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A phase I/II trial of weekly nab-paclitaxel for pretreated non-small-cell lung cancer patients without *epidermal growth factor receptor* mutations and *anaplastic lymphoma kinase* rearrangement

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Abstract

Aim: We investigated the efficacy, safety and optimal schedule of nanoparticle albumin-bound paclitaxel monotherapy as second- or third-line treatment for non-small-cell lung cancer patients without *epidermal growth factor receptor* mutation and *anaplastic lymphoma kinase* rearrangement.

Methods: Patients with pretreated advanced non-small-cell lung cancer without *epidermal growth factor receptor* mutation and *anaplastic lymphoma kinase* rearrangement were included. The patients were administered 100 mg/m^2 of nanoparticle albumin-bound paclitaxel on days 1, 8, 15 and 22 (level 0) or on days 1, 8 and 15 (level −1) every 4 weeks during phase I of the trial. The primary endpoint was objective response rate. The estimated objective response rate was 15% and the threshold was 5% with an α error of 0.05 and β error of 0.2 in phase II.

Results: The recommended schedule was determined as level −1 in phase I. The characteristics of the 55 patients enrolled in phase II were as follows: median age = 66 years, male/female = 40/15, second/third line = 34/21 and adenocarcinoma/squamous cell carcinoma/large cell carcinoma/others = 34/17/2/2. Objective response rate was 7.3% (95% confidence interval, 2.0–17.6%). Median progression-free survival was 3.4 months. Treatment-related grade 3 or 4 toxicities were neutropenia (36.4%), febrile neutropenia (5.5%) and pulmonary infection (3.6%). Three patients had grade 2 pneumonitis and one treatment-related death occurred due to adult respiratory distress syndrome.

Conclusion: This study failed to meet predefined primary endpoints for pretreated patients with advanced non-small-cell lung cancer without *epidermal growth factor receptor* mutation and *anaplastic lymphoma kinase* rearrangement.

KEYWORDS

cytotoxic chemotherapy, nanoparticle albumin-bound paclitaxel, non-small cell lung cancer, pretreated NSCLC, wild-type

1 | INTRODUCTION

Nanoparticle albumin-bound paclitaxel (nab-PTX) showed a significantly higher overall response rate (ORR) than solvent-based paclitaxel (sb-PTX) in combination with carboplatin for patients with non-small cell lung cancer (NSCLC) as first-line treatment (33% *vs* 25%, $P = 0.001$). The frequency of some serious adverse events (AEs) in the nab-PTX arm, such as peripheral neuropathy and neutropenia, was less than that in the sb-PTX arm.[1] A 4-week cycle treatment (days 1, 8 and 15) of 125 mg/m^2 of nab-PTX for patients with naïve advanced NSCLC demonstrated efficacy and tolerability in phase I/II of the study; ORR and median time to progression were 30% and 5 months, respectively.[2] In addition, a phase II study of weekly nab-PTX in patients previously treated for advanced NSCLC demonstrated acceptable toxicity and promising activity; ORR and median progression-free survival (mPFS) were 31.7% (95% confidence interval [CI] of 19.3–44.1%) and 4.9 months (95% CI, 2.4–7.4 months), respectively.[3]

Epidermal growth factor receptor (EGFR) mutations may be predictive biomarkers for the effects of cytotoxic chemotherapy, according to some phase III randomized studies comparing the efficacy of EGFR-tyrosine kinase inhibitors with cytotoxic chemotherapies in NSCLC patients. In the INTEREST study, the ORR of docetaxel (DOC) was 21.1% for the *EGFR* mutant, whereas it was 9.8% for wild-type patients.[4] In the V-15-32 study, the ORR of DOC was 46% for the *EGFR* mutant, whereas it was 13% for wild-type patients.[5] In the TRIBUTE trial, the progressive disease rate of carboplatin and paclitaxel chemotherapy was 21% for the *EGFR* mutant, whereas it was 37% for wild-type patients.[6] However, in the DELTA study, comparing erlotinib with DOC in previously treated NSCLC patients, the ORRs of DOC were similar: 17.9% for the *EGFR*-unselected patients and 20.0% for wild-type patients.[7,8]

As the importance of individualized medicine increases, it is necessary to establish a treatment strategy that takes into consideration the presence or absence of driver mutations, such as *EGFR* or *anaplastic lymphoma kinase* (*ALK*). To date, no clinical trial prospectively examined the efficacy and safety of nab-PTX for previously treated NSCLC patients without *EGFR* or *ALK* mutations. We believed that the development of a superior second-line treatment was important for such cases.

With this background, we determined the recommended schedule of weekly nab-PTX in phase I of the study. Subsequently, in phase II, we evaluated the efficacy and safety of nab-PTX with the recommended schedule as second- or third-line treatment for patients with advanced NSCLC without any driver mutation.

2 | PATIENTS AND METHODS

2.1 | Patients

Patients aged ≥20 years were enrolled in the study. The inclusion criteria are as follows: histologically or cytologically confirmed advanced NSCLC; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; measurable lesions documented by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and adequate organ functions; and progressed after one or two chemotherapy regimens including platinum-doublet chemotherapy. The driver mutation status for each patient was also confirmed; *EGFR* mutation was negative and *ALK* fusion status was negative or unknown. Patients who had a history of sb-PTX or nab-PTX and had symptomatic brain or meningeal metastasis were excluded.

This study protocol was developed according to the Declaration of Helsinki, and ethical guidelines for clinical research were approved by the ethics review boards of Shikoku Cancer Center, Matsuyama, Japan [H25-71] and each participating institution. The unique ID issued by UMIN was UMIN000012404. Written informed consent was obtained from each patient before enrollment. All patients provided written informed consent before enrollment.

2.2 | Treatment and assessment in phase I

This study was an open-label, multicenter, single-arm prospective study.

In phase I, a 4-week cycle (dose level 0: days 1, 8, 15 and 22 or dose level −1: days 1, 8 and 15) of 100 mg/m^2 nab-PTX was administered until disease progression or unacceptable AEs were observed. The study treatment was started at dose level 0 and six patients were initially enrolled. If the predefined dose-limiting toxicity (DLT) was observed in zero or one patient, we determined the recommended schedule to be dose level 0, and subsequently proceeded to phase II. If DLT was observed in two patients, six additional patients were enrolled and evaluated at dose level 0. If DLT was observed in ≥3 out of six patients, we determined the recommended schedule to be dose level −1. If DLT was observed in ≤5 out of 12 patients, we determined the recommended schedule to be dose level 0. If DLT was observed in ≥6 out of 12 patients, we determined the recommended schedule to be dose level −1. The definition of DLTs is defined as follows; nab-PTX was not administered on days 8, 15 and 22 in the first cycle because of neutrophil count of < 1000/μL, platelet count of <50 000/μL, infection, peripheral neuropathy, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, blood bilirubin increased, creatinine increased, mucositis or diarrhea of ≥grade 2 or the other nonhematological toxicity of ≥ grade 3, the administration of nab-PTX on day 1 in the second cycle was late for 8 or more days because of neutrophil count of <1500/μL, platelet count of <100 000/μL, hemoglobin of <8.0 g/dL, blood bilirubin of ≥ 1.5 mg/dL or creatinine of >1.5 mg/dL, peripheral neuropathy or infection of ≥grade 2, pneumonitis of any grade, the other nonhematological toxicities of ≥grade 3 or ECOG PS 3 or more.

The primary endpoints of phase I were feasibility and determination of the recommended nab-PTX schedule.

2.3 | Treatment and assessment in phase II

In phase II, nab-PTX was administered according to the recommended schedule determined in phase I until disease progression and unacceptable AEs were observed. The primary endpoint of phase II was ORR and the secondary endpoints were overall survival (OS), PFS and

safety. Tumor response was assessed according to the RECIST v1.1. AEs were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0.

2.4 | Statistical analysis

The sample size was calculated according to Simon's optimal and minimax two-stage sequential design. The expected ORR and threshold ORR for this study were assumed to be 15% and 5%, respectively.[9] Given this assumption, calculation of the required number of subjects with $\alpha = 0.05$ (one-sided) and $\beta = 0.2$ yielded 52 patients; considering that some patients may be ineligible, the planned enrollment number for phase II was set at 55 patients. These 55 patients included patients enrolled in phase I with the recommended schedule. We considered weekly nab-PTX to be an effective treatment regimen, if complete response (CR) or partial response (PR) was confirmed in ≥9 patients from the total of 55.

3 | RESULTS

3.1 | Phase I

A total of five patients were enrolled in phase I. The patient characteristics in phase I are presented in Table 1. The recommended schedule of weekly nab-PTX was determined as level −1, because DLT was observed in four of five patients. The contents of DLTs were grade 3/4 neutropenia in three patients (60%) and grade 2 pneumonitis in one patient (20%).

3.2 | Phase II

A total of 55 patients were enrolled in phase II between April 2014 and July 2016. The patient characteristics in phase II are presented in Table 1. The median age was 66 years (range, 41–90 years). The proportion of male patients was 72.7% and the PS 0/1/2 was 12/39/4, respectively. Thirty-four (61.8%) patients were administered second-line therapy. Twenty patients (36.3%) previously received DOC treatment. In 21 patients, (38.2%) who previously received both first- and second-line treatments, DOC was most frequently administered as the second-line treatment (52.4%). The proportion of patients with adenocarcinoma and squamous cell carcinoma (Sq) was 34 (61.8%) and 17 (30.9%) patients, respectively.

3.3 | Efficacy

Treatment efficacy is summarized in Table 2. All 55 patients were eligible for efficacy analysis. Based on the investigator's assessment, four patients had a PR, and none demonstrated CR, yielding an ORR of 7.3% (95% CI, 2.0–17.6%). Twenty-six patients had stable disease (SD), yielding a disease control rate (DCR: CR + PR + SD) of 54.5% (95% CI, 40.6–68.0%). In addition, subanalysis of clinical concerned factors predicting ORR and DCR was conducted (Table 3). The patients with non-Sq histology tended to have better ORR and DCR. At the median follow-up time of 9.6 months (range, 2.1–34.8 months) for all patients, mPFS was 3.4 months (95% CI, 1.9–4.0 months) and median survival time was 10.6 months (95% CI, 6.9–17.8 months) (Figure 1). The median number of treatment cycles was three. Among all treated patients, nine

TABLE 1 Characteristics of patients in the study ($n = 60$)

	Phase I ($n = 5$)		Phase II ($n = 55$)	
Characteristics	***n***	**%**	***n***	**%**
Age (years)				
Median (range)	67 (61–71)		66 (41–90)	
Sex				
Male	5	100.0	40	72.7
Female	0	0.0	15	27.3
Smoking status				
Nonsmoker	2	40.0	12	21.8
Ex-smoker	1	20.0	39	70.9
Current smoker	2	40.0	4	7.3
ECOG performance status				
0	1	20.0	12	21.8
1	4	80.0	39	70.9
2	0	0.0	4	7.3
Histology				
Adenocarcinoma	4	80.0	34	61.8
Squamous cell carcinoma	1	20.0	17	30.9
Large cell carcinoma	0	0.0	2	3.6
Others	0	0.0	2	3.6
Disease stage				
IIIB	1	20.0	6	10.9
IV	4	80.0	37	67.3
Postoperative recurrence	0	0.0	12	21.8
Treatment line				
Second line	5	100.0	34	61.8
Third line	0	0.0	21	38.2
Previous treatment with docetaxel	1	20.0	20	36.4

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

TABLE 2 Objective response

Best response	***n***	**%**
CR	0	0
PR	4	7.3
SD	26	47.3
PD	24	43.6
NE	1	1.8
Response rate	**%**	**[95% CI]**
ORR	7.3	[2.0–17.6]
DCR	54.5	[40.6–68.0]

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; ORR, overall response rate; DCR, disease control rate; CI, confidence interval.

TABLE 3 Subanalysis of ORR and DCR

	No. of pts ($n = 55$)	ORR	[95% CI]	DCR	[95% CI]
Previous docetaxel treatment					
Yes	20	5.0	[0.1–24.8]	45.0	[23.1–68.4]
No	35	8.5	[1.8–23.1]	60.0	[42.1–76.1]
Treatment line					
Second line	34	8.8	[1.9–23.7]	61.8	[43.6–77.8]
Third line	21	4.7	[0.1–23.8]	42.9	[21.8–66.0]
Histology					
Nonsquamous	38	10.5	[2.9–24.8]	63.2	[46.0–78.2]
Squamous	17	0	[0–19.5]	35.3	[14.2–61.7]

Abbreviations: ORR, overall response rate; DCR, disease control rate; CI, confidence interval.

(16.4%) reduced the dose of nab-PTX. The median dose intensity (DI) was 62.5 mg/m^2 per week and the median relative DI (RDI) was 83.3%.

3.4 | Safety

All 55 patients enrolled in the study treatment were eligible for safety analysis. The major treatment-related toxicities are presented in Tables 4 and 5. The major nonhematologic toxicities (total/grade 3 or more) were peripheral sensory neuropathy (49.1%/1.8%), fatigue (27.3%/0%) and anorexia (27.3%/1.8%). The most frequent treatment-related grade 3 or 4 toxicities were neutropenia (36%), febrile neutropenia (5.5%) and pulmonary infection (3.6%). Five patients (9.1%) and one patient received granulocyte-colony-stimulating factor support and erythrocyte transfusion, respectively. Seven patients (13%) discontinued the study treatment because of grade 2 pneumonitis ($n = 3$), grade 3 AST/ALT elevation ($n = 1$), grade 4 sepsis ($n = 1$), grade 3 anorexia ($n = 1$) and grade 5 adult respiratory distress syndrome (ARDS) ($n = 1$).

Two deaths (3.6%) were observed during the protocol study. One patient developed grade 5 ARDS on day 26 of the second cycle.

TABLE 4 Treatment-related adverse events in phase II of the trial

Adverse event	Total (%)	Grade 3 or above (%)
	General	
Peripheral sensory neuropathy	49.1	1.8
Fatigue	27.3	0.0
Anorexia	27.3	1.8
Nausea	12.7	0.0
Myalgia	12.7	0.0
Peripheral motor neuropathy	9.1	1.8
Arthralgia	7.3	0.0
Vomiting	5.5	1.8
Pneumonitis	5.5	0.0
Febrile neutropenia	5.5	5.5
Pulmonary infection	3.6	3.6
Diarrhea	3.6	1.8
Sepsis	1.8	1.8
ARDS	1.8	1.8

Abbreviation: ARDS, adult respiratory distress syndrome.

TABLE 5 Treatment-related adverse events in phase II of the trial

Adverse event	Grade 3 or above (%)
Hematologic	
Neutropenia	36.4
Anemia	1.8
Thrombocytopenia	0.0
Biochemical	
Blood bilirubin increased	1.8
AST/ALT elevation	1.8
Hyponatremia	1.8
Hypokalemia	1.8

Abbreviations: ALT, alanine amino transferase; AST, aspartate amino transferase.

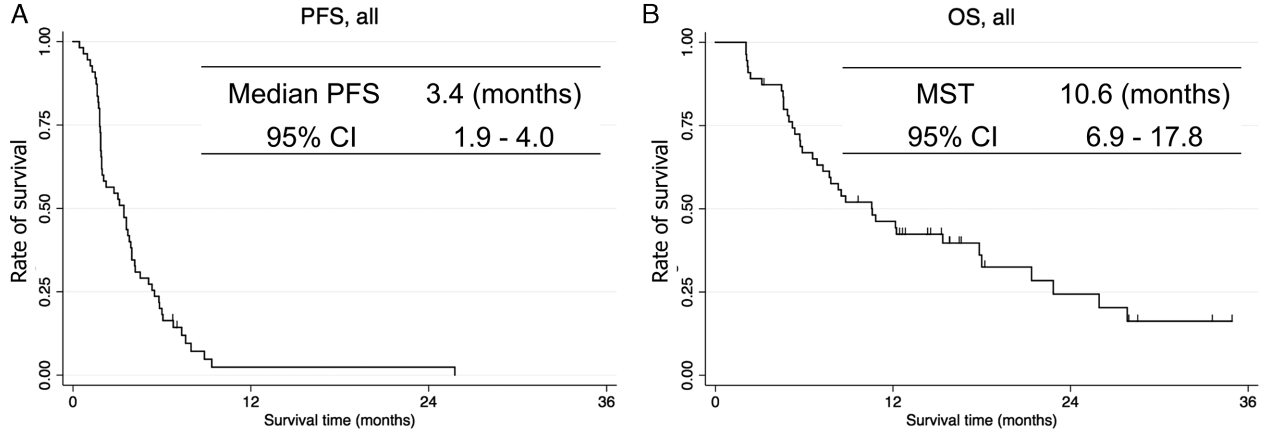

FIGURE 1 Progression-free survival and overall survival
Progression-free survival curve (A) and overall survival curve (B)
Abbreviations: PFS, progression-free survival; CI, confidence interval; OS, overall survival; MST, median survival time

TABLE 6 The treatment response and survival benefit

Author	*n*	Age, median (range)	Dose	ORR (%)	DCR (%)	mPFS [95% CI]	MST [95% CI]
Sakata et al.[3]	41	68	100 mg/m^2	31.7	65.9	4.9	11
		(43–77)	Q3w, days 1, 8 and 15			[2.4–7.4]	
Hu et al.[12]	56	59.6	100 mg/m^2	16.1	51.7	3.5	6.8
		(32–83)	Q4w, days 1, 8 and 15			[1.9–5.8]	[4.7–9.3]
Liu et al.[11]	55	52.5	150 mg/m^2	14.5	65.5	4.9	11
		(29–74)	Q3w, days 1 and 8			[2.4–7.4]	
Present study	55	66	100 mg/m^2	7.3	54.5	3.4	10.6
		(41–90)	Q4w, days 1, 8 and 15			[1.9–4.0]	[6.9–17.8]

Abbreviations: ORR, objective response rate; DCR, disease control rate; MST, median survival time; mPFS, median progression-free survival; CI, confidence interval.

Considering that the patient had increasing bilateral pleural effusion and exacerbation of dyspnea on day 1 of the second cycle and home oxygen therapy was introduced, his cancer may have progressed after the first cycle. Nevertheless, the patient received 2 mg oral dexamethasone to treat dyspnea, which was an inhibited agent in this protocol and the second treatment cycle was started. This case was considered to deviate from the study protocol. This deviation may have caused the patient's death. Thus, we considered this patient's demise to be probably a nab-PTX treatment-related death. The other patient died on day 10 of the fourth cycle, two days after day 8 of nab-PTX administration. Loss of consciousness occurred as the patient was going to the toilet at his home on day 9. He vomited, and subsequently experienced a cardiac arrest. In this case, AEs of nausea, vomiting and loss of appetite had not yet been reported. Despite emergency cardiopulmonary resuscitation, the patient died the next day. Computed tomography imaging of the head revealed no evidence of cerebral bleeding or infarction. Although grade 4 vomiting in this case was considered to be possibly related to nab-PTX treatment, the causal relationship between death and the treatment protocol is unknown.

3.5 | Poststudy chemotherapy

Overall, 70.9% (39/55) patients received subsequent systemic chemotherapy after poststudy treatment. The median number of poststudy treatment lines was one (range: 0–5). Drugs administered to the patients were as follows: nivolumab (30.9%), DOC (18.2%), S1 (12.7%), pemetrexed (10.9%) and vinorelbine (10.9%).

4 | DISCUSSION

We performed a prospective, multicenter phase I/II study of weekly nab-PTX therapy in patients with advanced NSCLC without *EGFR* mutations or *ALK* rearrangement who were previously treated with platinum-doublet chemotherapy. Although the level −1 schedule was not investigated in phase I, the proportion of AEs as the cause of discontinuation of therapy and dose reduction in phase II was 9/55 (16.4%) and 7/55 (13%) patients, respectively. The incidence of non-hematologic toxicities of grade ≥3 with the level −1 schedule was < 5%, except for febrile neutropenia (5.5%). Hematological toxicity was mild, with an incidence of 36.4% for grade ≥3 neutropenia. In contrast, the incidence of grade ≥3 neutropenia was 90.1% and that of febrile neutropenia was 19.1% in the DOC arm of phase III studies in previously treated Japanese patients with advanced NSCLC.[10] Considering these factors, the level −1 schedule was feasible and appropriate in this setting.

Although patients with histology of non-Sq tended to have better ORR in subanalysis, the experimental regimen yielded an ORR of 7.3% (95% CI, 2.0–17.6%) in total, which did not meet the primary endpoint of the study. In other clinical trials involving *EGFR*-mutated NSCLC patients, ORR was 14.5–31.7%, indicating good efficacy.[3,11,12] In the KTOSG trial 1301, indicating the proportion of cases with *EGFR* mutations, 56.1% patients had wild-type *EGFR* mutations, but the effectiveness analysis with or without *EGFR* mutation has not yet been investigated.[3] Although this may not be the only reason for the low ORR obtained in this study, targeting only wild-type *EGFR* patients may have resulted in this outcome.

In this study, the median DI was 62.5 mg/m^2/week. This value was 89.1 mg/m^2/week in the KTOSG trial 1301. The low DI may be one of the reasons for low ORR in our study. Although the prescribed DI was 75 mg/m^2/week, skipping treatment or dose reduction of nab-PTX may have resulted in the reduction of the RDI to 83.3%. The proportion of patients who skipped nab-PTX treatment on day 15 was 62/194 cycles (31.9%), which may be the main reason for the reduced RDI.

However, DCR, PFS and OS were not lower than those in other trials, where patients with *EGFR* mutation were included (Table 6).[3,11,12] The argument whether ORR is appropriate to determine the efficiency criteria in second- or third-line treatment is ongoing. Because PFS and OS of patients ≥70 years administered nab-PTX in the CA031 trial tended to be superior to those administered sb-PTX, a phase III trial (ABOUND .70+ trial) was conducted to investigate the efficacy and safety of weekly nab-PTX either continuously or with a 1-week interval, both in combination with carboplatin for patients aged ≥70 years.[13] The study showed that the 1-week break between treatment cycles significantly improved PFS (mPFS was 3.6 and 7.0 months [Hazard Ratio 0.48, $P < 0.0019$]) and ORR (23.9% and 40.3%; $P = 0.0376$). These findings support the safety and efficacy of first-line nab-paclitaxel/carboplatin in elderly patients with advanced NSCLC.

In preclinical data, it was shown that combination therapy with PTX/nab-PTX and angiogenesis inhibitor bevacizumab increased the antitumor effect as compared with PTX/nab-PTX monotherapy.[14] Actually, in advanced gastric cancer, angiogenesis inhibitor ramucirumab + PTX has been statistically significantly prolonged OS compared with PTX alone as a secondary treatment in patients who progressed after platinum-containing chemotherapy, and it is regarded as standard treatment.[15] In the future, it might be necessary to verify the effectiveness and safety of combination therapy of nab-PTX and angiogenesis inhibitor as a second-line chemotherapy in NSCLC.

This study failed to meet predefined primary endpoints for patients with advanced NSCLC, although the PFS and OS were comparable with those in previous reports and toxicity was acceptable. The weekly nab-PTX was not a promising treatment for NSCLC patients without *EGFR* or *ALK* mutations as a second- or third-line treatment setting.

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