

Phase I Study of Weekly Nab-Paclitaxel Plus Carboplatin And Concurrent Thoracic Radiotherapy in Elderly Patients with Unresectable Locally Advanced Non-Small-Cell Lung Cancer

Shota Omori

Shizuoka Cancer Center: Shizuoka Kenritsu Shizuoka Gan Center

Hideyuki Harada

Shizuoka Cancer Center: Shizuoka Kenritsu Shizuoka Gan Center

Keita Mori

Shizuoka Cancer Center: Shizuoka Kenritsu Shizuoka Gan Center

Yasushi Hisamatsu

Oita Prefectural Hospital: Oita Kenritsu Byoin

Yuko Tsuboguchi

Osaka City General Hospital: Osaka Shiritsu Sogo Iryo Center

Hiroshige Yoshioka

Kansai Medical University Hospital

Ryotaro Morinaga

Oita Prefectural Hospital: Oita Kenritsu Byoin

Haruko Daga

Osaka City General Hospital: Osaka Shiritsu Sogo Iryo Center

Takayasu Kurata

Kansai Medical University Hospital

Toshiaki Takahashi (✉ t.takahashi@scchr.jp)

Shizuoka Cancer Center <https://orcid.org/0000-0002-8188-2505>

Research Article

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Abstract

Few clinical studies have been designed for elderly patients with locally advanced non-small cell lung cancer (NSCLC). We conducted a phase I study to evaluate the tolerability of carboplatin/nab-paclitaxel and concurrent thoracic radiotherapy in elderly patients with locally advanced NSCLC. The eligibility criteria were: unresectable stage III NSCLC, performance status 0 or 1, and age ≥ 75 years. Eligible patients received 6 weeks of weekly carboplatin/nab-paclitaxel and concurrent thoracic radiotherapy with a total dose of 64 Gy in 32 fractions. Carboplatin was fixed to an area under the plasma concentration time curve (AUC) of 2 mg/mL/min, and the recommended dose of nab-paclitaxel was evaluated using a dose-escalation study (30 or 40 mg/m²). Tolerability at the recommended dose was evaluated in an expansion study. Nineteen patients were enrolled at four institutions, all of whom were eligible and assessable. The recommended nab-paclitaxel dose was set at 30 mg/m² because two patients experienced dose-limiting toxicity at 40 mg/m². The treatment completion rate of the 17 patients analyzed at the recommended dose was 100% (80% confidence interval (CI), 83.8–100%). The overall response rate was 76.5%, and the median progression free survival was 13.4 months (95% CI, 4.2–21.4 months). Common grade 3 and 4 toxicities included leukopenia (23.5%), neutropenia (17.6%), anemia (5.9%), and infection (5.9%). One treatment-related death due to pneumonitis was observed six months after the end of the study. In conclusion, carboplatin/nab-paclitaxel and concurrent thoracic radiotherapy show good tolerability and exhibit promising efficacy in elderly patients with locally advanced NSCLC. This trial was registered with the Japan Registry of Clinical Trials on March 11, 2019 (trial no. jRCTs042180077).

Introduction

Despite recent breakthroughs in therapy, lung cancer remains the leading cause of cancer-related deaths in Japan and around the world. Lung cancer caused approximately 74,300 deaths in Japan in 2018 [1] and 1.9 million deaths worldwide in 2017 [2], and the numbers are still increasing. Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of all lung cancer cases. Stage III NSCLC, also called locally advanced NSCLC, accounts for 15% of all lung cancer cases [1]. The standard treatment for patients with unresectable locally advanced NSCLC is definitive concurrent chemoradiotherapy. Based on the results of the PACIFIC trial, which demonstrated the efficacy of durvalumab after concurrent chemoradiotherapy, 12 months of durvalumab maintenance therapy has been considered for patients without disease progression [3]. In Japan, based on a randomized controlled trial conducted by the Japan Clinical Oncology Group (JCOG0301), low-dose carboplatin and concurrent thoracic radiotherapy are the standard treatment for elderly patients with unresectable locally advanced NSCLC [4]. However, this combined therapy requires 20 daily infusions of carboplatin, which is complicated and not widely used in Japanese clinical practice because of the increasing burden on the patient and limited health-care resources, including limited availability of hospital beds in the chemotherapy ward. Instead, weekly administrations of carboplatin/paclitaxel, which are more convenient, are often used in combination with thoracic radiotherapy in elderly patients. However, although weekly carboplatin/paclitaxel plus concurrent

radiotherapy showed acceptable efficacy and good safety in a randomized phase III study in non-elderly patients (75 years of age or younger) with locally advanced NSCLC [5], there are no prospective studies on this treatment in elderly patients with locally advanced NSCLC.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a cremophor-free formulation of paclitaxel with improved solubility and intratumor drug delivery [6]. In a phase III study, carboplatin/nab-paclitaxel showed a significantly higher objective response rate than carboplatin/paclitaxel in advanced NSCLC [7]. In addition, a preclinical study has shown that nab-paclitaxel is a more effective radiosensitizer than paclitaxel [8]. Based on these findings, we conducted a phase I study of carboplatin/nab-paclitaxel and concurrent thoracic radiotherapy to determine the recommended dose (RD) and to evaluate the tolerability and efficacy of this treatment in elderly patients with locally advanced NSCLC.

Materials And Methods

Clinical study design

This study was a multicenter, open-label, single-arm, prospective, phase I study that combined dose escalation and expansion to evaluate treatment tolerability, safety, and efficacy. This study was performed in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the institutional ethics committees of the participating institutes. As the Clinical Trials Act was revised during this clinical trial, this study was reviewed and approved by the certified review board of Shizuoka Cancer Center. All patients provided written informed consent prior to enrollment. The study was registered with the University Hospital Medical Information Network in Japan (UMIN 000014764) and the Japan Registry of Clinical Trials (jRCTs042180077).

Patient eligibility

Elderly patients with unresectable stage III NSCLC were eligible for this study. The eligibility criteria were as follows: (1) cytologically or histologically confirmed NSCLC; (2) clinical stage III (based on the 7th edition of the International Union for Cancer Control TNM classification [9]) and unresectable locally advanced tumor; (3) curative radiotherapy was feasible (including percent lung volume receiving at least 20 Gy [V20] \leq 35%, no contralateral hilar lymph node metastasis, no associated separate tumor nodule in the same lobe as the primary, no atelectasis of unilateral whole lung); (4) no prior chemotherapy or thoracic radiotherapy; (5) at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST ver1.1) [10]; (6) age \geq 75 years; (7) Eastern Cooperative Oncology Group performance status (ECOG-PS) score 0–1; (8) sufficient function of major internal organs (lung: a blood gas oxygen level in room air of \geq 70 torr; bone marrow: a neutrophil count of \geq 1,500/mm³, a hemoglobin content of \geq 9.0 g/dL, a platelet count of \geq 100,000/mm³; liver: aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels of \leq 100 IU/mL, a total bilirubin concentration of \leq 1.5 mg/dL; kidneys: a creatinine concentration of \leq 1.2 mg/dL); (9) life expectancy of at least 90 days. All eligible patients underwent computed tomography (CT) scans of the thorax and abdomen within 28 days before

enrollment. Brain CT, magnetic resonance imaging, and positron emission tomography were performed within 42 days before enrollment. Patients who had active concomitant malignancy or radiographically confirmed interstitial pneumonia, active severe infection, or other serious comorbidities were excluded.

Treatment plan

Chemotherapy schedule

All patients received nab-paclitaxel and carboplatin weekly for 6 weeks (Fig. 1). Carboplatin was administered at a fixed area under the plasma concentration time curve (AUC) dose of 2 mg/mL/min via intravenous infusion for 60 min on days 1, 8, 15, 22, 29, and 36, and nab-paclitaxel was administered at a dose of 30 mg/m² (dose level 1) or 40 mg/m² (dose level 2) via intravenous infusion for 60 min on days 1, 8, 15, 22, 29, and 36. For chemotherapy administration, patients had to meet the following criteria: ECOG-PS 0–1, no fever suggestive of infection, no interruption of radiation therapy, a neutrophil count of $\geq 1,000/\text{mm}^3$, a platelet count of $\geq 75,000/\text{mm}^3$; a creatinine concentration of ≤ 1.2 mg/dL, and other non-hematologic toxicities of grade ≤ 2 except for electrolyte abnormalities without clinical symptoms.

Radiotherapy

All patients received linear accelerator photon beam radiation at 6–10 MV from day 1 onwards. The primary tumor and involved lymph nodes received 64 Gy in 2-Gy fractions over 6.5 weeks. Three-dimensional treatment planning systems were used in this study. The gross tumor volume (GTV) was delineated according to the primary tumor and any regional nodal involvement determined from CT and PET/CT information. The clinical target volume (CTV) was defined and contoured to 5–10 mm around the GTV. The planning target volume (PTV) included CTV plus a margin of ≥ 5 mm. Elective nodal irradiation was not performed in this study. Beam shaping was accomplished using a multileaf collimator. The dose was prescribed to the isocenter. Per-protocol PTV coverage was achieved when more than 95% of the PTV received 93% or more of the prescribed dose and when minimum margin values for both CTV and PTV were achieved. Normal tissue dosimetric constraints were as follows: maximum spinal cord dose was 52 Gy and 1 cc dose was 48 Gy; normal lung volume irradiated with ≥ 20 Gy was 35% of total lung volume minus GTV. The dose was calculated using heterogeneity correction. Intensity-modulated radiation therapy was not acceptable in this study. If any of the following interruption criteria were met, thoracic radiotherapy was interrupted: a neutrophil count of $< 500/\text{mm}^3$, a platelet count of $< 25,000/\text{mm}^3$, fever of $\geq 38^\circ\text{C}$ suggesting infection, grade 3 or 4 esophagitis or dermatitis, or any grade of pneumonitis.

Dose modification

Dose-limiting toxicity (DLT) was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. DLT was evaluated from day 1 to day 90 and included non-hematologic toxicities of grade 4, non-hematologic toxicities of grade 3 lasting for 3 days or longer that did not improve with proper supportive care (excluding laboratory abnormalities without

clinical symptoms), neutropenia of grade 4 lasting 8 days or more, febrile neutropenia, thrombocytopenia of grade 4 (or thrombocytopenia of grade 3 requiring platelet transfusion), skipping chemotherapy more than once, incompleteness of radiotherapy by day 58, pneumonitis of grade 2 during study treatment, or pneumonitis of grade 3 after study treatment. At least three patients were enrolled at each dose level. First, three patients received dose level 1 (nab-paclitaxel 30 mg/m²), and no inpatient dose escalation was allowed. If a DLT was observed in these first three patients, three more patients were enrolled at this dose level and dose escalation to the next dose level continued if less than three out of six patients experienced a DLT. The maximum tolerated dose (MTD) was defined as the level before the one at which a DLT was observed in two out of three or three out of six patients. The RD was defined as the level below the MTD. If the MTD was not reached by dose level 2, this level was considered the RD.

Evaluation of efficacy and safety

All eligible patients underwent complete blood cell count, blood chemistry test, and chest X-ray once a week during the study period. CT was performed every 6–12 weeks during the first year and every 12–24 weeks thereafter. All responses were defined according to RECIST version 1.1. Progression-free survival (PFS) was defined as the time from enrollment to the date of confirmation of progressive disease or the date of death from any cause (whichever occurred earlier). Overall survival (OS) was defined as the time from enrollment until death from any cause. Toxicity was assessed according to NCI-CTCAE version 4.0.

Statistical analysis

The primary endpoint of the dose expansion study was the treatment completion rate. Treatment completion was defined as the receipt of at least five doses of nab-paclitaxel plus carboplatin and 64 Gy of thoracic radiotherapy within 58 days from the start of treatment. We considered tolerability and safety to be the most important aspects for elderly Japanese patients because severe lung toxicities have been reported in these patients [11, 12]. In addition, we considered that the regimen to be effective if the tolerability was the same as that of carboplatin/paclitaxel in non-elderly patients with locally advanced NSCLC [5].

Based on the results of a previous comparative phase III study using carboplatin/paclitaxel in non-elderly patients [5], the expected treatment completion rate for the present study was assumed to be 85%, with 60% set as the lower limit of interest. Based on this assumption, the study was designed to have a power of 90% and a one-sided alpha error of 0.10, resulting in a requirement of 20 patients. However, because patient enrollment was slower than planned, we changed the power from 90–80% after the start of the study. Consequently, the required number of patients was 14, and the planned number of registrations was 15. The expansion study included patients from the dose-escalation study treated at the RD. Secondary endpoints of the expansion study were the response rate, PFS, OS, 2-year survival rate, location of progression, and safety. PFS and OS were estimated using the Kaplan–Meier method. All statistical analyses were performed using JMP 10 for Windows (SAS Institute Inc., Cary, NC, USA) and R4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Post-study treatment

Initially, the enrolled patients were followed up without anticancer treatment after the end of the study. However, as durvalumab was approved as a maintenance therapy for locally advanced NSCLC patients who were treated with platinum-based definitive chemoradiotherapy and had no disease progression after chemoradiotherapy, durvalumab maintenance therapy after study treatment was allowed since February 2019.

Results

Dose-escalation study

Between July 2014 and December 2016, eight patients, all of whom were eligible and assessable, were enrolled in the dose-escalation study (Fig. 2). Their baseline characteristics were as follows. The median age was 82.5 years (range, 75–88 years). All patients were male, and six of them were previous or current smokers. Six of these patients had an ECOG-PS score of 0, and four had stage IIIA. Five of the patients were diagnosed with adenocarcinoma, two with squamous cell carcinoma, and one with other non-small cell carcinoma. DLT was not observed in the first three patients treated at dose level 1 (nab-paclitaxel, 30 mg/m²). At dose level 2 (nab-paclitaxel, 40 mg/m²), both enrolled patients experienced DLT: a 79-year-old male patient experienced a grade 3 lung infection, and an 88-year-old male patient experienced grade 3 pneumonitis. The additional three patients enrolled at dose level 1 did not experience DLT. Therefore, we determined that dose level 2 was the MTD, and dose level 1 (nab-paclitaxel, 30 mg/m²) was recommended as the dose for the expansion study (Fig. 2).

Expansion study and patient characteristics

Between May 2017 and December 2018, 11 patients at four institutions, all of whom were eligible and assessable, were enrolled in the expansion study (Fig. 2). In total, 17 patients, including the six patients who had received treatment at the RD in the dose-escalation study, were evaluated for tolerability, safety, and efficacy. The baseline characteristics of the 17 patients are shown in Table 1. The median age was 81 years (range, 75–86 years). Fifteen (88%) patients were male, and 13 (76%) were previous or current smokers. Ten (59%) of these patients had an ECOG-PS of 0, and 8 (47%) had stage IIIA (UICC 7th edition). Eleven (65%) patients were diagnosed with adenocarcinoma, four (24%) with squamous cell carcinoma, and two (12%) with other non-small cell carcinoma. Three patients had tumors harboring the L858R mutation in epidermal growth factor receptor (*EGFR*) exon 21, and one patient had deletions in *EGFR* exon 19.

Treatment delivery

Treatment delivery is shown in Table 2. Regarding chemotherapy administration, 65% of the patients received all six cycles, and 100% of the patients completed at least five cycles of weekly nab-paclitaxel plus carboplatin. Full-dose thoracic radiotherapy (64 Gy) was completed in 100% of the patients.

Therefore, the defined treatment completion rate of the 17 patients analyzed at the RD was 100% (80% confidence interval, 83.8–100%). The lower bound of the 80% confidence interval was above the 60% threshold; therefore, the null hypothesis was rejected. Three patients received durvalumab maintenance therapy after the study.

Toxicity

All 17 patients who received treatment at the RD were eligible for safety analysis. Adverse events from days 1 to 90 are shown in Table 3. Common grade 3 and 4 toxicities included leukopenia (23.5%), neutropenia (17.6%), anemia (5.9%), and infection (5.9%). Adverse reactions at a median follow-up period of 15.1 months are shown in Table 4. Grade 3 and 4 toxicities associated with the study treatment were not experienced. One treatment-related death due to pneumonitis was observed six months after the end of the study. The deceased patient was an 82-year-old male, and his V20 value was 32.9%.

Efficacy

On the basis of the investigators' assessment, among the 17 patients who received the study treatment at the RD, 13 patients showed a partial response and none showed a complete response. The overall response rate in all 17 patients was 76.5%. After a median follow-up period of 13.3 months (range, 11.1–16.1 months) for censored cases, the median PFS was 13.4 months (95% CI, 4.2–21.4 months) (Fig. 3). Survival data were immature due to a lack of events (7 at the data cutoff).

Discussion

This was the first prospective phase I study designed to evaluate the tolerability of concurrent chemoradiotherapy with nab-paclitaxel plus carboplatin in elderly patients with unresectable locally advanced NSCLC. In the dose-escalation study, we determined that dose level 2 (nab-paclitaxel, 40 mg/m²) was the MTD, and dose level 1 (nab-paclitaxel, 30 mg/m²) was recommended for the expansion study. In the subsequent expansion study, the treatment completion rate was high (100%) and a promising efficacy at the RD was demonstrated.

Although there was one treatment-related death (out of 17 patients, 5.9%) six months after the end of study treatment, most toxicities were less likely to occur than reported previously in elderly and non-elderly patients with unresectable locally advanced NSCLC (Supplemental Table 1). Notably, carboplatin/nab-paclitaxel plus concurrent radiotherapy was associated with a lower incidence of grade 3 or worse neutropenia and thrombocytopenia than daily low-dose carboplatin plus concurrent radiotherapy, from the results of the JCOG0301 study [4]. Furthermore, chemoradiotherapy with carboplatin/nab-paclitaxel was associated with a lower incidence of grade 3 or worse pneumonitis than carboplatin/S-1 plus concurrent radiotherapy [13]. Kawano et al. reported a suitable safety profile of chemoradiotherapy with nab-paclitaxel at 50 mg/m² and carboplatin AUC of 2 mg/mL/min for non-elderly patients (≤ 74 years) with locally advanced NSCLC, although the recommended doses were different from those in our study [14]. The safety profile of our study is comparable to that reported for

non-elderly patients, and we consider the mild toxicities to have contributed to the high treatment completion rate in our study.

In terms of efficacy, carboplatin/nab-paclitaxel with concurrent thoracic radiotherapy resulted in a response rate of 76.5% and median PFS of 13.4 months (95% CI, 4.2–21.4 months), which are comparable to those in previous studies (Supplemental Table 2). In a previous preclinical study, nab-paclitaxel was shown to be a potent radiosensitizer [8] and to have increased antitumor activity, with fewer adverse effects than paclitaxel [6]. Several recent prospective clinical studies have shown that chemoradiotherapy using carboplatin/nab-paclitaxel is promising for non-elderly patients. In a phase II single-arm study in non-elderly patients with locally advanced NSCLC, Kawano et al. reported a response rate of 76.8% and a PFS of 11.8 months [14]. Based on these findings, nab-paclitaxel has potential as an alternative anticancer drug to paclitaxel for chemoradiotherapy in elderly patients with locally advanced NSCLC. Several prospective studies using another anticancer drug in elderly patients with locally advanced NSCLC have been conducted. However, due to the high incidence of pulmonary toxicities or non-platinum chemotherapy regimen not adapted to durvalumab, neither of these treatments was further developed. In a study using chemoradiotherapy with pemetrexed, although the objective response of the primary endpoint was met with 80.5%, grade 3 or higher pneumonitis was observed in 8 out of 41 patients (19.5%) [12]. Therefore, it was concluded that chemoradiotherapy with pemetrexed should be prescribed to elderly patients with caution. Chemoradiotherapy with vinorelbine was also associated with a high incidence of severe pneumonitis and was therefore not further developed [11]. While good results have been achieved with S-1 chemoradiotherapy, this regimen was not developed as it is platinum-free and durvalumab maintenance therapy is not available [15]. Chemoradiotherapy with carboplatin/S-1 also produced a high incidence of severe pneumonitis and was not further developed [13]. In this context, this study demonstrated an excellent tolerability with less severe lung toxicities in a platinum-combined chemotherapy regimen for which durvalumab maintenance therapy is indicated, demonstrating the potential of this new therapeutic strategy for elderly patients with locally advanced NSCLC.

This study had some potential limitations. First, the study cohort was relatively small, and the statistical power was reduced due to slow recruitment. However, all 17 patients achieved treatment completion; thus, carboplatin/nab-paclitaxel and concurrent thoracic radiotherapy is clearly well tolerated in elderly patients with locally advanced NSCLC. Second, as durvalumab maintenance therapy was not used initially, only a few patients were treated with durvalumab. Data on the efficacy and safety of durvalumab maintenance therapy in the elderly are inadequate, and further investigation is needed.

In conclusion, weekly nab-paclitaxel plus carboplatin combined with concurrent thoracic radiotherapy is associated with a high treatment completion rate and exhibits promising safety and efficacy in elderly patients with locally advanced NSCLC. Based on the study results, a randomized phase III study of chemoradiotherapy for elderly patients with locally advanced NSCLC comparing weekly nab-paclitaxel plus carboplatin with daily carboplatin (JCOG1914) is currently enrolling.

Declarations

Consent for publication:

Not applicable

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and the 1964 Helsinki declaration and its later amendments or with comparable ethical standards. This study was reviewed and approved by the certified review board of Shizuoka Cancer Center and registered with the Japan Registry of Clinical Trials on March 11, 2019 (trial no. jRCTs042180077).

Consent to participate:

All patients provided written informed consent before enrollment.

Conflicts of interest: Shota Omori received honoraria from Taiho-Pharma, Chugai-Pharma, Daiichi-Sankyo, Amgen, AstraZeneca, Ono-Pharma, and Novartis outside the submitted work. Hideyuki Harada received honoraria from AstraZeneca, Chugai-Pharma, Daiichi-Sankyo, Novartis, Eli Lilly, Pfizer and Brain lab outside the submitted work. Hiroshige Yoshioka received honoraria from Taiho-Pharma, Delta-Fly Pharma, Eli Lilly, Chugai-Pharma, AstraZeneca, Ono-Pharma, MSD, Novartis, and Kyowa Hakko Kirin, Daiichi-Sankyo, Nippon Kayaku, Otsuka-Pharma, Pfizer outside the submitted work. Haruko Daga received honoraria from Chugai-Pharma and Ono-Pharma and research funding from AstraZeneca, Chugai-Pharma, and Pfizer outside the submitted work. Takayasu Kurata received honoraria from AstraZeneca, Ono-Pharma, Bristol-Myers Squibb, Chugai-Pharma, Eli Lilly, Boehringer Ingelheim, and MSD research funding from MSD, AstraZeneca, Eli Lilly, Takeda-Pharma, and Ono-Pharma outside the submitted work. Toshiaki Takahashi received honoraria from AstraZeneca, Boehringer Ingelheim, Chugai-Pharma, Eli Lilly, MSD, Ono-Pharma, Roche Diagnostics, and Pfizer, and research funding from AstraZeneca, Boehringer Ingelheim, Chugai-Pharma, Eli Lilly, Ono-Pharma, MSD, and Pfizer, outside the submitted work. The other authors declare no conflict of interests.

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Authors' contributions: Shota Omori: developing the study concept and design, recruitment of patients, writing the manuscript, responsibility for the integrity of the data and accuracy of the data analysis; Hideyuki Harada: developing the study concept and design, recruitment of patients, and reviewing the manuscript; Keita Mori (Primary biostatistician of the study): developing the study concept and design, statistical analysis, and reviewing the manuscript; Yasushi Hisamatsu: recruitment of patients and reviewing the manuscript; Yuko Tsuboguchi: recruitment of patients and reviewing the manuscript; Hiroshige Yoshioka: recruitment of patients and reviewing the manuscript; Ryotaro Morinaga: recruitment of patients and reviewing the manuscript; Haruko Daga: recruitment of patients and reviewing the manuscript; Takayasu Kurata: recruitment of patients and reviewing the manuscript; Toshiaki Takahashi

(Corresponding Author): recruitment of patients, reviewing the manuscript, and supervising this clinical trial.

Availability of data and material: The remaining data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Consent for publication: Not applicable

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Tables

Table 1. Characteristics of patients who received study treatment at the recommended dose.

Table 2. Treatment administered at the recommended dose.

	N = 17	%
Chemotherapy cycles		
<4	0	0%
5	6	35%
6	11	65%
Radiotherapy Completion	17	100%
Treatment Completion*	17	100%

*: Treatment completion was defined as the receipt of at least five doses of chemotherapy and 64 Gy of thoracic radiotherapy within 58 days from the start of treatment.

Age, y	
Median	81
Range	75-86
Sex	
Male	15
Female	2
ECOG Performance Status	
0	10
1	7
Smoking status	
Previous/current	13
Never smoker	4
Histology	
Adenocarcinoma	11
Squamous carcinoma	4
Others	2
Stage at diagnosis (UICC 7 Th)	
IIIA	8
IIIB	9
EGFR mutation status	
Wild type	6
Mutant	4
Unknown	7
Lung V20, %	
Median	23.9
Range	17.0-34.0

Abbreviation: ECOG, Eastern Cooperative Oncology Group; UICC, Union for

Table 3. Adverse events from day 1 to day 90 in patients who received study treatment at the recommended dose.

Toxicity	n = 17					
	Grade					
	Any	1	2	3	4	≥ 3 (%)
Hematologic						
Leukopenia	16	2	10	3	1	4 (23.5%)
Neutropenia	11	3	5	3	0	3 (17.6%)
Anemia	16	11	4	1	0	1 (5.9%)
Thrombocytopenia	10	10	0	0	0	0
Nonhematological						
Anorexia	10	9	1	0	0	0
Nausea	5	4	1	0	0	0
Vomiting	2	2	0	0	0	0
Fatigue	7	5	2	0	0	0
Constipation	12	10	2	0	0	0
Diarrhea	0	0	0	0	0	0
Alopecia	1	1	0	-	-	-
Peripheral sensory neuropathy	1	1	0	0	0	0
Arthralgia	0	0	0	0	-	0
Fever	1	1	0	0	0	0
Infection	1	-	-	1	0	1 (5.9%)
Febrile neutropenia	0	-	-	0	0	0
Radiation dermatitis	16	13	3	0	0	0
Esophagitis	13	7	6	0	0	0
Pneumonitis	7	4	3	0	0	0
AST increased	3	3	0	0	0	0
ALT increased	3	3	0	0	0	0
Creatinine increased	3	2	1	0	0	0
Hyponatremia	7	6	-	1	-	1 (5.9%)

Table 4. Adverse reactions after day 90 in patients who received study treatment at the recommended dose.

Toxicity	Dose level 1 (n = 17)						
	Grade						
	Any	1	2	3	4	5	≥ 3 (%)
Nonhematological							
Radiation dermatitis	6	6	0	0	0	0	0
Esophagitis	4	4	0	0	0	0	0
Myelitis	0	0	0	0	0	0	0
Pneumonitis	17	12	4	0	0	1	1 (5.9%)
Pulmonary fibrosis	0	0	0	0	0	0	0
Cough	2	1	1	0	-	-	0
Dyspnea	1	1	0	0	0	0	0
Tracheal stenosis	0	0	0	0	0	0	0
Myocarditis	0	0	0	0	0	0	0
Pericardial effusion	0	-	0	0	0	0	0
Infection	0	-	-	0	0	0	0

Figures

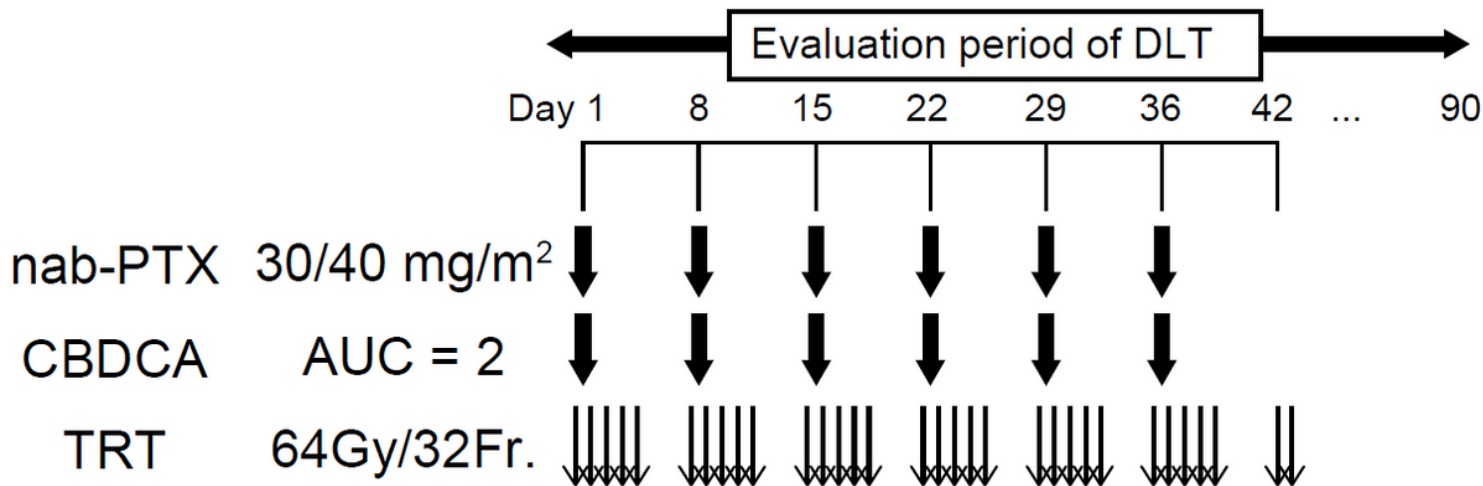
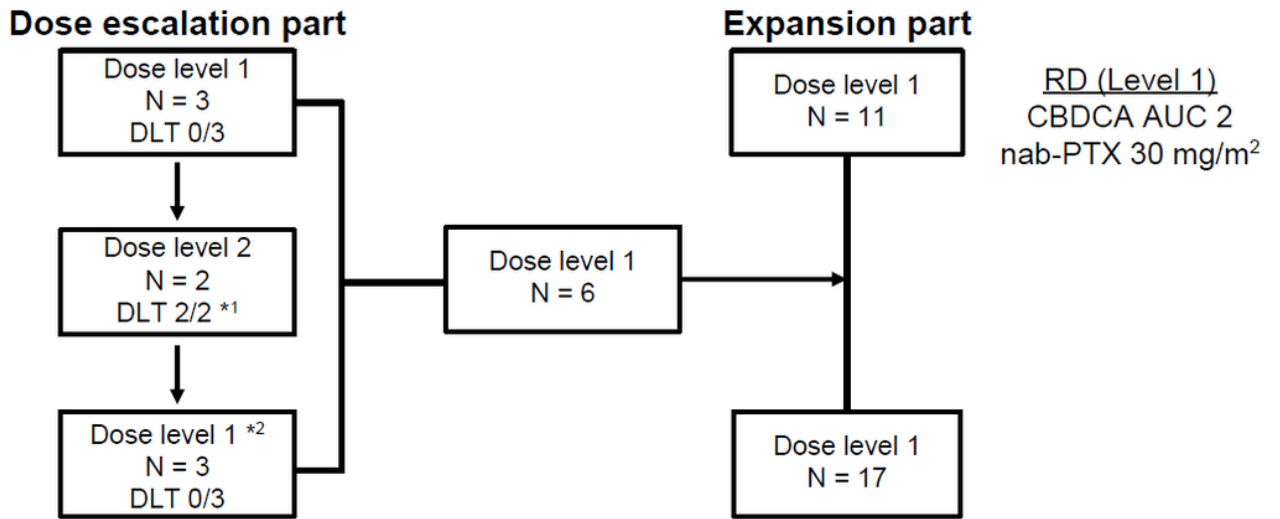


Figure 1

Treatment schema. Patients received nab-paclitaxel (30 or 40 mg/m²) and carboplatin (AUC 2 mg/mL/min) weekly for 6 weeks with concurrent thoracic radiotherapy (64 Gy/32 Fr.). DLT, dose-limiting toxicity; nab-PTX, nab-paclitaxel; CBDCA, carboplatin; AUC, area under the plasma concentration time curve; TRT, thoracic radiotherapy; fr., fraction.



*1: DLT were lung infection of grade 3, and pneumonitis of grade 3
 *2: Additional registration due to DLT occurrence of level 2

Figure 2

Flow chart of participant recruitment. In total, 17 patients, including the six patients who had received treatment at the RD in the dose-escalation study, were evaluated for tolerability, safety, and efficacy. DLT, dose-limiting toxicity; RD, recommended dose.

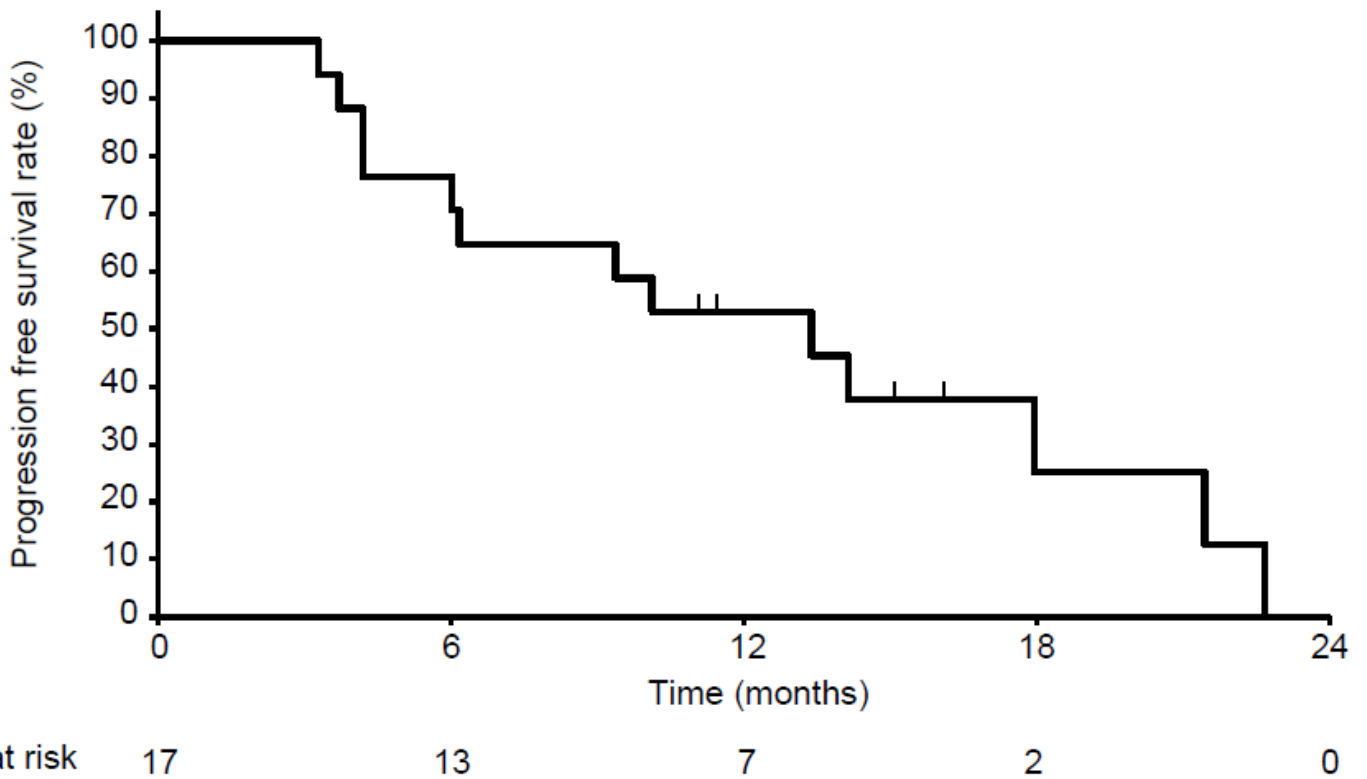


Figure 3

Kaplan–Meier plot of progression-free survival of 17 patients treated with the recommended dose of the study treatment. The median progression-free survival was 13.4 months (95% confidence interval, 4.2–

21.4 months)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalTableselderyCRTP12021.0508SO.docx](#)