Table 1
Patient characteristics at baseline.

	nab-PC ($n=74$)	sb-PC ($n=75$)	All patients ($n=149$)
Age (years)			
Median (min, max)	65.0 (37, 79)	64.0 (36, 77)	65.0 (36, 79)
Age categories, *n* (%)			
<70 years	59 (80%)	59 (79%)	118 (79%)
≥70 years	15 (20%)	16 (21%)	31 (21%)
Gender, *n* (%)			
Male	51 (69%)	50 (67%)	101 (68%)
Female	23 (31%)	25 (33%)	48 (32%)
Smoking status, *n* (%)			
Never smoked	13 (18%)	22 (29%)	35 (23%)
Smoked but had quit smoking	46 (62%)	32 (43%)	78 (52%)
Smoked and currently smokes	15 (20%)	21 (28%)	36 (24%)
ECOG performance score, *n* (%)			
0 (fully active)	35 (47%)	36 (48%)	71 (48%)
1 (restrictive but ambulatory)	39 (53%)	39 (52%)	78 (52%)
Histology of primary diagnosis			
Adenocarcinoma	55 (74%)	58 (77%)	113 (76%)
Squamous cell carcinoma	10 (14%)	7 (9%)	17 (11%)
Large cell carcinoma	1 (1%)	1 (1%)	2 (1%)
Other	8 (11%)	9 (12%)	17 (11%)
Stage at random assignment			
IIIB	19 (26%)	22 (29%)	41 (28%)
IV	55 (74%)	53 (71%)	108 (72%)

administered on day 1. Treatment for at least six cycles was encouraged but could continue in the absence of progressive disease (PD) and unacceptable toxicity at the investigator's discretion.

2.3. Treatment assessment

The primary end point of the study was ORR, determined by blinded independent radiologists using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. ORR was defined as the proportion of occurrence of either a confirmed complete response (CR) or a partial response (PR). Tumor response assessments by spiral computed tomography scans were made at 6-week intervals until PD. Secondary endpoints included PFS and OS. PFS was defined as the time from randomization to PD or any cause of death, whichever occurred first. Patients who did not have PD or had not died at the end of follow-up were censored at the last known time when the patient was progression free. OS was followed for a total of 18 months after discontinuation of the treatment, which was defined as the time from randomization to any cause of death. Patients that were alive at the end of follow-up were censored at the last known time that the patient was alive. Adverse events were graded according to NCI-CTCAE (version 3.0) throughout the treatment.

2.4. Statistical analysis

The analysis population for efficacy was the intent-to-treat (ITT) population, which included all randomized Japanese patients. PFS and OS were estimated using the Kaplan–Meier method, the 95% confidence interval (CI) for the median was calculated. Retrospective analyses were performed for the response to *nab*-PC vs sb-PC to explore the potential subgroup for patients with SCC and non-SCC. All patients who received at least one dose of study drug were evaluated for safety.

3. Results

3.1. Patients characteristics

A total of 149 patients were valid for ITT analyses and 147 patients for safety analyses. The baseline characteristics of patients were well balanced between the *nab*-PC and the sb-PC arm. The majority of patients were male and smokers. The majority of patients (76%) had adenocarcinoma (Table 1).

3.2. Efficacy results

Efficacy results are shown in Table 2. The ORR based on the blinded radiological assessment was 35% (95% CI: 24.3–46.0%) in the *nab*-PC arm, and 27% (95% CI: 16.7–36.7%) in the sb-PC arm (response rate ratio = 1.318; 95% CI: 0.810–2.143). In the subgroup of patients with SCC histology, ORR was 50% (95% CI: 18.7–81.3%) for the *nab*-PC arm and 43% (95% CI: 9.9–81.6%) for the sb-PC arm (response rate ratio = 1.167; 95% CI: 0.406–3.355) (Table 3). The Kaplan–Meier curves of PFS and OS are shown in Fig. 2. The median PFS was 6.9 months (95% CI: 5.4–8.3 months) in the *nab*-PC arm compared to 5.6 months (95% CI: 5.4–6.9 months) in the sb-PC arm (HR = 0.845; 95% CI: 0.539–1.325). The median OS for the *nab*-PC arm was approximately 1 month longer vs the sb-PC arm (16.7 vs 15.9 months; HR = 0.930; 95% CI: 0.608–1.425).

3.3. Safety results

The grade 3 or higher major treatment-related adverse events are shown in Table 4. There was more grade ≥3 anemia (32% vs 9%) and thrombocytopenia (14% vs 3%) in the *nab*-PC arm, and there was less sensory neuropathy (3% vs 13%) with *nab*-PC vs sb-PC. Grade ≥2 and ≥3 sensory neuropathy was less in the *nab*-PC arm than

Table 2
Efficacy outcomes.

	nab-PC ($n=74$)	sb-PC ($n=75$)
Overall response rate, *n* (%)	26 (35%)	20 (27%)
95% CI[a]	24.3, 46.0	16.7, 36.7
$p_{nab\text{-}PC}/p_{sb\text{-}PC}$[b] (95% CI[a])	1.318 (0.810, 2.143)	
Median progression-free survival (months)	6.9	5.6
95% CI[a]	5.4, 8.3	5.4, 6.9
Hazard ratio$_{nab\text{-}PC/sb\text{-}PC}$ (95% CI[a])	0.845 (0.539, 1.325)	
Median overall survival (months)	16.7	15.9
95% CI[a]	12.2, 22.3	11.2, n/c
Hazard ratio$_{nab\text{-}PC/sb\text{-}PC}$ (95% CI[a])	0.930 (0.608, 1.425)	

[a] CI, confidence interval.
[b] $p_{nab\text{-}PC}/p_{sb\text{-}PC}$, response rate ratio.

Table 3
Overall response rate by histology.

	Squamous		Non-squamous[a]	
	nab-PC ($n=10$)	sb-PC ($n=7$)	*nab*-PC ($n=64$)	sb-PC ($n=68$)
Overall response rate, *n* (%)	5 (50%)	3 (43%)	21 (33%)	17 (25%)
95% CI[b]	18.7, 81.3	9.9, 81.6	21.3, 44.3	14.7, 35.3
$p_{nab\text{-}PC}/p_{sb\text{-}PC}$[c] (95% CI[b])	1.167 (0.406, 3.355)		1.313 (0.764, 2.254)	

[a] Adenocarcinoma, large cell carcinoma, not otherwise specified.
[b] CI, confidence interval.
[c] $p_{nab\text{-}PC}/p_{sb\text{-}PC}$, response rate ratio.

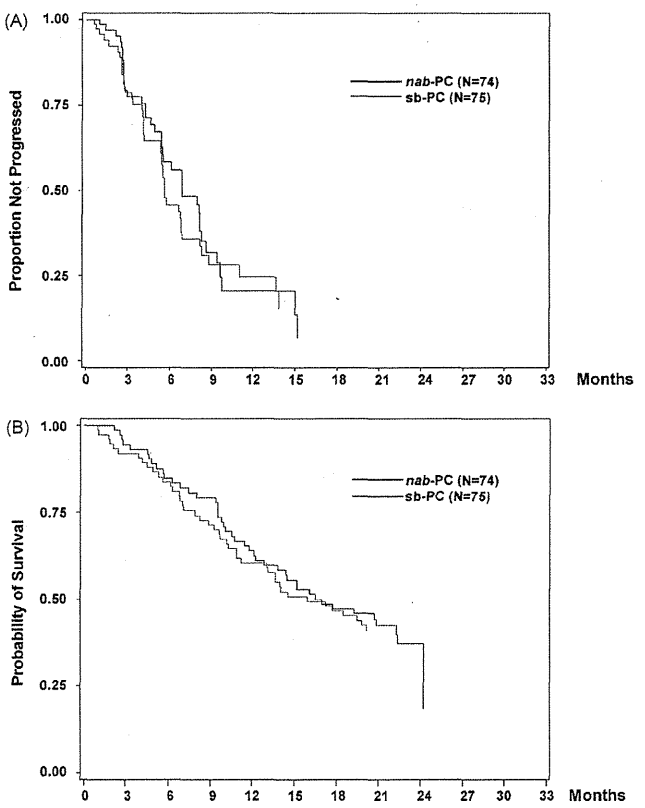

Fig. 2. Kaplan–Meier estimates for progression-free survival (A) and overall survival (B).

Table 4
Treatment-related adverse events occurred in ≥40% in each arm.

Adverse events	*nab*-PC (%) ($n=72$)		sb-PC (%) ($n=75$)		*p*-Value*
	All grade	Grade ≥3	All grade	Grade ≥3	
Hematologic adverse events					
Leukopenia	93	49	79	37	0.185
Neutropenia	90	69	85	75	0.582
Anemia	86	32	61	9	<0.001
Thrombocytopenia	81	14	55	3	0.016
Nonhematologic adverse events					
Alopecia	93	0	83	0	N.A.
Fatigue	74	3	67	8	0.276
Decreased appetite	69	11	72	3	0.053
Nausea	68	1	52	0	0.490
Sensory neuropathy	64	3	81	13	0.032
Constipation	54	1	40	3	>0.999
Arthralgia	42	0	68	7	0.059
Myalgia	29	0	60	7	0.059

N.A., not applicable.
* *p*-value for the comparison of ≥grade 3 AEs between the *nab*-PC arm and the sb-PC arm were obtained using Fisher's test and used to monitor for adverse safety signals at a statistical significance level of $p=0.05$.

the sb-PC arm (Grade ≥2, 18% vs 39%; Grade ≥3, 3% vs 15%). Study treatment was terminated due to adverse events less frequently in the *nab*-PC arm (21%) than the sb-PC arm (28%). There were no treatment-related deaths in both arms.

4. Discussion

The subset analyses evaluated the efficacy outcomes and safety profile of 149 Japanese patients enrolled in the CA031 study. Sample size was based on the primary end point of ORR for the whole patient population, such that the present study was not powered to detect for subgroup analyses. Despite the limitation of small sample size, the efficacy analysis showed that the ORR was higher in the *nab*-PC arm compared to the sb-PC arm. In addition, there was a non-significant trend toward improved PFS and OS in the *nab*-PC arm compared to the sb-PC arm. We acknowledge that the results of this unplanned retrospective analysis should be considered as exploratory. However, the present analysis indicated that these efficacy outcomes were generally consistent with those of the whole population of this phase III study [10], supporting the concept that weekly *nab*-P in combination with C is effective for the Japanese patients as first-line treatment of advanced NSCLC.

The ORR by histologic type was also evaluated in this analysis. It has been reported that Pemetrexed studies showed different survival outcomes based on histologic types (SCC vs non-SCC), which indicates that histologic type should be considered in determining the treatment strategy [5]. In the subgroup of patients with SCC, ORR for *nab*-PC compared favorably with that of sb-PC in this setting. This finding suggests that the results of clinical response to *nab*-PC in Japanese patients might not have been greatly different from that in the whole patient population [10]. However, given the small Japanese sample, further study is needed to determine the effect of the use of *nab*-PC treatment on SCC patients in a greater number of cases.

Interestingly, patient survival seemed to favor the Japanese population over the whole population in both arms (median 16.7 vs 12.1 months for *nab*-PC arm; median 15.9 vs 11.2 months for sb-PC arm). In the CA031 study, patient characteristics for Japanese patients mainly differed by PS, histologic type and post-study treatment across regions. In Japanese patients enrolled in the CA031 study, histological subtype of adenocarcinoma was more prevalent vs whole population (76% vs 49%), the percentage of patients with PS of 0 was higher (48% vs 23%), and a large proportion of Japanese patients received multiple post-study treatments (85% vs 54%) including EGFR–tyrosine kinase inhibitor (EGFR–TKI), which might have been attributed to longer patient survival than whole population in each of the arms.

The safety profile of *nab*-PC was acceptable and found to have no clinically significant issue for Japanese patients. The treatment-related adverse events associated with *nab*-PC were similar with that of sb-PC. Although some differences were seen in the incidence of grade ≥3 hematologic toxicities for the *nab*-PC arm vs the sb-PC arm and myelosuppression was the major reason for dose reduction, dose delay, or dose not given in the *nab*-PC arm, the

treatment could be continued. The incidence of grade ≥3 anemia was higher in the *nab*-PC arm compared to the sb-PC arm. A few patients (11%) required only a single blood transfusion, although one (1%) required two. However, the majority of anemia cases resolved without requiring transfusion. Although the incidence of grade ≥3 thrombocytopenia was also higher with *nab*-PC arm compared with sb-PC arm, there was no increase in hemorrhagic events in the *nab*-PC arm. The clinical issue for the use of sb-P has been reported to be sensory neuropathy, resulting in the discontinuation of the treatment. To date, there are few effective drugs for neuropathy [17]. Even if patients are switched to other chemotherapeutic treatment, it does not readily resolve. Hence, symptom management related to sb-P is a clinically important component of cancer care. In the present analysis, *nab*-PC was associated with lower sensory neuropathy in terms of both frequency and severity (both grade ≥2 and grade ≥3). One possible explanation would be the difference in the administration schedule and the amount of paclitaxel per dose. Based on the results, treatment with weekly *nab*-P plus C is beneficial and anticipated to maintain QOL in NSCLC patients during treatment.

5. Conclusion

The weekly *nab*-P 100 mg/m^2 in combination with C (AUC = 6) in Japanese patients with previously untreated stage III/IV NSCLC yielded encouraging efficacy results. Further, it was generally well tolerated with less neuropathic toxicity as first-line treatment for NSCLC.

The *nab*-PC treatment could be an alternative to sb-PC in the treatment of advanced NSCLC regardless of histology, and may have the potential for the treatment of SCC, where there is an unmet medical need.

Conflict of interest statement

Miyako Satouchi, Hiroshi Sakai, Nobuyuki Yamamoto, Naoyuki Nogami, Koji Takeda and Tetsuya Mitsudomi have received honoraria from Taiho Pharmaceuticals. Koji Takeda and Tetsuya Mitsudomi have received consulting fees from Taiho Pharmaceuticals. Isamu Okamoto has received research funding from Celgene. Tetsuya Mitsudomi has received research funding from Taiho Pharmaceuticals. The other authors have declared no conflicts of interest.

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Appendix.

The following Japanese institution participated in the trial: KKR Sapporo Medical Center (Sapporo), Tohoku University Hospital (Miyagi), Saitama Cancer Center (Saitama), Saitama Medical University International Medical Center(Saitama), National Cancer Center Hospital East (Chiba), Tokyo Medical University Hospital (Tokyo), Nippon Medical School Hospital (Tokyo), National Cancer Center Hospital (Tokyo), Kitasato University Hospital (Kanagawa), Shizuoka Cancer Center (Shizuoka), Aichi Cancer Center Hospital (Aichi), Kanazawa University Hospital (Ishikawa), National Hospital Organization Kinki-Chuo Chest Medical Cente (Osaka), Kinki University Faculty of Medicine (Osaka), Osaka Prefectural Medical Center for Respiratory and Allergic Diseases (Osaka), Osaka City General Hospital (Osaka), Hyogo Cancer Center (Hyogo), National Hospital Organization Shikoku Cancer Center (Ehime), National Kyushu Cancer Center (Fukuoka), Kameda Medical Center (Chiba), Kanagawa Cancer Center (Kanagawa).

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Efficacy and safety analysis according to histology for S-1 in combination with carboplatin as first-line chemotherapy in patients with advanced non-small-cell lung cancer: updated results of the West Japan Oncology Group LETS study

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Background: A phase III study (Lung Cancer Evaluation of TS-1) previously demonstrated noninferiority in terms of overall survival (OS) at interim analysis for carboplatin–S-1 compared with carboplatin–paclitaxel for first-line treatment of advanced non-small-cell lung cancer (NSCLC).

Patients and methods: A total of 564 patients were randomly assigned to receive either carboplatin on day 1 plus oral S-1 on days 1–14 or carboplatin–paclitaxel on day 1 every 21 days. Updated results and *post hoc* subgroup analysis according to tumor histology are presented.

Results: The updated analysis revealed a median OS of 15.2 months in the carboplatin–S-1 arm and 13.1 months in the carboplatin–paclitaxel arm, with a hazard ratio (HR) of 0.956 [95% confidence interval (CI) 0.793–1.151], consistent with the previous primary analysis. Median OS was 14.0 months in the carboplatin–S-1 arm and 10.6 months in the carboplatin–paclitaxel arm (HR 0.713; 95% CI 0.476–1.068) for patients with squamous cell carcinoma (SCC), with corresponding values of 15.5 and 13.9 months (HR 1.060; 95% CI 0.859–1.308) for those with non-SCC.

Conclusions: These results establish the efficacy and safety of carboplatin–S-1 in patients with advanced NSCLC regardless of tumor histology.

Key words: carboplatin, histology, non-small-cell lung cancer, S-1, squamous cell carcinoma

introduction

Lung cancer is the leading cause of death related to cancer worldwide, with non-small-cell lung cancer (NSCLC) accounting for 85% of lung cancer cases [1]. Most NSCLC cases are categorized into two distinct histological subtypes: squamous cell carcinoma (SCC) and non-SCC. Treatment with pemetrexed–cisplatin was associated with a longer overall survival (OS) compared with that with gemcitabine–cisplatin in patients with non-SCC but not in those with SCC [2]. The addition of bevacizumab, a monoclonal antibody specific for vascular endothelial growth factor, to carboplatin and paclitaxel improved survival compared with chemotherapy alone in patients with non-SCC, but such treatment was contraindicated for patients with SCC because of an increased risk of fatal bleeding events [3–5]. Furthermore, the recent identification of oncogenic alterations, such as mutation of the epidermal growth factor receptor (EGFR) gene or the fusion of the genes for echinoderm microtubule-associated protein–like

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4 (EML4) and anaplastic lymphoma kinase (ALK), and of the association of such gene alterations with a clinically relevant response to corresponding tyrosine kinase inhibitors (TKIs), has had a profound impact on the treatment of advanced NSCLC [6–10]. Almost all cases of NSCLC harboring *EGFR* mutations or *ALK* rearrangements are non-SCC, with adenocarcinomas being most common. Treatment options for non-SCC have thus increased, whereas the contribution of new drugs to the treatment of SCC has been minimal. The poor outlook for advanced NSCLC patients with SCC has prompted a search for new chemotherapeutic agents and combination regimens.

S-1 (TS-1; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) is an oral fluoropyrimidine anticancer agent that combines tegafur as the effector drug with two modulators, gimeracil, and oteracil potassium, in a molar ratio of 1 : 0.4 : 1 [11, 12]. We have recently completed a multicenter randomized phase III study comparing carboplatin and S-1 with standard carboplatin and paclitaxel combination therapy as first-line treatment in patients with advanced NSCLC [13]. The primary objective of the Lung Cancer Evaluation of TS-1 (LETS) study —determination of the noninferiority of carboplatin and S-1 compared with carboplatin and paclitaxel in terms of OS—was met at the planned interim analysis. On completion of the initially planned 2 years of follow-up, at which time an adequate number of events had been obtained, we updated the survival data of the LETS study. Given that histology (SCC or non-SCC) has recently become a key factor in the selection of chemotherapy regimens for the treatment of advanced NSCLC, we also assessed the efficacy and safety data according to the histological subtype of NSCLC by performing subgroup analyses that were not predefined in the study protocol but which address a clinically important issue.

patients and methods

patients

The design and results of the LETS study were published in 2010 [13]. In brief, the study group comprised patients aged 20–74 years who had a histopathologic diagnosis of stage IIIB or IV NSCLC, an Eastern Cooperative Oncology Group performance status of 0 or 1, and preserved functions of major organ systems. Patients had not previously received chemotherapy, and they were randomly assigned in a 1 : 1 ratio to receive carboplatin–S-1 or carboplatin–paclitaxel. In the carboplatin–S-1 group, carboplatin was given as a continuous i.v. infusion (area under the curve, 5) on day 1, and S-1 (80 mg/m^2 in two divided doses) was given orally on days 1–14. Treatment was repeated every 3 weeks for up to six cycles. Patients in the carboplatin–paclitaxel group received carboplatin (area under the curve, 6) and paclitaxel (200 mg/m^2) by continuous i.v. infusion on day 1 every 3 weeks. Treatment was repeated for up to six cycles. The primary end point was OS. Secondary end points were tumor response, safety, quality of life (QOL), and progression-free survival (PFS). Written informed consent was obtained from all patients before treatment, and the study protocol was approved by the institutional ethics committee of each of the participating institutions.

In this *post hoc* investigation, OS and PFS in the intention-to-treat population were determined from updated survival data. In addition, subgroup analyses were carried out to compare overall response rate (ORR), OS, and PFS between the treatment groups according to histological subtype (SCC versus non-SCC) of NSCLC. To assess the impact of post-study treatments with potential effects on survival, we analyzed the data according to treatment line and drugs administered (docetaxel and EGFR-TKIs). Treatment-related adverse events were also assessed according to each subgroup. QOL was assessed with the lung cancer subscale of Functional Assessment of Cancer Therapy-Lung (FACT-L) [14] and the neurotoxicity subscale of FACT/Gynecology Oncology Group-Neurotoxicity (FACT/GOG-Ntx) version 4 [15]. The maximum attainable scores on the lung cancer and neurotoxicity subscales were 28 and 44, respectively, with which a patient was considered to be asymptomatic. Patients were asked to complete each instrument at the time of enrollment and at 6 and 9 weeks after the initiation of treatment.

statistical analysis

The definition of survival was similar to that used in the initial description of the LETS study [13]. OS was defined as the interval from the date of randomization until the date of death from any cause or the final date of follow-up. At the time of data cutoff, data on survivors and on patients who were lost to follow up were censored on the final date of follow-up. PFS was defined as the interval from the date of randomization until the date on which progressive disease was first confirmed by imaging or the date of death from any cause, whichever came first. If no events had occurred, data were censored at the most recent date of follow-up.

Survival curves in each treatment group and subgroup were estimated with the Kaplan–Meier method. The 95% confidence interval (CI) for median survival was calculated with the method of Brookmeyer and Crowley. A Cox proportional-hazards model was used to calculate the hazard ratio (HR) and CI and to examine the interaction effects between study treatment and subgroup. Longitudinal QOL data were analyzed with a linear mixed-effects model. All statistical analyses were carried out with SAS for Windows, release 9.2 (SAS Institute, Cary, NC). A P value of <0.05 was considered statistically significant.

results

baseline characteristics

A total of 564 patients were enrolled into the phase III study, and 282 patients were treated in each of the carboplatin–paclitaxel and carboplatin–S-1 arms. At the time of the updated analysis, the median follow-up time was 33.4 months (range 2.1–43.6 months) and a total of 446 deaths (carboplatin–paclitaxel, $N = 219$; carboplatin–S-1, $N = 227$) had occurred. The median OS was 15.2 months (95% CI 12.3–17.8 months) in the carboplatin–S-1 group and 13.1 months (95% CI 11.7–14.9 months) in the carboplatin–paclitaxel group, with an HR for death of 0.956 (95% CI 0.793–1.151). The median PFS was 4.1 months (95% CI 3.8–4.7 months) in the carboplatin–S-1 group and 4.8 months (95% CI 4.3–5.2 months) in the carboplatin–paclitaxel group, with an HR for progression or death of 1.035 (95% CI 0.875–1.224). Of the 564 randomized patients in the phase III study population, 114 patients had SCC (carboplatin–paclitaxel, $N = 59$; carboplatin–S-1, $N = 55$) and 450 had non-SCC (carboplatin–paclitaxel, $N = 223$; carboplatin–S-1, $N = 227$). The CONSORT diagram for the study is shown in supplementary Figure S1, available at *Annals of Oncology* online. Baseline patient characteristics for both histological subtypes were generally well balanced between the treatment groups (Table 1).

Table 1. Patient demographics and characteristics according to histological subtype of NSCLC

Characteristic	Squamous		Nonsquamous	
	CBDCA–S-1 ($N = 55$)	CBDCA–PTX ($N = 59$)	CBDCA–S-1 ($N = 227$)	CBDCA–PTX ($N = 223$)
Age, median, years (range)	66 (39–74)	65 (43–74)	64 (38–74)	62 (36–74)
Sex, *N* (%)				
Male	48 (87.3)	51 (86.4)	169 (74.4)	165 (74.0)
Female	7 (12.7)	8 (13.6)	58 (25.6)	58 (26.0)
ECOG PS, *N* (%)				
0	18 (32.7)	14 (23.7)	68 (30.0)	77 (34.5)
1	37 (67.3)	45 (76.3)	159 (70.0)	146 (65.5)
Clinical stage, *N* (%)				
IIIB	20 (36.4)	27 (45.8)	48 (21.1)	41 (18.4)
IV	35 (63.6)	32 (54.2)	179 (78.9)	182 (81.6)
Smoking status, *N* (%)				
Smoker	52 (94.5)	56 (94.9)	178 (78.4)	174 (78.0)
Nonsmoker	3 (5.5)	3 (5.1)	49 (21.6)	49 (22.0)

CBDCA, carboplatin; PTX, paclitaxel; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 2. Summary of OS, PFS, and response rate according to histological subtype of NSCLC

	Squamous		Nonsquamous	
	CBDCA–S-1 ($N = 55$)	CBDCA–PTX ($N = 59$)	CBDCA–S-1 ($N = 227$)	CBDCA–PTX ($N = 223$)
ORR, *N* (%)	15 (27.3)	20 (33.9)	42 (18.5)	61 (27.4)
Disease control rate, *N* (%)	44 (80.0)	45 (76.3)	156 (68.7)	162 (72.6)
Median PFS (months)	4.37	4.87	4.14	4.77
95% CI	3.65–5.79	3.98–5.72	3.65–4.77	4.18–5.23
HR (95% CI)	0.938 (0.642–1.371)		1.063 (0.881–1.282)	
Median OS (months)	14	10.6	15.5	13.9
95% CI	11.4–16.7	8.7–12.6	11.7–18.4	12.1–16.8
HR (95% CI)	0.713 (0.476–1.068)		1.060 (0.859–1.308)	

efficacy results based on histology

Efficacy results according to histological subtype of NSCLC are shown in Table 2. For the non-SCC cohort, ORR was significantly higher in the carboplatin–paclitaxel arm than in the carboplatin–S-1 arm (27.4% versus 18.5%; $P = 0.027$, chi-square test), with a response rate ratio of 0.680 (95% CI 0.4805–0.960), whereas the overall disease control (complete response + partial response + stable disease) rate was similar in both treatment groups (72.6% versus 68.7%, respectively; $P = 0.393$). The ORR was 33.9% and 27.3% ($P = 0.444$), with a response rate ratio of 0.805 (95% CI 0.460–1.408), for carboplatin–paclitaxel and carboplatin–S-1, respectively, in patients with SCC. No significant interaction was noted for ORR between histology and treatment ($P = 0.686$).

The median PFS was 4.8 months with carboplatin–paclitaxel and 4.1 months with carboplatin–S-1 in patients with non-SCC (HR 1.063; 95% CI 0.881–1.282). The median PFS was similar with carboplatin–paclitaxel or carboplatin–S-1 in patients with SCC (4.9 versus 4.4 months, respectively; HR 0.938; 95% CI 0.642–1.371). No interaction was observed between histology and treatment effect for PFS ($P = 0.547$).

Figure 1 shows Kaplan–Meier analysis of OS according to treatment arm for SCC and non-SCC subgroups. Patients with SCC experienced a longer median OS in the carboplatin–S-1 group than in the carboplatin–paclitaxel group (14.0 versus 10.6 months, respectively; HR 0.713; 95% CI 0.476–1.068). Patients with non-SCC assigned to carboplatin–S-1 had a median OS of 15.5 months, whereas those assigned to carboplatin–paclitaxel had a median OS of 13.9 months (HR 1.060; 95% CI 0.859–1.308). These data were suggestive of a positive interaction between histology and treatment of OS, but it did not achieve statistical significance ($P = 0.093$).

safety results based on histology

Treatment-related adverse events according to histological subtype are shown in Table 3. Regardless of histology, carboplatin–S-1 was associated with a higher incidence of thrombocytopenia of grade 3 or 4 and a lower incidence of leukopenia, neutropenia, and febrile neutropenia of grade 3 or 4 compared with carboplatin–paclitaxel, consistent with the results previously reported for the intention-to-treat population [13].

QOL results based on histology

In general, results for QOL were similar for both histological subtypes of NSCLC (Figure 2). In patients with SCC, the adjusted mean FACT-L scores at 6 and 9 weeks were 20.8 and 21.1, respectively, for carboplatin–S-1 and 21.0 and 20.8 for carboplatin–paclitaxel ($P = 0.723$ between treatment arms). In

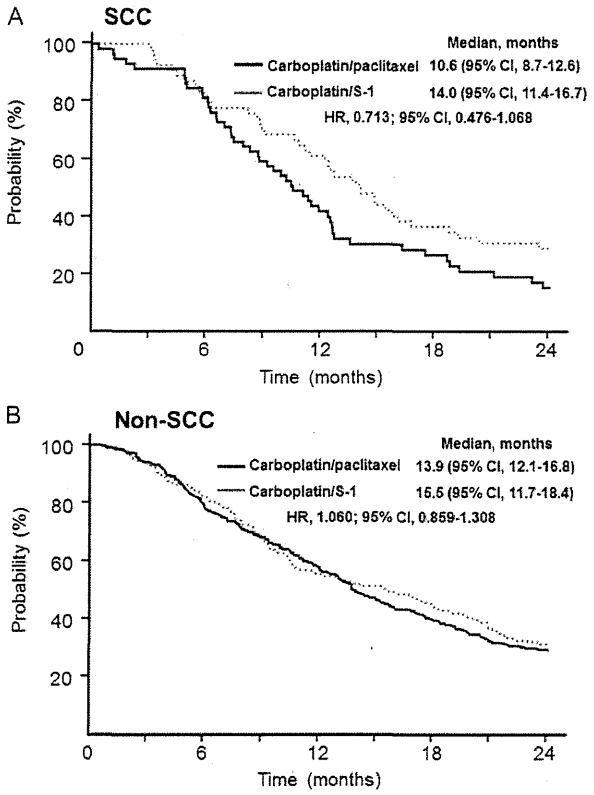

Figure 1. Kaplan–Meier curves for OS according to histological subtype of NSCLC. (A) SCC and (B) Non-SCC.

patients with non-SCC, the corresponding adjusted mean scores were 21.1 and 21.5 for carboplatin–S-1 and 21.3 and 21.3 for carboplatin–paclitaxel ($P = 0.702$). FACT/GOG-Ntx scores differed significantly between treatment arms regardless of histology. For SCC, the adjusted means were 41.1 and 41.5 at 6 and 9 weeks, respectively, for carboplatin–S-1 and 36.9 and 35.4 for carboplatin–paclitaxel ($P < 0.001$). For non-SCC, the adjusted means were 41.2 and 40.9 for carboplatin–S-1 and 38.6 and 37.6 for carboplatin–paclitaxel ($P < 0.001$).

post-study treatment based on histology

There were no major differences in post-study treatment between the two arms regardless of histological subtype (Table 4). The percentage of patients with SCC who received docetaxel as second-line treatment, however, was significantly higher for the carboplatin–S-1 arm than for the carboplatin–paclitaxel arm (58.2% versus 30.5%; $P = 0.003$, chi-square test).

discussion

The present updated analysis confirmed the noninferiority of carboplatin and S-1 compared with carboplatin and paclitaxel for the treatment of advanced NSCLC in terms of OS after completion of 2 years of follow-up and the occurrence of an adequate number of events, as planned in the original protocol. First-line treatment with carboplatin and S-1 showed a

Table 3. Treatment-related adverse events according to histological subtype of NSCLC

Event	Squamous						Nonsquamous					
	CBDCA/S-1 (*N* = 55)			CBDCA/PTX (*N* = 59)			CBDCA/S-1 (*N* = 224)			CBDCA/PTX (*N* = 221)		
	All	G3	G4	All	G3	G4	All	G3	G4	All	G3	G4
Hematologic (%)												
Leukopenia	55	2	0	85	24	7	55	6	1	86	31	2
Neutropenia	56	18	6	85	19	49	59	18	2	91	35	43
Anemia	96	13	6	85	19	3	84	16	3	82	13	2
Thrombocytopenia	91	27	16	76	12	3	86	17	13	59	6	2
Nonhematologic (%)												
Febrile neutropenia	4	4	0	19	17	2	1	1	0	4	4	0
Nausea	64	2	0	44	2	0	62	2	0	50	2	0
Vomiting	38	0	0	24	0	0	33	2	0	24	1	0
Diarrhea	40	2	0	17	0	0	31	4	0	22	1	0
Neuropathy: sensory	16	0	0	81	5	0	16	1	0	81	3	0
Arthralgia	9	0	0	59	0	0	8	0	0	69	3	0
Alopecia	11	0	0	73	0	0	9	0	0	78	0	0

favorable risk-benefit profile regardless of NSCLC histology compared with carboplatin and paclitaxel. As a first-line treatment of patients with SCC, carboplatin and S-1 showed a tendency to improve OS, with a 3.4-month increase in median OS, compared with carboplatin and paclitaxel (14.0 versus 10.6 months; HR 0.713; 95% CI 0.476–1.068). This outcome is of particular interest because of the limited therapeutic options for this patient population compared with patients with non-SCC. The current National Comprehensive Cancer Network (NCCN) guidelines highlight only cisplatin–gemcitabine and cisplatin–cetuximab–vinorelbine as treatment options for recurrence and distant metastases in patients with SCC [2, 16, 17]. Treatment of patients with SCC with gemcitabine–cisplatin versus pemetrexed–cisplatin yielded a median OS of 10.8 versus 9.4 months [2]. In the First-Line Erbitux in Lung Cancer (FLEX) trial, cetuximab–platinum-based chemotherapy was associated with a longer median OS in patients with SCC (10.2 versus 8.9 months) compared with chemotherapy alone [17]. The survival results for SCC patients treated with carboplatin and paclitaxel in our phase III trial are thus similar to those of recent previous studies. In this regard, given the historical context of NSCLC studies focusing on SCC, the survival advantage observed with carboplatin and S-1 in SCC patients is promising and warrants the performance of additional phase III studies for confirmation.

It is unclear whether the possible survival benefit conferred by carboplatin and S-1 in SCC patients is due to an intrinsic superiority of this drug combination compared with carboplatin and paclitaxel, to a reduced toxicity, or to other factors. Carboplatin–S-1 was as effective as carboplatin–paclitaxel in terms of response rate and PFS in patients with SCC. For such patients, carboplatin–S-1 was associated with a significantly lower rate of febrile neutropenia compared with carboplatin–paclitaxel (4% versus 19%, respectively; $P = 0.017$, chi-square test) as well as with a lower rate of neuropathy. SCC patients in the carboplatin–S-1 arm received docetaxel more

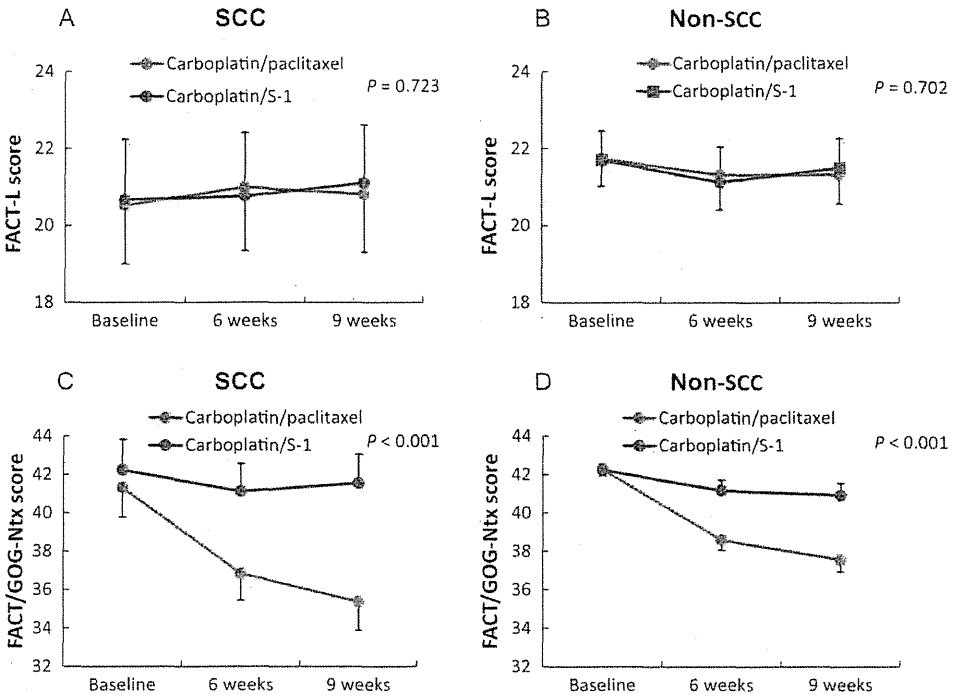

Figure 2. QOL assessments according to histological subtype of NSCLC. Assessments were carried out with the seven-item FACT-L (A and B) and 11-item FACT/GOG-Ntx (C and D) subscales for patients with SCC (A and C) or with non-SCC (B and D). Data are presented as least-square means and 95% CIs. Higher scores indicate a better QOL. *P* values were determined by analysis of variance.

Table 4. Post-treatment rate according to histological subtype of NSCLC

	Squamous			Nonsquamous		
	CBDCA–S-1 (*N* = 55)	CBDCA–PTX (*N* = 59)	*P*	CBDCA–S-1 (*N* = 227)	CBDCA–PTX (*N* = 223)	*P*
Second-line, *N* (%)	43 (78.2)	39 (66.1)	0.15	168 (74.0)	156 (70.0)	0.34
Docetaxel, *N* (%)	32 (58.2)	18 (30.5)	0.003	107 (47.1)	99 (44.4)	0.56
EGFR-TKI, *N* (%)	7 (12.7)	6 (10.2)	0.67	122 (53.7)	102 (45.7)	0.09

P values were determined by the chi-square test.

frequently as a second-line treatment than did those in the carboplatin–paclitaxel arm (58.2% versus 30.5%, respectively, $P = 0.003$), possibly because the former patients were in better condition as a result of a better tolerated first-line regimen. The reduced toxicity of carboplatin–S-1, especially with regard to neuropathy and neutropenia, may thus have allowed for more frequent application of second-line treatment with docetaxel, which has been shown to improve survival over best supportive care for the second-line setting in phase III trials [18]. Kaplan–Meier survival curves for the patients with SCC began to diverge shortly after the end of the study treatment, suggesting that the higher percentage of active second-line treatment in the carboplatin–S-1 arm of the SCC cohort may have contributed to the improved survival outcome. Given the increasing number of active drugs available for second-line treatment, subsequent therapies instituted after disease progression can have a substantial impact on OS in advanced NSCLC [19]. If multiple drugs with no large differences in effectiveness are indicated for NSCLC, treatment strategies should take into account the overall treatment plan envisioned for a given patient, including second-line and subsequent therapies as well as first-line chemotherapy.

In conclusion, we have presented the results of updated survival analysis and subgroup analysis by histology for the first phase III study of the combination of carboplatin and S-1 for the treatment of chemotherapy-naïve patients with advanced NSCLC. This regimen is therapeutically beneficial and well tolerated in such patients with either SCC or non-SCC histology. Given its efficacy and favorable toxicity profile, the combination of carboplatin and S-1 is a feasible platinum-based option to which molecularly targeted agents can be added. We are currently conducting a phase II trial of carboplatin and S-1 in combination with bevacizumab for patients with previously untreated advanced non-SCC NSCLC [20]. Furthermore, on the basis of the promising results showing a survival advantage for

SCC patients, carboplatin and S-1 should be considered among first-line treatment options for NSCLC patients with SCC.

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disclosure

The authors have declared no conflicts of interest.

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ORIGINAL REPORT

Phase III Study Comparing Amrubicin Plus Cisplatin With Irinotecan Plus Cisplatin in the Treatment of Extensive-Disease Small-Cell Lung Cancer: JCOG 0509

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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Clinical trial information: UMIN000000720 (registered at University Hospital Medical Information Network Clinical Trials Registry).

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ABSTRACT

Purpose
This randomized phase III trial was conducted to confirm noninferiority of amrubicin plus cisplatin (AP) compared with irinotecan plus cisplatin (IP) in terms of overall survival (OS) in chemotherapy-naive patients with extensive-disease (ED) small-cell lung cancer (SCLC).

Patients and Methods
Chemotherapy-naive patients with ED-SCLC were randomly assigned to receive IP, composed of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 every 4 weeks, or AP, composed of amrubicin 40 mg/m^2 on days 1, 2, and 3 and cisplatin 60 mg/m^2 on day 1 every 3 weeks.

Results
A total of 284 patients were randomly assigned to IP (n = 142) and AP (n = 142) arms. The point estimate of OS hazard ratio (HR) for AP to IP in the second interim analysis exceeded the noninferior margin (HR, 1.31), resulting in early publication because of futility. In updated analysis, median survival time was 17.7 (IP) versus 15.0 months (AP; HR, 1.43; 95% CI, 1.10 to 1.85), median progression-free survival was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.16 to 1.73), and response rate was 72.3% (IP) versus 77.9% (AP; $P = .33$). Adverse events observed in IP and AP arms were grade 4 neutropenia (22.5% *v* 79.3%), grade 3 to 4 febrile neutropenia (10.6% *v* 32.1%), and grade 3 to 4 diarrhea (7.7% *v* 1.4%).

Conclusion
AP proved inferior to IP in this trial, perhaps because the efficacy of amrubicin as a salvage therapy was differentially beneficial to IP. IP remains the standard treatment for extensive-stage SCLC in Japan.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide,[1] and small-cell lung cancer (SCLC) accounts for almost 13% of all new cases.[2] More than half of these patients are diagnosed with extensive-disease (ED) SCLC.[3] SCLC refers to a rapidly proliferating tumor that is highly sensitive to chemotherapy. However, rapid emergence of clinical drug resistance has resulted in poor prognosis, with almost all such patients dead within 2 years of initial diagnosis.[3] Thus, there is a need for new and effective therapeutic options for ED-SCLC.

The combination of etoposide and cisplatin (EP) has been standard treatment for ED-SCLC for decades. In 2002, a phase III trial conducted by the Japan Clinical Oncology Group (JCOG 9511) demonstrated the superiority of irinotecan plus cisplatin (IP) over EP for patients with ED-SCLC.[4] Median survival time (MST) and 1-year survival for the IP and EP arms were 12.8 versus 9.4 months and 58.4% versus 37.7%, respectively, but patients in the IP arm experienced a significantly higher proportion of grade 3 to 4 diarrhea. Although two randomized phase III trials have failed to confirm the superiority of IP over EP for chemotherapy-naive patients with SCLC in North America and Australia,[5-7] IP is considered equivalent to EP and one of the standard ED-SCLC regimens in Japan.

Amrubicin is a completely synthetic anthracycline derivative that is converted to an active metabolite, amrubicinol, and it is a potent topoisomerase

II inhibitor.[7] The high degree of therapeutic activity of amrubicin is caused by the selective distribution of amrubicinol, which is 10× to 100× more cytotoxic than its parent compound, amrubicin.[8,9]

A phase II study of amrubicin as single-agent therapy for previously untreated ED-SCLC yielded a response rate (RR) of 76%, complete response (CR) rate of 9%, and MST of 11.7 months,[10] similar to outcomes for platinum-based doublets at the time. Moreover, a phase I/II study of amrubicin plus cisplatin (AP) recommended administration of amrubicin 40 mg/m^2 on days 1, 2, and 3 with cisplatin 60 mg/m^2 on day 1 every 3 weeks. An RR of 87.8% and MST of 13.6 months were demonstrated in the patients treated with the recommended dose.[11] The major toxicity of the AP regimen was hematologic, which was acceptable because of the absence of febrile neutropenia (FN). Moreover, the incidence of grade 3 to 4 diarrhea, a concern with IP, was only 4.9%. Therefore, we believed AP might be a new effective treatment option for ED-SCLC, with a more favorable toxicity profile than IP. We undertook a multicenter, randomized, phase III noninferiority trial of AP compared with IP in previously untreated patients with ED-SCLC.

PATIENTS AND METHODS

Patient Selection

Patients were considered eligible if they met the following criteria: histologically or cytologically demonstrated ED-stage SCLC (defined as ≥ one of following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion, pericardial effusion), chemotherapy naive, age 20 to 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to1, no prior chemotherapy or radiotherapy for any cancers, and adequate organ function, defined as leukocyte count ≥ 4,000/mm^3, hemoglobin ≥ 9.0 g/dL, platelet count ≥ 100,000/mm^3, total bilirubin ≤ 2.0 mg/dL, AST ≤ 100 IU/L, ALT ≤ 100 IU/L, serum creatinine ≤ 1.5 mg/dL, and partial pressure of arterial blood gas without oxygen inhalation ≥ 70 torr. Patients had normal ECG and were asked to respond to a quality-of-life (QOL) questionnaire before enrollment. Patients were excluded if they had other unrelated invasive malignancies requiring ongoing therapy, serious tumor-related complication, active bacterial or fungal infection, diarrhea, intestinal paralysis or obstruction, evidence of interstitial pneumonia or pulmonary fibrosis on chest x-ray, received or expected to receive long-term treatment (≥ 50 days) with nonsteroidal anti-inflammatory drugs or steroids, serious cardiac disease, serious psychiatric disorder, pregnancy, active gastroduodenal ulcer, or history of myocardial infarction within 12 months. All enrolled patients provided written informed consent to participate in the study.

Treatment Plan

Patients were randomly assigned at a one-to-one ratio to receive either AP or IP. Random assignment was adjusted according to the following stratification factors: ECOG PS, institution, and sex. The IP regimen consisted of four cycles of irinotecan 60 mg/m^2 intravenously (IV) on days 1, 8, and 15 and cisplatin 60 mg/m^2 IV on day 1. Cycle length for this arm was 4 weeks. The AP regimen initially consisted of four cycles of amrubicin 40 mg/m^2 IV on days 1, 2, and 3 and cisplatin 60 mg/m^2 IV on day 1 every 3 weeks. However, because of the high incidence of severe hematologic toxicities, the protocol was revised to reduce the initial dose of amrubicin to 35 mg/m^2 in the AP group after 66% of patients (94 of 142) in the AP arm had been enrolled. The subsequent cycles of both arms were begun if absolute leukocyte count ≥ 3,000/μL, platelet count ≥ 100,000/μL, serum creatinine ≤ 1.5 mg/dL, and treatment-related nonhematologic toxicities (excluding alopecia, weight loss, and hyponatremia) had been resolved to grade ≤ 1. In regard to dose modification, if during the previous course the patient presented with thrombocytopenia (platelet count < 20,000/mm^3) and/or grade 3 nonhematologic toxicity including FN and diarrhea, the dose of irinotecan was reduced by 10 mg/m^2 and the dose of amrubicin by 5 mg/m^2 in the next cycle. The dose of cisplatin was reduced by 20 mg/m^2 for subsequent courses in the event of any of the following toxicities: creatinine > 1.5 to ≤ 2.0 mg/dL, grade 3 nonhematologic toxicity, grade ≥ 2 neuropathy (sensory or motor), and grade ≥ 2 muscle or joint pain. Prophylactic administration of granulocyte colony-stimulating factor was not allowed in the first cycle. After the fourth cycle, initially prophylactic cranial irradiation (PCI) was conducted as per institutional policy. However, because of the report at the 2007 Annual Meeting of the American Society of Clinical Oncology stating that addition of PCI for ED-SCLC responders significantly extended survival,[12] the protocol was revised just 4 months after the start of patient enrollment so that patients with CR or tumor elimination would additionally receive PCI.

Response and Toxicity Evaluations

Baseline evaluation consisted of complete medical history and physical examination, ECG, ECOG PS, complete blood count, blood chemistry, blood gas analysis, computed tomography (CT) scan of the chest, CT or ultrasound of the abdomen, magnetic resonance imaging or CT of the brain, and bone scan or positron emission tomography. During treatment within the study, complete blood count, blood chemistry, and complete physical examination with clinical assessment were performed at least every week. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 3). Chest x-ray was performed every cycle during protocol treatment, whether or not there was evidence of progression. All responses were defined according to RECIST (version 1.0). We evaluated patient QOL twice—once at baseline and once after completion of the second course (8 weeks in IP arm, 6 weeks in AP arm after treatment initiation)—using a QOL questionnaire for patients with cancer treated with anticancer drugs (QOL-ACD) and QOL Questionnaire Core 30 (QLQ-C30; diarrhea score). The primary metric used to analyze QOL was a comparison between arms in terms of improvement of physical status score over baseline QOL questionnaire.

End Points

The objective of this randomized phase III study was to establish the noninferiority of AP compared with IP as first-line therapy in patients with ED-SCLC. The primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), RR, adverse events (AEs), grade 3 to 4 diarrhea, and QOL.

Study Design and Statistical Analysis

This trial was a multicenter randomized trial. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review board of each participating institution.

The trial was designed to achieve at least 70% power to confirm noninferiority of AP compared with IP, with a noninferiority margin of 1.31 in terms of hazard ratio (HR), MST of 12.8 months in both arms, and one-sided α = 0.05. We believed 3 months would be the maximum allowable noninferiority margin in the case of a less-toxic regimen with a different toxicity profile—a profile that we had expected from the phase I/II study. An MST 3 months shorter than that of the IP arm would correspond to an HR of 1.31. The planned sample size was 282 patients, determined by the methods of Schoenfeld and Richter,[13] with 3 years of accrual and 3 years of follow-up. Because of an insufficient accrual rate during the study, the accrual period was revised to 4 years.

An interim analysis was scheduled because of the futility of the trial at the halfway mark of registration. The results from the interim analysis were reviewed by the JCOG Data and Safety Monitoring Committee, and investigators were blinded for the results. After the first interim analysis, the protocol was revised to add second interim analysis after all patients had been registered. Multiplicity for the primary end point was adjusted using O'Brien-Fleming–type alpha spending function.[14] The primary end point—OS—was analyzed using stratified Cox regression analysis with PS (0 *v* 1) and sex (male *v* female) as strata for all eligible patients. Except for the primary analysis, OS and PFS were analyzed using unstratified Cox regression analysis. OS and PFS were estimated using the Kaplan-Meier method. RRs were compared using Fisher's exact test. QOL scores were analyzed using logistic regression with covariate, treatment arm, and QOL scores at baseline. All *P* values are two sided, except for the primary analysis of the noninferiority hypothesis. Statistical analyses were conducted using SAS software (version 9.1 or 9.2; SAS Institute, Cary, NC).

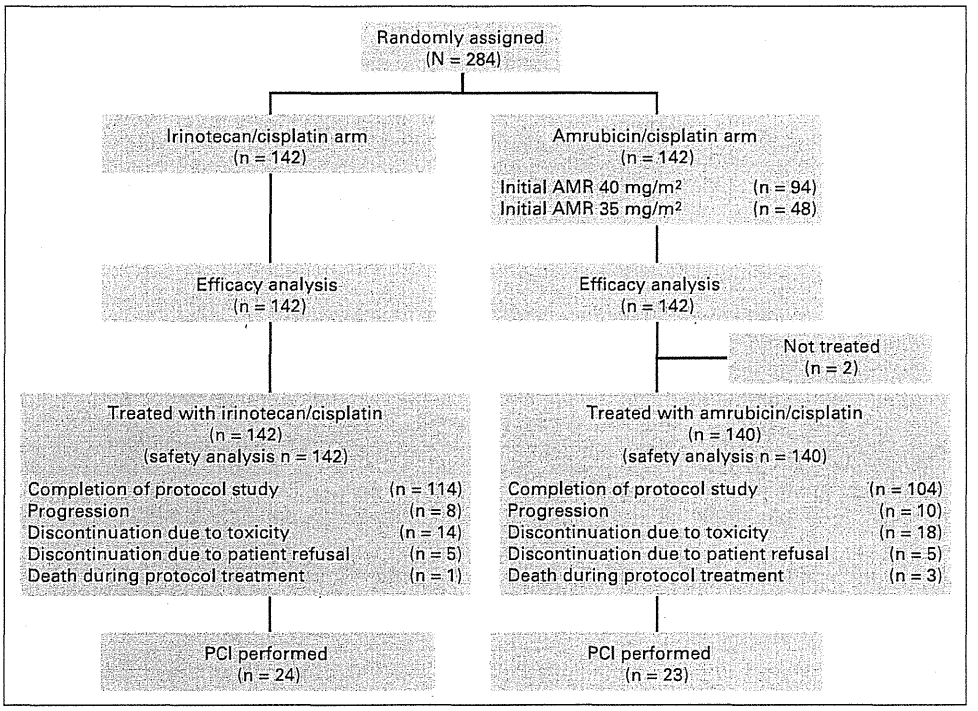

Fig 1. CONSORT diagram. AMR, amrubicin; PCI, prophylactic cranial irradiation.

RESULTS

From May 2007 to December 2010, 284 patients from 35 institutions were enrolled onto the study. All patients were deemed eligible; 142 patients were randomly assigned to the IP arm and 142 to the AP arm (Fig 1). Baseline characteristics were well balanced between the arms (Table 1). All 284 patients were included in the analysis for OS, PFS, and response. Patients who received at least one cycle of study treatment (n = 282) were assessable for toxicity analysis.

Treatment Delivery

Table 2 lists the number of cycles delivered. There were no significant differences between the two arms in treatment delivery. Two patients in the AP arm did not receive any protocol treatment. For the remaining 142 and 140 patients, the proportions receiving the planned four cycles of chemotherapy were 81% and 73.2% in the IP and AP arms, respectively. In the AP arm, 67% (63 of 94) of those who received an initial dose of 40 mg/m^2 completed four cycles, whereas in the AP arm, 85.4% of those who received 35 mg/m^2 completed four cycles; 4.9% (seven of 142) in the IP group and 7% (10 of 142) in the AP group received < two thirds of the planned dose of cisplatin. The interruption rates before protocol completion in the IP and AP arms were 19.7% and 26.8%, respectively; 13.4% and 16.2% of the patients in the IP and AP arms, respectively, had their treatment interrupted because of toxicity. In the IP and AP arms, 24 and 23 patients underwent PCI, respectively.

Toxicity

Table 3 lists grade ≥ 3 major toxicities. The most common grade ≥ 3 AEs in the AP arm were myelosuppression and FN. Diarrhea represented the predominant type of grade ≥ 3 toxicity in the IP arm. Myelosuppression was improved by reducing the initial dose of amrubicin: grade 3 to 4 leukopenia (from 77.2% to 62.5%), neutropenia (from 96.7% to 93.8%), anemia (from 43.5% to 22.9%), thrombocytopenia (from 35.9% to 10.4%), and FN (from 37% to 22.9%).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	IP Arm (n = 142) No.	IP Arm (n = 142) %	AP Arm (n = 142) No.	AP Arm (n = 142) %
Sex				
Male	120	84.5	119	83.8
Female	22	15.5	23	16.2
Age, years				
Median	63		63	
Range	39-70		29-70	
ECOG PS				
0	78	54.9	80	56.3
1	64	45.1	62	43.7
Measurable lesions				
None	1	0.7	2	1.4
Yes	141	99.3	140	98.6
Smoking status				
Nonsmoker	3	2.1	3	2.1
Smoker	139	97.9	139	97.9
Metastasis (overlapped)				
Lung	9	6.3	14	9.9
Bone	25	17.6	31	21.8
Brain	32	22.5	41	28.9
Liver	35	24.6	45	31.7
Others	68	47.9	64	45.1

Abbreviations: AP, amrubicin plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; IP, irinotecan plus cisplatin.

Table 2. Delivered Cycles

No. of Cycles	IP Arm (n = 142) No.	IP Arm (n = 142) %	AP Arm (n = 142) No.	AP Arm (n = 142) %
0	0	0.0	2	1.4
1	7	4.9	8	5.6
2	10	7.0	14	9.9
3	10	7.0	14	9.9
4	115	81.0	104	73.2

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin.

One treatment-related death occurred in the IP arm (resulting from infection), and two occurred in the AP arm (one resulting from infection, and other resulting from pulmonary hemorrhage).

Efficacy

In the first interim analysis, the HR was 1.25 (99.9% CI, 0.28 to 5.59; information time, 0.16). The second interim analysis was conducted after completion of patient accrual based on the data as of May 2011. It showed that the median OS for AP (15.0 months) was much worse than that for IP (18.3 months) and that the HR was 1.41 (96.3% CI, 1.03 to 1.93) in stratified Cox regression. The point estimate of HR in OS for AP to IP exceeded the noninferiority margin (HR, 1.31); therefore, the Data Safety Monitoring Committee recommended early publication because of futility according to the preplanned decision rule that a point estimate of HR of AP to IP exceed the noninferiority margin (HR > 1.31). The Bayesian predictive probability that noninferiority would be shown with statistical significance at the end of this trial was 16.2%. Median PFS was 5.7 (IP) versus 5.2 months (AP; HR, 1.43; 95% CI, 1.13 to 1.82). RR was 72.3% (IP) versus 77.9% (AP; $P = .33$). Even updated analysis, as of May 2012, showed OS to be inferior in the AP arm (17.7 *v* 15.0 months; HR, 1.43; 95% CI, 1.10 to 1.85; Fig 2A). Median PFS was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.12 to 1.80; Fig 2B). The initial dose reduction in amrubicin had no impact on any efficacy results when the dose was reduced to 35 mg (Table 4).

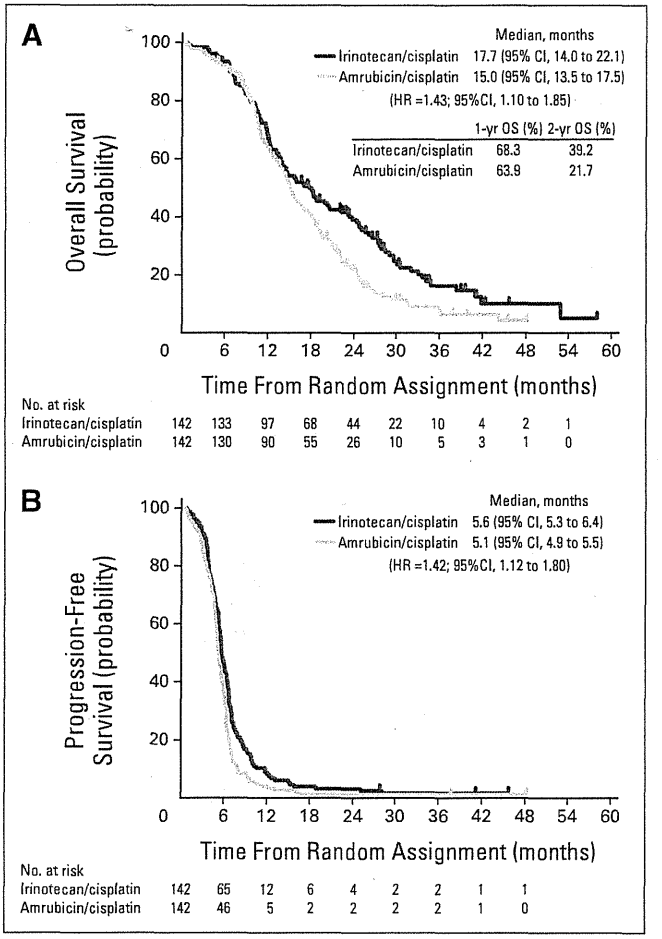

Fig 2. (A) Overall and (B) progression-free survival for intent-to-treat population ($n = 284$). *HR, hazard ratio.*

Table 3. Toxicities

Toxicity	Regimen by Grade (%) IP Arm (n = 142)* All	IP Arm 3	IP Arm 4	AP Arm (n = 140)† All	AP Arm 3	AP Arm 4
Hematologic						
Leukopenia	88.7	20.4	2.1	98.6	46.4	25.7
Neutropenia	95.8	35.9	22.5	99.3	16.4	79.3
Anemia	85.9	16.9	6.3	91.4	23.6	12.9
Thrombocytopenia	12.0	1.4	0.7	59.3	15.7	11.4
Nonhematologic						
FN	10.6	9.9	0.7	32.1	31.4	0.7
Fatigue	61.3	3.5	0.7	64.3	3.6	0.0
Nausea	78.9	6.3	0.0	79.3	4.3	0.0
Vomiting	37.3	3.5	0.0	34.3	2.1	0.0
Diarrhea	63.4	7.7	0.0	26.4	1.4	0.0
Hyponatremia	74.6	14.8	4.9	79.3	15.7	6.4
Cardiovascular events	0.0	0.0	0.0	0.0	0.0	0.0

Abbreviations: AP, amrubicin plus cisplatin; FN, febrile neutropenia; IP, irinotecan plus cisplatin.
*One treatment-related death (0.7%).
†Two treatment-related deaths (1.4%).

The QOL questionnaire was completed in most cases: 282 of 284 patients at baseline and 272 patients at the end of the second course. The proportion of improvement in physical status in terms of QOL—the primary metric used to analyze QOL—was 37.1% in the IP arm versus 31.7% in the AP arm (odds ratio, 0.72; 95% CI, 0.43 to 1.22; $P = .23$). There was no significant difference in QOL improvement.

Poststudy Treatment

Table 5 summarizes poststudy treatment. Overall, 93.7% of IP-arm patients and 92.1% of AP-arm patients received additional therapy; 89.4% of patients in the IP arm and 87.1% of those in the AP arm received second-line chemotherapy, whereas 59.2% of those in the IP arm and 62.1% of those in the AP arm received third-line chemotherapy, indicating no substantial difference in the percentage receiving poststudy treatment. Nonetheless, 61 and 34 patients in the IP arm were administered single-agent amrubicin in their second- or third-line therapy, respectively. These figures are higher than those observed in the AP arm.

Table 4. Summary of Survival and Response

Survival/ Response	Before Amrubicin Dose Revision		After Amrubicin Dose Revision	
	IP Arm (n = 97)	AP Arm (n = 94)	IP Arm (n = 45)	AP Arm (n = 48)
ORR				
No.	72 of 97	70 of 93*	30 of 44*	39 of 47*
%	74.2	75.3	68.2	83.0
PFS				
Median	6.0	5.3	5.4	5.0
95% CI	5.5 to 6.6	4.9 to 5.7	4.8 to 6.4	4.7 to 5.7
OS				
Median	17.7	14.9	18.0	15.6
95% CI	13.9 to 22.1	13.1 to 16.8	12.2 to NE	12.4 to 20.7

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*One patient excluded because of no measurable lesions.

DISCUSSION

The outcomes in our study did not satisfy the primary end point, showing OS in the AP arm to be significantly inferior to that in the IP arm. The MST for AP was favorable (15 months), reproducing the outcomes obtained in the phase I/II study. The MST for IP was approximately 5 months beyond that shown in JCOG 9511. AP may simply be inferior to IP in the first line in that the platinum–topoisomerase I inhibitor partnership between cisplatin and irinotecan may be more synergistic. Although there was only a 0.5-month difference in median PFS, the IP arm displayed a much longer MST (ie, postprogression survival of IP arm was longer); two conceivable reasons for this are the advancements in support therapy and the influence of poststudy treatment.

Table 5. Poststudy Therapy

Chemotherapy	Second Line		Third Line	
	IP Arm (n = 127)	AP Arm (n = 122)	IP Arm (n = 84)	AP Arm (n = 87)
IP	7	10	0	3
Irinotecan	3	24	7	19
Cisplatin, irinotecan, and etoposide	10	13	2	2
Carboplatin plus irinotecan	1	4	0	9
Irinotecan plus other	0	1	3	4
Amrubicin	61	2	34	12
AP	0	4	0	1
Carboplatin plus amrubicin	1	0	0	0
Cisplatin plus etoposide	9	11	4	1
Carboplatin plus etoposide	22	29	25	24
Etoposide	1	0	0	0
Carboplatin, etoposide, and other	0	1	0	0
Topotecan	12	23	6	5
Carboplatin	0	0	0	1
Carboplatin plus other	0	0	1	4
Other	0	0	2	2

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin.

The incidence of the greatest toxicity concern in JCOG 9511, grade 3 to 4 diarrhea, was 7.7% in this study (16.0% in JCOG 9511). The incidence of diarrhea was lower, which was most likely the result of advances in support therapy. That said, the impact of poststudy treatment should garner the most attention as a reason for the inability to demonstrate survival extension or noninferiority in our study.

Analysis of subsequent therapies administered in this study revealed that ultimately, two thirds of all patients in the IP arm received single-agent amrubicin as a subsequent therapy. There was no difference between the two arms in terms of the percentage of patients who received subsequent therapies, suggesting that amrubicin, used in a large percentage of patients in the IP arm as postprotocol therapy, contributed to an extension in OS.

Several studies have examined the use of amrubicin as secondary treatment for SCLC.[15-18] A phase II study by Inoue et al[15] comparing amrubicin with topotecan, considered to be standard secondary treatment, indicated the possibility that amrubicin might be superior to topotecan. A phase III study conducted by Jotte et al[16] did not show any significant difference between topotecan and amrubicin as second-line chemotherapy in terms of OS (MST: amrubicin, 9.2 months; topotecan, 9.9 months; HR, 0.89; 95% CI, 0.73 to 1.06); however, outcomes with amrubicin were significantly better in terms of RR and PFS, and OS was better in subanalysis only among patients experiencing refractory relapse (MST: amrubicin, 6.2 months; topotecan, 5.7 months; HR, 0.77; 95% CI, 0.79 to 1.0; $P = .047$). Although topotecan is the most evidence-based second-line therapy for SCLC,[19,20] amrubicin has come into widespread use in Japan as a result of many reports on its use among Japanese patients (ie, RR and PFS compare favorably, and survival is quite respectable).

Amrubicin is a topoisomerase II inhibitor, suggesting that it may not be effective in patients for whom etoposide (also topisomerase II inhibitor) or EP has failed. Irinotecan is a topoisomerase I inhibitor, and amrubicin may be effective in those for whom IP has failed (unlike in those for whom EP has failed). Accordingly, the possibility remains that the frequent use of amrubicin in poststudy treatment may have extended survival even beyond that expected. This may be a reason why IP therapy showed significantly better survival than AP therapy in our study. In this phase III trial, AP proved to be inferior to IP, but the results seen here do not negate the activity of this agent in SCLC and perhaps underscore the particular value of amrubicin as second- or third-line therapy in this setting.

The AP arm showed reproducible, favorable survival in the form of 15-month MST and noninferiority to EP in a phase III study conducted in China (MST: AP, 11.79 months; EP, 10.28 months),[21] suggesting that AP is rather effective. However, considering that hematotoxicity and FN, even after reduction of the dose to 35 mg/m^2, were relatively serious, and considering the excellent effect of amrubicin monotherapy in relapse treatment, we are unable to recommend AP as standard first-line therapy for ED-SCLC. Therefore, IP therapy showed favorable OS and toxicity profile, indicating, as expected, its continuing presence as one of the standard first-line therapies for ED-SCLC in Japan.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Data analysis and interpretation: Miyako Satouchi, Taro Shibata, Kazuhiko Nakagawa, Tomohide Tamura
Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

Topoisomerase I: An enzyme that acts on the topology of native DNA by changing the supercoiled structure of DNA. Topoisomerase I makes a nick in one DNA strand, twists it around the other, and religates the nicked strand.

Topoisomerase II: An enzyme that catalyzes the ATP-dependent transport of one segment of DNA duplex through another DNA duplex. Topoisomerases change the topology of DNA by controlling the essential functions of separating intertwined daughter chromosomes.

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Appendix

Overall survival (OS) was defined as the time from random assignment to death resulting from any cause and censored at the last follow-up date. Progression-free survival (PFS) was defined as the interval from random assignment to diagnosis of progression or death resulting from any cause and censored at the last date on which progression-free status was evaluated.

The response rate was the proportion of patients evaluated as having a complete or partial response as overall response among all eligible patients with evaluable lesions. Proportion of grade 3 to 4 diarrhea was defined the number of patients who experienced at least one grade 3 to 4 diarrhea event by Common Terminology Criteria for Adverse Events (version 3) from the first day of protocol treatment to 30 days after protocol treatment. Quality of life was compared in terms of a proportion of patients whose quality-of-life scores improved during protocol treatment.

CIs for OS and PFS proportions were estimated using Greenwood's formula, and those of median OS and median PFS were estimated using the method of Brookmeyer and Crowley. Hazard ratios were estimated using Cox regression.

Is Consolidation Chemotherapy after Concurrent Chemo-Radiotherapy Beneficial for Patients with Locally Advanced Non–Small-Cell Lung Cancer?

A Pooled Analysis of the Literature

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Introduction: The purpose of this study was to evaluate whether consolidation chemotherapy (CCT) after concurrent chemo-radiotherapy is beneficial for patients with locally advanced non–small-cell lung cancer (LA-NSCLC).

Methods: We systematically searched PubMed for phase II/III trials published before December 31, 2011, examining survival of LA-NSCLC treated with concurrent chemo-radiotherapy. Median overall survival and other study characteristics were collected from each study and pooled. We extracted log-transformed hazards and standard errors under the assumption that survival follows an exponential distribution, and computed a pooled median overall survival and a 95% confidence interval (CI) using random-effects model. Collected trial arms were categorized as having CCT or not having it, CCT+ and CCT−, respectively.

Results: Forty-one studies were identified including seven phase III studies and 34 phase II studies with 45 arms (CCT+: 25; CCT−: 20). Clinical data were comparable for clinical stage, performance status, cancer histology, sex, and median age between the two groups. There was no statistical difference in pooled mOS between CCT+ (19.0 month; 95% CI, 17.3–21.0) and CCT− (17.9 month; 95% CI, 16.1–19.9). Predicted hazard ratio of CCT+ to CCT− was 0.94 (95% CI, 0.81–1.09; $p = 0.40$). There were no differences between the two groups with regard to grade 3–5 toxicities in pneumonitis, esophagitis, and neutropenia. These models estimated that addition of CCT could not lead to significant survival prolongation or risk reduction in death for LA-NSCLC patients.

Conclusion: The pooled analysis based on a publication basis failed to provide evidence that CCT yields significant survival benefit for LA-NSCLC.

Key Words: Non–small-cell lung cancer, Chemo-radiotherapy, Consolidation chemotherapy, Locally advanced.

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Lung cancer continues to be the leading cause of cancer-related deaths worldwide, with approximately 1.4 million deaths per year.[1] Non–small-cell lung cancer (NSCLC) represents more than 80% of all lung tumors, and approximately 35% of patients with NSCLC present with stage III locally advanced non–small cell lung cancer disease (LA-NSCLC). Previous clinical trials of LA-NSCLC demonstrated that concurrent administration of two cycles of chemotherapy with thoracic radiotherapy (TRT) improved overall survival (OS) compared with radiotherapy (RT) alone and/or sequential chemo-RT.[2–4] Thus the standard treatment for patients with LA-NSCLC is recognized as concurrent chemo-RT with curative intent. Despite recent progress, cure rates remain low for those diagnosed with LA-NSCLC, and the prognosis for the vast majority of LA-NSCLC patients still remains poor. Therefore, new strategies such as radiation methods, radiation dose, optimal chemotherapy regimen, prophylactic cranial irradiation, and molecular targeted agents, are needed to improve clinical outcome.[5] The addition of consolidation chemotherapy (CCT) is another attractive approach.

Recently, close attention has been paid to the efficacy of maintenance chemotherapy after platinum combination chemotherapy for metastatic NSCLC patients and postoperative adjuvant chemotherapy for early-stage NSCLC patients. In fact, several randomized studies and their systematic reviews/meta-analyses have already indicated the efficacy of maintenance[6,7] and adjuvant chemotherapy.[8–10] For LA-NSCLC patients, however, little is known about the efficacy of CCT and few randomized studies have been reported. The Hoosier Oncology Group recently performed a randomized phase III study and reported that CCT with docetaxel increased toxicities without significant survival benefit.[11] There is currently insufficient evidence indicating CCT improves OS of patients with LA-NSCLC.

The purpose of this study is to evaluate, through a pooled analysis of publications, whether CCT after concurrent chemo-RT is beneficial for patients with LA-NSCLC in terms of survival prolongation.

MATERIALS AND METHODS

Literature Search and Data Extraction

We performed a systematic search of PubMed for phase II/III trials examining survivals of LA-NSCLC patients treated with concurrent chemo-RT. All trials that had been reported by December 31, 2011, were targeted. Systematic search was performed using the key words, *non-small cell lung cancer, radiation or RT, concurrent or concomitant, phase II or phase III*. All searches were limited to English language and studies with no less than 30 patients per arm. Chemotherapy regimens scheduled in the concurrent phase were limited to platinum combination therapies. When a study had multiple arms and at least one of them fulfilled the requirements, it was included in our analysis. Studies that did not analyze survival data, or that analyzed only patients with poor performance status (PS; Eastern Cooperative Oncology Group score ≥ 2/Karnofsky score ≤ 70) or high-risk complications, or elderly patients (age ≥ 70 years) were excluded. Studies, in which randomization and survival analyses were performed only on patients with no disease progression after induction chemo-RT were excluded because these trials would strongly be biased toward longer OS. We also excluded trial arms in which surgery or induction chemotherapy was offered in addition to the concurrent chemo-RT.

Collected trial arms were categorized as having (CCT+) or not having (CCT−) CCT. We defined CCT as systemic chemotherapy sequentially performed after concurrent chemo-RT. Arms, in which triweekly carboplatin plus paclitaxel were used after low-dose weekly carboplatin plus paclitaxel with concurrent TRT, were included in CCT+ group in this analysis. CCT+ group was further divided into two patterns of CCT: continuous CCT (CCCT), which continues treatment with at least one of the agents given in the initial therapy and switch CCT (SCCT), which switches to a different agent. For each trial, data on sample size, OS, chemotherapy regimens, doses of RT, delivery of treatment, frequency of grade 3–5 toxicities (neutropenia, leukopenia, esophagitis, pneumonitis, and treatment-related death) were collected. Median OS, and 1-, 2-, and 3-year OS rates were determined using reported data or survival curves. We also recorded data of patient characteristics included in studies (age, sex, histology and stage of cancer, and PS) and study characteristics (trial phase, chemotherapy regimen, and period and region in which study was conducted) to assess heterogeneity across studies.

All phase II/III studies were retrieved independently by two investigators (KT and SY) to assess the reliability of data extraction. After selection of potentially appropriate trials, the investigators reviewed each other's selected trials and excluded inappropriate trials with the agreement of both. Disagreements were adjudicated by a third reviewer after referring to the original articles.

Statistical Analysis

To estimate 95% confidence interval (CI) for median (mOS), the observed mOS was considered as an approximate estimate of the median of an exponential distribution. To examine the bias and validity of this estimation, we compared measured and estimated values of 1-, 2-, and 3-year survival rates and calculated the discrepancy among them by mean prediction error and root mean squared error.[12,13]

For each study, hazard was calculated as the natural logarithm of 2 divided by the mOS. We combined log-transformed hazards and standard errors (SEs) from individual studies and computed a pooled mean and SE of the log-transformed hazard using a random-effects model. Comparison of the pooled survival between CCT− and CCT+ was performed by meta-regression analysis. Because two study characteristics, *region* and *period*, were found to be associated with survival, we performed additional meta-regression analysis adjusted for them. Pooled mOS with 95% CI was calculated as the natural logarithm of 2 divided by the pooled hazard, which was converted back from the pooled log-transformed value computed in the random-effects model. Hazard ratio (HR) was obtained by taking the ratio of the pooled hazards estimated in the meta-regression analysis. The I^2 statistics were used to assess heterogeneity across studies, and I^2 less than 25, I^2 of 25 or more, but less than 50, and I^2 of 50 or more were interpreted as signifying low-level, intermediate-level, and high-level heterogeneity, respectively.[14] The survival benefit of CCT was analyzed in all studies, and also in subgroups according to study character using a forest plot of HRs. We used Student's t test, Kruskal–Wallis test, or Pearson's χ^2 test to examine a difference in the distribution of targeted values among trial arms, or in the proportion of targeted trial arms.

A p value less than 0.05 was considered statistically significant, and all reported p values were two-sided. The Eggers' test and Begg's funnel plots were calculated using Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, NJ). All other statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL) or SAS version 9 (SAS Inc., Cary, NC).

RESULTS

Patient Characteristics and Treatment Administrations in Each Study

We identified 41 studies[2,4,15–53] (7 phase III studies and 34 phase II studies) including 45 arms with 3479

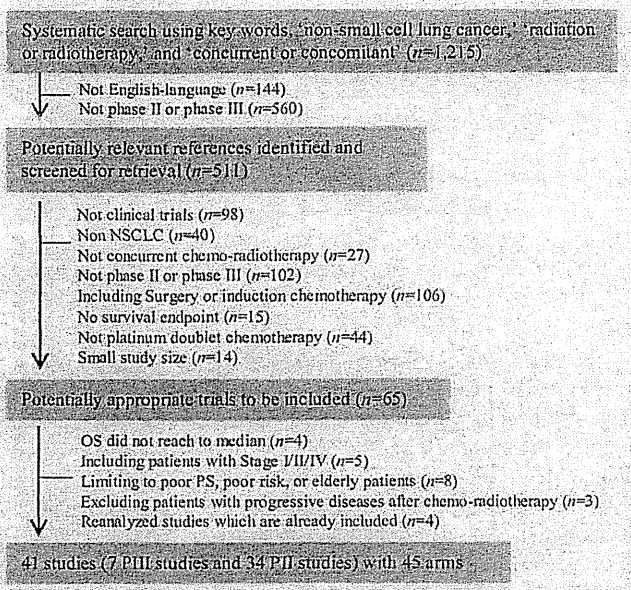

FIGURE 1. Flowchart showing retrieved citations from literature searches and the number of trials analyzed. NSCLC, non–small-lung cancer; PS, performance status.

patients, which examined survivals of LA-NSCLC patients treated with concurrent chemo-RT (Fig. 1; and Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A439). All 41 studies reported mature data on mOS and 1-year OS, whereas 40 studies reported data on 2-year OS, and 32 studies did on 3-year OS.

Among studies analyzed, 25 arms (1707 patients) were designed to perform CCT after concurrent chemo-RT (CCT+ group), whereas 20 arms (1772 patients) were designed for only concurrent chemo-RT (CCT− group). In CCT+ group, four arms (247 patients) were designed for SCCT and other 21 arms (1460 patients) for CCCT. The data on included patients and administered treatments of the two groups are shown in Table 1. There was no statistical difference between the two groups in clinical data of included patients, such as age, sex, histology and clinical stage of cancer, and PS. The planned doses of TRT were comparable between the two groups (62–63 Gy on average in both groups; Table 1). In concurrent phases, approximately 80% to 90% of patients had completed RT/chemotherapy in both groups. Regarding CCT, 1 to 4 (average: 2.3) cycles had been planned in CCT+ arms, and among them, 0.7 to 3.1 (average: 1.5) cycles were actually delivered (Table 1).

TABLE 1. Differences of Patient Characteristics and Treatment Administrations between Study Arms with and without CCT

	Arms without CCT		Arms with CCT		
Patients Characteristics	**Mean**	**SD**	**Mean**	**SD**	***p*[a]**
Age					
Median age	61.71	2.72	60.58	3.24	0.22
Sex					
Female, %	21.96	12.54	23.79	12.92	0.63
Histology					
Squamous cell carcinoma, %	47.56	9.94	43.67	12.20	0.26
Adenocarcinoma, %	35.60	8.85	36.02	12.51	0.90
Stage					
IIIA, %	35.68	19.21	33.19	18.35	0.67
IIIB, %	63.27	19.29	66.31	18.61	0.52
PS, %[b]					
0	46.43	25.72	42.89	19.94	0.65
1	50.38	21.70	52.92	16.01	0.70
2	4.28	6.97	4.36	11.48	0.98
Treatment Administrations					
Concurrent phase					
Planned TRT dose (Gy)	62.85	5.99	62.70	3.50	0.96
Patients who completed TRT (%)	85.65	10.89	89.18	7.66	0.29
Patients who completed chemotherapies (%)	86.15	13.03	79.16	14.47	0.14
Consolidation phase					
No. of planned CCT cycles	—	—	2.32	0.90	—
Median no. of delivered CCT cycles	—	—	1.88	0.90	—
Mean no. of delivered CCT cycles	—	—	1.53	0.64	—

[a]Statistical differences were calculated using Student's *t* test across trial arms.
[b]KPS was converted to Eastern Cooperative Oncology Group PS as follows: KPS 90–100; PS 0, KPS 70–80; PS 1, KPS 60–70; PS 2.
TRT, thoracic radiotherapy; CCT, consolidation chemotherapy; PS, performance status; SD, standard deviation; KPS, Karnofsky performance score.