Original Study

Long-Term and Low-Grade Safety Results of a Phase III Study (PARAMOUNT): Maintenance Pemetrexed Plus Best Supportive Care Versus Placebo Plus Best Supportive Care Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non–Small-Cell Lung Cancer☆

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Abstract

Updated long-term, low-grade (grade 1/2) safety and quality of life (QoL) results from the randomized, double-blind maintenance phase of the PARAMOUNT trial are reported. These results showed a low incidence of low-grade adverse events and uncompromised QoL, demonstrating a well-tolerated safety profile for long-term pemetrexed maintenance.

Introduction: In the PARAMOUNT ("A Phase 3, Double-Blind, Placebo-Controlled Study of Maintenance Pemetrexed plus Best Supportive Care vs. Best Supportive Care Immediately Following Induction Treatment with Pemetrexed Plus Cisplatin for Advanced Non-Squamous Non–Small-Cell Lung Cancer") trial, patients with advanced nonsquamous non–small-cell lung cancer (NS-NSCLC) benefited from pemetrexed maintenance therapy after induction therapy with pemetrexed and cisplatin by extending survival, delaying disease progression, and maintaining quality of life (QoL). However, low-grade 1 or 2 toxicities during long-term maintenance treatment may become burdensome and impact QoL. **Materials and Methods:** Patients in this double-blind study (n = 539), who had completed 4 induction cycles (pemetrexed with cisplatin) without progressive disease (PD) and had an ECOG performance status of 0/1, were randomized 2:1 to pemetrexed maintenance (500 mg/m^2, day 1) plus best supportive care (BSC) or placebo plus BSC until PD. Adverse events (by maximum Common Terminology Criteria for Adverse Events [CTCAE] grade) and QoL (EuroQol 5-dimensional [EQ-5D] scale) were assessed. **Results:** A median of 4 maintenance cycles was administered (range, pemetrexed 1-44; mean ± SD 7.9 ± 8.3; placebo 1-38; mean ± SD 5.0 ± 5.2), with 28% of pemetrexed and

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12% of placebo patients receiving ≥ 10 maintenance cycles. The pemetrexed dose intensity was 94%. More patients receiving pemetrexed (12%) than placebo discontinued because of possible drug-related CTCAEs (4%; $P = .005$). Overall, pemetrexed was associated with significantly more ($P < .05$) low-grade events (grade 1/2 nausea, grade 2 anemia, edema, and neutropenia) than placebo. Overall, the incidence of low-grade fatigue, anemia, and neutropenia decreased with long-term pemetrexed exposure; however, renal events increased across treatment arms. EQ-5D analyses demonstrated no treatment-by-time interaction or overall treatment differences between the 2 arms. **Conclusion:** PARAMOUNT demonstrated a low incidence of low-grade toxicities with long-term pemetrexed exposure without compromising QoL in patients with NS-NSCLC.

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Introduction

Maintenance therapy, which is initiated after 4 cycles of platinum-based induction therapy in patients with advanced non–small-cell lung cancer (NSCLC), delays disease progression, extends survival, and maintains health-related quality of life (QoL).[1,2] Continuation maintenance therapy is the ongoing administration of the non-platinum component of the initial chemotherapy regimen until progressive disease (PD).[3] Patients with NSCLC who are candidates for maintenance therapy are those without PD after induction therapy and with a good ECOG performance status (PS 0/1). Patient safety and QoL are important concerns in this clinical setting[4,5] and have been evaluated as endpoints in NSCLC clinical trials investigating maintenance pemetrexed[6-10] and other agents.[11-16] These studies have shown that global QoL is maintained during long-term treatment.

Treatment with pemetrexed continuation maintenance therapy after induction treatment with pemetrexed combined with cisplatin significantly reduced the risk of disease progression and death compared with placebo (progression-free survival [PFS], hazard ratio [HR], 0.62; 95% CI, 0.49-0.79; $P < .0001$; overall survival [OS], HR, 0.78; 95% CI, 0.64-0.96; $P = .0195$) in the advanced nonsquamous (NS)-NSCLC setting.[6,8] In the PARAMOUNT trial, the incidence of adverse events (AEs) reported at the primary database lock to evaluate PFS was consistent with previously reported safety profiles of pemetrexed as a single agent.[6,8,10] Additionally, pemetrexed was well tolerated as a maintenance treatment, with similar EuroQol 5-dimensional (EQ-5D) scale scores between treatment arms, suggesting preservation of QoL.[7]

Safety analyses from clinical trial data have generally focused on high-grade (grade 3 or 4) and acute short-term events. Because the occurrence of low-grade (grade 1 or 2) toxicities during long-term maintenance therapy (eg, fatigue or nausea) may become burdensome and compromise overall QoL, the present report has provided an updated analysis of low-grade toxicity and QoL results of pemetrexed maintenance compared with placebo in the PARAMOUNT trial from the final database lock (March 19, 2012).

Materials and Methods

Study Design and Treatment Plan

PARAMOUNT, a phase III, multicenter, randomized, double-blind, placebo-controlled study, consisted of induction and continuation maintenance treatment phases. Previous publications have provided a full description of the study design and treatment plan.[6,7] In brief, in the double-blind maintenance phase, 539 eligible patients (patients who had completed 4 cycles of induction therapy, had not progressed, and had an ECOG PS of 0/1) were randomized 2:1 to pemetrexed 500 mg/m^2 (ALIMTA [LY231514], Eli Lilly and Company, Indianapolis, IN) plus best supportive care (BSC) or placebo plus BSC. BSC was administered at the discretion of the physician and was designed to alleviate patient symptoms by methods other than prescribed antineoplastic agents. All patients received vitamin B_{12} and folic acid supplementation and prophylactic dexamethasone during the induction and maintenance treatment phases. Treatment delays were permitted for ≤ 42 days to allow sufficient time for recovery from study drug-related toxicity.[8]

Patients discontinued maintenance therapy at the occurrence of disease progression, unacceptable toxicity, or at the on request of the patient or physician. All patients were followed up until death or study closure.

Statistical Analysis

The primary and secondary endpoint results from the PARAMOUNT trial (ie, PFS, OS, tumor response rate, patient-reported outcomes using the EQ-5D QoL tool, resource use, and toxicity) were previously published.[6-8] The long-term safety, resource use, and patient-reported QoL data from the final database lock have been updated in the present study.

The mean pemetrexed dose was calculated as the overall dose administered divided by the treatment duration. The planned dose divided by the treatment duration yielded the planned mean pemetrexed dose. The pemetrexed weekly dose intensity was calculated as follows: (actual mean dose/planned mean dose) × 100%.

Patients were included in the safety analysis if they had been randomized to the maintenance phase and treated with ≥ 1 dose of pemetrexed or placebo. Safety was summarized for all randomized patients by treatment group as follows: the incidence of possible study drug-related Common Terminology Criteria for Adverse Events (CTCAE, version 3.0), treatment discontinuation, and dose delays occurring in all cycles of maintenance therapy. Additionally, we evaluated the incidence of selected clinically relevant, possible study drug-related events commonly associated with pemetrexed treatment (ie, anemia, fatigue, neutropenia, and renal events) during

maintenance cycles 1 through 11. Additional analyses are presented for fatigue.

The patient-reported EQ-5D QoL analysis included all patients who had provided a baseline assessment and ≥ 1 subsequent assessment. The EQ-5D QoL instrument has been previously described.[17,18] The UK index score is generated from the 5 descriptive questions in the EQ-5D QoL questionnaire related to mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The visual analog scale (VAS) is the part of the instrument that allows patients to rate their present health on a scale from 0 to 100. The UK index and VAS scores were analyzed using a mixed-effects analysis of variance model. The mean changes from baseline by treatment group were compared at each maintenance cycle using the paired *t* test. The changes in ECOG PS from baseline were assessed by treatment group, the same as in a previous publication.[7]

Results

Patient Characteristics

The baseline patient and disease characteristics were well balanced between the treatment arms. The median age was 60 years in the pemetrexed maintenance arm and 62 years in the placebo arm. Most patients were male (pemetrexed 56%; placebo 62%), white (pemetrexed 94%; placebo 95%), had stage IV disease (pemetrexed 91%; placebo 90%), and reported a history of smoking (pemetrexed 76%; placebo 80%). Most patients had an ECOG PS of 1 (pemetrexed 69%; placebo 67%) and stable disease after induction therapy (pemetrexed 53%; placebo 53%).

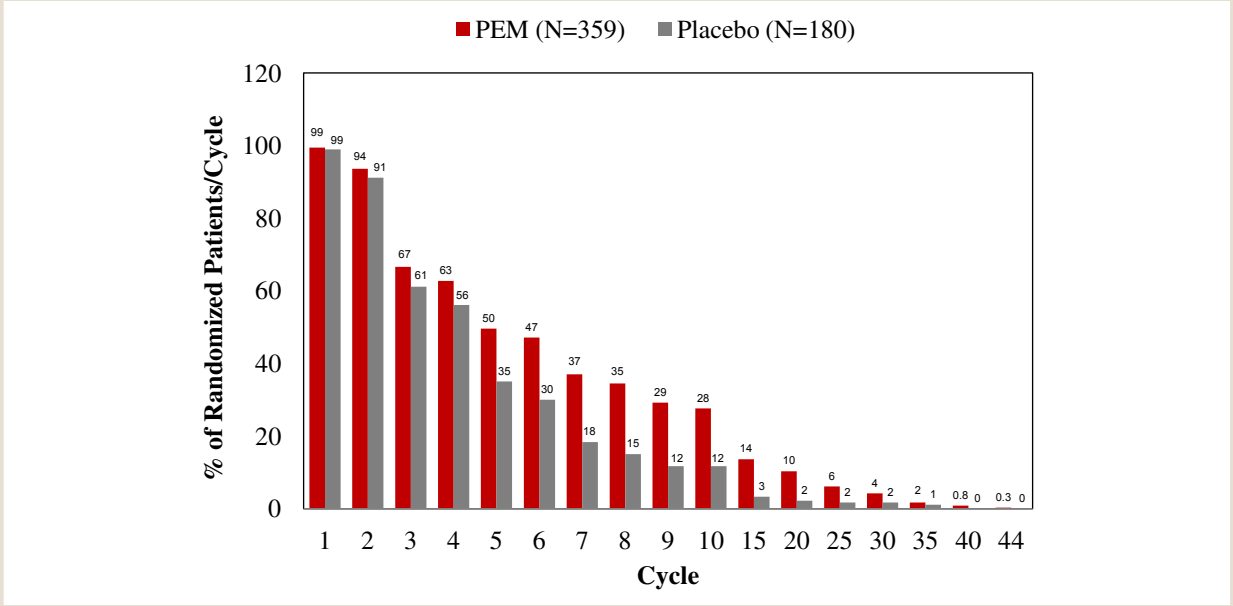
The patients were randomized 2:1 to either pemetrexed 500 mg/m^2 plus BSC (n = 359) or placebo plus BSC (n = 180) maintenance therapy. A median number of 4 maintenance cycles was administered in both treatment arms (pemetrexed, range, 1-44, mean ± SD, 7.9 ± 8.3; placebo range, 1-38, mean ± SD, 5.0 ± 5.2). The pemetrexed dose intensity was 94%. As summarized in Figure 1, 28% of the patients in the pemetrexed arm received ≥ 10 cycles of maintenance therapy (ie, a total of ≥ 14 pemetrexed cycles, which included 4 cycles of pemetrexed combined with cisplatin as induction therapy [data not shown]). In the placebo arm, 12% of patients received ≥ 10 maintenance cycles. As expected, the number of randomized patients who received maintenance therapy progressively declined with each cycle. At the final data cutoff date, the median follow-up period for the entire population was 12.5 months (95% CI, 11.1-13.7) and 24.3 months (95% CI, 23.2-25.1) for alive patients.

Safety

The incidence of possible study drug-related CTCAE toxicity by grade occurring in all cycles of maintenance therapy stratified by treatment arm is listed in Table 1. Overall, the incidence of any grade 1 CTCAE was similar between treatment arms (pemetrexed 14.8%; placebo 13.3%). Nausea was the only grade 1 toxicity with a significantly greater incidence in the pemetrexed arm than in the placebo arm (8.9% vs. 1.1%, respectively; $P < .001$). The overall incidence of grade 2 CTCAEs was significantly greater in the pemetrexed arm than in the placebo arm (23.4% vs. 12.8%, respectively; $P < .01$), and the incidence of nausea, anemia, edema, and neutropenia was significantly greater in the pemetrexed arm than in the placebo arm ($P < .05$ for all).

The incidence of other common low-grade toxicities, such as rash, mucositis/stomatitis, and conjunctivitis, did not significantly

Figure 1 Summary of Maintenance Cycles Administered. The Percentage of Randomized Patients Per Maintenance Cycle (Cycles 1-44) in the Pemetrexed and Placebo Groups. Percentages (> 1%) Were Rounded to the Nearest Whole Number



Abbreviation: PEM = pemetrexed.

Table 1 Study Drug-Related Adverse Events[a] by Maximum CTCAE Toxicity Grade Occurring in ≥ 2% of Patients During Maintenance Therapy (Cycles 1-44)

	Pemetrexed (n = 359)			Placebo (n = 180)		
CTCAE	Grade 1 (%)	Grade 2 (%)	Grade 3/4 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3/4 (%)
Any CTCAE	14.8	23.4[b]	11.7[c]	13.3	12.8	4.5
Fatigue	8.9	9.7	5.3[c]	5.6	5.0	1.1
Nausea	8.9[b]	5.8[b]	0.6	1.1	1.1	0.0
Anemia	4.2	10.0[b]	6.7[c]	1.1	3.3	0.6
Edema	4.2	3.6[b]	0.0	3.3	0.0	0.0
Mucositis/stomatitis	3.9	2.2	0.6	1.1	1.1	0.0
Neuropathy/sensory	4.5	0.6	0.6	5.0	1.1	0.6
Neutropenia	1.9	3.6[b]	6.1[c]	0.0	0.6	0.0
Leukopenia	1.4	1.7	2.2	0.0	0.0	0.0
ALT (SGPT)	0.8	1.7	0.3	0.0	0.6	0.0
Renal toxicities	3.1	3.9	0.8	1.7	0.6	0.0
Rash	2.2	0.6	0.0	2.2	0.0	0.0
Conjunctivitis	0.6	0.8	0.0	0.0	0.0	0.0

Abbreviations: ALT = alanine aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; SGPT = serum glutamic pyruvic transaminase.
[a]Events starting during induction remaining and ongoing during maintenance therapy without any change in severity were excluded.
[b]Statistical significance limit of $P < .05$ versus placebo.
[c]Statistical significance limit of $P < .05$ versus placebo for grade 3 only.

differ between the treatment arms (Table 1). The overall incidence of CTCAE grade 3/4 was greater in the pemetrexed arm than in the placebo arm (11.7% vs. 4.5%, respectively; Table 1). Most of these events were grade 3 (pemetrexed 10.6%; placebo 2.8%; $P = .001$), and the incidence of grade 4 events was both low and similar between treatment arms (pemetrexed 1.1%; placebo 1.7%). The incidence of grade 3/4 fatigue, anemia, and neutropenia was significantly greater in the pemetrexed arm than in the placebo arm.

Figure 2 presents the incidence of possible study drug-related CTCAE toxicity (by cycle) for neutropenia, renal, anemia, and fatigue events (all grades) in cycles 1 through 11. At any given cycle, < 15% of patients in the pemetrexed arm experienced any of the specified grade 1 or 2 events.

For neutropenia, the overall incidence of grade 1 or 2 events was low (≤ 3%) in both treatment arms ($P > .05$ for all; Figure 2A). Renal toxicity was experienced by < 6% of the patients in both treatment arms, and the difference was not statistically significant. Unlike other toxicities, the incidence of grade 1 renal toxicity events increased with the number of maintenance cycles in both treatment arms (Figure 2B), although the differences were not significant. The incidence of grade 2 anemia was significantly greater with pemetrexed than with placebo in cycles 2 and 3 (10.1% vs. 4.3% and 7.9% vs. 1.8%, respectively; $P < .05$ for all), followed by a decreasing trend. In contrast, an increasing trend of grade 2 anemia was seen in the placebo arm from cycles 3 to 11 (Figure 2C).

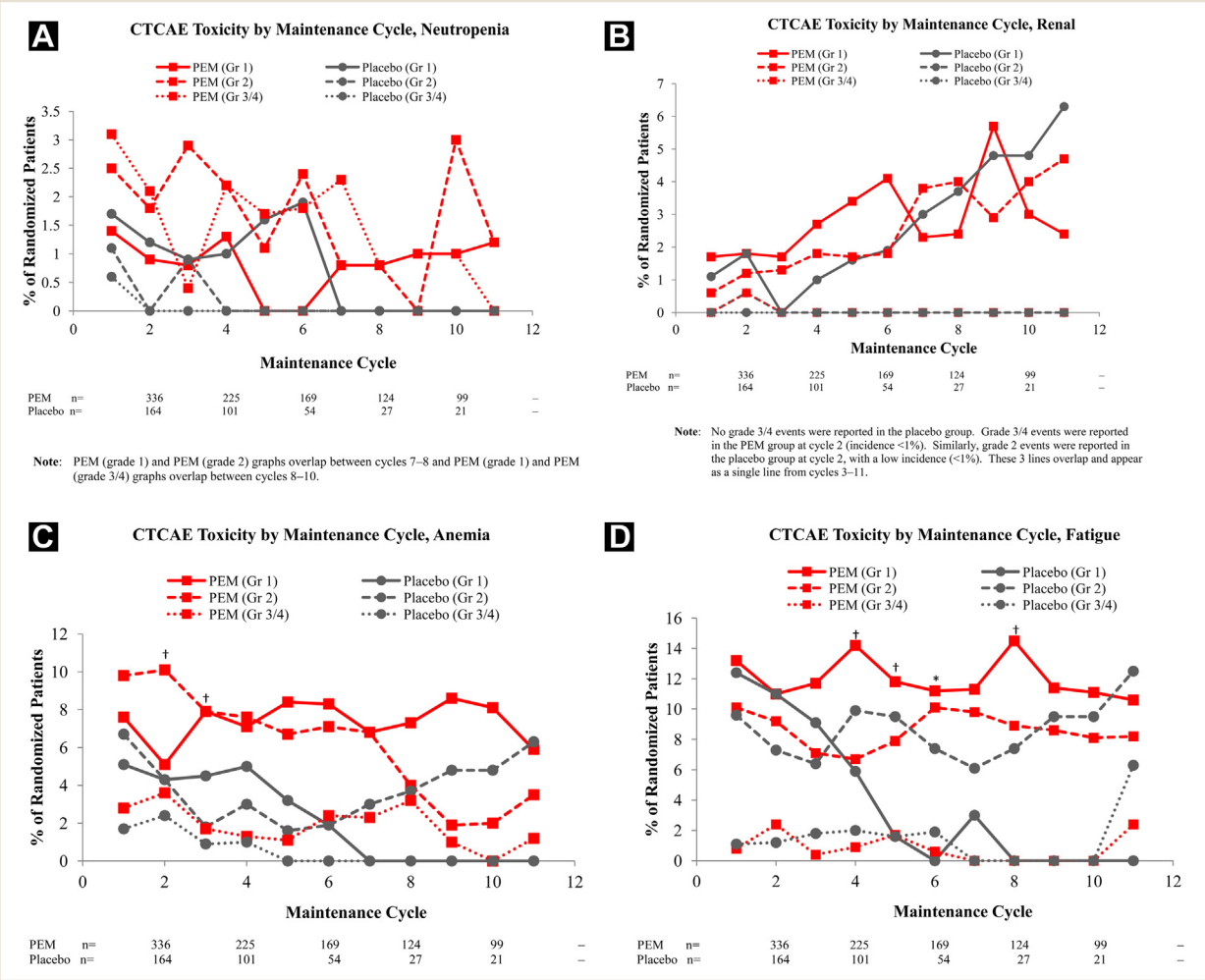
Fatigue was the most frequently reported any grade toxicity (23.9% vs. 11.7% for pemetrexed vs. placebo, respectively; $P < .001$). The incidence of grade 1/2 fatigue ranged from 6.7% to 14.5% for pemetrexed and 0% to 12.5% for placebo in cycles 1 through 11 (Figure 2D). Compared with placebo, the patients in the pemetrexed arm experienced significantly more grade 1 fatigue at cycles 4, 5, 6, and 8 ($P < .05$ for all). However, 8.9% and 12.2% of patients assigned to the pemetrexed and placebo arms, respectively, had fatigue as a prerandomization condition, implying that these patients had first experienced fatigue in the induction phase (data not shown).

The onset of fatigue, regardless of causality, was further investigated (Figure 3). Of the pemetrexed-treated patients who reported any grade of fatigue during the study period, most (74%) had first experienced fatigue during the induction phase. Only 26% of the patients reported fatigue onset during the maintenance phase. In addition, most patients experienced the onset and maximum grade of fatigue in the same cycle, primarily during the induction phase (data not shown).

Treatment Discontinuation

A similar percentage of pemetrexed- and placebo-treated patients discontinued maintenance treatment (97.5% and 98.9%, respectively; Table 2). Fewer patients in the pemetrexed arm discontinued treatment because of PD than did patients in the placebo arm (69.4% vs. 84.4%, respectively). A significantly greater percentage of patients in the pemetrexed arm than in the placebo arm discontinued treatment because of possible study drug-related CTCAEs (12.0% vs. 4.4%, respectively; $P = .005$; Table 2). Patients discontinued treatment because of CTCAEs of grade 1/2 (pemetrexed 6.4%; placebo 1.7%), grade 3/4 (pemetrexed 5.3%; placebo 1.7%), and grade 5 (pemetrexed 0.3%; placebo 1.1%). Of the 43 patients who discontinued pemetrexed, more than one half (61%) discontinued during cycles 1 through 6 (data not shown). Renal toxicity was the most commonly reported possible study drug-related event leading to discontinuation (n = 16 [4.5%]; n = 13, grade 1/2, and n = 3, grade 3 events), of which only 1 event was reported as serious. The second-most common event leading to discontinuation was asthenia/fatigue (n = 8 [2.2%]; 3 with grade 1/2 and 5 with grade 3), of which none were considered serious. In the placebo arm, 1 patient each (0.6%) discontinued because of an event related to renal function and fatigue.

Figure 2 Possible Study Drug-Related Common Terminology Criteria for Adverse Events (CTCAE) Toxicity by Maintenance Cycle. Incidence of (A) Neutropenia, (B) Renal, (C) Anemia, and (D) Fatigue Events by Grade for Patients in Each Group (Pemetrexed [PEM], n = 357; Placebo, n = 178) for Maintenance Cycles 1 Through 11. *$P < .01$ and †$P < .05$ for Pemetrexed Grade Specified versus Corresponding Placebo Grade



Abbreviation: Gr = grade.

Dose Delays

More patients in the pemetrexed maintenance arm than in the placebo arm experienced dose delays due to possible study drug-related CTCAEs (18.7% vs. 11.1%, respectively). The most common CTCAEs leading to those delays in the pemetrexed versus placebo arms, respectively, were anemia/hemoglobin decrease (5.6% vs. 1.7%), neutropenia (4.5% vs. 3.9%), events associated with renal function (2.8% vs. 1.7%), and asthenia/fatigue (2.5% vs. 0.6%).

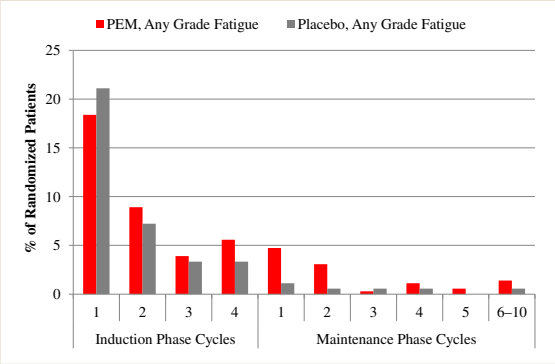
Resource Utilization

In general, the use of supportive care was greater in the pemetrexed arm than in the placebo arm. The percentage of patients who received red blood cell (RBC) transfusions was significantly greater in the pemetrexed arm than in the placebo arm (16.2% vs. 5.6%; $P < .001$). The use of other transfusions, such as plasma or platelets, was not significantly different between the 2 treatment arms. In addition, more patients in the pemetrexed arm than in the placebo arm received concomitant antibiotics during maintenance therapy (30.1% vs. 18.9%, respectively; $P = .005$). Concomitant use of granulocyte or granulocyte macrophage colony-stimulating factor (CSF) was 7.0% in the pemetrexed arm and 0.6% in the placebo arm ($P < .001$). The percentage of patients with ≥ 1 hospitalization was similar for both treatment arms (24.8% vs. 20.0%). However, significantly more patients in the pemetrexed arm than in the placebo arm were hospitalized because of study drug-related CTCAEs (10.9% vs. 3.3%; $P = .003$).

ECOG PS

Overall, the PS changes in the pemetrexed and placebo treatment arms did not differ significantly. Most patients in both treatment arms were able to maintain their PS from the baseline assessment at randomization throughout the maintenance phase (pemetrexed 76% vs. placebo 79%). Likewise, the balance was equal between

Figure 3 Onset of Fatigue. Percentage of Randomized Patients With Onset of Fatigue (Any Grade), Regardless of Causality, During Induction and Continuation Maintenance Phases. Of 359 Patients Randomized to Pemetrexed (PEM) Maintenance and 180 Randomized to Placebo, 7 (2%) and 1 (1%) Developed Fatigue Onset Beyond Cycle 11 Through the End of the Study



treatment arms for both improvements in PS from baseline (pemetrexed 8%; placebo 9%) and worsened PS (pemetrexed 16%; placebo 12%). Overall, 32.1% of all patients had a PS of 0% and 67.3% a PS of 1 at baseline; 12.1% of those patients improved to a PS of 0.

Quality of Life

The updated EQ-5D measures, including the UK index and VAS scores, from the final data cutoff date are listed in Table 3. The overall *P* value was used to compare the difference in the average change from the baseline QoL parameters between the treatment arms. The interaction *P* value was used to measure whether the pemetrexed and placebo profiles differed over time. All interaction term *P* values were > .05, demonstrating that the QoL parameters for the pemetrexed and placebo treatment arms did not significantly differ from randomization through the last assessment after treatment discontinuation. Although the mean scores for 2 individual parameters (self-care and usual activities) favored pemetrexed over placebo, no statistically significant differences were observed in the patient-reported QoL measures.

Table 2 Reasons for Treatment Discontinuation From Maintenance Therapy

Reasons for Discontinuation	Pemetrexed (n = 359)	Placebo (n = 180)
All randomized patients	97.5	98.9
Progressive disease	69.4	84.4
Adverse event		
Regardless of cause	19.5[a]	8.3
Possible study drug-related	12.0[a]	4.4
Serious adverse event		
Regardless of cause	6.7	2.8
Possibly study drug-related	3.3	1.7
Investigator decision	0.8	1.1
Subject decision	5.8	4.4
Death	2.2	2.2
Study disease	0.8	0.6
Adverse event/toxicity	1.1	0.6
Study drug-related	0.3	1.1

Data presented as %.
[a]Statistical significance limit of $P < .01$ versus placebo.

Table 3 Quality of Life Update: Repeated Measures Analysis of UK Index and VAS Scores (EQ-5D) During Maintenance Therapy

Quality of Life Parameters	Overall *P* Value Between Treatment Groups	Interaction *P* Value[a]
Mobility	.090	.475
Self-care	.003	.614
Usual activities	.051	.553
Pain/discomfort	.964	.374
Anxiety/depression	.851	.739
VAS health state score	.515	.977
UK population-based index score	.241	.770

Abbreviations: EQ-5D = EuroQoL 5-dimensional; UK = United Kingdom; VAS = visual analog scale.
[a]*P* value for treatment by cycle interaction.

Discussion

The safety data reported for maintenance studies have generally been limited to the incidence of high-grade (grade 3/4) toxicities.[3,10,12,14,19,20] However, the incidence of low-grade (grade 1/2) toxicities is equally important during long-term maintenance treatment because these events may impact health-related QoL and the ability of patients to continue treatment. To our knowledge, PARAMOUNT is the only trial that reports both grade 1/2 and 3/4 toxicities, making it difficult to effectively compare the incidence of grade 1/2 toxicities across studies.

In the present analysis, the overall low incidence (≤ 10%) of grade 1 or 2 events commonly associated with pemetrexed maintenance treatment included gastrointestinal, fatigue, and hematologic toxicities. The grade 3/4 incidence of these same events was < 7% (Table 1). Other clinically relevant toxicities associated with pemetrexed (skin and renal events) were less frequent, primarily low-grade, and comparable between the treatment arms. When comparing 2 chemotherapy agents evaluated in the maintenance setting, pemetrexed and gemcitabine, the incidence of low-grade fatigue, anemia, neutropenia, and rash observed with pemetrexed was numerically lower than that reported for gemcitabine.[20]

The percentage of patients receiving ≥ 10 cycles of maintenance in the pemetrexed arm (28%) demonstrated that maintenance therapy was well tolerated for an extended period. The discontinuation rate because of possible study drug-related CTCAEs was nearly 3 times greater in the pemetrexed arm (12.0%) than in the placebo arm (4.4%). The most common event leading to discontinuation from the pemetrexed arm was grade 1/2 renal events (3.6%). More than one half of the discontinuations in the

pemetrexed arm were due to low-grade events and occurred within the first 6 cycles, suggesting that discontinuation is likely to occur earlier, rather than later. No evidence was found that long-term (> 6 cycles) maintenance treatment will lead to an increased discontinuation rate because of drug-related events (cumulative effect). Although direct comparisons could not be made between the safety profiles of drugs with different mechanisms of action, such as a chemotherapy and epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), a trial investigating maintenance erlotinib (an EGFR-TKI) compared with placebo reported a similar difference in discontinuation rates between the 2 arms (5% vs. 2%, respectively; 2.5 times more discontinuations with the active treatment).[14]

Clinically relevant CTCAEs associated with pemetrexed treatment in the first 11 maintenance cycles were further explored in an analysis by cycle (Figure 2). Toxicities occurring beyond maintenance cycle 11 were not assessed due to the low number of patients receiving > 10 cycles, particularly in the placebo arm (Figure 1). Although the incidence of low-grade toxicities was significantly greater among patients receiving pemetrexed (grade 2 anemia and grade 1 fatigue) at the early maintenance cycles, the patients who continued pemetrexed for > 6 cycles reported neutropenia and anemia less frequently. This could have resulted from either earlier discontinuation of maintenance therapy for the subgroup of patients affected by toxicity and/or overall adequate management of anemia and neutropenia, resulting in an increased number of RBC transfusions and the use of CSF in the pemetrexed arm. Unlike other toxicities (eg, anemia, fatigue, and neutropenia), relatively small increases the incidence of in low-grade renal events were observed in the first 11 maintenance cycles. However, the incidence of renal-related events was not statistically different in patients receiving pemetrexed versus those receiving placebo, either in the first 11 cycles or across all maintenance cycles. In addition, the analysis of patient outcomes after renal events in the PARAMOUNT study suggested that a clinically significant majority of patients receiving pemetrexed with mild-to-moderate renal dysfunction were able to recover (data not shown). As expected, the type, grade, and incidence of any AE observed in the present study were not significantly affected by maintenance therapy, further supporting pemetrexed use as long-term, single-agent therapy for patients with advanced NS-NSCLC.

From a patient's and clinician's perspective, cancer-related fatigue is one of the most common and distressing adverse effects of cancer treatment and can significantly stress and impair a patient's daily performance.[21] Fatigue was the most commonly reported study drug-related toxicity during PARAMOUNT maintenance treatment. In randomized patients who experienced fatigue during the study, we further assessed whether fatigue was first experienced in the induction or maintenance phase (Figure 3). Differentiating the occurrence of AEs by phase of onset can be informative to fully characterize the safety profile during the maintenance phase.[19] Within the patient population randomized to pemetrexed who experienced any grade of fatigue, regardless of causality, during the induction and/or maintenance phases, only 26% first experienced fatigue as a new event during the maintenance phase.

Dose delays due to possible study drug-related CTCAEs were numerically greater with pemetrexed; however, no clinically or statistically significant differences were observed compared with placebo. This was an expected finding in a study comparing an active cytotoxic agent against placebo.

Resource use during continuation maintenance therapy was consistent with observations from a previous report of resource use in PARAMOUNT.[7] The use of RBC transfusions, antibiotics, and CSF, as well as hospitalizations due to study drug-related CTCAEs, was significantly greater in the pemetrexed maintenance arm than in the placebo arm, although the magnitude of the differences between treatments was small (6%-11%).

In our previously published EQ-5D results, no overall treatment differences in QoL were observed between the pemetrexed and placebo arms.[7] Repeated measures analyses showed no treatment-by-time interaction and no overall treatment differences between arms; these final data support the initial PARAMOUNT QoL results (Table 3). The EQ-5D QoL profiles were similar between the treatment arms and correlated with similar changes in the ECOG PS from baseline in the pemetrexed and placebo arms. Overall, the PARAMOUNT trial demonstrated that pemetrexed maintenance after pemetrexed and cisplatin induction therapy significantly improves both OS and PFS,[6] with a long-term safety profile that does not compromise the QoL of patients with advanced NS-NSCLC. The low-grade safety results we have presented further support long-term treatment with pemetrexed in the continuation maintenance clinical setting.

Conclusion

The present updated long-term safety report included data from the final database lock and offers supportive safety evidence of pemetrexed maintenance therapy after pemetrexed combined with cisplatin first-line induction therapy in patients with advanced NS-NSCLC, with a low incidence of the grade 1/2 and 3/4 CTCAEs generally associated with pemetrexed. For any specific toxicity type, ≤ 10% of patients randomized to pemetrexed experienced grade 1 or 2 events during maintenance therapy. As expected, a greater incidence of CTCAEs occurred with pemetrexed than with placebo. However, overall tolerability was not affected by long-term pemetrexed maintenance therapy, and patient QoL and PS were preserved. Overall, the PARAMOUNT trial has shown that pemetrexed continuation maintenance therapy is clinically beneficial to patients by prolonging survival[6,8] and does not pose any significant safety concerns, even when administered as long-term treatment.

Clinical Practice Points

- Continuation maintenance therapy has been associated with delayed disease progression and prolonged survival in patients with advanced NSCLC who have not experienced disease progressed after induction treatment and who have a good ECOG PS.[1,2]
- In PARAMOUNT, pemetrexed maintenance therapy significantly reduced the risk of disease progression and improved survival compared with placebo,[6] patient QoL was not compromised, and patients were able to maintain their PS.[7]

- Overall, pemetrexed maintenance offers a favorable risk/benefit profile for patients with NS-NSCLC, with improved survival benefits and no unexpected safety concerns.
- Pemetrexed maintenance treatment was well tolerated, and the toxicities were consistent with previously reported safety profiles.[6,8,10]
- The low incidence of low- and high-grade toxicity events observed with long-term administration of pemetrexed maintenance therapy further validates the safety and tolerability of pemetrexed in a continuation maintenance clinical setting.

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