

Pemetrexed and Cisplatin for Advanced Non-squamous Non-small Cell Lung Cancer in Japanese Patients: Phase II Study

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Abstract. *Background:* Although pemetrexed/cisplatin (P-C) is a standard treatment for advanced non-squamous non-small cell lung cancer (Nsq-NSCLC), neither its efficacy nor the effects of potential differences between driver mutations, such as the anaplastic lymphoma kinase (ALK) translocation and epidermal growth factor receptor (EGFR) mutations, have been thoroughly examined. *Patients and Methods:* A single-arm phase II study of P-C was conducted in Japanese patients with chemo-naïve advanced Nsq-NSCLC. Patients received four cycles of pemetrexed (500 mg/m²) combined with cisplatin (75 mg/m²) on day 1 every three weeks. The primary end-point was the response rate (RR) and the secondary end-points were toxicity, progression-free survival (PFS), and overall survival (OS). *Results:* A total of 50 patients were analyzed (males, 68%; adenocarcinoma, 80%). The RR was 44.0%. The median PFS and OS were 4.3 months and 22.2 months, respectively. Toxicities were mild, and no new toxicity profiles were identified. Among the 39 out of 50 samples, six (15.4%) presented ALK translocation and nine (23.1%) presented EGFR mutations; of the remaining patients, 24 (61.5%) were wild-type for both ALK and EGFR. Objective response was observed in two out of six patients with ALK translocations, six out of nine with EGFR mutations, and in 11 (45.8%) wild-type patients. *Conclusion:* The combination of pemetrexed and cisplatin was effective and safe in Japanese patients with Nsq-NSCLC.

We did not observe obvious differences in the efficacy of P-C between patients with ALK translocation or EGFR mutation and those with wild-type genotype.

Lung cancer is the major cause of cancer-related deaths worldwide. Approximately 85% of lung tumors are non-small cell lung cancers (NSCLC), 70% of which are either inoperable, locally advanced or metastatic (1). Two-drug combinations of a third-generation agent (docetaxel, paclitaxel, gemcitabine, vinorelbine, and pemetrexed) with a platinum compound (cisplatin and carboplatin) are the standard treatment options for advanced NSCLC (2-5).

Pemetrexed (Alimuta[®]; Eli Lilly and Company, Indianapolis, IN, USA) is a multitargeted antifolate that inhibits thymidylate synthase (TYMS), dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase (6).

Randomized phase III clinical trials have demonstrated that pemetrexed is efficacious both in combination with cisplatin (P-C) for first-line treatment of NSCLC—having non-inferior efficacy and better tolerability than for the combination of gemcitabine and cisplatin (4)—and as a single-agent in second-line treatment (7). Moreover, in patients with non-squamous NSCLC (Nsq-NSCLC), pemetrexed has superior efficacy compared with other standard treatments, and the combination therapy with cisplatin leads to superior overall survival (OS) compared with gemcitabine and cisplatin, and is one of the most common regimens for treatment of metastatic Nsq-NSCLC (8).

Adenocarcinoma is the major histological type of Nsq-NSCLC. More than 75% East Asian never-smokers with lung adenocarcinoma harbor targetable oncogenic mutations, including epidermal growth factor receptor (EGFR) mutations, fusions of echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase

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(ALK; 5.8%) (9, 10). Therefore, ethnic differences and driver mutations are important factors in NSCLC (particularly adenocarcinoma) treatment.

Recent reports revealed the impact of *EGFR* mutations, and *ALK* translocation on the efficacy of pemetrexed and P-C therapies (11-14). Moreover, ethnicity is a prognostic factor; East and South Asian patients had longer survival compared with that in the entire study population (Whites, African descent, East Asians, and others) in a phase III study (15) –and may be a predictive biomarker of enhanced sensitivity to pemetrexed. Although P-C provided tolerability in a phase I/II study of malignant pleural mesothelioma in Japan (16), its overall efficacy, and that according to tumor genotype, has not been well-evaluated in Japanese patients with Nsq-NSCLC.

We conducted this prospective study to evaluate the efficacy and safety of P-C in Japanese patients with Nsq-NSCLC, and to determine whether the *EGFR* mutation or *ALK* translocation impacted the treatment outcome in these patients.

Patients and Methods

Eligibility. Patients with histologically- or cytologically-confirmed Nsq-NSCLC were eligible for this study. Additional eligibility criteria were as follows: clinical stage IIIB, IV, or recurrent disease, no prior chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate bone marrow, renal, and hepatic function. Patients with unstable brain metastases, uncontrolled pleural effusion or ascites, active infection, active concomitant malignancy or interstitial pneumonia were excluded. The study protocol was approved by the Institutional Review Board at our center (UMIN000002847). All patients signed written informed consent before enrollment.

Treatment plan. Patients received pemetrexed (500 mg/m²) intravenously (*i.v.*) for over 10 min followed by cisplatin (75 mg/m², *i.v.*) over 2 h on day 1 of a 21-day cycle. This combination therapy was repeated for up to four cycles. Patients were instructed to take oral multivitamin supplement (1 g/day) containing 500 mg folic acid beginning one week before the first treatment until 22 days after the last pemetrexed administration; vitamin B12 (1000 mg) was injected intramuscularly every nine weeks during the same period.

The second and subsequent treatment cycles were initiated only when the following criteria were satisfied on day 1 of the cycle: white blood cells $\geq 3,000/\text{mm}^3$ or neutrophils $\geq 1,500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, PS ≤ 1 , creatinine ≤ 1.5 mg/dl, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq 100\text{IU/l}$, total bilirubin ≤ 1.5 mg/dl, body temperature (BT) $< 38^\circ\text{C}$, no interstitial pneumonia, non-hematological toxicity $\leq \text{G1}$. Pemetrexed was reduced to 400 mg/m² in the subsequent cycles if chemotherapy induced either grade 4 leukopenia or neutropenia for more than five days or grade 4 thrombocytopenia or thrombocytopenia requiring platelet transfusion, grade 3 febrile neutropenia or grade 3 non-hematological toxicities. Cisplatin was reduced to 60 mg/m² in the subsequent cycles if these toxicities recurred after the dose reduction of pemetrexed or if serum creatinine was more than 2.0 mg/dl.

Patients would be withdrawn from the study if these toxicities recurred after the reduction in cisplatin dose, or if the next cycle was delayed because of toxicity for more than 43 days

Evaluation of tumor response and toxicity. Complete patient histories, physical examinations, complete blood cell counts, serum electrolytes and chemistry were performed before initiation of treatment and before each treatment cycle. Tumor status and response were assessed by radiological examination, including computed tomography, at baseline and after every two treatment cycles. Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.0) (17) were used to define the antitumor effects, and toxicity was assessed based on the National Cancer Institute Common Toxicity Criteria (version 3.0) (18).

Detection of oncogene driver mutations. Genomic DNA was extracted from tumors embedded in paraffin blocks or from tumor cells from aspirates of pleural effusions, or biopsied superficial lymph nodes or subcutaneous metastases. Mutations in *EGFR* exons 19 and 21 were detected by the Cycleave real-time quantitative PCR technique, and the *ALK* translocation was examined using fluorescence *in situ* hybridization or highly sensitive immunohistochemistry (IHC) to detect the *ALK* fusion protein (19).

Statistical analysis. This study was a prospective, single-center, single-arm study (UMIN000002847) of first-line combination therapy with P-C. The primary end-point was the response rate (RR) and the secondary endpoints were toxicity, progression-free survival (PFS), and overall survival (OS).

A Simon's minimax two-stage phase II design (20) was used to define minimum sample sizes for statistical significance: assuming an expected overall RR of $\geq 50\%$ and a minimum acceptable RR of 30%, 22 patients would be required as the first step. Our plan further stipulated that if at least seven out of the 22 patients responded to the therapy, another 24 patients would be required as the second step. If at least 17 of the 46 patients responded, the treatment would be declared sufficiently promising. OS was recorded as the time from registration until either death or conclusion of the analysis; PFS was the time from registration to documented progression or death from any cause, whichever occurred first. Survival analyses were performed using the Kaplan-Meier method. All statistical analyses were performed using the SPSS 17.0 statistical software (Dr SPSS II for Windows, Standard version 17.0; SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics. From November 2009 until January 2010, 50 patients with Nsq-NSCLC were enrolled. Patients' characteristics are listed in Table I. The median age was 60 years (range 28-74), and there were 34 males and 16 females. Thirty-one patients had PS 0 and 19 patients had PS 1. Forty-one patients (82.0%) had adenocarcinoma. *EGFR* mutation status was analyzed in 46 patients; nine patients (19.6%) harbored an activating mutation in *EGFR*. *ALK*-translocation was identified in six (15.4%) out of 39 patients analyzed. Six patients were positive by FISH, five out of six patients were positive by IHC, but the remaining patients were not evaluable by IHC.

Table I. *Patients' characteristics.*

Characteristic	N=50
Age, years	
Median (range)	60 (28-74)
Gender	
Male/female	34/16
Stage	
IIIB/IV/recurrence	5/40/5
History of smoking	
Non-smoker/smoker	14/36
Histology	
Adenocarcinoma/other	41/9
Performance status (ECOG)	
0/1	31/19
<i>EGFR</i> mutation status	
Positive/negative/unknown	9/37/4
<i>ALK</i> translocation status	
Positive/negative/unknown	6/33/11

ECOG: Eastern Cooperative Oncology Group; *EGFR*: epidermal growth factor receptor; *ALK*: anaplastic lymphoma kinase.

Response and survival. Fifty patients were analyzed. There were no complete responses, 22 partial responses, 17 cases of stable disease, 10 of progressive disease, and one case was non-evaluable because of grade 5 pneumonitis during the first treatment cycle. Thus, the overall RR was 44.0% [95% confidence interval (CI)=30.0%-58.0%], and the disease control rate (DCR) was 78.0% (95% CI=66.0%-90.0%; Table II). At the median follow-up period of 19.0 months (range=1.4-35.2 months), the median PFS and OS were 4.3 months (95% CI=3.9-4.8 months; Figure 1A) and 22.2 months (95% CI=13.4-31.0 months; Figure 2B), respectively.

Treatment delivery. Thirty-three (66.0%) patients completed four cycles of P-C therapy. The median number of chemotherapy cycles administered throughout the study was four (range=1-4 cycles). However, one patient had dose reduction of cisplatin because of elevated serum creatinine level, two patients had dose reduction of pemetrexed because of infection (one patient) and fatigue (one patient).

Toxicity. Toxicity was evaluated in all patients in all cycles (Table III). Grade 3 or 4 neutropenia was observed in eight patients (16%) and grade 3 infection in three (6%), but there were no cases of febrile neutropenia. In addition, grade 3 or 4 anemia was observed in eight patients (16%), and grade 3 elevations of serum creatinine level were observed in two patients. Furthermore, one patient (2%) experienced grade 5 pneumonitis after one cycle.

Subgroup analysis by *ALK* fusion status and *EGFR* mutation status. Among the 39 out of 50 patients, we identified *ALK*

Table II. *Response rates.*

Response	N=50
CR	0
PR	22
SD	17
PD	10
NE	1
RR	44.0%
DCR	78.0%

NE, Not evaluable; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate.

translocations in six patients (15.4%), *EGFR* mutations in nine (23.1%), and wild-type *ALK* and *EGFR* in 24 patients (61.5%) (referred to as WT/WT). However, we were unable to examine *ALK* translocation in 11 patients and *EGFR* mutations in four patients because of insufficient material. Objective responses were observed in two patients with *ALK* translocation, six with *EGFR* mutation, and 11 (45.8%) of the WT/WT group. However, there were no significant differences in PFS by genotype. The median PFS in the *ALK* translocation, *EGFR* mutation and WT/WT subgroups were 3.0 months (95% CI=0.0-8.3 months), 5.5 months (95% CI=4.7-6.4 months) and 4.0 months (95% CI=2.9-5.1 months), respectively (Figure 1B). Median OS had not yet been reached in the patients with *EGFR* mutation and *ALK* translocation, and was 15.8 months in WT/WT patients (95% CI=2.9-28.8 months; Figure 2B).

Discussion

The impact of ethnicity and oncogene driver mutations on advanced NSCLC treatment has only recently begun to be considered. Although there have been several phase II and III studies of P-C for Nsq-NSCLC worldwide, there are no data for Japanese patients. In our phase II study of Japanese patients with Nsq-NSCLC, we observed that the efficacy of P-C in terms of overall RR and median PFS was comparable to those for other ethnicities, and we did not identify any new safety concerns. In our study, the overall RR was 44.0%, and the median PFS was 4.3 months, whereas in global studies, these values were 30.9%-45% and 5.3-6.3 months, respectively (4, 21, 22). Toxicities were mostly very mild; the major toxicities were myelosuppression, and the incidence of either grade 3 or grade 4 neutropenia or anemia were 16%. However, the toxicity profile was similar to that of previous studies: grade 3 or grade 4 neutropenia, 15.1%-58.3%; anemia, 5.6%-20% (4, 21, 22).

The median OS of our whole-patient sample was 22.2 months, which is significantly longer than that in previous

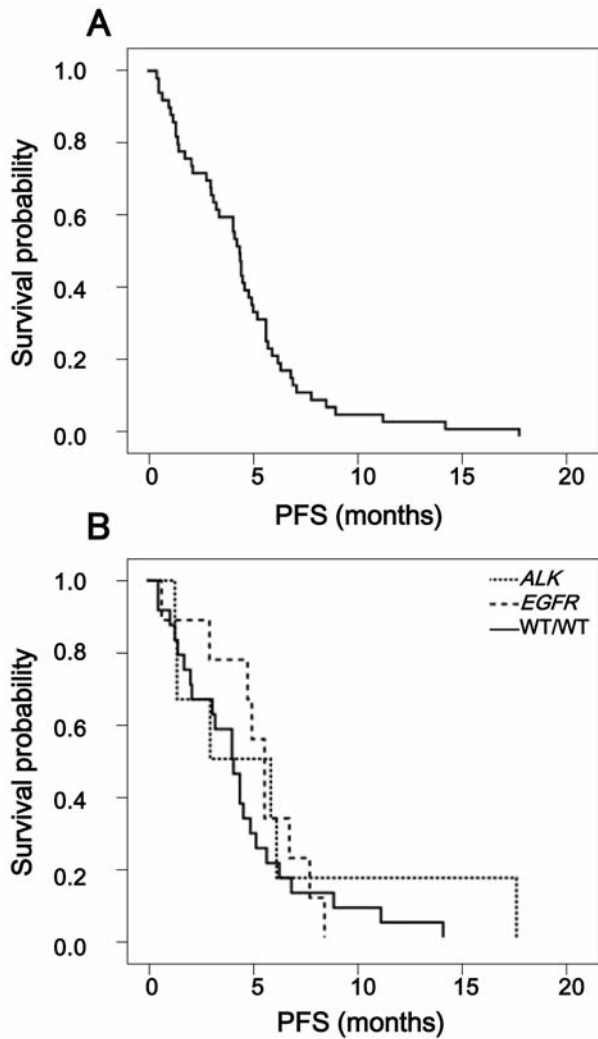


Figure 1. Kaplan-Meier curves for progression-free survival (PFS) (N=50). The median PFS (N=50) was 4.3 months (A). The median PFS in subgroups of with patients with anaplastic lymphoma kinase (ALK) translocation, epidermal growth factor receptor (EGFR) mutation, wild-type for both ALK and EGFR (WT/WT) were 3.0, 5.5 and 4.0 months, respectively (B).

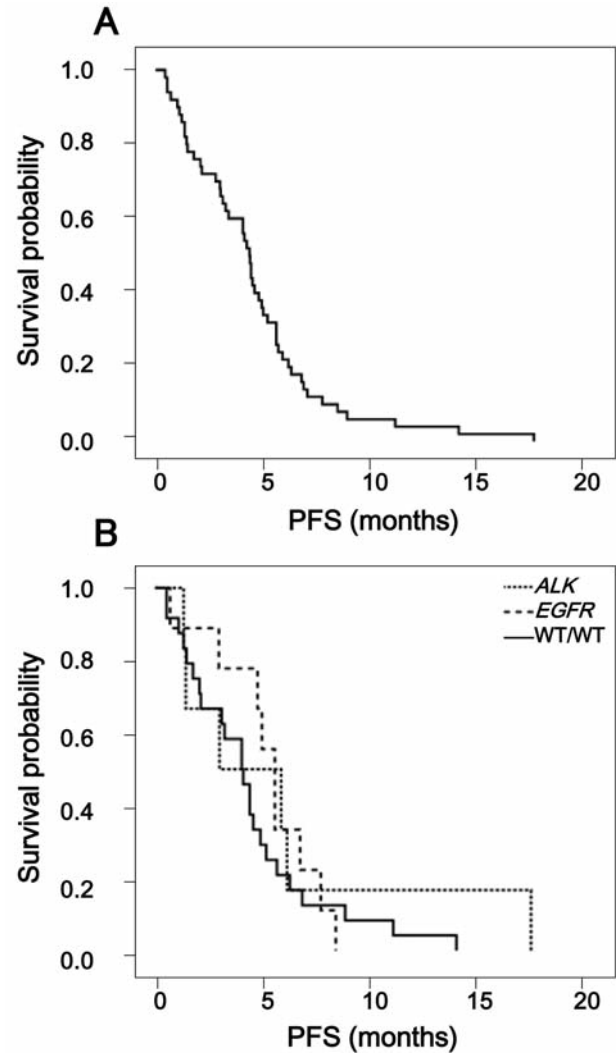


Figure 2. Kaplan-Meier curves for overall survival (OS) (N=50). The overall median OS (N=50) was 22.2 months (A). The median OS had not yet been reached in the patients with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocation, but was 15.8 months in wild-type for both ALK and EGFR (WT/WT) patients (B).

reports (8.9-11.8 months) (4, 21, 22). Ethnic differences might have resulted in this discrepancy. Similar results were observed in a subset analysis of a previous global phase III study reporting that East Asian patients with Nsq-NSCLC (Taiwan and Korea) had longer median OS (21.2 months) than that of the population overall (23). In subset analysis of our study, patients with *EGFR* mutations or *ALK* translocations exhibited longer median OS compared with that in WT/WT patients. The driver mutation status and target therapy after the discontinuation of P-C may be related to prolonged survival. All patients with *ALK* translocations

received *ALK* inhibitors for second-line or third-line treatment, and all patients with *EGFR* mutations received *EGFR* tyrosine kinase inhibitor for second-line treatment.

Some reports correlate *EGFR* mutations with the efficacy of pemetrexed. NSCLC cells with activating mutations in *EGFR* had lower TYMS expression than those with wild-type *EGFR* (24). In one study, patients with *EGFR* mutations receiving pemetrexed monotherapy responded more favorably and also had longer PFS than those with wild-type *EGFR* (14). TYMS is key folate enzyme targeted by pemetrexed and TYMS levels may correlate inversely with sensitivity to pemetrexed (25). In

Table III. Hematological and non-hematological toxicities (N=50) experienced with pemetrexed-cisplatin therapy.

Toxicity	Grade*					
	1	2	3	4	5	≥ Grade 3(%)
Hematological toxicity						
Leucopenia	18	11	1	0	0	2
Neutropenia	10	15	7	1	0	16
Anemia	21	16	3	5	0	16
Thrombocytopenia	9	3	0	2	0	4
Non-hematological toxicity						
Nausea	34	6	0	0	0	0
Vomiting	5	0	0	0	0	0
Diarrhea	5	1	1	0	0	0
Constipation	22	13	0	0	0	0
Rash	4	11	0	0	0	0
Elevated creatinine	12	1	2	0	0	0
Elevated aspartate aminotransferase	16	5	0	0	0	0
Elevated alanine aminotransferase	17	4	0	0	0	0
Infection	-	-	3	0	0	7
Pneumonitis	0	0	0	0	1	2

*National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (18).

Table IV. Patients' characteristics by genotype.

Characteristic	All patients N=50	ALK translocation (n=6)	EGFR mutation (n=9)	WT/WT (n=24)
Age, years				
Median (range)	60 (28-74)	38 (28-67)	65 (37-72)	57 (41-73)
Gender				
Male/female	34/16	4/2	5/4	17/7
Stage				
IIIB/IV/recurrence	5/40/5	0/3/3	1/8/0	3/19/2
History of smoking				
Non-smoker/smoker	14/36	5/1	4/5	5/19
Histology				
Adenocarcinoma/other	41/9	6/0	9/0	18/6
Performance status (ECOG)				
0/1	31/19	6/0	8/1	14/10

ECOG: Eastern Cooperative Oncology Group, WT: wild-type.

our study, the RR was higher in the nine patients with EGFR mutations than in the entire study population (6/9 *vs.* 44.0%), although there were no differences in PFS.

ALK translocation has been identified as a driver mutation in NSCLC (26), and ALK tyrosine kinase inhibitors such as crizotinib have had a profound impact on the treatment of advanced NSCLC (27). Several retrospective studies report conflicting results on the efficacy of pemetrexed in ALK-positive patients. Camidge *et al.* reported that ALK-positive patients respond to pemetrexed with a better RR and longer PFS than WT patients (11). However, one of the largest

retrospective analyses of pemetrexed-based chemotherapy documented no difference in PFS with respect to ALK status (13). In the phase III study of ALK-positive NSCLC comparing crizotinib, pemetrexed and docetaxel, overall RR and PFS were higher in the pemetrexed arm than in the docetaxel arm: 29.3% *vs.* 6.9% and 4.2 months *vs.* 2.6 months, respectively (28). Moreover, patients with ALK re-arrangements had lower TYMS expression than those with normal ALK loci. In our study, RR was lower in the six patients with ALK translocations than in the entire study population (6/9 *vs.* 44.0%), but there were no differences in PFS.

However, it is difficult to conclude on the mechanism of sensitivity to P-C therapy on the basis of the TYMS level in tumor tissue because of the lack of TYMS evaluation in our study. In addition, our study was too small to conclude whether particular genotypes correlate with the efficacy of P-C.

In conclusion, P-C therapy was effective and well-tolerated in Japanese patients with Nsq-NSCLC. We did not observe any obvious differences in the efficacy of P-C treatment between patients with *ALK* translocation or *EGFR* mutation status and these wild-type for these genes.

Disclosure

The Authors have declared no conflicts of interest.

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