ORIGINAL ARTICLE

Prospective phase II study of cisplatin plus pemetrexed with maintenance of pemetrexed for advanced non-squamous cell non-small cell lung cancer in Japan

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Keywords

Cisplatin plus pemetrexed; continuation maintenance; Japanese patients; non-small cell lung cancer; non-squamous cell.

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Abstract

Background: A previous study showed a survival benefit with maintenance therapy with pemetrexed in patients with advanced non-small cell lung cancer (NSCLC). However, it remains unclear whether continuation maintenance therapy with pemetrexed is beneficial in Japanese patients. Here, we present our phase II study that assessed the efficacy and safety of cisplatin plus pemetrexed as induction chemotherapy, followed by maintenance therapy with pemetrexed in advanced NSCLC patients in Japan.

Methods: Chemotherapy-naïve patients received 500 mg/m² pemetrexed and 75 mg/m² cisplatin on day one every three weeks for four cycles. In patients who responded to therapy or achieved stable disease, pemetrexed was continued until disease progression. The primary endpoint of this study was the progression-free survival rate at six months (PFS-6).

Results: Of the 35 patients initially enrolled in the study, 18 (51%) received maintenance chemotherapy with pemetrexed. The median PFS was 6.7 months, and the PFS-6 was 60% (95% confidence interval [CI], 42–76%). Median overall survival (OS) was 15.5 months (95% CI, 8.3–22.7 months). The median PFS and OS in patients who received maintenance chemotherapy with pemetrexed were 9.5 months and 25.3 months, respectively. The most frequently noted severe toxicity during induction chemotherapy was neutropenia, which occurred in seven patients. Two patients discontinued maintenance therapy owing to prolonged grade 2 edema in one patient and grade 3 neutropenia in another.

Conclusion: Continuation maintenance chemotherapy with pemetrexed is associated with a survival benefit in patients who have completed induction chemotherapy for non-squamous NSCLC.

Introduction

Lung cancer is a leading cause of cancer-related deaths worldwide.^{1,2} More than 70% of lung cancer patients are diagnosed with advanced non-small cell lung cancer (NSCLC), and the prognosis for these patients remains poor.³

Third generation platinum-based cytotoxic agents – including paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan – have been established as standard therapies and yield similar improvements in survival in patients with

advanced NSCLC.^{4–6} A phase II trial showed that pemetrexed, a multi-targeted antifolate, was active in recurrent and progressive NSCLC.⁷ A previous phase III trial demonstrated that pemetrexed showed similar efficacy and a significantly better safety profile compared to standard docetaxel when used as second-line therapy for NSCLC.⁸ A randomized phase III study of cisplatin plus pemetrexed in patients with advanced NSCLC demonstrated that this regimen significantly improved survival compared to the reference arm of cisplatin plus gemcitabine in patients with adenocarcinoma (12.6 vs.

10.9 months) and large cell carcinoma histology (10.4 vs. 6.7 months).⁹ This study suggested that cisplatin plus pemetrexed was another alternative doublet regimen that can be implemented as first-line chemotherapy for advanced NSCLC, and that NSCLC patients with non-squamous cell histology may benefit from pemetrexed. Platinum-based chemotherapy has clinical benefits for patients with advanced NSCLC, demonstrating a response rate (RR) of nearly 30%, median progression-free survival (PFS) at six months of 40%, and one-year survival rate (1y-SR) of 50%.^{10–14} However, the efficacy of these treatments has reached a plateau.

Previous studies have demonstrated the utility and safety of switch or continuation maintenance chemotherapy after induction treatment with platinum-based chemotherapy.^{15,16} Niho *et al.* reported that first-line carboplatin, paclitaxel, and bevacizumab, followed by bevacizumab, led to a significantly longer PFS than carboplatin plus paclitaxel in Japan.¹⁷ In that study, patients who achieved non-progressive disease (non-PD) with induction chemotherapy received subsequent bevacizumab until PD was seen. However, this study did not demonstrate the efficacy of bevacizumab as continuation therapy. With regard to maintenance chemotherapy with cytotoxic agents, very few clinical studies have evaluated the utility of maintenance therapy after platinum doublet chemotherapy for advanced NSCLC in the Japanese patient population. Therefore, it is unclear whether continuation maintenance chemotherapy would be useful in Japanese patients with advanced NSCLC.

Here, we assessed the efficacy and safety of continuation maintenance therapy with pemetrexed following cisplatin plus pemetrexed as induction therapy in chemotherapy-naïve Japanese patients with advanced non-squamous NSCLC.

Methods

Eligibility

Chemotherapy-naïve patients with histologically or cytologically diagnosed stage IIIB or IV non-squamous cell NSCLC were eligible to participate in this study. Other criteria included: age of 20 to 74 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; neutrophil count ≥ 1500 ; hemoglobin ≥ 9.0 g/dl; platelet count $\geq 100\,000$; aspartate aminotransferase and alanine aminotransferase ≤ 100 IU/L; bilirubin ≤ 1.5 mg/dl; creatinine clearance ≥ 60 ml/min; arterial oxygen pressure ≥ 60 mmHg; and an estimated life expectancy > 12 weeks.

Exclusion criteria were: the presence of symptomatic brain metastases; active infection; interstitial pneumonia or pulmonary fibrosis, as determined by computed tomography; uncontrolled diabetes mellitus; uncontrolled cardiovascular disease; chronic liver disease; active concomitant cancer;

severe allergy; and inability or unwillingness to be administered folic acid, injection of vitamin B12, or corticosteroids.

Study design

The primary endpoint of the study was the progression-free survival rate six months after registration (PFS-6), and the secondary endpoints were RR, disease control rate (DCR), rate of survival one year after registration (1y-SR), and the toxicity profile. All patients provided written informed consent before enrolment, and the institutional review board of each participating institution approved the protocol. This study was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. This study was registered with University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) (<http://www.umin.ac.jp/ctr/index.htm>, identification number UMIN000002686) on 2 November 2009.

Study treatment

Patients received 500 mg/m² pemetrexed and 75 mg/m² cisplatin once every three weeks for four cycles as induction therapy until PD or treatment discontinuation. For patients who had a complete response (CR), partial response (PR), or achieved stable disease (SD) from induction chemotherapy, 500 mg/m² pemetrexed was continued until PD or treatment discontinuation. Patients were given 500 µg folic acid orally every day beginning one week before registration and continuing throughout the study. Patients were also given 1000 µg vitamin B12 intramuscularly one week before registration, and again once every nine weeks while the patients were receiving pemetrexed. No restrictions were placed on treatment after the end of the study period.

Treatment assessment

The response to induction therapy with cisplatin plus pemetrexed was evaluated by computed tomography every eight weeks until PD occurred, and was assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1. Complete restaging studies were performed after the completion of induction chemotherapy. The DCR was defined as the rate of CR plus PR plus SD. SD was defined as no change in measurable lesions for at least eight weeks. Overall survival (OS) was defined as the interval between the date of registration and the date of death from any cause. The PFS rate at six months was defined as the proportion of patients who were progression-free and alive six months after the date of registration. The 1y-SR was defined as the proportion of patients who were alive one year after registration for this study. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

Epidermal growth factor receptor gene (EGFR) analysis

We examined epidermal growth factor receptor (EGFR) mutation status with the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp test (PNA-LNA; Mitsubishi Chemical Medience, Tokyo, Japan) using paraffin sections of biopsy samples or cytological specimens from patients diagnosed with NSCLC.

Echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene analysis

Fluorescence in situ hybridization (FISH) (SRL Inc., Tokyo, Japan) was performed to identify the echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene in histological specimens from patients who had positive results for ALK using the high-sensitivity immunohistochemistry technique.

Thymidylate synthase (TS) expression analysis

The thymidylate synthase (TS) immunoreactive population was evaluated according to positive tumor cell percentage and staining intensity as follows: negative if <1%, weakly positive (+1) if between 1% and 50%, moderately positive (+2) if 50% to 79%, and strongly positive (+3) if ≥80%.

Statistical considerations

With regard to our primary endpoint, a Simon two-stage optimal design was used to determine the total number of patients required for the present study. According to previous phase III studies, including the IPASS study (an open-label randomized trial of gefitinib compared to carboplatin plus paclitaxel for advanced lung adenocarcinoma patients) and the E4599 trial (an ECOG Study of bevacizumab with carboplatin plus paclitaxel for advanced non-squamous cell NSCLC patients), the PFS-6 of carboplatin plus paclitaxel ranges from 35% to 40%.^{18,19} We set a PFS-6 of 60% in enrolled patients and a rate of 35% as the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.2$. The estimated accrual number was at least 31 cases. PFS and OS were estimated via the Kaplan–Meier method. Statistical analyses were performed using SPSS software, v. 19.0 (IBM, Chicago, IL, USA).

Results

Patient characteristics

From December 2009 to November 2011, 35 eligible non-squamous cell NSCLC patients were enrolled in the study and

Table 1 Patient characteristics (*n* = 35)

Characteristic	No. of patients (%)
Median age, years (range)	63 (43–74)
Gender	
Male	24 (69)
Female	11 (31)
Smoking status	
Never	9 (26)
Former/current	26 (74)
Performance status (ECOG)	
0	17 (49)
1	18 (51)
Stage	
IIIB	7 (20)
IV	28 (80)
Histology	
Adenocarcinoma	32 (91)
Others†	3 (9)
EGFR mutation	
Exon 19	2 (6)
Exon 18	2 (6)
Wild type	31 (88)
ALK (by HSIHC)	
Positive	2‡ (6)
Negative	30 (85)
Unknown	3§ (9)
TS expression	
Positive (+1–+3)	3¶ (9)
Negative	29 (82)
Unknown	3§ (9)

†Three patients had non-squamous cell non-small cell lung cancer histology. ‡One patient was found to have the echinoderm microtubule-associated protein-like 4-ALK fusion gene using the fluorescence in situ hybridization technique. §ALK and TS expression was unable to be examined in three patients because of insufficient specimens. ¶Strong positive (+3) was found in one patient and weakly positive (+1) was found in two. ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HSIHC, high-sensitivity immunohistochemistry; TS, thymidylate synthase.

received at least one cycle of protocol induction chemotherapy. Patient characteristics are shown in Table 1. Approximately 90% of patients had histopathologically diagnosed lung adenocarcinoma. Activating EGFR mutations, including exon 19 deletion mutations, were detected in two patients (6%), and exon 18 mutations were detected in two patients. Among patients harboring an EGFR mutation, ALK and TS expression were not found in any patients. Of the 35 enrolled patients, we were unable to examine ALK and TS expression in three patients because of insufficient specimens. ALK was examined using high-sensitivity immunohistochemistry in 32 patients, and was positive in two cases (6%). One patient was revealed to be EML4-ALK-positive by FISH, and the other was negative. TS expression was examined in 32 patients and found in three cases. Two patients showed

Table 2 Response to cisplatin plus pemetrexed therapy ($n = 35$)

Response	No. of patients	Response rate (%)	95% CI
CR	0	0	
PR	16	46	
SD†	6	17	
PD	9	26	
NA‡	4	11	
Overall response rate	16	46	29–63
Disease control rate§	22	63	45–79

†Stable disease was confirmed and sustained for eight weeks or longer.

‡One patient developed a grade 5 adverse event, two switched to other chemotherapy regimens, and one switched radiotherapy before response assessment. §Disease control rate was defined as the rate of CR plus PR plus SD. CI, confidence interval; CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.

weakly positive TS expression, and one patient had strongly positive expression. ALK was not found in any patients who had TS expression.

Patient disposition

Patient disposition is shown in the Participant Flow Diagram (Supplementary material). Seventeen patients (49%) did not receive maintenance therapy. Progressive disease was observed in nine patients. Three patients developed prolonged grade 3 adverse events, and two developed grade 4 and 5 severe adverse events. Three patients switched to other treatments before response assessment during the induction phase. One patient required palliative chest radiotherapy after two cycles of protocol induction chemotherapy. Two patients with prolonged grade 2 fatigue were switched to carboplatin and pemetrexed after one cycle of protocol induction chemotherapy at the discretion of the attending physicians. Finally, 18 patients (51%) received protocol maintenance therapy with pemetrexed. All patients discontinued maintenance therapy. Sixteen patients were confirmed to have PD. Two patients discontinued protocol therapy owing to prolonged adverse events: one developed grade 2 edema in 10 cycles of maintenance therapy, and the second developed grade 3 neutropenia in six cycles of maintenance therapy.

Response and survival

Objective tumor RRs are described in Table 2. The overall RR was 46% and the DCR was 63%. No patient achieved a CR. Three patients, including one who developed grade 5 toxicity, switched to off-protocol therapy with carboplatin plus pemetrexed or radiotherapy before response assessment and were excluded from the study. Three patients, including prolonged grade 3 toxicity, had PR, SD, and PD in each to

Figure 1 Kaplan–Meier plot of progression-free survival (PFS) ($n = 35$). Median PFS was 6.7 months (95% confidence interval, 5.7–7.7 months).

protocol induction chemotherapy. Additionally, one patient developed a grade 4 severe adverse event and also had PD.

The median follow-up time was 15.8 months (95% confidence interval [CI], 13.1–18.6 months). As of July 2013, all patients were confirmed to have PD or had died. Twenty-nine patients received subsequent chemotherapy or palliative radiotherapy after confirmation of PD, and two patients received best supportive care because their performance status was 3 at the time that PD was confirmed. One patient died of grade 5 neutropenic infection during the course of protocol induction chemotherapy.

The median PFS was 6.7 months (95% CI, 5.7–7.7 months) and the median OS was 15.5 months (95% CI, 8.3–22.7 months) (Figs 1, 2). Twenty-four patients were alive one year after registration. Of the patients treated with continuation maintenance therapy, one patient was confirmed to have PD less than six months after registration. PFS-6 was 60% (95% CI, 42–76%), and the 1y-SR was 69% (95% CI, 51–83%). Among the 18 patients who received maintenance therapy, the median number of treatment cycles was seven (range, one to 18). The median PFS and OS were 9.5 months and 25.3 months in patients with maintenance chemotherapy and 3.3 months and 9.3 months in patients without maintenance chemotherapy, respectively.

One of two patients harboring activating EGFR mutations, including exon 19 deletion mutations, had PD to induction chemotherapy, and another patient who received one cycle of protocol maintenance chemotherapy had SD in the induction phase. They showed PRs in response to subsequent gefitinib therapy after failure of protocol treatment, and continued the therapy without disease progression. One patient who was revealed by FISH to have the EML4-ALK fusion gene

Figure 2 Kaplan-Meier plot of overall survival (OS) ($n = 35$). Median OS was 17.9 months (95% confidence interval, 10.0–25.8 months).

achieved a PR to induction chemotherapy and received 18 cycles of maintenance chemotherapy followed by subsequent chemotherapy with docetaxel after the failure of protocol therapy. The other patient, who did not have the EML4-ALK fusion gene, had SD in response to induction therapy. This patient discontinued protocol treatment owing to confirma-

tion of PD at the time of the full re-staging before the maintenance phase, and subsequently received erlotinib. Three patients who had TS expression had PD in the induction phase of chemotherapy, and none of them received maintenance therapy.

Toxicity

All patients were evaluated for toxicity during the induction and maintenance phases (Tables 3, 4). Major adverse events associated with induction chemotherapy with cisplatin plus pemetrexed were leukopenia, neutropenia, and nausea. The most severe adverse event, including grade 3 to grade 5 toxicities, was neutropenia, which occurred in 20% of the patients. One patient developed grade 4 febrile neutropenia on day eight after administration of the initial cycle of induction chemotherapy. This patient died two days later of respiratory failure as a result of bacterial pneumonia. One patient developed increasing grade 4 levels of aspartate aminotransferase and alanine aminotransferase, one patient developed prolonged grade 3 anemia, and two patients developed prolonged grade 3 neutropenia during the induction phase of chemotherapy. Eventually, these four patients discontinued protocol treatment before the maintenance phase. Among the 18 patients who received protocol maintenance therapy, one patient each discontinued protocol therapy because of pro-

Table 3 Adverse events during the induction phase ($n = 35$)

Toxicity	No. of patients Grade 1	No. of patients Grade 2	No. of patients Grade 3	No. of patients Grade 4	No. of patients Grade 5	No. of toxicities ≥ Grade 1 (%)	No. of toxicities ≥ Grade 3 (%)
Leukopenia	14	7	2	3	1	27 (77)	6 (17)
Neutropenia	14	7	2	4	1	28 (80)	7 (20)
Thrombopenia	7	1	0	1	0	9 (26)	1 (3)
Anemia	8	4	1	0	0	13 (37)	1 (3)
Elevated AST/ALT	8	5	0	1	0	14 (40)	1 (3)
Pneumothorax	0	2	0	0	0	2 (6)	0 (0)
Nausea	11	8	1	0	0	20 (57)	1 (3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4 Adverse events during maintenance phase ($n = 18$)

Toxicity	No. of patients Grade 1	No. of patients Grade 2	No. of patients Grade 3	No. of patients Grade 4	No. of patients Grade 5	No. of toxicities ≥ Grade 1 (%)	No. of toxicities ≥ Grade 3 (%)
Leukopenia	3	2	2	0	0	7 (39)	2 (11)
Neutropenia	3	1	1	1	0	6 (33)	2 (11)
Thrombopenia	2	2	0	0	0	4 (22)	0 (0)
Anemia	2	2	0	0	0	4 (22)	0 (0)
Elevated AST/ALT	5	2	0	0	0	7 (39)	0 (0)
Edema	4	2	0	0	0	6 (33)	0 (0)
Fatigue	8	4	0	0	0	12 (67)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

longed grade 3 neutropenia and prolonged grade 2 edema. Most other toxicities observed during induction and maintenance therapies were mild.

Discussion

Our study met its primary endpoint of a PFS-6 of 60%, and we observed markedly long survival and tolerable toxicity in patients treated with the continuation maintenance therapy of pemetrexed following induction with cisplatin plus pemetrexed.

Our study is the first trial to assess the efficacy and safety of cisplatin plus pemetrexed followed by pemetrexed in Japanese patients with advanced NSCLC. A recent randomized phase III trial (the PARAMOUNT study) demonstrated a significant extension in PFS and OS in patients with advanced non-squamous cell NSCLC who received cisplatin plus pemetrexed followed by pemetrexed compared to a placebo control group.^{20,21} The PARAMOUNT study was the first trial to prove the efficacy of this treatment regimen as first-line therapy in patients with advanced NSCLC. There were 359 patients randomized in this study, and approximately 95% of them were white. Previously, Ciuleanu *et al.* reported that switch maintenance therapy with pemetrexed was well tolerated and improved survival after induction treatment with platinum-doublet chemotherapy.¹⁶ At the time of planning our phase II study, the efficacy and safety of maintenance therapy with pemetrexed after induction chemotherapy with cisplatin plus pemetrexed had not been assessed in Japan.

Our study was designed for patients with non-squamous NSCLC histology. Before the results of the PARAMOUNT study were presented, Scagliotti *et al.* reviewed two phase III studies of NSCLC and reported that patients with non-squamous histology received a survival advantage from pemetrexed treatment.²² We planned the present study for patients with advanced non-squamous NSCLC histology in response to the results of these reports.

We set the primary endpoint of the present study as the PFS-6. It has not yet been demonstrated whether or not the PFS rate is an appropriate index of efficacy for treatment with added maintenance therapy. In principle, maintenance therapy is the administration of treatment after a defined number of chemotherapy cycles in patients whose tumors have not progressed. Treatment can be continued in one of two ways: using a compound from the induction regimen, or using an agent with a different mode of action than the drugs used in the first-line regimen. These two approaches are called “continuation” or “switch” maintenance therapy, respectively, and these terms are now commonly used in discussions about maintenance therapy. However, it is not clear whether maintenance therapy is part of first-line therapy or an early second-line therapy. Maintenance therapy is likely best considered as an optional treatment for patients who

complete induction chemotherapy. For these reasons, positioning of maintenance therapy for treatment for NSCLC is unclear, and we accordingly did not set the primary endpoint as the PFS period, but rather as the PFS ratio. However, further investigation is required to validate whether the PFS-6 is an appropriate metric to evaluate the utility of maintenance chemotherapy.

For the present study, we set the maximum number of treatment cycles of induction chemotherapy at four. According to the American Society of Clinical Oncology 2011 guidelines, first-line platinum doublet chemotherapy should be administered for a maximum of six cycles to advanced NSCLC patients who show a good response, including a CR or PR.²³ In previous clinical trials, first-line platinum doublet chemotherapy was administered for a median of three to five cycles.^{4–6,9–14} On the basis of these previous clinical trial data, we designed an induction chemotherapy regimen of four cycles of cisplatin plus pemetrexed in this study.

We think it is unclear whether cisplatin plus pemetrexed is a reasonable induction chemotherapy regimen in the Japanese patient population. Only half of the enrolled patients in our study completed protocol induction chemotherapy and received maintenance chemotherapy. Furthermore, nearly a quarter of patients discontinued protocol induction chemotherapy for reasons other than PD. In contrast, approximately 60% of enrolled patients were able to receive continuation maintenance chemotherapy with pemetrexed in the PARAMOUNT study. Considering these results, it is difficult to conclude that cisplatin plus pemetrexed is an acceptable chemotherapy regimen for induction treatment in the Japanese patient population. A recent phase II study of carboplatin plus pemetrexed followed by pemetrexed maintenance therapy in Japanese patients with advanced non-squamous cell NSCLC met its primary endpoint for RR with 51% and showed a PFS of 6.3 months and OS of 24.3 months. Ninety percent of enrolled patients completed four cycles of induction chemotherapy. In that study, severe adverse events, including grade 3 or 4 neutropenia, were observed in more than 30% of the patients, which is a rate somewhat higher than in our study. However, the majority of patients continued to receive induction chemotherapy.²⁴ Further studies are needed to assess whether carboplatin plus pemetrexed or cisplatin plus pemetrexed is the more appropriate chemotherapy regimen for induction treatment in Japan.

It is unclear whether our present protocol regimen conferred a benefit for EML4-ALK fusion gene-positive NSCLC and whether it was unsuitable for TS expression-positive NSCLC. One patient who was found to have the EML4-ALK fusion gene had a good response to induction chemotherapy and continued long cycle maintenance therapy. In contrast, all patients who had TS expression failed induction chemotherapy owing to early tumor progression. Several investigators reported that lower TS expression was observed in lung

adenocarcinoma compared to other histological types of NSCLC and that higher levels of TS expression in NSCLC cells reduced sensitivity to pemetrexed.^{25–27} Gandara *et al.* reported at the 2012 American Society of Clinical Oncology annual meeting that there were lower levels of TS expression in ALK-positive NSCLC.²⁸ These reports may suggest that continuation maintenance therapy with pemetrexed is more beneficial for patients harboring the EML4-ALK fusion gene. Unfortunately, the small sample size of our study meant that we were unable to fully investigate the association of EML4-ALK and TS expression with the sensitivity of NSCLC to chemotherapy regimens that include pemetrexed. Further prospective studies are needed to validate the usefulness of pemetrexed for advanced NSCLC patients harboring the EML4-ALK fusion gene.

Two limitations of the present study warrant mention. First, our uncontrolled study design and lack of randomization prevented any determination of whether the maintenance chemotherapy group was superior to the non-maintenance chemotherapy group. Second, molecular information was limited, including data about the EML4-ALK fusion gene and TS expression. Further investigation will be required to assess whether our maintenance treatment is beneficial for patients harboring EML4-ALK and overexpression of TS.

Conclusion

In conclusion, continuation maintenance therapy with pemetrexed showed great efficacy and tolerability in patients with advanced non-squamous NSCLC who completed cisplatin plus pemetrexed as first-line chemotherapy. However, further investigation is needed to assess whether cisplatin plus pemetrexed is an acceptable regimen for induction chemotherapy in the Japanese patient population.

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Disclosure

No authors report any conflict of interest.

References

- 1 Parkin DM. Global cancer statistics in the year 2000. (Published erratum appears in *Lancet Oncol* 2001; 2: 596) *Lancet Oncol* 2001; 2: 533–43.
- 2 Travis WD, Rekhtman N, Riley GJ *et al.* Pathologic diagnosis of advanced lung cancer based on small biopsies and cytology: a paradigm shift. *J Thorac Oncol* 2010; 5: 411–4.
- 3 Travis WD, Travis LB, Devesa SS. Lung cancer. (Published erratum appears in *Cancer* 1995; 75: 2979) *Cancer* 1995; 75 (1 Suppl): 191–202.
- 4 Kelly K, Crowley J, Bunn PA Jr *et al.* Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol* 2001; 19: 3210–8.
- 5 Fossella F, Pereira JR, von Pawel J *et al.* Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003; 21: 3016–24.
- 6 Weick JK, Crowley J, Natale RB *et al.* A randomized trial of five cisplatin-containing treatments in patients with metastatic non-small-cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol* 1991; 9: 1157–62.
- 7 Smit EF, Mattson K, von Pawel J, Manegold C, Clarke S, Postmus PE. ALIMTA (pemetrexed disodium) as second-line treatment of non-small-cell lung cancer: a phase II study. *Ann Oncol* 2003; 14: 455–60.
- 8 Hanna N, Shepherd FA, Fossella FV *et al.* Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; 22: 1589–97.
- 9 Scagliotti GV, Parikh P, von Pawel J *et al.* Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008; 26: 3543–51.
- 10 Ohe Y, Ohashi Y, Kubota K *et al.* Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007; 18: 317–23.
- 11 Delbaldo C, Michiels S, Rolland E *et al.* WITHDRAWN: second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease. *Cochrane Database Syst Rev* 2012; (4): CD004569.
- 12 Ardizzone A, Boni L, Tiseo M *et al.* Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst* 2007; 99: 847–57.
- 13 D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol* 2005; 23: 2926–36.
- 14 Rajeswaran A, Trojan A, Burnand B, Giannelli M. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of

- metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. *Lung Cancer* 2008; **59**: 1–11.
- 15 Zhou C, Wu YL, Chen G *et al.* Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12**: 735–42.
 - 16 Ciuleanu T, Brodowicz T, Zielinski C *et al.* Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009; **374**: 1432–40.
 - 17 Niho S, Kunitoh H, Nokihara H *et al.* Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. *Lung Cancer* 2012; **76**: 362–7.
 - 18 Sandler A, Gray R, Perry MC *et al.* Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. (Published erratum appears in *N Engl J Med* 2007; **356**: 318) *N Engl J Med* 2006; **355**: 2542–50.
 - 19 Mok TS, Wu YL, Thongprasert S *et al.* Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947–57.
 - 20 Paz-Ares L, de Marinis F, Dediu M *et al.* Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2012; **13**: 247–55.
 - 21 Paz-Ares L, de Marinis F, Dediu M *et al.* Final overall survival (OS) results of the phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo (plb) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced nonsquamous (NS) non-small cell lung cancer (NSCLC). 2012 ASCO Annual Meeting Proceedings. *J Clin Oncol* 2012; **30**: (Suppl 18S). (Abstract LBA7507).
 - 22 Scagliotti G, Hanna N, Fossella F *et al.* The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist* 2009; **14**: 253–63.
 - 23 Azzoli CG, Temin S, Aliff T *et al.* 2011 focused update of 2009 American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2011; **29**: 3825–31.
 - 24 Kim YH, Hirabayashi M, Togashi Y *et al.* Phase II study of carboplatin and pemetrexed in advanced non-squamous, non-small-cell lung cancer: Kyoto Thoracic Oncology Research Group Trial 0902. *Cancer Chemother Pharmacol* 2012; **70**: 271–6.
 - 25 Tanaka F, Wada H, Fukui Y, Fukushima M. Thymidylate synthase (TS) gene expression in primary lung cancer patients: a large-scale study in Japanese population. *Ann Oncol* 2011; **22**: 1791–7.
 - 26 Takezawa K, Okamoto I, Okamoto W *et al.* Thymidylate synthase as a determinant of pemetrexed sensitivity in non-small cell lung cancer. *Br J Cancer* 2011; **104**: 1594–601.
 - 27 Ozasa H, Oguri T, Uemura T *et al.* Significance of thymidylate synthase for resistance to pemetrexed in lung cancer. *Cancer Sci* 2010; **101**: 161–6.
 - 28 Gandara DR, Huang E, Desai S *et al.* Thymidylate synthase (TS) gene expression in patients with ALK positive (+) non-small cell lung cancer (NSCLC): implications for therapy. 2012 ASCO Annual Meeting Proceedings. *J Clin Oncol* 2012; **30** (Suppl. 15S) (Abstract 7582).

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Participant flow diagram.