelle Gasco, Eli Lilly, for editorial assistance.

Appendix

Table A1. Patient and Disease Characteristics of All Randomly Assigned Patients*

Characteristic	Pemetrexed (n = 359)		Placebo (n = 180)	
	No.	%	No.	%
Sex				
Male	201	56	112	62
Female	158	44	68	38
Age at random assignment, years				
Median	61		62	
Range	32-79		35-83	
Age group, years				
< 65	238	66	112	62
≥ 65	121	34	68	38
Race/ethnicity				
Asian	16	4	8	4
African	4	1	1	0.6
White	339	94	171	95
Smoking status				
Smoker	274	76	144	80
Nonsmoker	83	23	34	19
Unknown	2	0.6	2	1
ECOG PS at randomization				
0	113	31	60	33
1	245	68	118	66
2-3†	1	0.3	2	1
Disease stage before maintenance therapy‡				
IIIB	31	9	18	10
IV	328	91	162	90
Best tumor response to induction therapy				
Complete/partial response	159	44	75	42
Stable disease	190	53	95	53
Progressive disease†	1	0.3	2	1
Unknown†	9	3	8	4
Histologic classifications§‖				
Bronchoalveolar	6	2	2	1
Adenocarcinoma	304	85	158	88
Large-cell carcinoma	24	7	12	7
Other or indeterminate¶	25	7	8	4

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

*Data derived from reporting database at the time of overall survival datalock. The database was open throughout the study; thus, small changes in patient numbers reported here and in Table 1 of Paz-Ares et al[17] are the result of study sites correcting or updating demographic data as needed.

†Randomized 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.

§Grouped by WHO classification of lung tumors.

‖Patients with squamous cell carcinoma were not eligible to enroll.

¶The subcategory of "Other" represents patients with a primary diagnosis of non–small-cell lung cancer whose disease did not clearly qualify as adenocarcinoma or large-cell carcinoma and includes non–small-cell lung cancer not otherwise specified, poorly differentiated, and mucinous adenocarcinoma.

Table A2. Summary of Postdiscontinuation Therapy

Postdiscontinuation Therapy	Pemetrexed (n = 359)		Placebo (n = 180)		
	No.*	%	No.*	%	*P*
Patients receiving postdiscontinuation therapy	231	64	129	72	.099
Erlotinib†	142	40	78	43	.405
Docetaxel†	116	32	78	43	.013
Gemcitabine	36	10	15	8	.640
Vinorelbine	28	8	11	6	.597
Investigational drug	20	6	8	4	.683
Carboplatin	18	5	8	4	.835
Paclitaxel	9	3	6	3	.587
Pemetrexed†‡	7	2	7	4	.249
Cisplatin	5	1	4	2	.490
Bevacizumab	6	2	1	0.6	.433
Gefitinib	3	0.8	2	1	1.000
Afatinib	2	0.6	2	1	.604
Placebo	4	1	0		.307

*Data expressed as percentage of randomly assigned patients. Systemic therapies used in ≥ 1% of patients in either arm are shown.
†Approved second-line therapies.
‡All patients had received induction therapy with pemetrexed.