Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online March 28, 2014

DOI: 10.1634/theoncologist.2013-0411

Title: Randomized Phase II Trial Comparing Carboplatin Plus Weekly Paclitaxel and Docetaxel Alone in Elderly Patients With Advanced Non-Small Cell Lung Cancer: North Japan Lung Cancer Group Trial 0801

Authors: Makoto Maemondo,[a] Akira Inoue,[b] Shunichi Sugawara,[c] Toshiyuki Harada,[d] Yuji Minegishi,[e] Kazuhiro Usui,[f] Koji Miwa,[g] Naoto Morikawa,[h] Mariko Kambe,[i] Kenji Ube,[j] Kana Watanabe,[a] Osamu Ishimoto,[c] Tomohiro Sakakibara,[b] Akihiko Gemma,[e] Toshihiro Nukiwa[k]

[a]Miyagi Cancer Center, Natori, Japan; [b]Tohoku University Hospital, Sendai, Japan; [c]Sendai Kousei Hospital, Sendai, Japan; [d]Hokkaido Social Insurance Hospital, Sapporo, Japan; [e]Nippon Medical School, Tokyo, Japan; [f]NTT Medical Center Tokyo, Tokyo, Japan; [g]Tsuboi Cancer Center Hospital, Kooriyama, Japan; [h]Iwate Medical University School of Medicine, Morioka, Japan; [i]Senseki Hospital, Higashimatsushima, Japan; [j]Iwate Prefectural Central Hospital, Morioka, Japan; [k]South Miyagi Medical Center, Miyagi, Japan

UMIN-CTR Identifier: UMIN000002616

Sponsor(s): Self-funding

Principal Investigator: Makoto Maemondo

IRB Approved: Yes

Disclosures

Akira Inoue: AstraZeneca, Eli Lilly, Chugai (H, uncompensated). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

Standard first-line chemotherapy for elderly non-small cell lung cancer (NSCLC) patients has been monotherapy with vinorelbine or gemcitabine. Docetaxel has also been considered as an alternative option for the elderly population in Japan. We have previously demonstrated the high efficacy of carboplatin plus weekly paclitaxel for elderly NSCLC patients. Consequently, we conducted a randomized phase II study to select the proper regimen for a future phase III trial.

Methods

Eligible patients were aged 70 years or older with newly diagnosed advanced NSCLC. Patients were randomly assigned either to a combination of carboplatin (area under the curve: 6 mg/mL per minute) with weekly paclitaxel (70 mg/m^2) (CP regimen) or to single-agent docetaxel (60 mg/m^2). The primary endpoint of this study was objective response rate. Secondary endpoints were progression-free survival, overall survival, and toxicity profile.

Results

Among 83 eligible patients (41 to CP, 42 to docetaxel), the objective response rates were 54% (95% confidence interval: 39%–69%) and 24% (95% confidence interval: 11%–37%) and median progression-free survival was 6.6 months and 3.5 months in the CP arm and the docetaxel arm, respectively. Severe neutropenia, febrile neutropenia, and nausea were

significantly frequent in the docetaxel arm, whereas toxicities in the CP arm were generally moderate. One treatment-related death was observed in the docetaxel arm.

Conclusion

The CP regimen achieved higher activity with less toxicity than single-agent docetaxel. Considering the results of this phase II trial and the IFCT-0501 trial, we have selected the CP regimen for a future phase III trial in elderly patients with advanced NSCLC.

Discussion

The objective response rate (ORR) of carboplatin (area under the plasma curve: 6 mg/mL per minute) with weekly paclitaxel (70 mg/m^2) (CP regimen) met the primary endpoint of this study, achieving a higher response rate than single-agent docetaxel in this population of elderly patients with non-small cell lung cancer (NSCLC). In addition, the CP regimen achieved longer progression-free survival with less toxicity excluding moderate anemia and thrombocytopenia in comparison with docetaxel. Consequently, we have selected the CP regimen as a candidate for a future phase III trial.

Although monotherapy with third-generation agents has been regarded as the preferred treatment option for elderly patients with NSCLC [1–6], Quoix et al. recently reported the results of IFCT-0501, a phase III study comparing a similar CP regimen (carboplatin [area under the plasma curve: 6 mg/mL per minute] plus weekly paclitaxel at 90 mg/m^2) with monotherapy with either vinorelbine or gemcitabine in an elderly population [7]. IFCT-0501 demonstrated significant superiority to the CP regimen in terms of the efficacy (ORR and overall survival); however, severe toxicity in the CP arm, including a treatment-related death (TRD) rate of 4.4%, was of concern. The dose of paclitaxel in the current study was 70 mg/m^2, and this could explain the lower toxicity of CP. No TRDs have been observed in the CP arm of this study or in our previous study using the same regimen.

Regarding the efficacy of CP, the ORR and progression-free survival in this study (54% and 6.6 months) are consistent with results achieved with the same regimen in our previous study (55% and 6.0 months) [8]. Because the evaluation of response in this study was performed by centralized review blinded as to the treatment, we believe the results were not biased. Furthermore, the ORR of the docetaxel arm in this study (24%) was quite consistent with previous results achieved with docetaxel in Japanese phase III trials with elderly NSCLC patients (23% in WJTOG9904 and 25% in JCOG0802) [6, 9]. Importantly, the rate of febrile neutropenia, an independent and poor prognostic factor in elderly NSCLC patients receiving chemotherapy, has been consistently high ($>$10%) in the docetaxel arm in the current study and in previous Japanese studies. In addition, one TRD was observed in the docetaxel arm in this study. All of these observations suggest that monotherapy with docetaxel might be more toxic than CP for elderly patients.

Trial Information

Disease:	Lung cancer – NSCLC
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	None
Type of study - 1:	Phase II
Type of study - 2:	Randomized
Primary Endpoint:	Objective Response Rate
Secondary Endpoint:	Progression Free Survival
Secondary Endpoint:	Overall Survival
Investigator's Analysis:	Active and should be pursued further

Drug Information

Drug 1: **Generic/Working name:**	Carboplatin
Drug class:	Platinum compound
Dose:	AUC 6.0 per
Route:	IV
Schedule of Administration:	day 1, every 4 weeks

Drug 2: **Generic/Working name:**	paclitaxel
Drug class:	Tubulin / Microtubules targeting agent
Dose:	70 mg (mg) per squared meter (m2)
Route:	IV
Schedule of Administration:	day1, 8, and 15, every 4 weeks
Drug 3: **Generic/Working name:**	docetaxel
Drug class:	Tubulin / Microtubules targeting agent
Dose:	60 mg (mg) per squared meter (m2)
Route:	IV
Schedule of Administration:	every 3 weeks

Patient Characteristics

Number of patients, male:	62
Number of patients, female:	21
Stage:	Stage III 16, IV 60, postoperative recurrence 7
Age:	Median (range): 76 (70-87)
Number of prior systemic therapies:	Median (range): 0
Performance Status:	ECOG 0 — 38 1 — 45 2 — 0 3 — 0 unknown — 0
Other:	Not Collected

Primary Assessment Method

Control Arm: Non-small cell lung cancer

Number of patients screened:	42
Number of patients enrolled:	42
Number of patients evaluable for toxicity:	42
Number of patients evaluated for efficacy:	42
Response assessment CR:	0%
Response assessment PR:	24%
Response assessment SD:	48%
Response assessment PD:	21%
Response assessment other:	7%
(Median) duration assessments PFS	3.5 months, CI: 2.5-4.6
(Median) duration assessments OS	11.8 months, CI: 6.5-17.1
Experimental Arm: Total Patient Population	
Evaluation method:	Other
Control Arm: Total Patient Population	
Evaluation method:	Other

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades
*No Change from Baseline/No Adverse Event							
Neutrophils/granulocytes (ANC/AGC)	0%	2%	22%	30%	44%	0%	100%

Regarding hematologic toxicity, the incidence of anemia and thrombocytopenia were slightly higher in the CP arm, although that of neutropenia and febrile neutropenia were significantly higher in the docetaxel arm. As to nonhematological toxicity, severe intestinal toxicity is more common in the docetaxel arm than the CP arm. Neurotoxicity in the CP arm was not severe. The total incidence of severe nonhematologic toxicities was higher in the docetaxel arm than the CP arm. One TRD due to neutropenia, pneumonia, and lethal arrhythmia was observed in the docetaxel arm.

Serious Adverse Events

Name	Grade	Attribution
neutropenia, pneumonia, and lethal arrhythmia	5	Probable

Assessment, Analysis, and Discussion

Completion: Study completed

Pharmacokinetics / Pharmacodynamics: Not Collected

Investigator's Assessment: Active and should be pursued further

Discussion

The objective response rate (ORR) of the current CP regimen was 54% (95% confidence interval: 39%–69%), which met the primary endpoint of this study. By comparison, the ORR of docetaxel was 24% (95% confidence interval: 11%–37%). In comparison with docetaxel, the CP regimen achieved longer PFS with less toxicity, excluding moderate anemia and thrombocytopenia. From these results, we have selected the CP regimen as a candidate in a future phase III trial for the elderly NSCLC population.

Although therapeutic recommendations are undergoing a re-evaluation, first-line chemotherapy for elderly patients with NSCLC has usually been monotherapy with agents such as vinorelbine or gemcitabine [1–6]. However, Quoix et al. recently reported the results of IFCT-0501, a phase III study comparing a similar CP regimen (with a carboplatin dose of area under the plasma curve of 6 mg/mL per minute on day 1 and paclitaxel at 90 mg/m^2 on days 1, 8, and 15 of each 4-week cycle) to monotherapy with vinorelbine or gemcitabine in elderly patients with a diagnosis of NSCLC. CP demonstrated a significant superiority in terms of efficacy (ORR and overall survival) [7]; however, severe toxicity in the CP arm, including a TRD rate of 4.4%, was of concern. Guided by our previous studies, we chose a paclitaxel dose of 70 mg/m^2 [8, 10], and this may be responsible for the lower toxicity observed with CP. TRDs were not observed in the CP arm in this study or in our previous study using the same regimen.

Regarding the efficacy of CP, the ORR and PFS in this study (54% and 6.6 months) are consistent with the results using the same regimen in our previous study (55% and 6.0 months) [8]. Because the evaluation of response in this study was performed by a centralized review blinded to the treatment, we believe the results were not biased. In fact, the ORR of docetaxel in this study (24%) was consistent with previous results using docetaxel in Japanese phase III trials for elderly NSCLC patients (23% in WJTOG9904 and 25% in JCOG0802) [6, 9]. Furthermore, despite patients in docetaxel arm receiving more subsequent chemotherapy, including a platinum doublet after their protocol treatment, the overall survival was still shorter than that of patients in the CP arm, suggesting that the most active regimen should be administered first. In addition, although the survival data of the CP arm in this study was much better than that achieved in IFCT-1501, a similar survival difference has also been observed in previous studies comparing Japanese patients with Western patients treated with the same chemotherapy regimen [11–13]. Because the efficacy of the carboplatin-based doublet was significantly superior to monotherapy in both IFCT-1501 and the current study, we believe elderly NSCLC patients with good performance status should be treated with proper doublet regimens as a standard of care.

Regarding toxicities due to paclitaxel, severe peripheral neuropathy is of the most concern. Ramalingam has reported the results in an elderly subgroup with advanced NSCLC from a previous phase III study that compared weekly paclitaxel (100 mg/m^2) with the standard 3-week paclitaxel (225 mg/m^2) schedule, both combined with carboplatin (area under the plasma curve: 6 mg/mL per minute). In this report, neurotoxicity of grade 3 or higher was lower in the weekly arm (9.5% in the standard arm vs. 5.5% in the weekly arm) [14]. Furthermore, nab-paclitaxel was recently approved for advanced NSCLC with a similar weekly schedule

that also showed a significantly lower rate of neurotoxicity compared with paclitaxel with the 3-week schedule, suggesting weekly administration may represent one approach to overcome the neurotoxicity related to paclitaxel. We chose a paclitaxel dose of 70 mg/m^2 based on our previous study because we had observed a favorable toxicity profile (greater than grade 3 neuropathy was 0%–3%) [8, 10]. We believe that the dose chosen for this study was appropriate for elderly NSCLC patients.

Other toxicities, including myelosuppression, grade 3 or higher neutropenia, neutropenic fever, and grade 3 or higher intestinal toxicities, were more common in the docetaxel arm, although rates of grade 3 or higher anemia and thrombocytopenia were slightly higher in the CP arm. Importantly, the rates of febrile neutropenia, an independent and poor prognostic factor in NSCLC patients receiving chemotherapy [16], has been consistently high ($>$10%) in the docetaxel arm in the current study and in previous Japanese studies. Given these observations and the fact that one TRD was observed in the docetaxel arm in this study, we infer that docetaxel might be more toxic than CP in elderly patients.

Our study has some limitations. First, because it is a phase II study, we cannot draw definite conclusions from this study alone. However, considering these results together with the positive results of a similar CP regimen in the recent IFCT-0501 trial, we believe that the CP regimen described is worthy of further investigation. Although the progression-free survival (PFS) of patients in the docetaxel arm in this study (3.5 months) may seem shorter than that of previous Japanese studies (5.5 months in WJTOG9904 and 4.4 months in JCOG0804), the median number of treatment cycles (i.e., four) was similar among these trials, suggesting that the difference may have occurred by chance or be related to some difference in the patient populations. We would note, however, that even if the PFS of docetaxel arm were 1 month longer than the current result, this would still appear inferior to the CP regimen that has demonstrated a PFS value in at least two trials of more than 6 months with a favorable risk-benefit ratio.

In conclusion, carboplatin plus weekly paclitaxel achieved higher activity with less toxicity in elderly patients with advanced NSCLC compared with monotherapy with docetaxel. Considering these results together with the results of the IFCT-0501 trial, we will select the CP regimen for use in a future phase III trial.

References

1. Azzoli CG, Baker S Jr., Temin S et al. American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009;27:6251–6266.
2. Ng R, de Boer R, Green MD. Undertreatment of elderly patients with non-small-cell lung cancer. Clin Lung Cancer 2005;7:168–174.
3. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Groups. J Natl Cancer Inst 1999;91:66–72.
4. Gridelli C, Perrone F, Gallo C et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003;95:362–372.
5. Gridelli C, Aapro M, Ardizzoni A et al. Treatment of advanced non-small-cell lung cancer in the elderly: Results of an international expert panel. J Clin Oncol 2005;23:3125–3137.
6. Kudoh S, Takeda K, Nakagawa K et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006;24:3657–3663.
7. Quoix E, Zalcman G, Oster JP et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079–1088.
8. Sakakibara T, Inoue A, Sugawara S et al. Randomized phase II trial of weekly paclitaxel combined with carboplatin versus standard paclitaxel combined with carboplatin for elderly patients with advanced non-small-cell lung cancer. Ann Oncol 2010;21:795–799.
9. Abe T, Yokoyama A, Takeda K et al. Randomized phase III trial comparing weekly docetaxel (D)-cisplatin (P) combination with triweekly D alone in elderly patients (pts) with advanced non-small cell lung cancer (NSCLC): An intergroup trial of JCOG0803/WJOG4307L. J Clin Oncol 2011;29(suppl):7509a.
10. Inoue A, Usui K, Ishimoto O et al. A phase II study of weekly paclitaxel combined with carboplatin for elderly patients with advanced non-small cell lung cancer. Lung Cancer 2006;52:83–87.
11. Gandara DR, Kawaguchi T, Crowley J et al. Japanese-US common-arm analysis of paclitaxel plus carboplatin in advanced non-small-cell lung cancer: A model for assessing population-related pharmacogenomics. J Clin Oncol 2009;27:3540–3546.
12. Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–2550.
13. 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;76:362–367.
14. Ramalingam S, Perry MC, La Rocca RV et al. Comparison of outcomes for elderly patients treated with weekly paclitaxel in combination with carboplatin versus the standard 3-weekly paclitaxel and carboplatin for advanced nonsmall cell lung cancer. Cancer 2008;113:542–546.
15. Socinski MA, Bondarenko I, Karaseva NA et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase III trial. J Clin Oncol 2012;30:2055–2062.
16. Rikimaru T, Ichiki M, Ookubo Y et al. Prognostic significance of febrile episodes in lung cancer patients receiving chemotherapy. Support Care Cancer 1998;6:396–401.

Figures and Tables

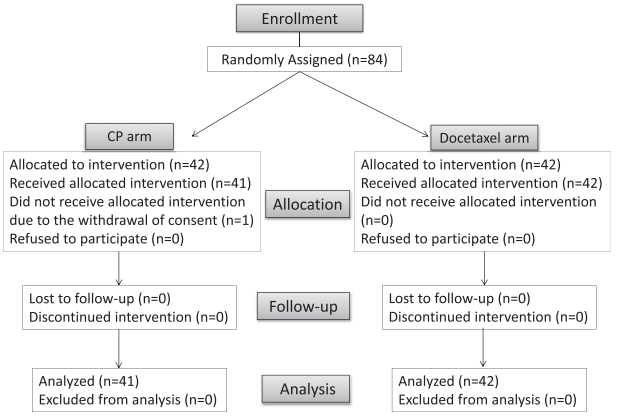

Figure 1. Enrollment.

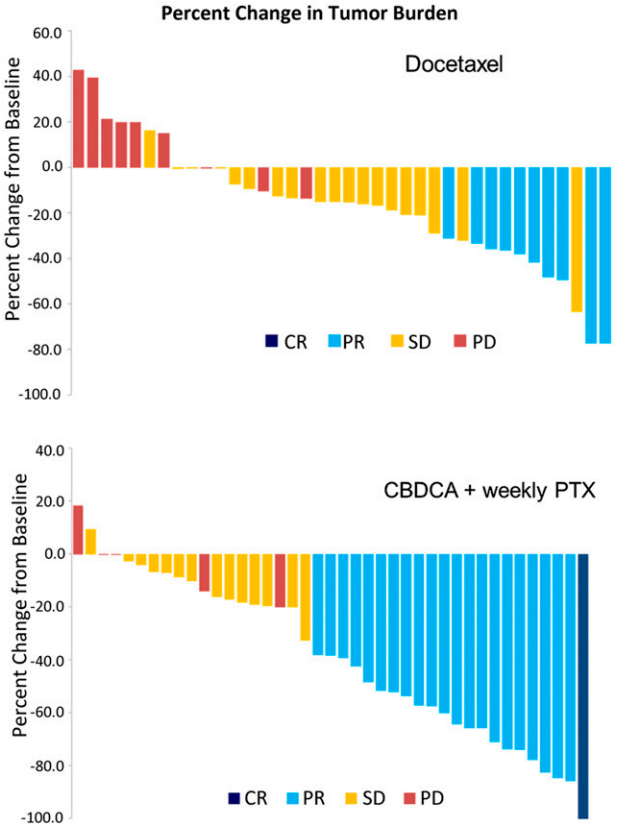

Figure 2. Waterfall plots of the docetaxel arm and the CP arm in this study.

Abbreviations: CBDCA, carboplatin; CP, carboplatin with weekly paclitaxel; CR, complete response, PD, progressive disease; PR, partial response; PTX, paclitaxel; SD, stable disease.

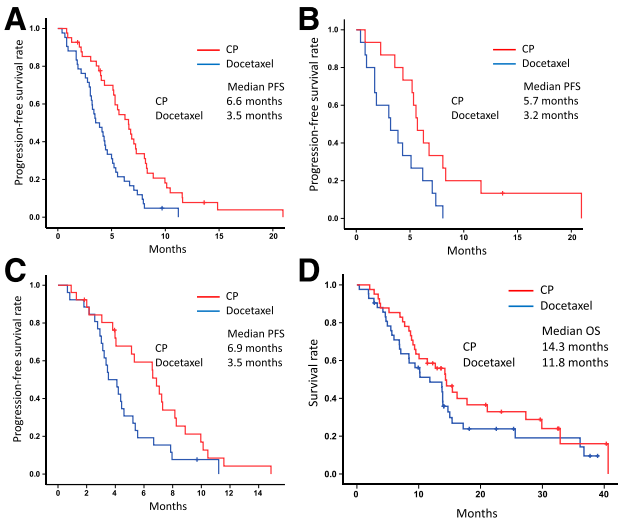

Figure 3. Survival rates. (A–C): Progression-free survival. (D): Overall survival.
Abbreviations: CP, carboplatin with weekly paclitaxel; OS, overall survival; PFS, progression-free survival.

Table 1. Patient characteristics

Characteristic	CP arm	Docetaxel arm
Gender, *n* (%)		
Male	35 (85)	27 (64)
Female	6 (15)	15 (36)
Age		
Median	76	77
Range	70–86	70–87
EGFR gene status, *n* (%)		
Wild	29 (71)	27 (64)
Mutant	2 (5)	2 (5)
Unknown	10 (24)	13 (31)
Performance status, *n* (%)		
0	19 (46)	19 (45)
1	22 (54)	23 (55)
Clinical stage, *n* (%)		
IIIA	0 (0)	1 (2)
IIIB	8 (20)	7 (17)
IV	29 (70)	31 (74)
Postoperative recurrence	4 (10)	3 (7)
Histology, *n* (%)		
Adenocarcinoma	23 (56)	23 (55)
Squamous cell	15 (37)	14 (33)
Large cell	0 (0)	1 (2)
Undifferentiated	3 (7)	4 (10)

Abbreviations: CP, carboplatin with weekly paclitaxel.

Table 2. Response

Result	CP arm	Docetaxel arm
Response, *n* (%)		
CR	1 (2)	0 (0)
PR	21 (51)	10 (24)
SD	14 (34)	20 (48)
Progressive disease	5 (12)	9 (21)
Not evaluable	0 (0)	3 (7)
Objective response rate (CR + PR) (95% confidence interval)	54% (39–69)	24% (11–37)
Disease control rate (CR + PR + SD)	88%	71%

Abbreviations: CP, carboplatin with weekly paclitaxel; CR, complete response, PR, partial response; SD, stable disease.

Table 3. Hematological and nonhematological toxicity

	CP arm ($n = 41$)						Docetaxel arm ($n = 42$)					
	CTCAE grade						CTCAE grade					
Toxicity	**1**	**2**	**3**	**4**	**5**	**Grade 3–4 (%)**	**1**	**2**	**3**	**4**	**5**	**Grade 3–4 (%)**
Hematological toxicity												
Anemia	9	24	4	2	0	14.6	26	9	2	1	0	7.1
Thrombocytopenia	11	8	2	2	0	9.8	4	0	0	0	0	0
Neutropenia	2	14	18	5	0	56.1	0	3	5	28	0	78.6
Febrile Neutropenia			1	0	0	2.4			10	0	1[a]	26.2
Nonhematological toxicity												
Nausea	12	6	1	0	0	2.4	15	3	6	0	0	14.3
Vomiting	2	2	0	0	0	0	5	0	0	0	0	0
Diarrhea	3	1	1	0	0	2.4	4	3	2	0	0	4.8
Peripheral neuropathy	7	5	1	0	0	2.4	2	0	0	0	0	0
Arthralgia, myalgia	5	0	0	0	0	0	2	0	0	0	0	0
Allergic reaction	2	1	0	0	0	0	5	0	0	0	0	0
Fatigue	2	2	0	0	0	0	5	2	0	1	0	2.4
Hypoalbuminemia	22	6	0	0	0	0	15	14	2	0	0	4.8
AST elevation	8	0	0	0	0	0	11	1	1	0	0	2.4
ALT elevation	7	1	1	0	0	2.4	10	3	0	0	0	0
Fever	3	1	0	0	0	0	3	0	0	0	0	0
Infection	2	3	2	0	0	4.8	3	0	1	0	0	2.4
Interstitial pneumonia	0	1	0	0	0	0	0	1	0	0	0	0
Ventricular tachycardia	0	0	0	0	0	0	0	0	0	0	1	2.4

[a]Treatment-related death.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CP, carboplatin with weekly paclitaxel; CTCAE, Common Terminology Criteria for Adverse Events.

Table 4. Postprotocol chemotherapy

Therapy	CP arm		Docetaxel arm	
Non-PD patients at data cutoff point	***n* = 3**		***n* = 1**	
PD patients after the protocol treatment	***n* = 38**		***n* = 41**	
	n	**%**	***n***	**%**
Combined regimen	4	10.5	14[a]	34.1
CBDCA + PTX	0	0	7	17.1
CBDCA + PEM	1	2.6	3	7.3
CBDCA + S-1	1	2.6	1	2.4
CBDCA + GEM	0	0	1	2.4
GEM + VNR	1	2.6	4	9.8
CPT + S-1	1	2.6	1	2.4
Monotherapy	16[a]	42.1	14[a]	34.1
Docetaxel	9	23.7	0	0
PEM	6	15.8	6	14.6
S-1	3	7.9	5	12.2
VNR	2	5.3	1	2.4
GEM	0	0	2	4.9
AMR	0	0	3	7.3
CPT	0	0	4	9.8
EGFR-TKI	2[a]	5.3	6	14.6
Gefitinib	2	5.3	3	7.3
Erlotinib	1	2.6	3	7.3
Any second-line chemotherapy	20	52.6	21	51.2
Any third-line chemotherapy	4	10.5	11	26.8
Any fourth-line or later chemotherapy	2	5.3	9	22.0

[a]Includes patient who received multiple regimens.
Abbreviations: AMR; amrubicin; CBDCA, carboplatin; CP, carboplatin with weekly paclitaxel; CPT; irinotecan; GEM, gemcitabine; PD, progressive disease; PEM, pemetrexed; PTX, paclitaxel; VNR, vinorelbine.