Phase II trial of Pemetrexed Continuation – Maintenance after Carboplatin-based Induction in Untreated Non-squamous Non-small Cell Lung Cancer

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Abstract. *Aim: We conducted a phase II study to evaluate the efficacy and safety of pemetrexed continuation-maintenance after carboplatin-based induction for advanced non-squamous non-small cell lung cancer (NSCLC). Patients and Methods: Thirty-four patients with advanced or recurrent non-squamous NSCLC received carboplatin (area under the concentration-time curve 6 mg/ml×min) plus pemetrexed (500 mg/m^2) on day 1 tri-weekly. After four cycles of induction, patients without disease progression received pemetrexed maintenance until disease progression or unacceptable toxicity. Results: Twenty-five patients completed induction and 22 received maintenance. The 1-year survival, objective response and disease control rates were 70.3%, 32.4% and 88.2%, respectively. The median progression-free survival and overall survival of all patients were 5.2 and 23.3 months. The incidental rates of grade 3 or more severe adverse events were low. Conclusion: This regimen appears to be an appropriate option for chemonaïve patients with advanced non-squamous NSCLC.*

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Lung cancer is the leading cause of cancer death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases and most patients are found to have locally advanced or metastatic diseases at the time of diagnosis. Maintenance chemotherapy is increasingly being approved as a new treatment paradigm to improve the outcome of advanced NSCLC.

Pemetrexed has become recognized as the most promising candidate drug for both switching maintenance (2) and continuation maintenance (3) use because of its efficacy and low cumulative toxicity. A phase III trial (PARAMOUNT) comparing pemetrexed maintenance with best supportive care after four cycles of induction pemetrexed-plus-cisplatin in patients with non-squamous NSCLC demonstrated benefits both in progression-free (PFS) and overall (OS) survival by pemetrexed continuation maintenance (3, 4).

Carboplatin was developed to reduce some toxicities of cisplatin and is often preferred in combination treatments because of the lower incidence of serious side-effects and more convenient administration. Although several meta-analyses suggested that cisplatin-based chemotherapy is slightly superior in antitumor efficacy and survival benefit to carboplatin-based chemotherapy, the latter has less severe emesis and nephrotoxicity than the former, except for thrombocytopenia (5-7). In a Norwegian phase III study, combination of carboplatin plus pemetrexed was shown to be an appropriate first-line treatment option for chemonaïve patients with advanced non-squamous NSCLC because it provided similar survival benefit and health-related quality-of-life with less hematological toxicity and less need for supportive care when compared with carboplatin plus gemcitabine (8). This study used 500 mg/m^2 of pemetrexed

and an area under the curve (AUC) of 5 mg/ml min of carboplatin. On the other hand, a Japanese dose-finding phase I study concluded the same recommended dose for pemetrexed and an AUC of 6 mg/ml min for carboplatin (9).

To our knowledge, there is no study evaluating the efficacy and safety of pemetrexed continuation maintenance after carboplatin-based induction. Therefore, we conducted a phase II study to evaluate whether carboplatin could substitute for cisplatin as the partner of pemetrexed in the induction phase of therapy, in terms of efficacy and safety for advanced non-squamous NSCLC.

Patients and Methods

Objectives and study design. This trial was an open-label, single-arm, multi-centered, phase II study. The primary objective was to investigate the 1-year survival rate. Secondary objectives were to investigate the safety, the objective response rate (ORR) during induction chemotherapy and PFS, defined as the time from enrollment to disease progression or death. The study protocol was approved by each Institutional Ethics Committee, and adhered to the principles outlined in the Guideline for Good Clinical Practice (January 1997) and Declaration of Helsinki (1996). Written informed consent was obtained from all patients before commencement of the study.

Patient selection. Patients were enrolled when they met all the following entry criteria: (i) histologically- or cytologically-confirmed non-squamous NSCLC; (ii) chemotherapy-naïve stage IIIB/IV or postoperative recurrence; (iii) age ≥20 years; (iv) measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (10); (v) a Karnofsky performance status (KPS) of 70-100; (vi) adequate hematological (absolute white blood cell count ≥4000/μl, neutrophil count ≥2000/μl, platelets ≥100,000/μl, and hemoglobin ≥9.5 g/d), renal (serum creatinine ≤1.2 mg/dl and creatinine clearance calculated by Cockcroft-Gault formula ≥60 ml/min), liver (serum total bilirubin ≤1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤3.0 × upper limit of normal (ULN), and respiratory functions (SpO_2 ≥93% under room air); (vii) estimated life expectancy of more than three months; (viii) written informed consent. Patients with asymptomatic brain metastases, concurrent palliative extra-thoracic radiotherapy, and recurrence one year after postoperative adjuvant chemotherapy were also eligible. On the other hand, exclusion criteria were: (i) clinically significant complications or unstable medical conditions; (ii) pregnancy, lactation, suspicion of being pregnant; (iii) other active neoplasm.

Treatment plan. Carboplatin (AUC 6 mg/ml×min, day 1) and pemetrexed (500 mg/m^2, day 1) were administered intravenously (*i.v.*) every three weeks. The glomerular filtration rate and carboplatin dose were calculated using Cockcroft-Gault and Calvert formule, respectively. Serum creatinine concentrations of the enzyme method were calibrated to those of the non-adjusted Jaffé's method by adding 0.2 mg/dl. After four cycles, patients without progressive disease underwent maintenance therapy of pemetrexed (500 mg/m^2, day 1) every three weeks. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Unless all the starting criteria defined in the protocol were met, administration of drugs on days 1 was postponed. Discontinuation criteria of protocol treatment included: (i) delay of the start of the next course greater than three weeks, (ii) necessity for second dose reduction, (iii) grade 2 or more interstitial pulmonary fibrosis or pneumonitis, (iv) grade 3 or more neurotoxicity, (v) documented disease progression and (vi) patient's refusal to continue the protocol therapy.

Assessments. Required baseline assessments included chest and abdominal computed tomography (CT), cranial CT or magnetic resonance imaging (MRI), and bone scintigraphy or positron emission tomography (PET) within four weeks before enrollment. Overall response was evaluated according to RECIST version 1.1 every cycle during the first two cycles and every two cycles thereafter. Toxicity was graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 (11).

Statistical analyses. We estimated the historical 1-year survival rate as being approximately 35% in patients with NSCLC treated only with four cycles of carboplatin and pemetrexed, based on the past randomized phase III study (8). An increase in the 1-year survival rate to 60% with the addition of pemetrexed maintenance would be considered significant. Assuming a two-sided α of 5% and a power of 80%, a study with 30 evaluable patients would detect the aforementioned treatment effect. Given the possibility of deviation from assessment, 33 patients were necessary. Interim analysis was not planned.

The evaluable population for overall response included all patients, defined as those without major protocol violation, who had received at least one cycle of chemotherapy and had at least two response assessments over six weeks after the enrollment, unless objective progressive disease (PD) was determined. Patients who received any protocol therapy without major protocol violation were considered evaluable for the 1-year survival rate, PFS and safety. Continuous variables are presented as the median values with the corresponding range. Categorical variables are summarized in frequency tables. Time-to-event end-points were computed using the method of Kaplan-Meier. Differences in PFS and OS between two groups were evaluated by the log-rank test. Univariate and Multivariate Cox proportional hazard analyses were applied to predict the prognostic factors affecting disease progression. All variables with $p<0.2$ in the univariate analysis were included in the multivariate analysis. Risk factors that showed significant effects in the Cox proportional hazard analysis are reported with relative risk (RR) and 95% confidence interval (CI). All statistical analyses were performed using StatMate statistical software (StatMate version IV; ATMS Co., Ltd., Tokyo, Japan). Statistical differences were considered significant if $p<0.05$.

Results

Patients' demographics. From December 2009 to March 2011, a total of 34 patients were enrolled from six medical Institutions in Osaka. The baseline characteristics are shown in Table I. Although examination of epidermal growth factor receptor (*EGFR*) mutation status was not mandatory, it was performed in 32 patients. As a result, five patents were found to have active mutations.

Table I. *Patients' characteristics*.

Age, years	
Median	67.5
Range	40-79
Gender	
Male	24
Female	10
Histology	
Adenocarcinoma	31
Other	3
EGFR mutation status	
Positive	5
Negative	27
Not examined	2
Stage	
IIIA	3
IIIB	1
IV	17
Postoperative recurrence	13
Karnofsky performance status	
70	10
80-90	13
100	11

EGFR: Epidermal growth factor receptor.

Treatment. Out of the 34 evaluable patients, 25 patients (73.5%) completed four cycles of induction chemotherapy. Nine patients dropped out during the induction phase because of PD (n=4), necessity for second dose reduction (n=2), patient's refusal (n=2), and physician's decision (n=1). During transition from the completion of the induction phase to the start of the maintenance phase, three patients dropped out because of PD (n=1), patient's refusal (n=1) and physician's decision (n=1). Finally, 22 patients (64.7%) received pemetrexed maintenance therapy. The median number of maintenance cycles delivered was 4 (range, 1 to over 32). There were two patients still on maintenance treatment as of November 30th 2012. Twenty patients discontinued maintenance treatment because of PD (n=12), physician's decision (n=5), patient's refusal (n=1), grade 5 pneumonitis (n=1), and hospital transfer (n=1).

Among the patients aged ≥70 years, 12 completed induction chemotherapy, 10 proceeded to maintenance therapy. Four patients dropped-out during the induction phase because of toxicities (n=1), patient's refusal (n=1), physician's decision (n=1), and PD (n=1). Two patients failed to proceed to maintenance therapy because of physician's decision (n=1) and patient's refusal (n=1).

Efficacy. The follow-up data were collected up to November 30th, 2012. The median follow-up time was 20.9 (range:2 - 32.3) months. At the time of data collection, 19 patients were dead, 13 still alive, and two had been lost follow-up.

The 1-year survival rate was 70.3% (95% CI=53.0 - 83.2%), which met the primary endpoint of this study. The 2-year survival rate was 45.5% (95% CI=28.7 - 63.5%). The median PFS and OS were 5.2 (95% CI=4.1 - 8.2) months (Figure 1A) and 23.3 (95% CI=15.5 to not available) months (Figure 1B) from enrollment in all 34 patients, and 9.0 (95% CI=5.2 - 12.1) months (Figure 1C) and 24.3 (95% CI=17.8 to not available) months (Figure 1D) from the start of maintenance therapy in 22 patients who proceeded to maintenance therapy. In 27 patients with wild-type *EGFR*, the median PFS and OS were 5.2 (95% CI=3.3 - 8.1) months (Figure 2A) and 21.0 (95% CI=10.4 - 27.1) months (Figure 2B) from enrollment. In 16 patients aged ≥70 years, the median PFS and OS were 5.4 (95% CI=3.7 - 10.0) months (Figure 2C) and 23.0 (95% CI=4.7 to not available) months (Figure 2D). In 10 patients with KPS 70, the median PFS and OS were 3.9 (95% CI=0.9 - 5.2) months (Figure 2E) and 6.3 (95% CI=2.0 to 24.2) months (Figure 2F).

In the univariate analysis, positive *EGFR* mutation status (*vs*. negative/unknown, p=0.02, RR=0.16) and better KPS grade of 80-100 (*vs*. 70, p=0.02, RR=0.30) were found to be significant predictive factors for longer PFS from enrollment. In the multivariate analysis, longer time to the best response (interval between enrollment and best response achievement, median 3.0 months, range=1.1 to 9.4 months) (p=0.01, RR=0.69) was also found to be a significant factor influencing longer PFS, in addition to positive *EGFR* mutation status (*vs*. negative/unknown, p=0.03, RR=0.17) and better KPS grade of 80-100 (*vs*. 70, p<0.01, RR=0.13) (Table II).

In the induction therapy, 1 and 10 patients achieved complete response and partial response, respectively. Nineteen remained with stable disease, but in 2 patients, disease progressed. Two patients were not evaluable. Consequently, the ORR and disease control rate (DCR) were 32.4% and 88.2%, respectively.

Safety. The incidental rates of grade 3-4 adverse events (AEs) were low. During the induction phase, grade 4 hematological AEs of neutropenia (n=3), reduced hemoglobin (n=1), and thrombocytopenia (n=4) were recorded. Red blood cell transfusion was required in one patient, and platelet transfusion in another. Severe grade 3 non-hematological AEs included aminotransferase increase (n=3), fatigue (n=2), anorexia (n=1) and lung infection (n=1) (Table III). During the maintenance phase, hematological AEs of grade 3-4 neutropenia (n=5) were observed. Severe non-hematological AEs included grade 3 aminotransferase increase (n=1) and grade 5 pneumonitis, probably due to pemetrexed (n=1) (Table IV). No patient experienced febrile neutropenia, and granulocyte-colony stimulating factor support was not required for any patient throughout the entire protocol treatment.

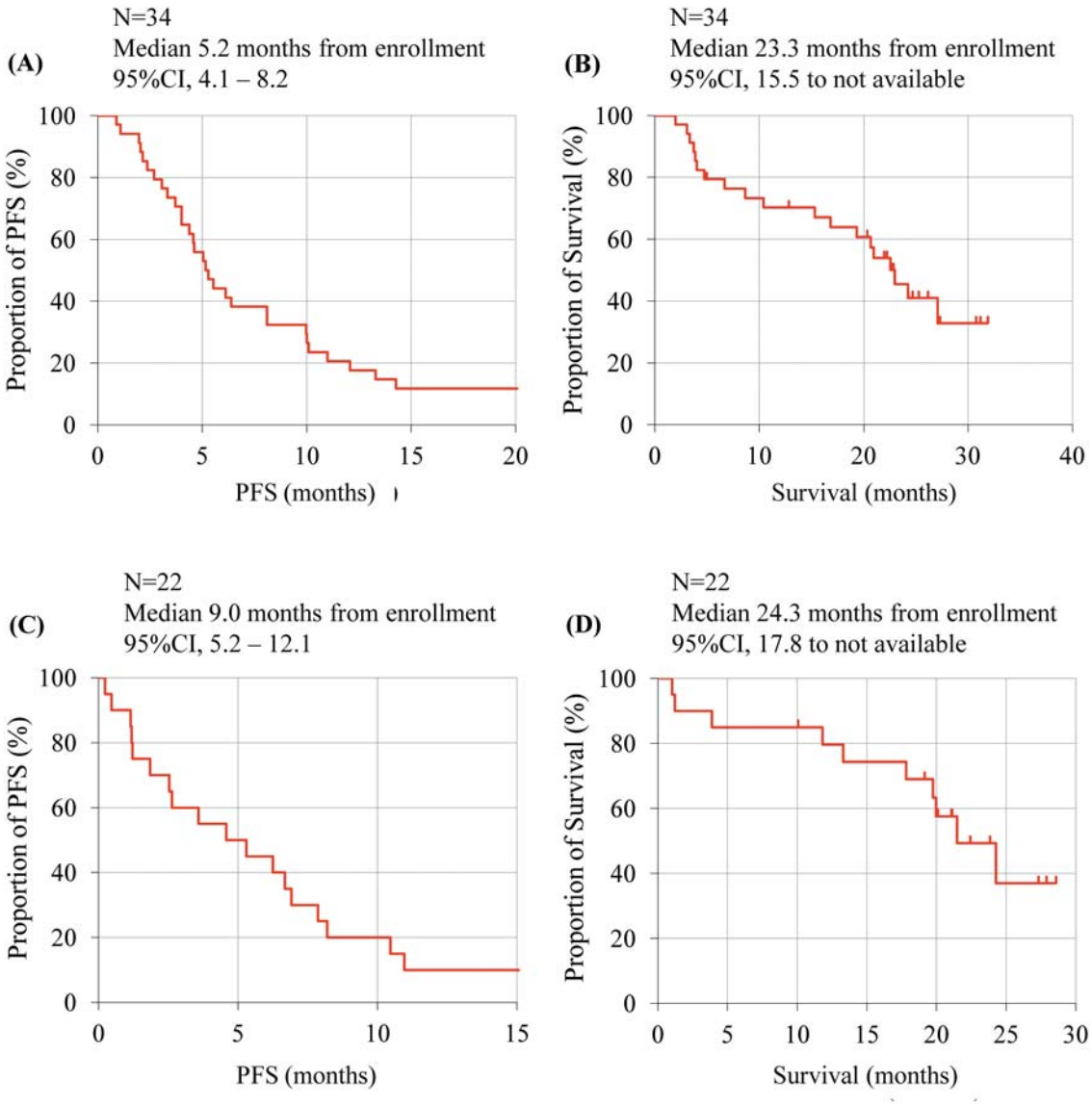

Figure 1. *Kaplan-Meier curves from the enrollment. Progression-free survival (PFS) and overall survival (OS) from enrollment for all 34 patients (A and B) and for the 22 patients who proceeded to maintenance therapy (C and D).*

In 16 patients aged ≥70 years, severe hematological AEs of neutropenia (5 of grade 3 and 2 of grade 4), reduced hemoglobin (2 of grade 4) and thrombocytopenia (5 of grade 3 and 2 of grade 4) were observed during the induction phase. Both of the two patients who received transfusion were aged ≥75 years. Few severe non-hematological AEs occurred, except for grade 3 fatigue (n=1), pneumonitis (n=1) and vasovagal episode (n=1).

Post-protocol treatment. Among 32 patients who discontinued the protocol therapy, 24 patients (75.0%) received post-protocol chemotherapy. Among the 20 patients who discontinued maintenance therapy, 13 received post-protocol chemotherapy. Docetaxel and erlotinib were most commonly used (n=10 and 8, respectively) (Table V).

Discussion

We showed the efficacy and safety of pemetrexed continuation maintenance following induction by pemetrexed plus carboplatin for patient with chemonaïve non-squamous NSCLC. The 1-year survival rate was 70.3% (95% CI=53.0 - 83.2%) and the lower limit (53.0%) was beyond the estimated threshold of 35.0%, thus our study successfully met its primary end-point.

The tumor response in our study (ORR=32.4% and

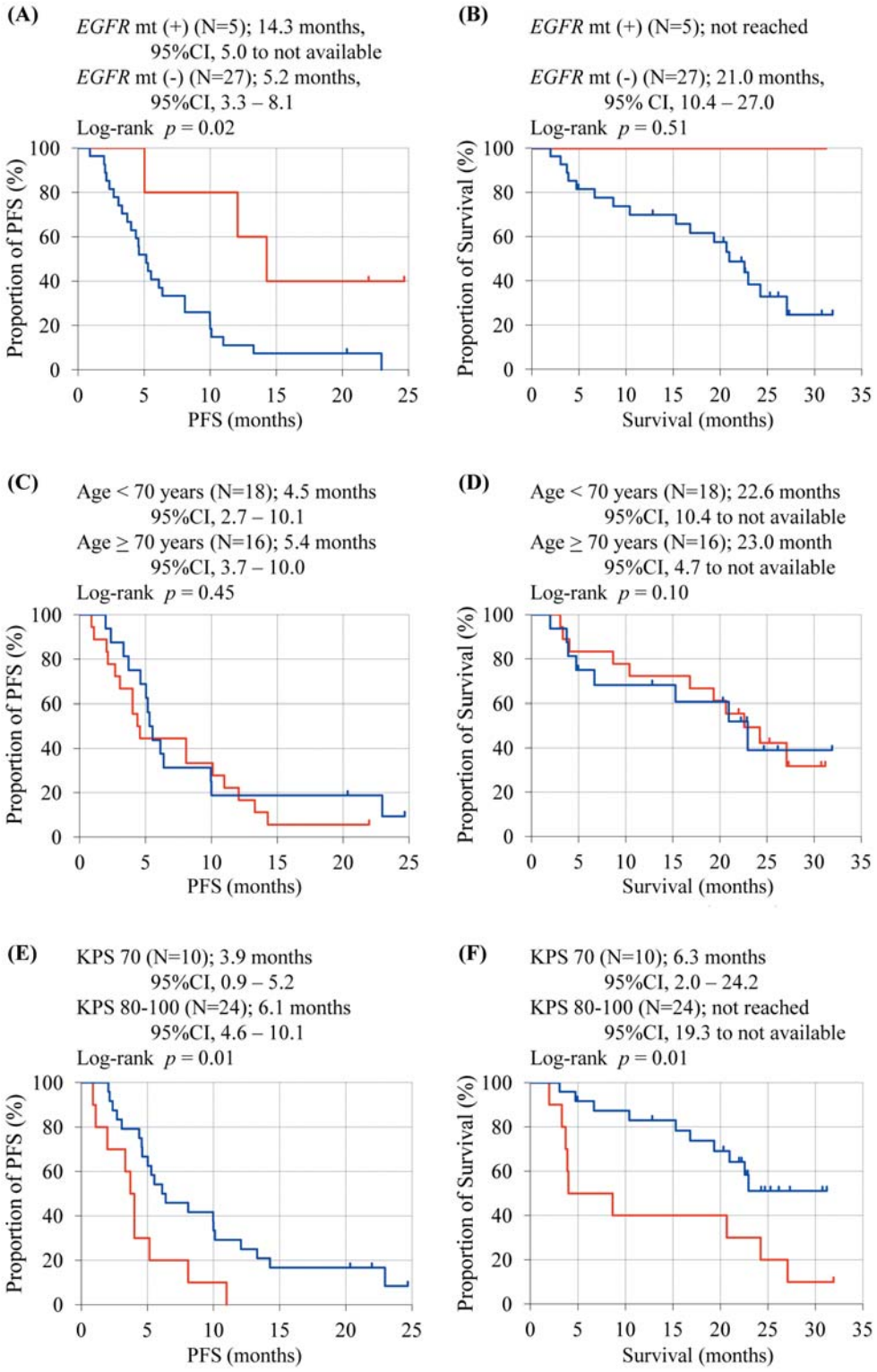

Figure 2. *Kaplan-Meier curves by subgroup. Progression-free survival (PFS; A) and overall survival (OS; B) from enrollment of five patients with active epidermal growth factor receptor mutation (EGFR mt) status (red) and 27 patients with wild-type (wt) EGFR (blue). Two patients with unknown EGFR mutation status were excluded from this analysis. PFS (C) and OS (D) from enrollment of 18 patients aged <70 years (red) and 16 patients aged ≥70 years (blue). PFS (E) and OS (F) from enrollment of 10 patients with Karnofsky performance status (KPS) 70 (red) and 24 patients with KPS 80-100 (blue).*

Table II. *Univariate and multivariate Cox proportional hazard analysis of factors influencing progression-free survival (PFS) from the beginning of maintenance therapy. PFS from the beginning of maintenance treatment was analyzed by univariate and multivariate Cox proportional hazard analysis (n=21). One patient whose disease had gradually progressed without tumor regression but who received maintenance therapy was excluded from the analysis because of lack of data on the time-to-best response. Univariate analysis of histology was not performed because all patients except one had adenocarcinoma.*

Risk factor	RR	95% CI	*p*-Value
Univariate			
Gender	0.64	0.24-1.69	0.37
Stage IV/postoperative recurrence	0.53	0.15-1.91	0.33
Time to the best response (months)	0.85	0.66-1.08	0.17
PR/CR	1.01	0.39-2.60	0.99
Age ≥70 year-old	0.93	0.36-2.41	0.88
EGFR mutation	0.17	0.04-0.76	0.02
KPS ≥80	0.37	0.13-1.03	0.06
Multivariate			
Time-to-the best response (months)	0.69	0.52-0.92	0.01
EGFR mutation	0.17	0.03-0.85	0.03
KPS ≥80	0.18	0.04-0.69	0.01

RR: Relative risk, CI: confidence interval, PR: partial response, CR: complete response, KPS: Karnofsky performance status.

Table III. *Adverse events during the induction phase (n=34).*

	All grades	Grade 3	Grade 4
Hematological			
Leukopenia	24	7	1
Neutropenia	23	11	3
Thrombocytopenia	25	6	4
Hemoglobin decrease	32	4	1
Non-hematological			
Aminotransferase increase	24	3	0
Anorexia	16	1	0
Nausea or vomiting	14	0	0
Fatigue	14	2	0
Constipation	14	0	0
Oral mucositis	4	0	0
Lung infection	1	1	0

DCR=88.2%) was not inferior to that (ORR=30.1% and DCR=74.5%) in PARAMOUNT. The survival from the start of maintenance in our study (PFS 9.0 months and OS 24.3 months) was longer than that (PFS 4.1 months and 13.9 months) in PARAMOUNT. The completion rate of four cycles of induction (73.5%) and the transition rate to maintenance (64.7%) in our study were slightly higher than those in PARAMOUNT (67.8% and 57.4%, respectively) (3, 4). Thus, pemetrexed-plus-carboplatin was equivalent to pemetrexed-plus-cisplatin as the induction regimen.

Table IV. *Adverse events during the maintenance phase (n=22).*

	All grades	Grade 3	Grade 4	Grade 5
Hematological				
Leukopenia	12	2	0	0
Neutropenia	10	3	2	0
Thrombocytopenia	4	0	0	0
Hemoglobin decrease	17	0	0	0
Non-hematological				
Aminotransferase increase	11	1	0	0
Nausea or vomiting	4	0	0	0
Constipation	3	0	0	0
Pneumonitis	2	0	0	1

Table V. *Post-protocol treatment (n=32).*

	n
Received post-protocol treatment	24
Radiotherapy	7
Chemotherapy	20
Docetaxel	10
Erlotinib	8
S-1	7
Vinorelbine	5
Gemcitabine	4
Bevacizumab	4
Pemetrexed	3
Carboplatin	2
Irinotecan	2
Gefitinib	1
None	6
Unknown	2

Two patients continue to receive protocol treatment.

During our study, a Japanese phase IV study of pemetrexed maintenance following four cycles of induction pemetrexed-plus-carboplatin (JACAL, n=109) reported that this regimen was effective and well-tolerable (12). The treatment regimen in JACAL was almost same as ours, except that the carboplatin dose was not adjusted by serum creatinine concentration measured by the enzyme method, resulting in a larger dose than ours. In JACAL, the ORR, DCR, completion rate of induction chemotherapy, transition rate into pemetrexed maintenance, median PFS and OS for the entire study period were 35.8%, 74.5%, 68.8%, 55.0%, 5.7 months and 20.2 months, respectively. The most common AEs were appetite loss (75.2%), nausea (74.3%) and fatigue (67.9%). Grade 3-4 neutropenia, thrombocytopenia and anemia were 56.9%, 41.3% and 31.2%, respectively (12). The response, PFS and OS were similar to ours. However, the completion rate of induction chemotherapy and the transition rate to maintenance therapy were slightly lower and the incidences of hematological AEs were higher than

ours. These differences between JACAL and our study are probably attributable to the difference in adjustment by serum creatinine concentration and suggest the validity of our dose setting for carboplatin.

Of note, a recent Japanese phase I study of this regimen for patients aged ≥75 years finally recommended 500 mg/m^2 of pemetrexed and AUC 5 mg/ml min of carboplatin without adjustment by serum creatinine concentration because grade 4 thrombocytopenia and febrile neutropenia were observed as dose-limiting toxicities in the cohort of the maximum-tolerated dose, pemetrexed at 500 mg/m^2 and carboplatin at an AUC of 6 mg/ml min (13). In our nine patients aged ≥75 years, grade 4 neutropenia and thrombocytopenia occurred only in one and grade 4 reduced hemoglobin in another two (data not shown). Thus, it is controversial whether our dose setting is feasible for patients aged ≥75 years.

Interestingly, multivariate analysis of patients who received maintenance therapy revealed that a longer time-to-the best response, positive *EGFR* mutation status and better KPS significantly led to a longer PFS from the start of maintenance therapy. Consistent with our result, a retrospective study showed that patients with active *EGFR* mutations had longer PFS by pemetrexed monotherapy than those with wild-type *EGFR* (3.9 months *vs*. 2.3 months, p=0.03) (14). On the other hand, the JACAL study did not show the superiority of positive *EGFR* mutation to wild-type *EGFR* in PFS (median 5.7 months *vs*. 6.9 months) (12). Thus, it remains controversial whether positive *EGFR* mutation status is predictive of a longer maintenance period without disease progression.

Considering a longer time to the best response as a predictive marker for a longer maintenance period, patients who responded slowly (late responders) maintained their response for a long time, whereas patients who responded early in the induction phase (early responders) experienced disease progression shortly after the maintenance phase started. Carboplatin would be the key drug in early responders, while pemetrexed would be so in late responders. Prolongation of PFS probably depends on whether pemetrexed is the key drug or not, regardless of the dependency on carboplatin. A similar phenomenon was repeated in the PARAMOUNT trial (3, 4). The PFS curve of the pemetrexed maintenance arm overlay that of the placebo maintenance arm within the initial one to two months after randomization, but thereafter the superiority of the pemetrexed maintenance arm became apparent. This observation might explain why patients with cisplatin-dependent but not pemetrexed-dependent disease progressed in the pemetrexed maintenance phase as early as the placebo maintenance and that only those with pemetrexed-dependent disease could benefit from pemetrexed maintenance therapy. Therefore, it is important to determine the true factor predicting for pemetrexed efficacy in order to select the population that really benefits from pemetrexed maintenance therapy.

In conclusion, pemetrexed continuation maintenance following pemetrexed-plus-carboplatin induction is a promising treatment for chemonaïve patients with advanced non-squamous NSCLC because of its good efficacy and less cumulative toxicities. This regimen could substitute for pemetrexed continuation maintenance following cisplatin-based induction.

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