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Original Article

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Pemetrexed Continuation Maintenance in Patients with Nonsquamous Non-small Cell Lung Cancer: Review of Two East Asian Trials in Reference to PARAMOUNT

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Purpose

A recent phase III study (PARAMOUNT) demonstrated that pemetrexed continuation maintenance therapy is a new treatment paradigm for advanced nonsquamous non-small cell lung cancer (NSCLC). The majority of patients enrolled in PARAMOUNT were Caucasian (94%). We reviewed efficacy and safety data from two clinical trials, which enrolled East Asian (EA) patients, to supplement data from PARAMOUNT on pemetrexed continuation maintenance therapy in patients with nonsquamous NSCLC.

Materials and Methods

Study S110 was a phase II, multicenter, randomized, controlled, open-label trial in never-smoker, chemonaïve, EA patients (n=31) with locally advanced or metastatic nonsquamous NSCLC (n=27). Study JMII was a multicenter, open-label, single-arm, post-marketing, clinical trial in Japanese patients (n=109) with advanced nonsquamous NSCLC. PARAMOUNT was a multicenter, randomized, double-blind, placebo-controlled trial in patients with advanced nonsquamous NSCLC.

Results

In EA patients with nonsquamous NSCLC, the median progression-free survival (PFS) for pemetrexed continuation maintenance therapy was 4.04 months (95% confidence interval [CI], 3.22 to 5.29 months) in study S110 and 3.9 months (95% CI, 3.2 to 5.2 months) in study JMII. The median PFS for pemetrexed continuation maintenance therapy in PARAMOUNT was 4.1 months (95% CI, 3.2 to 4.6 months). Pemetrexed continuation maintenance therapy in EA patients in studies S110 and JMII did not lead to any unexpected safety events, and was consistent with PARAMOUNT's safety profile.

Conclusion

The efficacy and safety data in the EA trials were similar to those in PARAMOUNT despite differences in patient populations and study designs. These data represent consistent evidence for pemetrexed continuation maintenance therapy in EA patients with advanced nonsquamous NSCLC.

Key words
Pemetrexed, Maintenance chemotherapy, Nonsquamous non-small cell lung carcinoma, Far East

Introduction

Treatment with a platinum-based doublet as first-line chemotherapy is the current standard-of-care in patients with non-small cell lung cancer (NSCLC) [1,2]. Extended first-line chemotherapy with a platinum-based doublet is not recommended as it leads to cumulative toxicities and provides no additional advantage to patients with NSCLC [1,3,4]. The goal of maintenance therapy is to improve progression-free survival (PFS) and overall survival (OS) while maintaining an adequate tolerability profile and quality of life. A well-tolerated, active maintenance treatment

Table 1. Patients and methods

	JMII	S110	PARAMOUNT
Study design	Multicenter, open-label, single-arm post-marketing clinical trial	Phase II, multicenter, randomized, controlled, open-label study	Global, phase III, multicenter, randomized, double-blind, placebo-controlled study
Histology of patient population			
Original analysis	NS NSCLC	SQ and NS NSCLC	NS NSCLC
Analysis for this review	NS NSCLC	NS NSCLC	NS NSCLC
Induction therapy	Pemetrexed 500 mg/m^2 and carboplatin AUC=6 every 21 days for 4 cycles	Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 every 21 days for 4 cycles	Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 every 21 days for 4 cycles
No. of patients enrolled/entered	111	86	1,022
No. of patients treated with induction therapy	109	70[a)]	939
No. of patients with NS disease	109	59	939
Randomization	No	Yes (prior to induction therapy)	Yes (prior to maintenance therapy)
Maintenance therapy	Pemetrexed 500 mg/m^2 every 21 days until PD	Optional cisplatin 75 mg/m^2 for first 2 cycles and pemetrexed 500 mg/m^2 every 21 days until PD/death/unacceptable toxicity	Pemetrexed 500 mg/m^2 and BSC every 21 days until PD/ unacceptable toxicity/decision of the patient or physician
No. of randomized patients to pemetrexed/treated with pemetrexed maintenance	60	24[b)]	359
No. of patients with NS disease	60	22	359
Comparator	NA	Gefitinib 250 mg orally every day until PD/death/unacceptable toxicity	Placebo and BSC every 21 days until PD/ unacceptable toxicity/decision of the patient or physician
No. of randomized patients to comparator group	NA	25[c)]	180
Efficacy endpoints			
Primary	PFS from enrollment date to PD or death (induction plus maintenance)	PFS from enrollment date to PD or death (induction plus maintenance); however, for the primary endpoint analysis, it was evaluated for the maintenance period only using a time-dependent Cox model	PFS from randomization date to PD or death (maintenance)
Secondary	OS, DCR, ORR, response rate in induction and DCR in maintenance	ORR, DoR, OS	OS, ORR

Table 1. Continued

	JMII	S110	PARAMOUNT
Baseline for efficacy and safety assessment	Enrollment	Randomization	Randomization
Efficacy analysis set	Treated patients with no significant protocol violation	Randomized and treated patients	Randomized patients
Safety analysis set	Patients who received at least one dose of pemetrexed and carboplatin induction therapy	Randomized and treated patients	Randomized patients
Adverse events assessment	AEs which onset newly or worsened in the entire treatment (induction+maintenance) in patients who received induction therapy AEs which onset newly in maintenance or worsened from baseline and induction period	AEs which onset newly in maintenance or worsened from baseline and induction period AEs which onset newly or worsened in the entire treatment (induction+maintenance) in patients who received the induction therapy	AEs which onset newly or worsened in the entire treatment (induction+maintenance) in patients who received the induction therapy AEs which onset newly in maintenance or worsened from baseline and induction period
PFS assessed in this manuscript	PFS for entire period – PFS for induction therapy period	PFS for maintenance period	PFS for only maintenance therapy

NS, nonsquamous; NSCLC, non-small cell lung cancer; SQ, squamous; AUC, area under curve; PD, progressive disease; BSC, best supportive care; NA, not applicable; PFS, progression-free survival; OS, overall survival; DCR, disease control rate; ORR, objective response rate; DoR, duration of response; AE, adverse event; PC/G, pemetrexed+cisplatin followed by gefitinib; PC/P, pemetrexed+cisplatin followed by pemetrexed. [a]Of 73 NSCLC patients who were enrolled and randomized, 70 patients received induction treatment, of which 59 patients (32 in the PC/G arm and 27 in the PC/P arm) had NS NSCLC, [b]Of 24 NSCLC patients in the pemetrexed maintenance arm in study S110, 22 patients had NS NSCLC, [c]Of 25 NSCLC patients in the gefitinib maintenance arm in study S110, 23 patients had NS NSCLC.

Table 2. Key eligibility criteria

	JMII	S110	PARAMOUNT
Age	≥ 20 yr	≥ 18 yr	≥ 18 yr
ECOG PS	0-1	0-1	0-1
Stage	IIIB/IV, post-operative recurrent disease	IIIB/IV	IIIB/IV
Histology	NS NSCLC	SQ and NS NSCLC	NS NSCLC
Smoking status	NA	Never-smoker[a)]	NA
EGFR mutation status	NA	Unknown	NA
CNS metastasis	Stable or treated brain metastasis allowed	Stable or treated brain metastasis allowed	Stable or treated brain metastasis allowed
Prior treatment history	Chemonaïve Adjuvant excluded Radiotherapy < 25% of the bone marrow	Chemonaïve Radiotherapy < 25% of the bone marrow	Chemonaïve Adjuvant excluded Radiotherapy < 25% of the bone marrow
Adequate organ function	Bone marrow reserve, renal, hepatic	Bone marrow reserve, renal, hepatic	Bone marrow reserve, renal, hepatic
Weight loss	NA	≤ 10% within 6 weeks prior to study entry	NA
Measurable lesions	Measurable lesions meeting RECIST ver. 1.0 criteria	At least 1 unidimensionally measurable lesion meeting RECIST ver. 1.0 criteria	At least 1 unidimensionally measurable lesion meeting RECIST ver. 1.0 criteria
Criteria for randomization and/or receiving maintenance therapy	Evidence of CR, PR or SD after 4 cycles of induction therapy	Four cycles of induction therapy	Documented radiographic evidence of a tumor response of CR, PR, or SD after 4 cycles of induction therapy
Life expectancy	At least 12 weeks	Less than 12 weeks	At least 12 weeks

ECOG PS, Eastern Cooperative Oncology Group performance status; NS, nonsquamous; NSCLC, non-small cell lung cancer; SQ, squamous; NA, not applicable/not available; *EGFR*, epidermal growth factor receptor; CNS, central nervous system; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease.
[a)]Defined as having smoked < 100 cigarettes during his/her life.

may benefit patients who have not progressed during first-line or induction treatment due to prolongation of tumor control. Maintenance therapy in advanced NSCLC, which comprises either continuation of non-platinum chemotherapy (continuation maintenance) or introduction of a new agent (switch maintenance), has been shown to be an effective strategy for improving survival and has become a recommended therapeutic option.

Pemetrexed, a multi-targeted antifolate, acts by disrupting the folate-dependent metabolic processes essential for cell replication [5] and is a standard-of-care option in the first-line treatment of nonsquamous NSCLC as a combination therapy with platinum [6], as a single agent for second-line therapy [7], and as switch maintenance therapy [8]. A *post hoc* subgroup analysis of results from a global, phase III trial (JMEN) supports pemetrexed as switch maintenance therapy in East Asian (EA) patients with advanced nonsquamous NSCLC, and was consistent with results from the overall population [9].

A recent global, phase III study (PARAMOUNT) demonstrated that pemetrexed continuation maintenance therapy resulted in improved OS and PFS versus placebo, leading to its regulatory approval as a new treatment option for advanced nonsquamous NSCLC [10,11], and its inclusion in the recent National Comprehensive Cancer Network guidelines for NSCLC [1]. However, the majority of patients enrolled in the PARAMOUNT study were Caucasian (94%) and further data are required to validate the efficacy of pemetrexed continuation maintenance therapy in EA patients.

Studies S110 [12] and JMII [13] were two clinical trials that investigated the efficacy and safety of pemetrexed continuation maintenance therapy in EA patients. The objective of this analysis was to review the efficacy and safety data from these two clinical trials in EA patients to supplement the data from PARAMOUNT on pemetrexed continuation maintenance therapy in patients with nonsquamous NSCLC.

Materials and Methods

1. Study design

The study designs for all three studies were reported previously [10,12,13]. Study S110 compared the efficacy and safety of pemetrexed and cisplatin as first-line treatment, followed sequentially by switch maintenance with gefitinib versus continuation maintenance with pemetrexed in patients with locally advanced or metastatic NSCLC in patients from China, Korea, and Taiwan [12]. Study JMII evaluated the efficacy and safety of pemetrexed plus carboplatin as induction therapy, followed by pemetrexed as maintenance therapy, in patients from Japan with advanced nonsquamous NSCLC [13]. PARAMOUNT was a global study conducted in patients with advanced nonsquamous NSCLC to compare the efficacy and safety of pemetrexed plus best supportive care (BSC) with placebo plus BSC as maintenance therapy following induction treatment with pemetrexed plus cisplatin combination chemotherapy [10].

2. Treatment plan

The treatment regimens for all three studies were reported previously [10,12,13]. Table 1 shows details of the study designs, the number of patients enrolled and randomized, and the number of patients treated during the induction and maintenance phases. Details of the drug manufacturers were published previously [10,12,13] and, in all of these studies, pemetrexed was administered intravenously (500 mg/m^2) on day 1 of a 3-week cycle as described in the pemetrexed label. All patients treated with pemetrexed received dexamethasone, folic acid, and vitamin B_{12}, except for the Japanese patients who did not receive dexamethasone as it was not per the pemetrexed label in Japan.

3. Eligibility criteria

Detailed eligibility criteria were reported previously [10,12,13]. The key eligibility criteria are presented in Table 2. These studies were conducted in accordance with the ethical principles originating in the Declaration of Helsinki, good clinical practices, and all applicable laws and regulations. The institutional review board at each site approved the study, and all subjects provided written informed consent before undergoing any study procedure.

4. Efficacy and safety assessments

PFS was the primary endpoint for all three studies, the definition of which was based on each study design, as previously reported [10,12,13]. To assess PFS for the maintenance period in studies JMII and S110, PFS of the induction period was subtracted from PFS for the entire period (induction plus maintenance). To assess PFS for the entire period in PARAMOUNT, PFS for the induction period was combined with PFS for the randomization period.

The secondary endpoints assessed in addition to the safety profile were OS, disease control rate (DCR), and overall response rate (ORR) in study JMII [13], and in study S110 [12], and ORR and OS in PARAMOUNT [10,11].

To assess the safety of maintenance therapy, two types of toxicities were evaluated: adverse events (AEs) with new onset or that deteriorated during the entire treatment period (induction plus maintenance) for patients who received the induction therapy, and AEs with new onset or that deteriorated during maintenance therapy for patients who received maintenance therapy.

5. Statistical methods

Detailed statistical methods for all three studies were reported previously [10,12,13]. Data from the investigational treatment arm of each study were used for this review: pemetrexed-cisplatin followed by pemetrexed (PC/P) arm in S110, pemetrexed plus carboplatin arm in JMII, and pemetrexed plus BSC maintenance arm in PARAMOUNT. For JMII and S110, only nonsquamous NSCLC patients were included in efficacy analyses, while all patients were included in safety analyses because the safety profile has not been shown to differ by histology. PARAMOUNT only enrolled nonsquamous patients and hence all results are for nonsquamous patients only.

Results

1. Baseline demographics and treatment

Table 3 shows the baseline demographic and disease characteristics of patients who received pemetrexed continuation maintenance therapy in the three studies. The majority of patients in study S110 were never-smokers, whereas the majority of patients in studies JMII and PARAMOUNT were past or current smokers. For the purpose of this analysis, only nonsquamous NSCLC patients (59 patients; 32 in pemetrexed-cisplatin followed by gefitinib [PC/G] and 27 in PC/P) were considered for efficacy analyses from study S110; all study S110 patients were included in safety analyses as there has been no evidence to date that toxicity varies by histology. *EGFR* mutation status, which was tested only in study JMII, is shown in Table 3.

Table 3. Baseline characteristics[a)]

Variable	JMII PCb/P (n=109)	S110 PC/P ind+mnt (n=27)	S110 PC/P mnt (n=22)	PARAMOUNT P+BSC mnt (n=359)
Age (yr)				
Median (range)	63 (38-78)	57.0 (29-75)	54.5 (29-74)	61 (32-79)
Gender				
Female	40 (36.7)	22 (81.5)	17 (77.3)	158 (44)
Male	69 (63.3)	5 (18.5)	5 (22.7)	201 (56)
Ethnic origin				
Asian	-	-	-	16 (4)
Japan	109 (100)	-	-	-
China	-	13 (48.1)	12 (54.5)	-
Korea	-	6 (22.2)	5 (22.7)	-
Taiwan	-	8 (29.6)	5 (22.7)	-
Caucasian	-	-	-	339 (94)
African	-	-	-	4 (1)
Stage of disease				
Stage IIIB	33 (30.3)	3 (11.1)	3 (13.6)	31 (9)
Stage IV	72 (66.1)	24 (88.9)	19 (86.4)	328 (91)
Recurrence	4 (3.7)	-	-	-
ECOG performance status				
0	37 (33.9)	8 (29.6)	8 (36.4)	115 (32)
1	72 (66.1)	19 (70.4)	14 (63.6)	243 (68)
2-3	-	-	-	1 (< 1)
Histological subtypes				
Adenocarcinoma	106 (97.2)[b)]	24 (88.9)	21 (95.5)	304 (85)
Large cell	3 (2.8)	1 (3.7)	-	24 (7)
Bronchoalveolar	-	-	-	6 (2)
Other	-	2 (7.4)	1 (4.5)	25 (7)
Smoking				
Ever	76 (69.7)	2 (7.4)	1 (4.5)	275 (77)
Never	33 (30.3)	25 (92.6)	21 (95.5)	82 (23)
Unknown	0	0	-	2 (< 1)
EGFR mutation status				
Positive	24 (22.0)	-	-	-
Negative	63 (57.8)	-	-	-
Unknown	3 (2.8)	-	-	-
Not done	19 (17.4)	-	-	-

Values are presented as number (%). PCb/P, pemetrexed+carboplatin followed by pemetrexed; PC/P, pemetrexed+cisplatin followed by pemetrexed; ind, induction; mnt, maintenance; P+BSC, pemetrexed+best supportive care; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer. [a)]Baseline characteristics prior to induction for studies JMII and S110, but prior to maintenance for PARAMOUNT randomization, [b)]Includes 1 patient reclassified as having squamous NSCLC after study entry and examination of *EGFR* gene type was not done.

Table 4. Summary of efficacy parameters for patients with nonsquamous disease

Efficacy parameter	JMII PCb/P	S110 PC/P	PARAMOUNT P+BSC mnt
Induction regimen	Carboplatin+pemetrexed	Cisplatin+pemetrexed	Cisplatin+pemetrexed
Induction sample size	106	27	939
Maintenance sample size	60 (56.6%)	22 (81.5%)	359 (66.6%)[a]
Efficacy during maintenance therapy			
Maintenance regimen	Pemetrexed	Pemetrexed	Pemetrexed
No.	60	22	359
Median PFS (95% CI, mo)	3.9 (3.2-5.2)	4.04 (3.22-5.29)	4.1 (3.2-4.6)
Efficacy during induction+maintenance period			
No.	106[b]	27	359[a]
Median PFS (95% CI, mo)	5.7 (4.4-7.3)	6.83 (5.78-7.98)	6.9 (6.2-7.5)
Median OS (95% CI, mo)[c]	20.2 (16.7-NA)	NR[d]	13.9 (12.8-16.0)
1-Year survival rate (95% CI, %)[c]	70.0 (60.4-77.8)	96.3 (76.5-99.5)	58 (53.0-63.0)
2-Year survival rate (95% CI, %)[c]	42.5 (32.8-51.8)	78.0 (54.7-90.2)	32 (27.0-37.0)
Subgroup analysis			
Median PFS (95% CI, mo), *EGFR* mutation-positive patients	5.7 (5.2-7.2)	NA[e]	NA[e]
Median PFS (95% CI, mo), *EGFR* mutation-negative patients	6.9 (4.3-7.8)	NA[e]	NA[e]

PCb/P, pemetrexed+carboplatin followed by pemetrexed; PC/P, pemetrexed+cisplatin followed by pemetrexed; P+BSC mnt, pemetrexed+best supportive care maintenance; PFS, progression-free survival; CI, confidence interval; OS, overall survival; NA, not available; NR, not reached; *EGFR*, epidermal growth factor receptor. [a]In PARAMOUNT, 939 patients were enrolled into the induction phase, and 539 patients (57.4%) (pemetrexed [n=359], placebo [n=180]) were randomized, [b]Efficacy assessment was performed on per-protocol set, which consisted of 106 treated patients without major protocol violations as reported in the JMII manuscript, [c]In PARAMOUNT, median OS, 1-year and 2-year survival rates are reported for the maintenance period but for the induction+maintenance period for S110 and JMII, [d]There were insufficient events to calculate median OS in study S110 due to censoring (72.9% cases were censored), [e]The *EGFR* mutation analysis was not performed in studies S110 and PARAMOUNT.

Table 5. Response rates and disease control rates for entire treatment period and during induction period for patients with nonsquamous disease

	Entire treatment period		Induction period	
	JMII (n=106)	S110 (PC/P) (n=27)	JMII (n=106)	S110 (PC/P) (n=27)
Best overall response[a]				
Complete response	0	0	0	0
Partial response	38 (35.8)	10 (37.0)	42 (39.6)	5 (18.5)
Stable disease	41 (38.7)	12 (44.4)	45 (42.5)	17 (63.0)
Progressive disease	20 (18.9)	3 (11.1)	15 (14.2)	2 (7.4)
Unknown	7 (6.6)	1 (3.7)	4 (3.8)	2 (7.4)
Early death from toxicity	NA	1 (3.7)	0	1 (3.7)
Disease control rate (CR+PR+SD)	74.5 (65.1-82.5)	81.5 (61.9-93.7)	82.1 (73.4-88.8)	81.5 (61.9-93.7)
Overall response rate (CR+PR)	35.8 (26.8-45.7)	37.0 (NA)	39.6 (30.3-49.6)	18.5 (6.3-38.1)

Values are presented as number (%) or percent (95% CI). PC/P, pemetrexed+cisplatin followed by pemetrexed; NA, not available/not applicable; CR, complete response; PR, partial response; SD, stable disease; CI, confidence interval. [a]The best overall response data for the entire treatment period were not captured in PARAMOUNT due to the unique study design.

Table 6. Adverse events grade ≥ 3 and possibly related to study drug across all studies during induction and/or pemetrexed maintenance period

Grade ≥ 3 AE	JMII[a]		S110[b]	PARAMOUNT[c,d,e]	
	PCb/P (n=109)	P maintenance (n=60)	PC/P (n=31)	P maintenance period (n=24)	P maintenance (n=359)
Patients with ≥ 1 laboratory AE	-	-	-	-	33 (9)
Hematologic AEs	-	-	6 (19.4)	3 (12.5)	-
Anemia	34 (31.2)	1 (1.7)	1 (3.2)	1 (4.2)	16 (4)
Neutropenia	62 (56.9)	3 (5.0)	5 (16.1)	2 (8.3)	13 (4)
Leukopenia	24 (22.0)	1 (1.7)	0	0	6 (2)
Thrombocytopenia	45 (41.3)	0	0	0	4 (1)
Non-hematologic AEs					
Alanine aminotransferase	7 (6.4)	2 (3.3)	1 (3.2)	0	1 (<1)
Aspartate aminotransferase	2 (1.8)	1 (1.7)	0	0	0
Hypokalemia	0	0	1 (3.2)	0	0
Hyponatremia	0	0	1 (3.2)	0	0
Metabolic/laboratory, other	0	0	2 (6.5)	0	0
Patients with ≥ 1 non-laboratory AE	-	-	-	-	32 (9)
Fatigue (asthenia, lethargy, malaise)	2 (1.8)	0	2 (6.5)	2 (6.5)	15 (4)
Nausea	1 (0.9)	0	3 (9.7)	0	1 (< 1)
Vomiting	3 (2.8)	0	4 (12.9)	0	0
Mucositis or stomatitis	0	0	0	0	1 (< 1)
Anorexia/appetite loss	6 (5.5)	0	1 (3.2)	0	1 (< 1)
Pain, any event	0	0	0	0	3 (< 1)
Infection	0	0	0	0	4 (1)
Neuropathy: sensory	0	0	0	0	1 (< 1)
Dyspnea	0	0	2 (6.5)	1 (4.2)	0
Rash	1 (0.9)	0	0	0	0
Pneumonitis	0	0	1 (3.2)	0	0
Fever	1 (0.9)	0	0	0	0

Values are presented as number (%). PCb/P, pemetrexed+carboplatin followed by pemetrexed; PC/P, pemetrexed+cisplatin followed by pemetrexed (10 patients also received optional cisplatin); AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; P, pemetrexed; TEAEs, treatment-emergent adverse events. [a]Toxicities in study JMII were TEAEs based on MedDRA ver. 14.1 and NCI-CTCAE ver. 3.0 preferred terms, [b]Toxicities in study S110 were based on NCI-CTCAE ver. 3.0; 4 patients had squamous NSCLC on PC/P induction+P maintenance and 2 patients had squamous NSCLC on PC/P maintenance period. There has been no evidence to date that toxicity varies by histology, [c]Toxicities in PARAMOUNT were TEAEs based on NCI-CTCAE ver. 3.0, [d]Among possibly drug-related AEs during the maintenance treatment period, no laboratory AEs of grade 5 (deaths) and 2 non-laboratory AEs of grade 5 (deaths) were recorded: 1 patient died in the pemetrexed group (pneumonia) and 1 patient died in the placebo group (sudden death—not otherwise specified), [e]For PARAMOUNT, the decimals are rounded off to be consistent with the original publication.

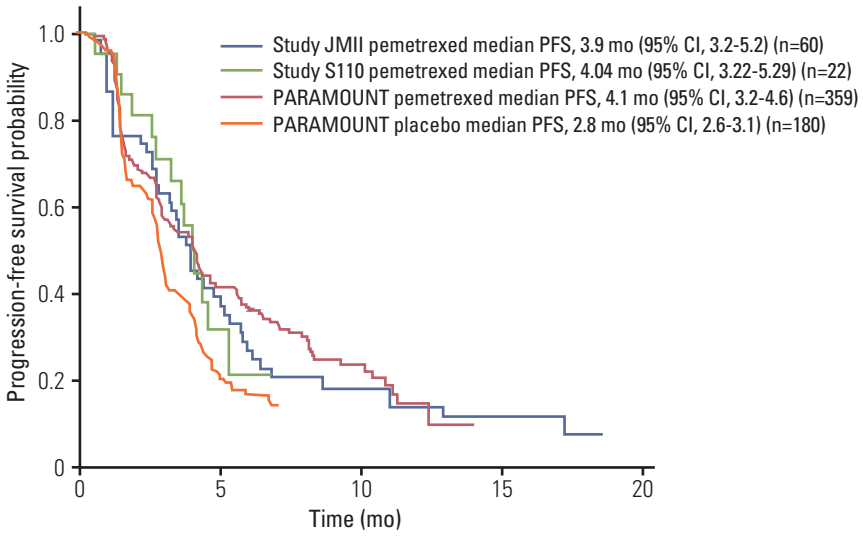

Fig. 1. Kaplan-Meier curve of progression-free survival for maintenance therapy post-induction. These are 4 curves superimposed on one plot and, as this was not a randomized study of 4 arms, they should not be directly compared. CI, confidence interval; PFS, progression-free survival.

2. Dose administration of pemetrexed maintenance therapy

The median number of cycles (range) in patients who received at least one cycle of pemetrexed treatment during the maintenance period in the three studies was as follows: study JMII (n=60), 4 (1, 14); study S110 (n=24), 4 (1, 10); and PARAMOUNT (n=333), 4 (1, 19).

3. Efficacy

PFS curves for pemetrexed continuation maintenance therapy post-induction are presented in Fig. 1. The median PFS during the maintenance period in studies JMII, S110, and PARAMOUNT was 3.9 months (95% confidence interval [CI], 3.2 to 5.2 months), 4.04 months (95% CI, 3.22 to 5.29 months), and 4.1 months (95% CI, 3.2 to 4.6 months), respectively (Table 4). The median PFS during the entire period (induction plus maintenance) in studies JMII, S110, and PARAMOUNT was 5.7 months (95% CI, 4.4 to 7.3 months), 6.83 months (95% CI, 5.78 to 7.98 months), and 6.9 months (95% CI, 6.2 to 7.5 months), respectively (Table 4).

In study JMII, the median OS during the entire period was 20.2 months (95% CI, 16.7 to not available). In study S110, the median OS could not be estimated due to a high censoring rate (72.9%); however, the 1-year survival rate from randomization at the start of induction therapy was 96.3% (95% CI, 76.5% to 99.5%). In PARAMOUNT, the median OS during the pemetrexed continuation maintenance period was 13.9 months (95% CI, 12.8 to 16.0 months), and the 1-year survival rate from randomization at the start of maintenance therapy was 58.0% (95% CI, 53.0% to 63.0%) [11].

The individual response rates during the induction period for JMII and S110 are reported in Table 5. The DCR for the entire period was 74.5% (95% CI, 65.1% to 82.5%) and 81.5% (95% CI, 61.9% to 93.7%), and the ORR was 35.8% and 37%, in studies JMII and S110, respectively (Table 5). Individual response rates and DCRs were not available for PARAMOUNT during the entire treatment period due to its unique study design. During the maintenance period, there was 44% complete/partial response, 53% stable disease, and 0.3% progressive disease.

4. Safety

AEs possibly related to study drug with grade ≥ 3 severity are reported by treatment period in Table 6. The incidence of hematologic AEs was higher than the incidence of non-hematologic and non-laboratory AEs in all three of the studies. Treatment-emergent or worsening AEs during the maintenance period were rare in studies JMII and S110. The most common non-laboratory AEs reported in all three of the studies were fatigue, nausea, and anorexia. The incidence of nausea and vomiting was also frequent during the induction period in studies JMII and S110 (Table 6).

Table 7. Summary of post-discontinuation anti-cancer therapy in studies JMII, S110, and PARAMOUNT

Post-study anti-cancer therapy[a]	JMII		S110[b]	PARAMOUNT[c]
	All treated patients (n=109)	Maintenance treated patients (n=60)	PC/P entire period (n=31)	Pemetrexed (n=359)
Any post-study anti-cancer therapy	86 (78.9)	50 (83.3)	25 (80.6)	231 (64)
Surgery	0	0	1 (3.2)	-
Radiotherapy	9 (8.3)	3 (2.8)	13 (41.9)	-
Chemotherapy (≥ 1 line)	-	-	18 (58.1)	-
Pemetrexed	11 (10.1)	4 (6.7)	0	7 (2)
Docetaxel	43 (39.4)	24 (40.0)	10 (32.3)	116 (32)
Other	59 (54.1)	32 (53.3)	11 (35.5)	96 (27)
Biological (targeted therapy)	34 (31.2)	19 (31.7)	18 (58.1)	-
Erlotinib	19 (17.4)	11 (18.3)	5 (16.1)	142 (40)
Gefitinib	16 (14.7)	8 (13.3)	14 (45.2)	3 (0.8)
Vandetanib	0	0	3 (9.7)	0
BIBW2992	0	0	4 (12.9)	0
Sorafenib	0	0	0	0
Cetuximab	0	0	1 (3.2)	0
Bevacizumab	8 (7.3)	4 (6.7)	1 (3.2)	6 (2)
Afatinib	0	0	0	2 (0.6)
Immunological	0	0	1 (3.2)	0
Investigational drug	9 (8.3)	8 (13.3)	0	20 (6)
Placebo	0	0	0	4 (1)

Values are presented as number (%). PC/P, pemetrexed+cisplatin followed by pemetrexed; NSCLC, non-small cell lung cancer. [a]Patients may have received ≥ 1 post-study anti-cancer therapy, [b]In study S110, post-discontinuation therapy details were reported for all NSCLC patients, [c]For PARAMOUNT, the decimals are rounded off to be consistent with the original publication.

5. Post-discontinuation anti-cancer therapy

A summary of post-discontinuation anti-cancer therapy for all three studies is reported in Table 7. There was a trend for higher use of post-discontinuation anti-cancer therapy in EA patients. Among the types of treatments, the use of docetaxel as post-discontinuation anti-cancer therapy was numerically higher compared with any other individual chemotherapy among all three of the studies. Also, use of the targeted therapies erlotinib and gefitinib was relatively high in all three of the studies.

Discussion

Our findings show that median PFS from the start of pemetrexed continuation maintenance therapy in two separate studies that enrolled Japanese, Chinese, and Korean patients was consistent with the median PFS observed in the PARAMOUNT study, which enrolled primarily Caucasian patients. Toxicity and safety results were consistent with those previously reported for PARAMOUNT, indicating that pemetrexed continuation maintenance therapy is well tolerated in EA patients with advanced, nonsquamous NSCLC.

In a follow-up of the PARAMOUNT study, it was reported that pemetrexed continuation maintenance therapy was well tolerated, which corresponded to known pemetrexed toxicities, and that resource use was low [14]. Studies JMII and S110 comprised different EA populations, study designs, and treatment regimens. Nonetheless, the additional data in the current analysis indicates consistent patient outcomes across clinical trials of pemetrexed continuation maintenance therapy. This additional data supports the findings of the PARAMOUNT study, and is consistent with another randomized phase II study, in which pemetrexed maintenance therapy resulted in promising PFS with an acceptable safety profile in a Middle Eastern population with advanced nonsquamous NSCLC [15]. Collectively, these data indicate

that pemetrexed maintenance therapy is efficacious among different ethnicities.

The results of this analysis are supported by a recent study, in which continuation maintenance therapy with pemetrexed and switch maintenance therapy with docetaxel were compared in patients with advanced nonsquamous NSCLC who did not experience disease progression after initial therapy with carboplatin and pemetrexed [16]. In that study, Karayama et al. [16] concluded that pemetrexed continuation maintenance therapy may be an effective treatment option for patients who have achieved disease control after induction therapy as switch maintenance with docetaxel was associated with both increased incidence of severe hematologic AEs and poor survival without toxicity.

A limitation of this analysis is that a comprehensive comparison of the AEs among the three studies could not be performed, since the AEs were defined differently in each study. The high incidence of hematologic toxicities in study JMII is probably due in part to weekly monitoring of laboratory measurements, whereas laboratory measurements were planned before day 1 of each cycle in the other two studies. The high incidence of hematologic toxicities in study JMII may also be due to the use of a different induction platinum regimen (i.e., carboplatin). The safety profile of pemetrexed in studies S110 and JMII was consistent with the safety profile of pemetrexed reported previously [8,9]. There were no noteworthy differences observed in the safety profile between the two EA trials and PARAMOUNT. Another limitation of this analysis is that limited data were available for EA patients treated with pemetrexed continuation maintenance therapy, since studies S110 and JMII enrolled fewer patients than PARAMOUNT. Also, the eligibility criteria, choice of platinum in the induction therapy, and study designs of the three studies were different, which prevented statistical comparison of data among the three studies.

Efficacy data from the three studies provide an insight on the expected outcomes for pemetrexed continuation maintenance therapy in EA patients with advanced nonsquamous NSCLC. Further studies on pemetrexed continuation maintenance therapy in EA patients are justified. To further establish the role of pemetrexed continuation maintenance as a new treatment paradigm in the global population, data from clinical trials, in addition to data from real-world clinical practice, are needed. These efforts may expand our insight on the role of pemetrexed continuation maintenance therapy in developing targeted treatment strategies for advanced nonsquamous NSCLC.

Conclusion

This analysis adds a moderate amount of data on EA patients for continuation maintenance with pemetrexed to complement the data from PARAMOUNT. The median PFS from the start of maintenance therapy in two separate phase II studies, JMII and S110, which collectively enrolled Japanese, Chinese, Taiwanese, and Korean patients, was consistent with the median PFS observed in PARAMOUNT, which enrolled primarily Caucasian patients. These results suggest that EA patients may benefit from pemetrexed continuation maintenance therapy to a similar degree that Caucasian patients benefit. Toxicity and safety results in studies JMII and S110 were consistent with those previously reported in PARAMOUNT, indicating that pemetrexed is a well-tolerated maintenance treatment in EA patients with advanced nonsquamous NSCLC. Continuation maintenance with pemetrexed is an effective and tolerable treatment for patients with chemonaïve advanced nonsquamous NSCLC.

Conflicts of Interest

Ms. Helen Barraclough, Dr. Sotaro Enatsu, Dr. Rebecca Cheng, and Dr. Mauro Orlando are full-time employees of, and minor stockholders in, Eli Lilly and Company. Dr. James Chin-Hsin Yang has acted as a consultant for Boehringer Ingelheim, Novartis, Pfizer, Clovis, Roche, Innopharma, and Eli Lilly and Company and has served on the Speakers Bureau for Boehringer Ingelheim, AstraZeneca, and Eli Lilly and Company. He currently consults for AstraZeneca, Bayer, Merck, and Optima and receives grant support from Boehringer Ingelheim. Dr. Myung-Ju Ahn, Dr. Nakagawa, and Dr. Tamura have no conflicts of interest to disclose.

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