original reports

Randomized Phase III Study of Pemetrexed Plus Cisplatin Versus Vinorelbine Plus Cisplatin for Completely Resected Stage II to IIIA Nonsquamous Non–Small-Cell Lung Cancer

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abstract

PURPOSE To evaluate the efficacy of pemetrexed plus cisplatin versus vinorelbine plus cisplatin as postoperative adjuvant chemotherapy in patients with pathologic stage II-IIIA nonsquamous non–small-cell lung cancer (NSCLC).

PATIENTS AND METHODS We performed a randomized, open-label, phase III study at 50 institutions within 7 clinical study groups in Japan. Patients with completely resected pathologic stage II-IIIA (TNM 7th edition) nonsquamous NSCLC were randomly assigned to receive either pemetrexed (500 mg/m^2, day 1) plus cisplatin (75 mg/m^2, day 1) or vinorelbine (25 mg/m^2, days 1 and 8) plus cisplatin (80 mg/m^2, day 1) with stratification by sex, age, pathologic stage, *EGFR* mutation, and institution. These treatments were planned to be given every 3 weeks for 4 cycles. The primary end point was recurrence-free survival in the modified intent-to-treat population, excluding ineligible patients.

RESULT Between March 2012 and August 2016, 804 patients were enrolled (402 assigned to vinorelbine plus cisplatin and 402 assigned to pemetrexed plus cisplatin). Of 784 eligible patients, 410 (52%) had stage IIIA disease and 192 (24%) had *EGFR*-sensitive mutations. At a median follow-up of 45.2 months, median recurrence-free survival was 37.3 months for vinorelbine plus cisplatin and 38.9 months for pemetrexed plus cisplatin, with a hazard ratio of 0.98 (95% CI, 0.81 to 1.20; 1-sided $P = .474$). Grade 3-4 toxicities reported more frequently for vinorelbine plus cisplatin than for pemetrexed plus cisplatin were febrile neutropenia (11.6% *v* 0.3%, respectively), neutropenia (81.1% *v* 22.7%, respectively), and anemia (9.3% *v* 2.8%, respectively). One treatment-related death occurred in each arm.

CONCLUSION Although this study failed to show the superiority of pemetrexed plus cisplatin for patients with resected nonsquamous NSCLC, this regimen showed a better tolerability as adjuvant chemotherapy.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Previous phase III studies have demonstrated the efficacy of postoperative cisplatin-based adjuvant chemotherapy for the treatment of non–small-cell lung cancer (NSCLC).[1-3] In a meta-analysis of 4,584 patients enrolled in a large-scale comparative study of cisplatin-based chemotherapy versus no chemotherapy as postoperative adjuvant therapy (the Lung Adjuvant Cisplatin Evaluation [LACE] trial), the hazard ratio (HR) against death in all patients was 0.89 (95% CI, 0.82 to 0.96), which corresponded to an absolute survival benefit of 5.4% at 5 years.[4] The survival benefit varied with pathologic stage (HR for stage IA, 1.40; stage IB, 0.93; stage II, 0.83; stage III, 0.83). Because subgroup analysis of the LACE study showed that among the various drugs coadministered with cisplatin, only vinorelbine significantly prolonged survival ($P < .001$), vinorelbine plus cisplatin has become standard as adjuvant chemotherapy in patients with resected NSCLC.[5]

The combination of pemetrexed plus cisplatin is a standard treatment of patients with metastatic nonsquamous NSCLC. A randomized phase III study demonstrated the noninferiority in overall survival of pemetrexed plus cisplatin compared with gemcitabine plus cisplatin in patients with untreated advanced NSCLC, with an HR of 0.94 (95% CI, 0.84 to 1.05).[6] In addition, subgroup analysis according to histology

showed that the combination of pemetrexed plus cisplatin was associated with significantly better survival compared with gemcitabine plus cisplatin in patients with adenocarcinoma (median survival time, 12.6 *v* 10.9 months, respectively; $P = .03$) and large-cell carcinoma (10.4 *v* 6.7 months, respectively; $P = .03$). In a phase III study of pemetrexed versus docetaxel for previously treated metastatic NSCLC, subgroup analysis for adenocarcinoma also showed that pemetrexed prolonged the survival time.[7] These results indicate that pemetrexed can be considered a key drug in the treatment of metastatic nonsquamous NSCLC.

Based on this background, we conducted the first, to our knowledge, randomized phase III study (JIPANG, an open-label phase III trial conducted at 50 study sites) to evaluate the efficacy of pemetrexed plus cisplatin versus vinorelbine plus cisplatin as adjuvant chemotherapy in patients with stage II-IIIA nonsquamous NSCLC (University Hospital Medical Information Network Clinical Trials Registry identifier: UMIN000006737; jRCTs041180023).[8]

PATIENTS AND METHODS

Patients

This trial enrolled patients with nonsquamous NSCLC who underwent complete surgical resections by lobectomy or pneumonectomy with resection of any involved N2 lymph nodes within the 3-8 weeks before enrollment. Eligible patients were age 20-75 years with histologically confirmed pathologic stage II or IIIA nonsquamous NSCLC (Union for International Cancer Control TNM classification, seventh edition), proven results of the *EGFR* gene mutation test, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic and organ function. Nonsquamous NSCLC was defined as adenocarcinoma, large-cell carcinoma (excluding large-cell neuroendocrine carcinoma), and adenosquamous carcinoma based on the WHO 2003 classification.[9] Key exclusion criteria were severe postoperative complications (eg, infection, respiratory failure), interstitial pneumonia on computed tomography of the chest, current pregnancy, and other severe comorbidity. Patients who received neoadjuvant chemotherapy or had planned to receive EGFR tyrosine kinase inhibitors were also excluded in this study. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional review board of each study institution. All patients provided written informed consent before participation.

Eligible patients were randomly assigned to receive either pemetrexed plus cisplatin or vinorelbine plus cisplatin in a 1:1 ratio. Staff at the West Japan Oncology Group Data Center (Osaka, Japan) used a computer program with a dynamic minimization method (EPS, Tokyo, Japan) that balanced sex (female *v* male), age (< 70 *v* ≥ 70 years), pathologic stage (II *v* IIIA), *EGFR* mutation status (mutant *v* wild type), and institution for randomization.

Procedures

Eligible patients received either pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) by intravenous infusion on day 1 or vinorelbine (25 mg/m^2) on days 1 and 8 and cisplatin (80 mg/m^2) on day 1 by intravenous infusion. Each cycle of treatment was repeated every 3 weeks until 4 cycles were completed. Patients assigned to pemetrexed plus cisplatin received vitamin B_{12} (1,000 μg intramuscularly at least every 9 weeks) starting from 1 week before treatment initiation and no later than the first day of treatment until 3 weeks after the last dose of pemetrexed; these patients also received folic acid supplementation (400 μg daily orally, from approximately 1 week before the first dose of chemotherapy until at least 3 weeks after the final dose).

In patients without recurrence, subsequent chemotherapy or postoperative radiotherapy was not permitted. We planned to follow up all patients for recurrence with chest radiographs and physical examination every 3 months for 3 years, then every 6 months through year 5, and then annually through year 10. In addition, chest computed tomography was performed every 6 months for 3 years and then every 12 months through year 5 and reviewed locally.

Outcomes

Initially, the primary end point was overall survival, defined as the time from random assignment to death from any cause. Secondary end points were recurrence-free survival (time from random assignment to disease recurrence or death, whichever occurred first), rate of treatment completion, and toxicity assessment according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 for up to 30 days beyond the last dose of any protocol treatment.

In a protocol amendment during the study, the primary end point was changed from overall survival to recurrence-free survival because, with developments in subsequent chemotherapy, death events were too few to evaluate survival at the completion of patient accrual. In addition, a meta-analysis showed that disease-free survival (time from random assignment to locoregional or distant recurrence or death from any cause) may represent a valid surrogate end point for overall survival in studies of adjuvant chemotherapy for NSCLC.[10]

Statistical Analysis

Efficacy analysis was performed for the modified intent-to-treat (m-ITT) population, which is determined as all randomly assigned patients excluding patients who did not meet eligibility criteria. For toxicity analyses, only patients who received at least 1 dose of chemotherapy were included. In the analysis of overall survival, patients who were alive at the time of final analysis were censored at the last date of contact. For recurrence-free survival, patients who did not experience a recurrence-free survival event at analysis were censored at the last date of disease assessment or contact. The 5-year survival rate of patients

treated with vinorelbine plus cisplatin as the control arm was estimated to be 50% based on previous reports.[4] Before the study protocol amendment, the 5-year survival rate was expected to improve by 8%. To perform the log-rank test under the chosen conditions ($\alpha = .05$ [1-sided], $1 - \beta = 0.8$, 3-year registration period, and 5-year follow-up after registration of the last patient), 426 events and 777 patients were required. After allowing for the exclusion of some patients from the analyses, a sample size of 400 patients per arm (total of 800 patients) was planned. Following the protocol amendment, the 3-year recurrence-free survival rate of patients in the control arm (vinorelbine plus cisplatin) was estimated at 50%, and the 3-year recurrence-free survival was expected to improve by 8% with an HR of 0.755 ($\alpha = .05$ [1-sided], $1 - \beta = 0.9$, 3-year follow-up after registration of the last patient). On the basis of the amended statistical setting, approximately 420 recurrence-free survival events were required. Event time was estimated using the Kaplan-Meier method, and Cox proportional hazards models stratified by the predefined factors (sex, age, pathologic stage, and *EGFR* mutation status) were used to estimate HRs and to test for differences in recurrence-free survival and overall survival between the treatment groups. *P* values of log-rank testing for recurrence-free survival and overall survival were denoted as 1-sided, whereas all other analyses were exploratory and thus 2-sided. CIs are at the 95% level.

RESULTS

A total of 804 patients were screened and enrolled in this study between March 14, 2012, and August 19, 2016, from 50 participating centers (Fig 1). Among these participants, 402 were assigned to vinorelbine plus cisplatin and 402 to pemetrexed plus cisplatin (intent-to-treat population). Sixteen patients did not start their assigned treatment (6 in the vinorelbine plus cisplatin group and 10 in the pemetrexed plus cisplatin group) for various reasons (summarized in Fig 1) but were included in the intent-to-treat analyses. Twenty patients (7 in vinorelbine plus cisplatin arm and 13 in pemetrexed plus cisplatin

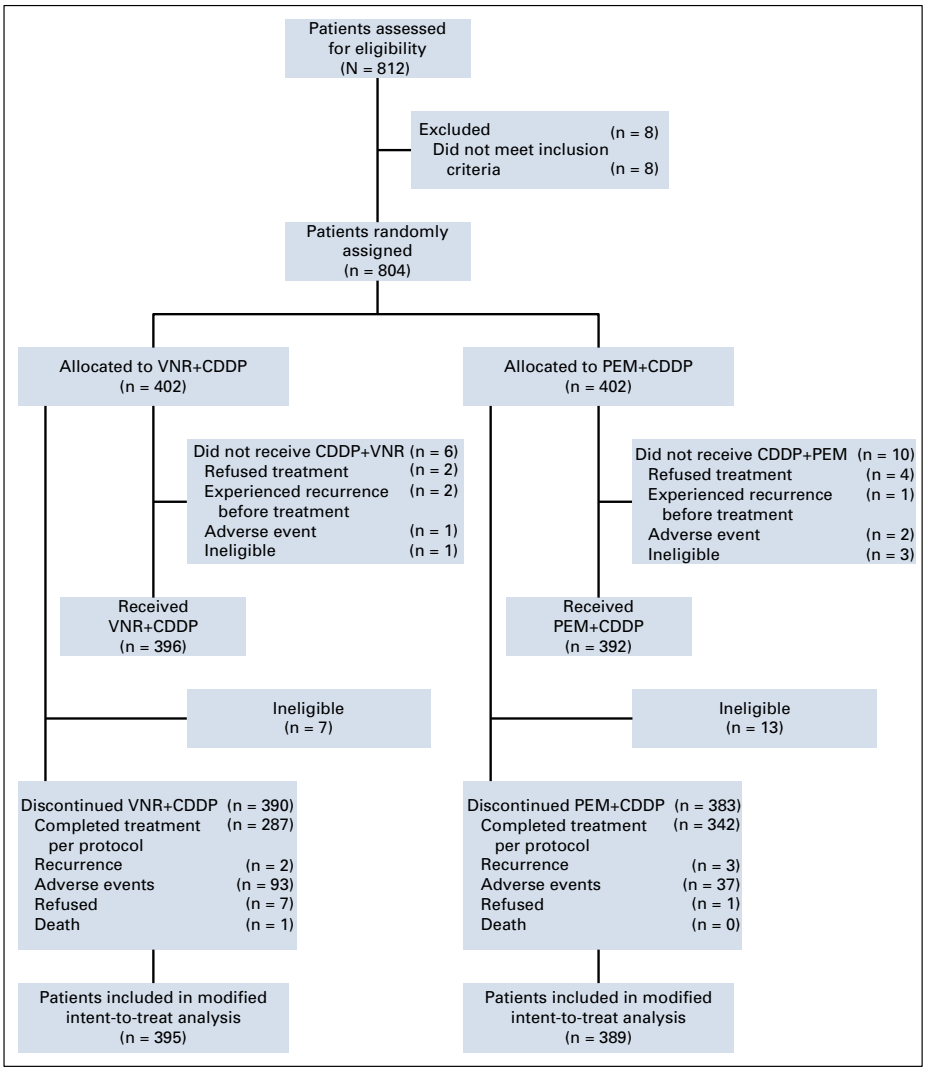

FIG 1. CONSORT diagram. CDDP, cisplatin; PEM, pemetrexed; VNR, vinorelbine.

arm) were deemed ineligible, most commonly because of an absence of nonsquamous histology (n = 10). Other reasons for ineligibility were incomplete resection (n = 3), history of malignancy (n = 3), inadequate nodal sampling (n = 2), serum bilirubin not evaluated within 14 days before enrollment (n = 1), and brain metastasis growing in follow-up magnetic resonance imaging (n = 1).

Patient characteristics were similar between the 2 arms in m-ITT population (Table 1). Pathologic stage IIIA was recorded for 410 (52%) of the 784 patients. Most patients had adenocarcinoma histology (752 [96%] of 784 eligible patients), and 192 patients (24%) had nonsquamous NSCLC harboring *EGFR*-activating mutations including deletion in exon 19 and L858R in exon 21. Most patients underwent lobectomy (772 [98%]), and 12 patients (2%) had pneumonectomy (9 in vinorelbine plus cisplatin arm and 3 in pemetrexed plus cisplatin arm).

The rate of completion of 4 cycles of treatment was 72.7% for the 395 patients assigned to vinorelbine plus cisplatin and 87.9% for the 389 patients assigned to pemetrexed plus cisplatin ($P < .001$). Median follow-up was 45.2 months (interquartile range, 34.7-57.1 months).

Disease recurrence or death was reported in 208 patients (53%) assigned to vinorelbine plus cisplatin and 199 patients (51%) assigned to pemetrexed plus cisplatin. Median recurrence-free survival in the m-ITT population did not differ significantly between the 2 arms (vinorelbine plus cisplatin: 37.3 months [95% CI, 28.8 to 52.5 months]; pemetrexed plus cisplatin: 38.9 months [95% CI, 28.7 to 55.3 months]), with an HR of 0.98 (95% CI, 0.81 to 1.20; 90% CI, 0.84 to 1.16; 1-sided $P = .474$; Fig 2A). Two-year recurrence-free survival was 60.7% (95% CI, 55.7% to 65.3%) in the vinorelbine plus cisplatin group and 58.3% (95% CI, 53.2% to 63.0%) in the pemetrexed plus cisplatin group. Three-year recurrence-free survival was 50.2% (95% CI, 45.0% to 55.2%) in the vinorelbine plus cisplatin group and 51.1% (95% CI, 45.8% to 56.0%) in the pemetrexed plus cisplatin group. Figure 3 shows the post hoc analysis of recurrence-free survival by various patient subgroups, with the exploratory nature of the analyses. In the subgroup analysis of *EGFR* mutation status, a significant interaction was observed ($P = .046$). In patients with nonsquamous NSCLC without *EGFR* mutations, recurrence-free survival in the m-ITT population tended to

TABLE 1. Patient Characteristics

	Vinorelbine Plus Cisplatin Group (n = 395)		Pemetrexed Plus Cisplatin Group (n = 389)	
Characteristic	**No.**	**%**	**No.**	**%**
Sex				
Male	235	59.5	227	58.4
Female	160	40.5	162	41.6
Median age, years (IQR)	65 (58-69)		64 (57-67)	
ECOG performance status				
0	306	77.5	295	75.8
1	89	22.5	94	24.2
Pathologic stage (seventh TNM classification)				
IIA	132	33.4	134	34.4
IIB	57	14.4	51	13.1
IIIA	206	52.2	204	52.4
Histology				
Adenocarcinoma	379	95.9	373	95.9
Others	16	4.1	16	4.1
EGFR-sensitive mutations				
Positive	95	24.1	97	24.9
Wild type	300	75.9	292	75.1
Surgery				
Pneumonectomy	9	2.3	3	0.8
Lobectomy	386	97.7	386	99.2
Median time from surgery, days (IQR)	42 (35-50)		43 (36-50)	

NOTE. Data are numbers and percentages, unless otherwise indicated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

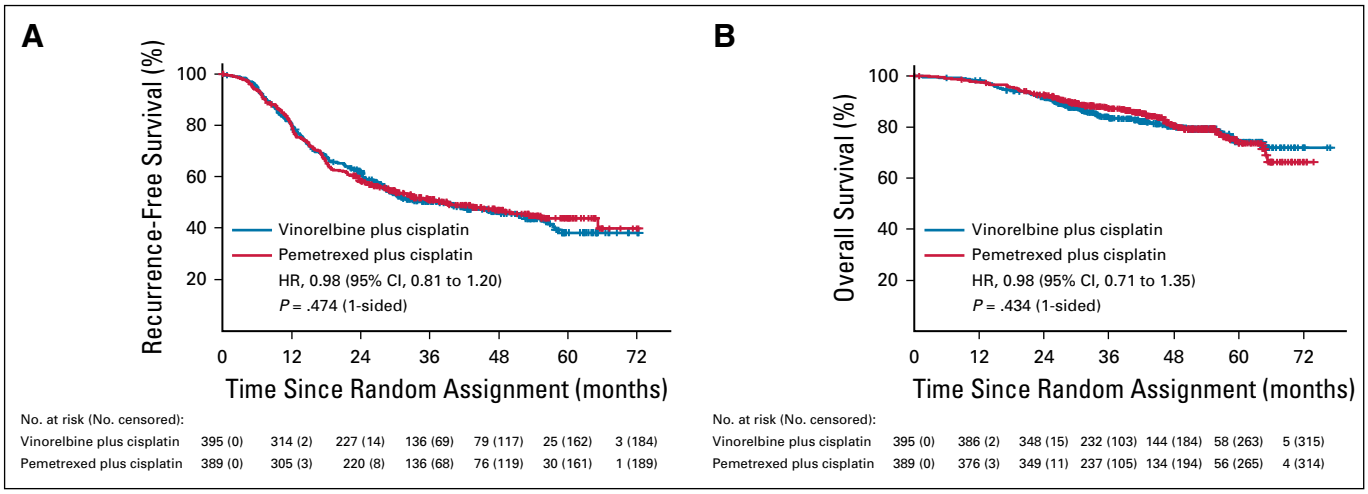

FIG 2. Kaplan-Meier curve for (A) recurrence-free survival and (B) overall survival in eligible patients (n = 784). HR, stratified hazard ratio by the predefined factors (sex, age, pathologic stage, *EGFR* mutation status).

be better in patients assigned to pemetrexed plus cisplatin (median, 65.2 months; 95% CI, 33.1 months to no upper limit) compared with patients assigned to vinorelbine plus cisplatin (median, 39.9 months; 95% CI, 28.2 to 56.0 months), although the difference was not significant, with an HR of 0.87 (95% CI, 0.69 to 1.09; Fig 4A). In patients with nonsquamous NSCLC harboring *EGFR* mutations, recurrence-free survival tended to be better in the group assigned to vinorelbine plus cisplatin (median, 30.4 months; 95% CI, 23.9 to 57.3 months) compared with the group assigned to pemetrexed plus cisplatin (median, 24.1 months; 95% CI, 18.2 to 32.7 months), although the difference was not statistically significant (HR, 1.38; 95% CI, 0.95 to 1.99; Fig 4B). No notable interaction was observed in the other patient subgroup. A total of 309 recurrences were observed, and recurrence sites in the vinorelbine plus cisplatin and pemetrexed plus cisplatin groups were reported as follows: regional lymph nodes (n = 75 [36.6%] and n = 73 [37.6%], respectively), pulmonary metastasis (n = 69 [33.7%] and n = 64 [33.0%], respectively), and brain metastasis (n = 51 [24.9%] and n = 46 [23.7%], respectively; Appendix Table A1, online only).

At the time of analysis, 75 patients in the vinorelbine plus cisplatin group and 71 patients in the pemetrexed plus cisplatin group had died. The estimated median overall survival time in both arms has not been reached to date,

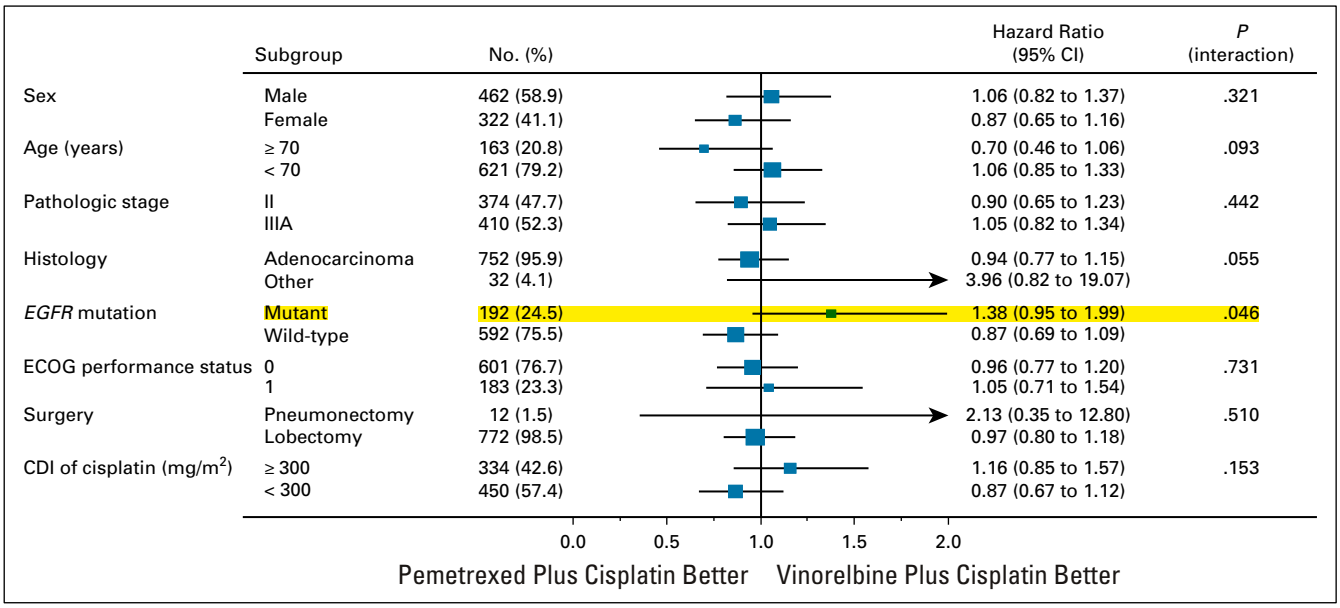

FIG 3. Subgroup analysis of recurrence-free survival by baseline characteristics. CDI, cumulative dose-intensity; ECOG, Eastern Cooperative Oncology Group.

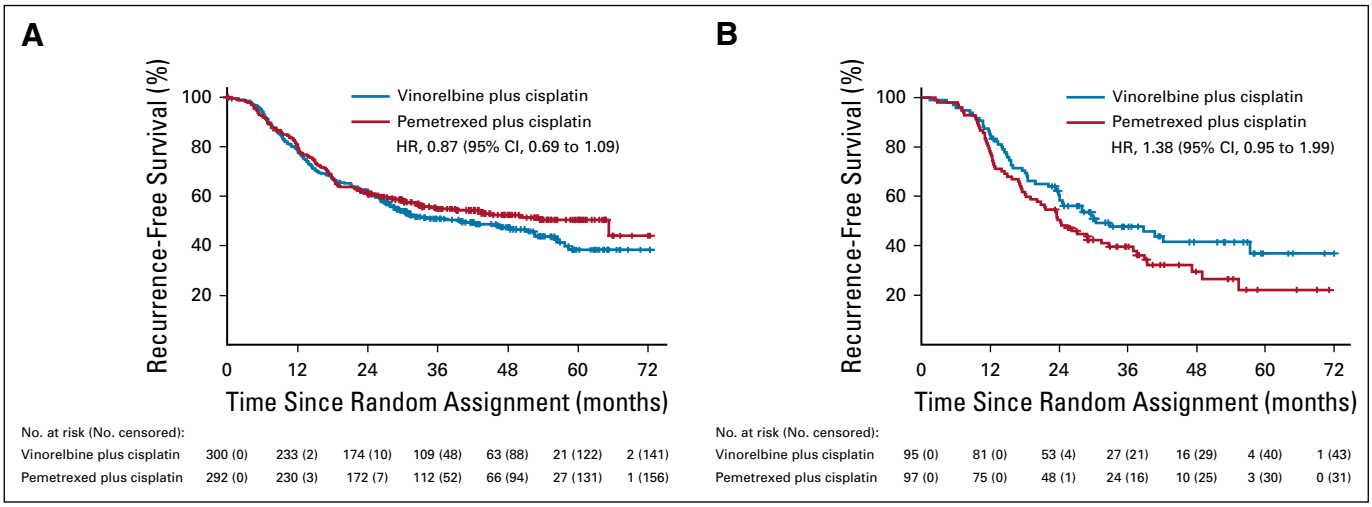

FIG 4. Recurrence-free survival in (A) patients with *EGFR* wild-type non–small-cell lung cancer (NSCLC; n = 592) and (B) patients with *EGFR*-mutant NSCLC (n = 192). HR, unstratified hazard ratio.

resulting in an estimated overall survival HR of 0.98 (95% CI, 0.71 to 1.35; 1-sided $P = .434$; Fig 2B). Three-year overall survival was 83.5% (95% CI, 79.2% to 87.0%) in the vinorelbine plus cisplatin group and 87.2% (95% CI, 83.8% to 90.2%) in the pemetrexed plus cisplatin group.

The 788 patients (396 patients receiving vinorelbine plus cisplatin and 392 receiving pemetrexed plus cisplatin) who underwent at least 1 treatment cycle were evaluated for adverse events. Table 2 lists the all-grade adverse events reported. The rates of any grade and grade 3-5 adverse events were 100% and 89.4% in vinorelbine plus cisplatin arm and 99.7% and 47.4% in pemetrexed plus cisplatin arm, respectively.

Grade 3-4 febrile neutropenia was observed in 46 patients (11.6%) receiving vinorelbine plus cisplatin and in 1 patient (0.3%) receiving pemetrexed plus cisplatin ($P < .01$). Grade 3-4 WBC count decrease, neutrophil count decrease, and anemia were more frequently observed in patients receiving vinorelbine plus cisplatin (202 [51.0%], 321 [81.1%], and 37 patients [9.3%], respectively) than in those receiving pemetrexed plus cisplatin (23 [5.9%], 89 [22.7%], and 11 patients [2.8%], respectively; $P < .01$). Rates of grade 4 WBC count decrease and neutrophil count decrease were also higher in the vinorelbine plus cisplatin arm (37 patients [9.3%] and 224 patients [56.6%], respectively) compared with pemetrexed plus cisplatin arm (1 patient [0.3%] and 13 patients [3.3%], respectively). One treatment-related death was observed in each arm (sudden death in a patient receiving vinorelbine plus cisplatin and pneumonitis in a patient receiving pemetrexed plus cisplatin).

DISCUSSION

This phase III study (JIPANG) failed to show the superiority of pemetrexed plus cisplatin to improve recurrence-free survival among patients with completely resected non-squamous NSCLC. To our knowledge, this is the first randomized phase III study comparing the efficacy of platinum-based chemotherapy regimens as adjuvant chemotherapy for NSCLC. Previous randomized studies have not established the optimal platinum-based chemotherapy regimen for patients with advanced NSCLC.[11,12] However, in the subgroup analysis of a randomized phase III study comparing pemetrexed plus cisplatin versus gemcitabine plus cisplatin for advanced NSCLC, the combination of pemetrexed plus cisplatin resulted in significantly better survival among patients with nonsquamous NSCLC.[6] The results of the JIPANG study indicate that the optimal platinum-based chemotherapy remains unclear in the adjuvant chemotherapy setting for resected non-squamous NSCLC. A post hoc subgroup analysis of a recent large randomized phase III study of adjuvant chemotherapy in patients with pathologic stage IB-IIIA NSCLC (Eastern Cooperative Oncology Group [ECOG] 1505 trial) by chemotherapy regimen also did not show any meaningful differences among 4 platinum-based chemotherapy regimens, including pemetrexed plus cisplatin.[13]

To date, 2 randomized phase II studies evaluating the combination of pemetrexed plus cisplatin as adjuvant chemotherapy have been reported. The TREAT study evaluated the feasibility of 4 cycles of cisplatin and pemetrexed every 3 weeks as adjuvant chemotherapy for patients with NSCLC.[14] The feasibility rate was better for the combination of pemetrexed and cisplatin (95.5%) compared with the combination of vinorelbine and cisplatin (75.4%; $P = .001$). In a 3-year follow-up of the TREAT study, there were no significant differences in efficacy between these 2 chemotherapy regimens.[15] The other randomized phase II study of pemetrexed in combination with cisplatin or carboplatin as adjuvant chemotherapy also

TABLE 2. Adverse Events in the Safety Population

	No. of Patients (%)						
	Vinorelbine Plus Cisplatin Group (n = 395)			Pemetrexed Plus Cisplatin Group (n = 392)			
Adverse Event	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	P[a]
Any adverse events	396 (100)	126 (31.8)	227 (57.3)	391 (99.7)	165 (42.1)	20 (5.1)	< .01
Neutrophil count decreased	378 (95.5)	97 (24.5)	224 (56.6)	306 (78.3)	76 (19.4)	13 (3.3)	< .01
WBC count decreased	375 (94.7)	165 (41.7)	37 (9.3)	280 (71.6)	22 (5.6)	1 (0.3)	< .01
Anorexia	318 (80.3)	43 (10.9)	0	322 (82.1)	42 (10.7)	0	.94
Nausea	313 (79.0)	30 (7.6)	0	309 (78.8)	28 (7.1)	0	.81
Anemia	303 (76.5)	37 (9.3)	0	208 (53.2)	11 (2.8)	0	< .01
Constipation	299 (75.5)	8 (2.0)	0	262 (66.8)	5 (1.3)	0	.41
Hyponatremia	278 (70.2)	34 (8.6)	4 (1.0)	261 (66.8)	26 (6.6)	4 (1.0)	.33
Fatigue	226 (57.1)	18 (4.5)	0	192 (49.0)	9 (2.3)	0	.08
Hypokalemia	210 (53.0)	21 (5.3)	1 (0.3)	197 (50.4)	15 (3.8)	1 (0.3)	.33
ALT increased	177 (44.8)	9 (2.3)	0	165 (42.2)	7 (1.8)	0	.62
Creatinine increased	156 (39.5)	0	0	122 (31.2)	0	1 (0.3)	.32
Alopecia	122 (30.1)	—	—	50 (12.8)	—	—	—
Phlebitis	102 (25.8)	—	—	9 (2.3)	—	—	—
Mucositis oral	81 (20.5)	1 (0.3)	0	48 (12.2)	0	0	.32
AST increased	77 (19.5)	5 (1.3)	0	87 (22.3)	1 (0.3)	1 (0.3)	.26
Fever	70 (17.7)	5 (1.3)	0	23 (5.9)	0	0	.03
Diarrhea	69 (17.4)	1 (0.3)	0	60 (15.3)	3 (0.8)	0	.31
Vomiting	67 (16.9)	4 (1.0)	0	82 (20.9)	3 (0.8)	0	.71
Weight loss	65 (16.4)	0	0	46 (11.7)	0	0	—
Platelet count decreased	47 (11.9)	5 (1.3)	0	46 (11.8)	6 (1.5)	0	.75
Febrile neutropenia	46 (11.6)	46 (11.6)	0	1 (0.3)	1 (0.3)	0	< .01
Blood bilirubin increased	42 (10.6)	0	0	40 (10.2)	1 (0.3)	0	.32
Rash	40 (10.1)	1 (0.3)	0	70 (17.9)	0	0	.32
Peripheral sensory neuropathy	34 (8.6)	0	0	12 (3.1)	0	0	—
Infection	29 (7.3)	6 (1.5)	1 (0.3)	24 (6.1)	2 (0.5)	1 (0.3)	.21
Dyspnea	20 (5.1)	2 (0.5)	1 (0.3)	18 (4.6)	0	1 (0.3)	.32
Arthralgia	13 (3.3)	0	0	8 (2.0)	0	0	—
Myalgia	8 (2.0)	0	0	10 (2.6)	0	0	—
Peripheral motor neuropathy	4 (1.0)	0	0	3 (0.8)	0	0	—
Thromboembolic event	3 (0.8)	2 (0.5)	0	8 (2.0)	5 (1.3)	1 (0.3)	.15
Pneumonitis	0	0	0	3 (0.8)	0	0	.32

NOTE. Data represent all reported toxicities.

[a]Grade 3-5 adverse events.

reported the treatment feasibility (feasibility rate: 59.4% for pemetrexed plus cisplatin and 50% for pemetrexed plus carboplatin).[16] These results suggest that the combination of pemetrexed and cisplatin is feasible as adjuvant chemotherapy. In the current JIPANG study, grade 3-4 toxicities reported more frequently for vinorelbine plus cisplatin than for pemetrexed plus cisplatin were febrile neutropenia, neutropenia, and anemia. In addition, the completion rate of 4 cycles of treatment was also higher in the pemetrexed plus cisplatin arm, compared with the vinorelbine plus cisplatin arm. However, patients receiving pemetrexed plus cisplatin have to receive vitamin B_{12} and folic acid supplementation 1 week before treatment initiation. Although this study did not evaluate quality of life, mild toxicities and higher completion rate of pemetrexed plus cisplatin as adjuvant chemotherapy were validated.

Currently, phase III studies evaluating anti–PD-1/PD-L1 inhibitors in patients with resected NSCLC are ongoing, and these study results may support the use of pemetrexed plus cisplatin as adjuvant chemotherapy in patients with resected nonsquamous NSCLC. However, in eighth edition of the TNM classification, most patients with stage IIA disease according to the seventh edition were restaged as stage IIB.[17] Therefore, these results may be directly useful for patients with pathologic stage IIB-IIIA nonsquamous NSCLC.

Although the overall survival data were immature, recurrence-free survival was not significantly different between the 2 platinum-based chemotherapy regimens in the current study. In the ECOG 1505 study, the prognosis of completely resected NSCLC was shown to be better than that in a previous phase III study evaluating platinum-based chemotherapy as adjuvant chemotherapy.[13] A study based on data from a Japanese lung cancer registry showed that stage-specific prognoses improved over 1 decade.[18] In addition, some Japanese phase II studies have reported a 5-year overall survival rate of approximately 70% in patients with stage II-IIIA NSCLC who underwent adjuvant chemotherapy.[19,20] These findings may have been influenced by recent advances in diagnostic and surgical procedures and the improved efficacy of chemotherapy for NSCLC, including molecular targeted therapies and immune checkpoint inhibitors. Therefore, it was considered acceptable to change the primary end point from overall survival to recurrence-free survival in the current study.

In the subgroup analysis of patients with nonsquamous NSCLC harboring *EGFR* mutations, recurrence-free survival tended to be better in patients in the vinorelbine plus cisplatin group compared with those in the pemetrexed plus cisplatin group. However, in patients with nonsquamous NSCLC without *EGFR* mutations, recurrence-free survival tended to be better in the pemetrexed plus cisplatin group. Pemetrexed acts as a multitarget antifolate agent, inhibiting 3 enzymes in the folate metabolic pathway. A previous study showed that the *EGFR* mutation status influenced the clinical benefit of adjuvant chemotherapy with tegafur-uracil, an antimetabolite that combines a fluorouracil prodrug and uracil, in patients with resected lung adenocarcinoma. In an in vitro study, *EGFR* mutant cells were less sensitive to fluorouracil compared with *EGFR* wild-type cells.[21] These data suggest that *EGFR* mutation status can influence the efficacy of chemotherapy in patients with NSCLC, even in patients with resected NSCLC. In patients with ALK-positive NSCLC, pemetrexed may produce a higher response rate than that observed in the population of all patients with NSCLC.[22] The findings of the current study also indicate that *EGFR* mutation status might influence the efficacy of adjuvant chemotherapy among patients with nonsquamous NSCLC.

In conclusion, although the JIPANG study failed to show the superiority of pemetrexed plus cisplatin in terms of recurrence-free survival, toxicity profiles favored this regimen. Therefore, this combination can be an option for postoperative adjuvant chemotherapy in patients with completely resected nonsquamous NSCLC. The results of the JIPANG study indicate that the optimal platinum-based chemotherapy is still unclear in the adjuvant chemotherapy setting for resected nonsquamous NSCLC.

AFFILIATIONS

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REFERENCES

1. Arriagada R, Bergman B, Dunant A, et al: Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 350:351-360, 2004
2. Winton T, Livingston R, Johnson D, et al: Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 352:2589-2597, 2005
3. Douillard JY, Rosell R, De Lena M, et al: Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial. Lancet Oncol 7:719-727, 2006
4. Pignon JP, Tribodet H, Scagliotti GV, et al: Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group. J Clin Oncol 26:3552-3559, 2008
5. Douillard JY, Tribodet H, Aubert D, et al: Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: Subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol 5:220-228, 2010
6. Scagliotti GV, Parikh P, von Pawel J, et al: Phase III study comparing cisplatin plus gemcitabine with Pemetrexed plus Cisplatin in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 26:3543-3551, 2008
7. 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 14: 253-263, 2009
8. Yamamoto N, Kenmotsu H, Yamanaka T, et al: Randomized phase III study of cisplatin with pemetrexed and cisplatin with vinorelbine for completely resected nonsquamous non-small-cell lung cancer: The JIPANG study protocol. Clin Lung Cancer 19:e1-e3, 2018
9. Travis WD, Brambilla E, Muller-Hermelink HK, et al: Pathology and genetics of tumours of the lung, pleura, thymus and heart, in Kleihues P, Sobin LH (eds): World Health Organization Classification of Tumours. Lyon, France, IARC Press, 2003, pp 35-44
10. Mauguen A, Pignon JP, Burdett S, et al: Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: A re-analysis of meta-analyses of individual patients' data. Lancet Oncol 14:619-626, 2013
11. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002
12. Ohe Y, Ohashi Y, Kubota K, et al: Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and Vinorelbine plus Cisplatin for advanced non-small-cell lung cancer: Four-arm cooperative study in Japan. Ann Oncol 18:317-323, 2007
13. Wakelee HA, Dahlberg SE, Keller SM, et al: Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): An open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 18:1610-1623, 2017
14. Kreuter M, Vansteenkiste J, Fischer JR, et al: Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: The TREAT study. Ann Oncol 24:986-992, 2013
15. Kreuter M, Vansteenkiste J, Fischer JR, et al: Three-year follow-up of a randomized phase II trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine (the TREAT Study). J Thorac Oncol 11:85-93, 2016
16. Schmid-Bindert G, Engel-Riedel W, Reck M, et al: A randomized phase 2 study of pemetrexed in combination with cisplatin or carboplatin as adjuvant chemotherapy in patients with completely resected stage IB or II non-small-cell lung cancer. Lung Cancer 90:397-404, 2015
17. Okami J, Shintani Y, Okumura M, et al: Demographics, safety and quality, and prognostic information in both the seventh and eighth editions of the TNM classification in 18,973 surgical cases of the Japanese Joint Committee of Lung Cancer Registry Database in 2010. J Thorac Oncol 14:212-222, 2019
18. Sawabata N, Miyaoka E, Asamura H, et al: Japanese lung cancer registry study of 11,663 surgical cases in 2004: Demographic and prognosis changes over decade. J Thorac Oncol 6:1229-1235, 2011
19. Iwamoto Y, Mitsudomi T, Sakai K, et al: Randomized phase II study of adjuvant chemotherapy with long-term S-1 versus cisplatin+S-1 in completely resected stage II-IIIA non-small cell lung cancer. Clin Cancer Res 21:5245-5252, 2015

20. Sonobe M, Okubo K, Teramukai S, et al: Phase II study of adjuvant vinorelbine and cisplatin in Japanese patients with completely resected stage II and III non-small cell lung cancer. Cancer Chemother Pharmacol 74:1199-1206, 2014
21. Suehisa H, Toyooka S, Hotta K, et al: Epidermal growth factor receptor mutation status and adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. J Clin Oncol 25:3952-3957, 2007
22. Shaw AT, Kim DW, Nakagawa K, et al: Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368:2385-2394, 2013

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Study of Pemetrexed Plus Cisplatin Versus Vinorelbine Plus Cisplatin for Completely Resected Stage II to IIIA Nonsquamous Non–Small-Cell Lung Cancer

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APPENDIX

TABLE A1. Sites of Recurrence

Site	Vinorelbine Plus Cisplatin Group (n = 205)		Pemetrexed Plus Cisplatin Group (n = 194)	
	No.	%	No.	%
Locoregional recurrence				
Bronchial stump	6	2.9	8	4.1
Regional lymph node	75	36.6	73	37.6
Supraclavicular lymph node	20	9.8	22	11.3
Distant recurrence				
Pleural or pericardial metastasis	26	12.7	25	12.9
Brain metastasis	51	24.9	46	23.7
Pulmonary metastasis	69	33.7	64	33.0
Liver metastasis	5	2.4	5	2.6
Bone metastasis	35	17.1	27	13.1
Other	62	30.2	46	23.7