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Highlights

•Compared advanced NSCLC phase III trials: pemetrexed–cisplatin with or without pem maintenance.

•4 cycles pem–cis followed by pem maintenance improves survival over 6 cycles pem–cis.

•Longer exposure to pem–cis or maintenance pem increases some toxicities, but overall incidence low.

Abstract

Objectives

Two phase III trials of advanced NSCLC patients were compared to examine relative efficacy and safety of differing treatment regimens. The JMDB trial investigated first-line pemetrexed–cisplatin (pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 every 21 days; maximum: 6 cycles). The PARAMOUNT phase III trial compared maintenance pemetrexed versus placebo after patients with nonsquamous NSCLC completed 4 cycles of first-line pemetrexed–cisplatin without disease progression.

Methods

Overall survival (OS) and progression-free survival (PFS), analyzed by Kaplan–Meier and Cox methods, and toxicity rates were compared between the PARAMOUNT arms and a selected homogeneous population from JMDB: 346 patients with disease and prior treatment characteristics matching the PARAMOUNT population.

Results

Outcomes for the PARAMOUNT placebo arm were similar to the JMDB homogeneous group (median PFS: 5.6 versus 6.2 months, $p = 0.117$, HR = 1.16; median OS: 14.0 versus 14.2 months, $p = 0.979$, HR = 1.00). The PARAMOUNT maintenance pemetrexed group had statistically superior efficacy compared with the JMDB homogeneous group (median PFS: 7.5 versus 6.2 months, $p < 0.00001$, HR = 0.66; median OS: 16.9 versus 14.2 months, $p = 0.003$, HR = 0.75). Patients who received pemetrexed maintenance (median 4 cycles, range 1–44) following 4 cycles of pemetrexed–cisplatin exhibited a higher incidence of drug-related serious adverse events compared with JMDB patients (median 6 cycles of pemetrexed–cisplatin) (10.6% versus 2.9%); grade 3/4 fatigue and renal toxicity were also higher in the pemetrexed arm of PARAMOUNT.

Conclusions

The across-trial comparison of a relevant JMDB study population with the two arms of the PARAMOUNT study supported the efficacy of the pemetrexed continuation maintenance strategy

and suggested the results are not influenced by limiting the pemetrexed–cisplatin induction treatment to four cycles. Although longer exposure to pemetrexed–cisplatin or maintenance pemetrexed increased some toxicities, the overall incidence remained low, underscoring the relative safety of these treatment regimens.

Keywords

- Carcinoma;
- Non-small cell lung;
- Pemetrexed;
- Cisplatin;
- Maintenance chemotherapy;
- Induction chemotherapy;
- Phase III clinical trial;
- Nonsquamous

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1. Introduction

Lung cancer is the most common type of cancer globally and the leading cause of cancer-related deaths for both men and women in the United States. Approximately 85% of lung cancers are non-small cell (NSCLC), and more than 70% of patients with NSCLC present with inoperable, locally advanced (Stage IIIB) or metastatic (Stage IV) disease [1].

Platinum-based doublet therapy is recommended for first-line treatment of patients with advanced NSCLC, with cisplatin preferred to carboplatin in Europe [2], [3] and [4]. In a large phase III study of pemetrexed–cisplatin versus gemcitabine–cisplatin, in patients with advanced NSCLC of all histologies (referred to here as "JMDB study"), a pre-specified subgroup analysis in patients with nonsquamous NSCLC showed pemetrexed–cisplatin to have superior survival compared with gemcitabine–cisplatin [5]. This differential efficacy based on histology, as well as a significant treatment-by-histology interaction for pemetrexed, was consistently detected across multiple studies [6]. These results led to a recommendation of pemetrexed–cisplatin for first-line treatment of patients with advanced nonsquamous NSCLC [2], [3] and [4].

Subsequently, pemetrexed versus placebo was investigated as switch maintenance treatment, and significant improvements of progression-free survival (PFS) and overall survival (OS) after induction with a non-pemetrexed platinum doublet were shown [7]. More recently, the PARAMOUNT study examined pemetrexed continuation maintenance therapy following four cycles of pemetrexed–cisplatin as induction treatment and found significantly improved PFS and OS when administered to non-progressing patients with advanced, nonsquamous NSCLC [8] and [9]. Current guidelines recommend maintenance single-agent pemetrexed for patients with stable disease (SD) or tumor response after four cycles of platinum-containing induction therapy [2], [3] and [4].

When evaluating results from trials testing the maintenance hypothesis, some might comment that patients received only four courses of induction treatment, whereas in clinical practice and in many guidelines, up to six cycles are recommended when the patient achieves objective response (and four cycles if patient achieves only disease stabilization). Consequently, it could be questioned if two more cycles of combination platinum chemotherapy could have accomplished the same outcome as the maintenance therapy.

This report compares the efficacy and safety results of patients with nonsquamous NSCLC treated with pemetrexed–cisplatin in the JMDB study with the two arms of the PARAMOUNT study. The PARAMOUNT placebo arm/JMDB population comparison will evaluate whether the first-line pemetrexed–cisplatin results are consistent between studies, and provide information regarding four versus six cycles of first-line pemetrexed–cisplatin. The JMDB population and the PARAMOUNT pemetrexed continuation maintenance arm comparison will investigate longer first-line treatment followed by the option of second-line therapy at tumor progression, versus four cycles of induction therapy followed by continuation maintenance therapy and optional second-line treatment at progression. The goal of both comparisons is to further elucidate optimal treatments and durations for patients with advanced nonsquamous NSCLC.

2. Methods

2.1. Patients and study design

Detailed descriptions of both trials have been previously published [5], [8] and [9]. In brief, the PARAMOUNT study enrolled 939 chemotherapy-naïve patients primarily from European centers with advanced (stage IIIB or IV) nonsquamous NSCLC to receive four 21-day cycles of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) induction therapy. 539 patients who completed four cycles of induction therapy with documented radiographic evidence of partial (PR) or complete (CR) tumor response or SD, and who had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, were then randomly assigned (2:1 ratio) to receive maintenance therapy with pemetrexed (500 mg/m^2) (n = 359) or placebo (9% sodium chloride) (n = 180). All randomized patients were included in the previously reported efficacy and safety analysis populations [8] and [9] and are included in the analyses described here.

The JMDB first-line study included 1725 chemotherapy-naïve advanced (stage IIIB or IV) NSCLC patients of any histology [5]. A subset of these patients was identified that matched the key criteria of the patient population of the PARAMOUNT study: nonsquamous NSCLC, treated with at least four 21-day cycles of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2), without ECOG PS >1 prior to completing the fourth cycle, and without radiologic evidence of disease progression at the time of completing the fourth cycle. Of the 378 patients identified, 346 were included in this selected homogeneous patient population used for the analyses here. The other 32 patients were not included because they had been enrolled at Taiwanese or Korean centers, and the PARAMOUNT comparator population did not include patients from those geographic areas [8]. Patients from this geography have a better prognosis than patients from non-East Asian geographies, with nearly double the median survival [10] and [11]. Neither study determined the EGFR mutation status of the patients.

For all randomized patients in PARAMOUNT, and for all patients in the JMDB homogeneous population, tumor assessments took place every six weeks according to both study protocols. After treatment discontinuation in JMDB, non-progressing patients continued to undergo tumor assessment at the same frequency (every six weeks) as patients on maintenance treatment in the PARAMOUNT study.

2.2. Statistical analyses

The post hoc meta-analysis presented entails a cross-trial comparison of PARAMOUNT and JMDB. All analyses were run for the two randomized arms of PARAMOUNT in comparison to the selected homogeneous population from JMDB. Detailed descriptions of the primary statistical analyses of both studies have been previously published [5], [8] and [9]. The following analyses were carried

out for the three treatment groups: Kaplan–Meier estimates (including medians) for PFS and OS; Cox hazard ratio estimates [with *p*-values and 95% confidence intervals (CIs)] for PFS and OS. Frequencies and percentages of key baseline characteristics, post-study treatment usage, and adverse events (AEs), serious AEs, and graded AEs were calculated. Both studies were registered with ClinicalTrials.gov: NCT00087711 (JMDB) and NCT00789373 (PARAMOUNT).

3. Results

The baseline and disease characteristics of the JMDB homogeneous population are similar to those published for the complete JMDB study population [5] and similar to those of the two PARAMOUNT arms (Table 1). Some notable differences between the PARAMOUNT and JMDB populations were the NSCLC stage percentages (stage IIIB NSCLC: 9% versus 21%, respectively), "Other or indeterminate histology" (approximately 6% versus 17%, respectively), and smoking status "Unknown" (1% versus 35%, respectively). In general, the distribution of patient and disease characteristics represented in these three groups is similar to that seen in other recent phase III studies [7], [12], [13] and [14].

Table 1.

Baseline patient and disease characteristics.[a]

	PARAMOUNT pemetrexed arm (*n* = 359)	**PARAMOUNT placebo arm (*n* = 180)**	**JMDB homogeneous population (*n* = 346)**
Median age, years	60	62	60
Age <70/≥70	85.5/14.5	77.8/22.2	85.5/14.2
Female/male (%)	44.0/56.0	37.8/62.2	36.7/63.3
ECOG performance status 0/1 (%)[b]	31.5/68.5	33.3/66.7	37.9/62.1
Stage IIIB/IV (%)	8.6/91.4	10.0/90.0	21.4/78.6
Adenocarcinoma/large cell/other or indeterminate (%)[b]	86.4/6.7/7.0	89.4/6.7/3.9	71.1/11.6/17.3
Smoking: ever/never/unknown (%)	76.3/23.1/0.6	80.0/18.9/1.1	51.4/13.3/35.3

Abbreviation. ECOG: Eastern Cooperative Oncology Group.

a

Percentages not totaling 100% are due to rounding or missing data. PARAMOUNT data were derived from the initial database lock.

b

The subcategory of “Other” 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 options

A comparison of dosage administration between the two studies (Table 2) reflects the differences expected due to study design. Among the homogeneous JMDB population, the median number of pemetrexed–cisplatin cycles was 6 (mean 5.5), with about 72% of the homogeneous population completing 6 cycles, 10% completing 5 cycles, and 18% completing 4 cycles. Patients randomized to maintenance in PARAMOUNT received 4 cycles of pemetrexed–cisplatin induction as per protocol. The two PARAMOUNT arms subsequently received maintenance cycles, with pemetrexed arm patients received a median of 4 cycles (range 1–44) and mean of 8 cycles, and the placebo arm patients received a median of 4 cycles (range 1–38) and mean of 5 cycles.

Table 2.

Treatment administration.

	PARAMOUNT pemetrexed arm[a] (*n* = 359)	**PARAMOUNT placebo arm[a] (*n* = 180)**	**JMDB homogeneous population (*n* = 346)[b]**
Patients treated	359	180	346
Median number of pem–cis cycles (range)	4 (4)	4 (4)[c]	6 (4–6)[d]
Mean number of pem–cis cycles	4.0	4.0	5.5
Patients completing ≥4 pem–cis cycles, *n* (%)	359 (100)	179 (99.4)	346 (100)
Patients completing ≥5 pem–cis cycles, *n* (%)	NA	NA	285 (82.4)
Patients completing 6 pem–cis cycles, *n* (%)	NA	NA	250 (72.3)[d]
Median number of pem maintenance cycles (range)	4 (1–44)	4 (1–38)	NA

	PARAMOUNT pemetrexed arm[a] (*n* = 359)	PARAMOUNT placebo arm[a] (*n* = 180)	JMDB homogeneous population (*n* = 346)[b]
Mean number of pem maintenance cycles (standard deviation)	7.9 (8.3)	5.0 (5.2)	NA

Abbreviations. Cis = cisplatin; pem = pemetrexed.

A The PARAMOUNT data summarize induction phase dose administration, that is, treatment prior to randomization to the maintenance phase. Four cycles of pemetrexed–cisplatin were stipulated by protocol.

B The JMDB trial stipulated a maximum of 6 cycles pemetrexed–cisplatin.

C Additionally, one patient on the placebo arm received 3 cycles which was considered a protocol violation.

D Additionally, one patient in this analysis subpopulation received 7 cycles which was considered a protocol violation. Patients in the analysis population who received <6 cycles did so due to patient/physician decision or intolerance of study treatment.

A comparison of the induction tumor response between the two studies (Supplemental Table SI) reveals that both studies exhibit a similar distribution of partial tumor response (42–47) and stable disease (48–53%) following pemetrexed–cisplatin as first-line therapy. The greater number of cycles of pemetrexed–cisplatin given to the JMDB patients (median 6) did not yield appreciably more patients with a tumor response (versus SD) than those from the PARAMOUNT study (4 cycles), nor did it yield a higher disease control rate.

OS and PFS times for nonsquamous patients treated with pemetrexed and cisplatin in the JMDB study were consistent with the results from the placebo arm of the PARAMOUNT study (Fig. 1, Table 3). There is no statistical difference between the median OS or PFS of the two groups (PFS unadjusted HR = 1.16, 95% CI = 0.96–1.39, $p = 0.117$; OS unadjusted HR = 1.00, 95% CI = 0.81–1.24, $p = 0.979$). In contrast, the PARAMOUNT pemetrexed continuation maintenance group is not only statistically superior to the PARAMOUNT placebo group (as previously reported) [8] and [9], but also to the JMDB group, with an unadjusted HR for PFS of 0.66 (95% CI 0.56–0.77), p-value <0.00001, and for OS of 0.75 (95% CI 0.63–0.91), p-value = 0.003. Patients receiving pemetrexed continuation maintenance therapy after 4 cycles of first-line pemetrexed–cisplatin displayed significantly improved PFS and OS over those patients who received only first-line pemetrexed–cisplatin (median 6 cycles). Survival rates reflected the benefit of pemetrexed maintenance with 67% and 35% of PARAMOUNT pemetrexed patients surviving to 1-year and 2-years, whereas only 60% and 25% of PARAMOUNT placebo patients and 59% and 26% of JMDB patients survived to those milestones (Table 3).

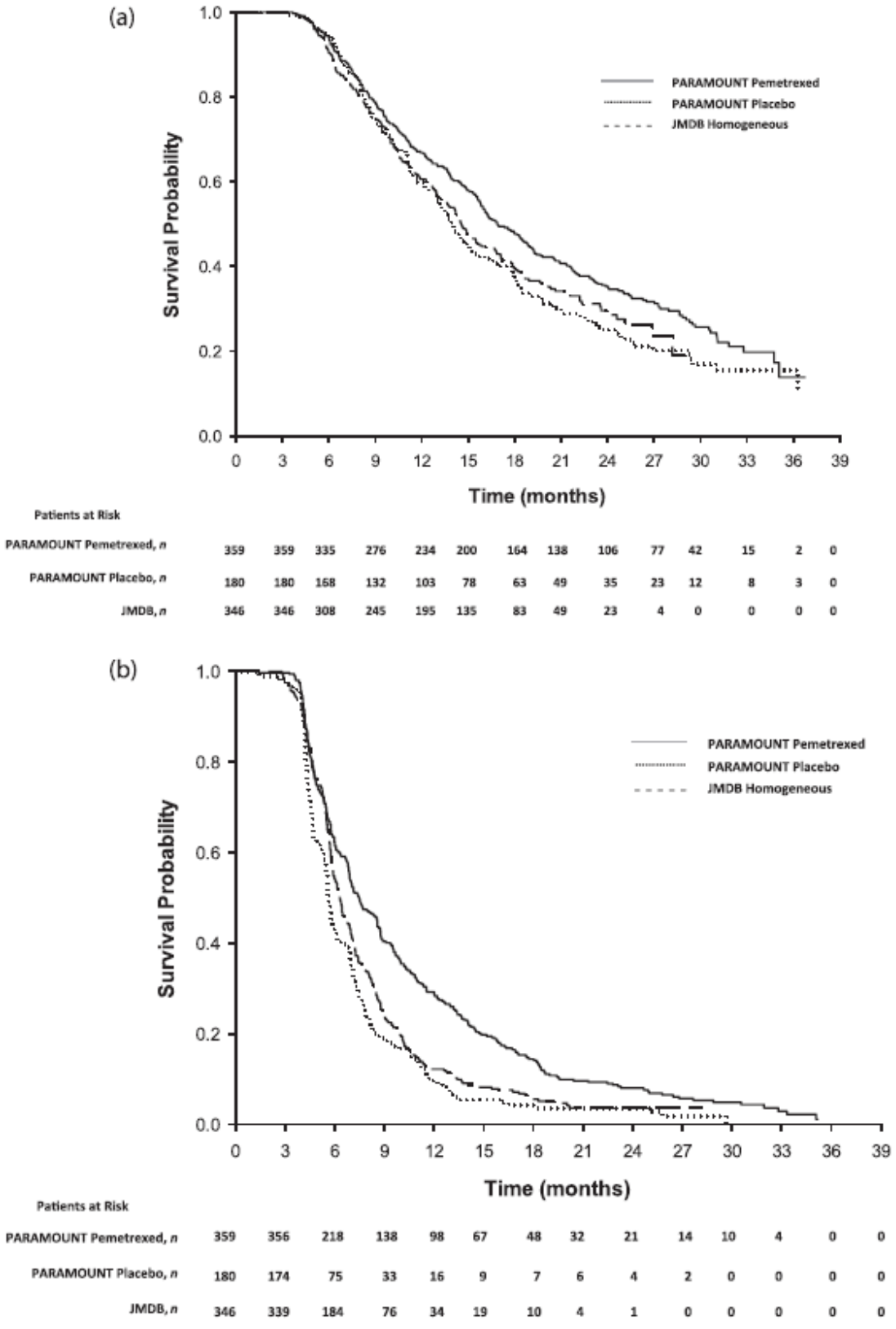

Fig. 1.

Kaplan–Meier plots of overall survival (OS) and progression-free survival (PFS) of PARAMOUNT arms and homogeneous JMDB population. (A) OS data are shown for PARAMOUNT arms as measured from the start of 4 cycles of pemetrexed–cisplatin (induction) treatment followed by randomization to pemetrexed continuation maintenance treatment or placebo. JMDB OS data are plotted from the onset of

pemetrexed–cisplatin treatment (up to 6 cycles). (B) PFS was compared among the three populations as 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.

Figure options

Table 3.

Efficacy summary.

	PARAMOUNT pemetrexed arm (*n* = 359)[a]	**PARAMOUNT placebo arm (*n* = 180)[a]**	**JMDB homogeneous population (*n* = 346)**
Progression-free survival			
Number of patients with events, *n* (%)	331 (92.2)	172 (95.6)	324 (93.6)
Number of patients censored, *n* (%)	28 (7.8)	8 (4.4)	22 (6.4)
Median PFS (95% CI), months	7.5 (6.9–8.6)	5.6 (5.5–6.0)	6.2 (5.9–6.5)
Comparison with JMDB first-line data			
Unadjusted log rank *p*-value	<0.00001	0.117	
Unadjusted HR (95% CI)	0.66 (0.56–0.77)	1.16 (0.96–1.39)	
1-year PFS rate (%)	29 (24–34) Comparison with JMDB: $p < 0.00001$	10 (6–15) Comparison with JMDB: $p = 0.729$	11 (8–14)
2-year PFS rate (%)	8 (5–11) Comparison with JMDB: $p = 0.009$	4 (2–7) Comparison with JMDB: $p = 0.772$	3 (1–6)
Overall survival			
Number of patients with events, *n* (%)	256 (71.3)	141 (78.3)	225 (65.0)

	PARAMOUNT pemetrexed arm (*n* = 359)[a]	PARAMOUNT placebo arm (*n* = 180)[a]	JMDB homogeneous population (*n* = 346)
Number of patients censored, *n* (%)	103 (28.7)	39 (21.7)	121 (35.0)
Median OS (95% CI), months	16.9 (15.8–19.0)	14.0 (12.9–15.5)	14.2 (12.9–15.1)
Comparison with JMDB first-line data			
Unadjusted log rank *p*-value	0.003	0.979	
Unadjusted HR (95% CI)	0.75 (0.63–0.91)	1.00 (0.81–1.24)	
1-year OS rate (%)	67 (62–71) Comparison with JMDB: *p* = 0.026	60 (52–67) Comparison with JMDB: *p* = 0.789	59 (53–64)
2-year OS rate (%)	35 (30–40) Comparison with JMDB: *p* = 0.026	25 (19–32) Comparison with JMDB: *p* = 0.745	26 (21–32)

Abbreviations. CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

A PARAMOUNT PFS and OS data are reported as measured from the beginning of the induction cycles.

Table options

Since differences in post-discontinuation therapy may impact OS results, Table 4 summarizes data for this parameter. Both JMDB and PARAMOUNT specified post-discontinuation therapy to be given upon disease progression at the investigator's discretion, with progression assessed radiologically every other 3-week cycle. Approximately 60% of patients from the JMDB trial, 64% of patients from PARAMOUNT pemetrexed maintenance arm, and 72% of patients from PARAMOUNT placebo maintenance arm received another line of systemic post-discontinuation therapy. For all three arms, two approved second-line treatments, erlotinib or docetaxel, were most frequently prescribed. However, a greater percentage of patients on the PARAMOUNT placebo arm received these two treatments, 92%, as compared to 62% of JMDB patients and 73% PARAMOUNT pemetrexed maintenance arm.

Table 4.

Summary of post-discontinuation systemic therapy.

	PARAMOUNT pemetrexed arm (*n* = 359)	PARAMOUNT placebo arm (*n* = 180)	JMDB homogeneous population (*n* = 346)
Received any post-discontinuation therapy, *n* (%)	231 (64.3)	129 (71.7)	207 (59.8)
Treatments			
Erlotinib	142 (39.6)	85 (47.2)	93 (26.9)
Docetaxel	121 (33.7)	80 (44.4)	122 (35.3)
Gemcitabine	37 (10.3)	16 (8.9)	55 (15.9)
Vinorelbine	29 (8.1)	11 (6.1)	41 (11.8)
Pemetrexed	8 (2.2)	7 (3.9)	16 (4.6)
Gefitinib	3 (0.8)	2 (1.1)	10 (2.9)
Other	88 (24.5)	34 (18.9)	133 (38.4)

Table options

In order to understand how treatment differences among the trial arms of the PARAMOUNT and JMDB studies impacted safety, AEs that emerged after completion of four cycles of first-line pemetrexed–cisplatin were examined (Table 5). A greater incidence of toxicities was observed for JMDB patients and in PARAMOUNT pemetrexed-treated arm patients than placebo arm patients as expected given the additional chemotherapy exposure: a median of two additional pemetrexed–cisplatin cycles for the JMDB population and a median of four (range 1–44; mean = 7.9, standard deviation 8.3) pemetrexed maintenance cycles for PARAMOUNT patients. Grade 3/4 anemia and fatigue, and low grade mucositis/stomatitis, edema, and renal toxicities, as well as drug-related serious adverse events, were all higher numerically among PARAMOUNT pemetrexed arm patients than JMDB patients in keeping with the greater total number of cycles received. Conversely, the incidence of grade 3/4 ototoxicity (inner ear/hearing AE), nausea, and vomiting was somewhat higher for the JMDB patients, likely due to the additional cisplatin exposure.

Table 5.

Drug-related adverse events by maximum CTCAE grade beginning after completion of 4 cycles of pemetrexed–cisplatin.[a]

Adverse events[b]	PARAMOUNT pemetrexed arm (*n* = 359)		PARAMOUNT placebo arm (*n* = 180)		JMDB homogeneous population (*n* = 346)	
	All grades	Grades 3 and 4	All grades	Grades 3 and 4	All grades	Grades 3 and 4
Hematologic toxicities, %						
Anemia	15.0	5.0	3.3	1.1	9.8	2.9
Leukopenia	5.0	2.2	0	0	4.9	0.9
Neutropenia	7.5	4.7	0.6	0	8.1	5.2
Thrombocytopenia	3.1	1.9	0	0	2.9	1.4
Non-hematologic toxicities, %						
Fatigue	16.7	4.7	6.1	1.1	8.1	1.4
Mucositis/stomatitis	7.2	0.6	2.2	0	2.0	0.3
Edema	6.7	0	2.2	0	1.2	0
Nausea	6.7	0.6	1.1	0	8.7	1.4
Neuropathy, sensory	5.6	0.6	6.7	0.6	6.9	0
Anorexia/decreased appetite	4.2	0.3	1.1	0	3.8	0.6
Vomiting	4.2	0.3	0.6	0	5.8	0.9
Diarrhea	3.6	0.3	1.7	0	2.9	0
Renal toxicities	5.6	1.1	1.7	0	0.6	0
Pyrexia	3.1	0	0	0	0	0
Ototoxicity	1.4	0	0	0	2.3	0.9
Febrile neutropenia	1.4	1.4	0	0	0.3	0.3

Adverse events[b]	PARAMOUNT pemetrexed arm (*n* = 359)		PARAMOUNT placebo arm (*n* = 180)		JMDB homogeneous population (*n* = 346)	
	All grades	Grades 3 and 4	All grades	Grades 3 and 4	All grades	Grades 3 and 4
Patients with ≥1 drug-related serious AE, %[c]	10.6		4.4		2.9	

Abbreviations. AE: adverse event; CTCAEs: Common Terminology Criteria for Adverse Events.

A Adverse events emerging after the completion of cycle 4 (cycle 5 or later for JMDB, and the first maintenance cycle for PARAMOUNT), that are either of special interest or occurring in ≥3% of patients (sum of all grades) are listed, with corresponding notation of percentage of grades 3 and 4 AEs. JMDB used CTCAE version 2.0, and PARAMOUNT used CTCAE version 3.0; hence, the maximum grade in the JMDB study was 4. Grade 5 events were possible in PARAMOUNT, but no grade 5 events were reported for any reported term.

B Some similar terms are combined: renal includes creatinine, glomerular filtration rate, renal/genitourinary – other, and renal failure. Fatigue includes asthenia, muscular weakness, and lethargy. Edema includes the terms: limb, head and neck, peripheral, and localized. Ototoxicity includes the terms: tinnitus, inner ear/hearing, and other auditory/hearing.

cSerious adverse events are defined as adverse events resulting in hospitalization, persitent or significant disability/incapacity, or death.

4. Discussion

The across-trial comparison of a relevant patient population in the JMDB study with the two arms of the PARAMOUNT study presented here support the efficacy of the pemetrexed continuation maintenance strategy, and suggests that the results are not influenced by limiting the pemetrexed–cisplatin induction treatment to four cycles.

Analyses of the survival data from the matched study populations showed that results from nonsquamous patients treated with pemetrexed–cisplatin in the JMDB first-line study were consistent with the results from the PARAMOUNT placebo group. The OS and PFS Kaplan–Meier curves of the two groups nearly overlapped, and the tumor responses of the two study populations to first-line pemetrexed–cisplatin were statistically indistinguishable. Since the homogeneous JMDB patient population received a median of six cycles of pemetrexed/cisplatin and the PARAMOUNT placebo patients received four cycles, the approximately two additional treatment cycles did not significantly impact survival in this patient population. This result is

consistent with other studies demonstrating that four cycles of first-line NSCLC treatment is sufficient to elicit an efficacy response [15], [16], [17] and [18].

As with all cross-trial comparisons, these conclusions should be viewed with caution since the trials were performed at different times and in different countries. Indeed, these differences likely contributed to the somewhat greater percentage of the PARAMOUNT placebo arm patients who received post-study therapy than those in the JMDB population (72% versus 60%), with more of the PARAMOUNT placebo patients receiving approved second-line therapy (92% versus 62% JMDB). However, in general, about two-thirds of the patients on both studies received another line of systemic therapy after discontinuing from the trial, indicating maintenance therapy does not substantially alter the likelihood of a patient receiving second-line treatment.

The PARAMOUNT and JMDB homogeneous populations also differed somewhat with respect to two baseline disease characteristics: histology and stage of disease. The higher proportion of patients in the JMDB homogenized population with “Other” or “Indeterminate” histology could be due to a higher proportion of cytological diagnosis, although recent studies enrolled a similar percentage of patients with Other/Indeterminate histology as in JMDB [19] and [20]. For the JMDB homogeneous population, a higher percentage of patients with Other/Indeterminate histology might imply some prognostic disadvantage, while a greater percentage of patients with disease stage IIIb might have provided a prognostic advantage. However, it is unlikely that these small imbalances would have introduced much prognostic heterogeneity into the cross-trial comparison, especially since patients with early disease progression were excluded from both PARAMOUNT and the JMDB homogeneous population. The similarity of outcomes between the JMDB homogeneous population and the PARAMOUNT control arm supports this conclusion.

Additional analyses found that PARAMOUNT pemetrexed continuation maintenance arm had statistically superior PFS and OS compared with the JMDB homogeneous population [unadjusted HRs: PFS 0.66 (0.56–0.77, $p < 0.00001$); OS 0.75 (0.63–0.91, $p = 0.003$)]. This result indicates a relative advantage of pemetrexed maintenance therapy immediately following four cycles of first-line pemetrexed–cisplatin versus up to six cycles of first-line pemetrexed–cisplatin followed by a watch-and-wait strategy, with patients in both groups having the option of second-line treatment upon progression. The Kaplan–Meier plots show greater separation of the OS and PFS curves on the latter portion of the curve, suggesting that more benefit is gained by patients who receive a greater number of maintenance cycles, and further supporting the hypothesis that six cycles of platin-based chemotherapy may not be as effective as four cycles followed by single-agent continuation maintenance. As expected, the greater chemotherapy exposure entailed somewhat greater incidence of toxicities on the PARAMOUNT maintenance pemetrexed arm than for the JMDB population, including anemia and fatigue. Furthermore, both the PARAMOUNT pemetrexed arm and the JMDB homogeneous group had greater incidence of toxicities than the PARAMOUNT placebo arm. However, the overall incidence of all grades and grade 3/4 toxicities emerging after four cycles of pemetrexed–cisplatin was low for both PARAMOUNT and JMDB (≤16.7% and ≤5.2%, respectively), and the toxicities were consistent with the known safety profile of pemetrexed–cisplatin [5], [6] and [21].

The superiority of the maintenance approach is likely due to a number of factors. First, it prolongs the administration of a drug shown to be well tolerated and effective during the administration of the platinum-based induction doublet. Additionally, it offers the improved safety of a single-agent treatment. Finally, the maintenance approach ensures that patients receive additional therapy. Recent reviews of the maintenance approach have underscored this advantage, noting that many factors including performance status deterioration often prevent patients from receiving second-line therapy at the time of disease progression [22] and [23].

To summarize, this cross-trial comparison showed that the PARAMOUNT placebo arm results are consistent with the JMDB homogeneous group treated with pemetrexed–cisplatin. The similar magnitude of the JMDB and PARAMOUNT placebo results suggests four cycles of pemetrexed–cisplatin yield maximal efficacy if a patient is to stop treatment until progression. However, additional results reveal that the most efficacious of the treatments was four cycles of pemetrexed–cisplatin followed by pemetrexed continuation maintenance. While this regimen increased some grade 3/4 toxicities (as did the additional cycles of pemetrexed/cisplatin in the JMDB population), the overall incidence of toxicities remained low. Overall, these data support the efficacy of first-line pemetrexed–cisplatin therapy for nonsquamous NSCLC as first identified in the landmark JMDB study, and support the administration of maintenance pemetrexed after the first-line treatment.

Conflict of interest

Authors M.D., C.G., L.G.P.-A., G.V.S., and M.T. have served as advisors or speakers for Eli Lilly and were financially compensated for their contributions. M.D., L.G.P.-A., and M.T. served in this capacity outside the scope of this manuscript. C.V.G., B.S.A., N.C., P.P., and W.J. are employed by Eli Lilly and Company and own Lilly stock. All other authors declare no conflict of interest.

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