TABLE 2. Impacts of Study Characteristics on mOS

Study Characteristics	No. of Arms	No. of Patients	mOS		
			Mean	SD	p^a
Trial phase					0.98
II	34	1936	19.36	5.91	—
III	11	1543	19.31	4.27	—
Proportion of stage IIIA patients[b]					0.046
≤33%	22	1674	17.7	3.44	—
>33%	23	1805	20.9	6.64	—
Period					0.022
1995–2000	12	738	16.40	3.80	—
2001–2005	14	978	19.08	4.87	—
2006–2011	19	1763	21.41	6.15	—
Region					0.035
Asian	22	1789	21.12	5.97	—
Non-Asian	23	1690	17.65	4.53	—
Platinum regimens in concurrent phase					0.48
CDDP	29	2524	18.93	5.77	—
CBDCA	16	955	20.11	5.08	—
Employment of third-generation drugs[c]					<0.01
Yes	25	1612	21.12	6.16	
No	20	1867	17.13	3.62	
Use of taxanes[d]					0.33
Yes	18	1122	20.32	5.26	
No	27	2357	18.70	5.67	

[a]Statistical differences were calculated using Student's *t* test or Kruskal–Wallis test across trial arms.
[b]Studies were divided into two groups with the median by proportion of stage IIIA patients.
[c]Third-generation drug was defined as irinotecan, paclitaxel, docetaxel, vinorelbine, gemcitabine, pemetrexed, or S-1.
[d]Taxane was defined as paclitaxel or docetaxel.
CDDP, cisplatin; CBDCA, carboplatin; mOS, median overall survival; SD, standard deviation.

Publication Bias

Potential publication bias was evaluated using the Eggers' test and Begg's funnel plots with log-transformed hazards calculated from mOS (horizontal axis) as the outcome and their SEs (vertical axis) as the index for accuracy (Supplementary Figure 1, Supplemental Digital Content 2, http://links.lww.com/JTO/A440). The funnel plots were symmetrical, with p values of 0.78, 0.17, and 0.21 in the Egger's test for all study arms, CCT− arms, and CCT+ arms, respectively. These data indicate that there is little evidence of publication bias.

Effects of Study Characteristics on Survival

As our study analyzed potentially heterogeneous study arms with different study characteristics, we next examined the influence of these study characteristics on mOS. We found four characteristics could be implicated in mOS: *proportion of stage IIIA patients*, *region* and *period* in which a study was conducted, and *use of third-generation drugs* (Table 2). As expected, studies which have larger proportion of stage IIIA patients tended to have longer mOS. Studies in Asian countries yielded significantly longer mOS (average: 21.2 month) than those in non-Asian countries (average: 17.7 months), most of which were European countries and the United States. In addition, mOS significantly improved during these 15 years: 16.4 months (1995–2000) versus 19.1 months (2001–2005) versus 21.4 months (2006–2011). Furthermore, studies using third-generation drugs tended to have longer mOS than those using only first- and/or second-generation drugs. Other factors such as *phase II or III* or *platinum regimens (cisplatin or carboplatin) in concurrent phase* did not significantly affect mOS of study arms (Table 2).

The distribution of study characteristics between CCT− and CCT+ is summarized in Supplementary Table 2 (Supplemental Digital Content 3, http://links.lww.com/JTO/A441). Although third-generation drugs were more frequently used in CCT+ than in CCT−, no significant difference was observed in the distribution of other study characteristics (Supplementary Table 2, Supplemental Digital Content 3, http://links.lww.com/JTO/A441).

No Survival Improvement of LA-NSCLC by CCT

mOS and corresponding 95% CI in each study arm are shown in Figure 2. I^2 values for assessing heterogeneity were 15.3, 31.5, and 36.7 in overall, CCT+, and CCT− arms, respectively. No statistical difference was observed in the distribution of mOS between CCT+ and CCT− (p = 0.82). Next, to calculate pooled mOS using random-effects

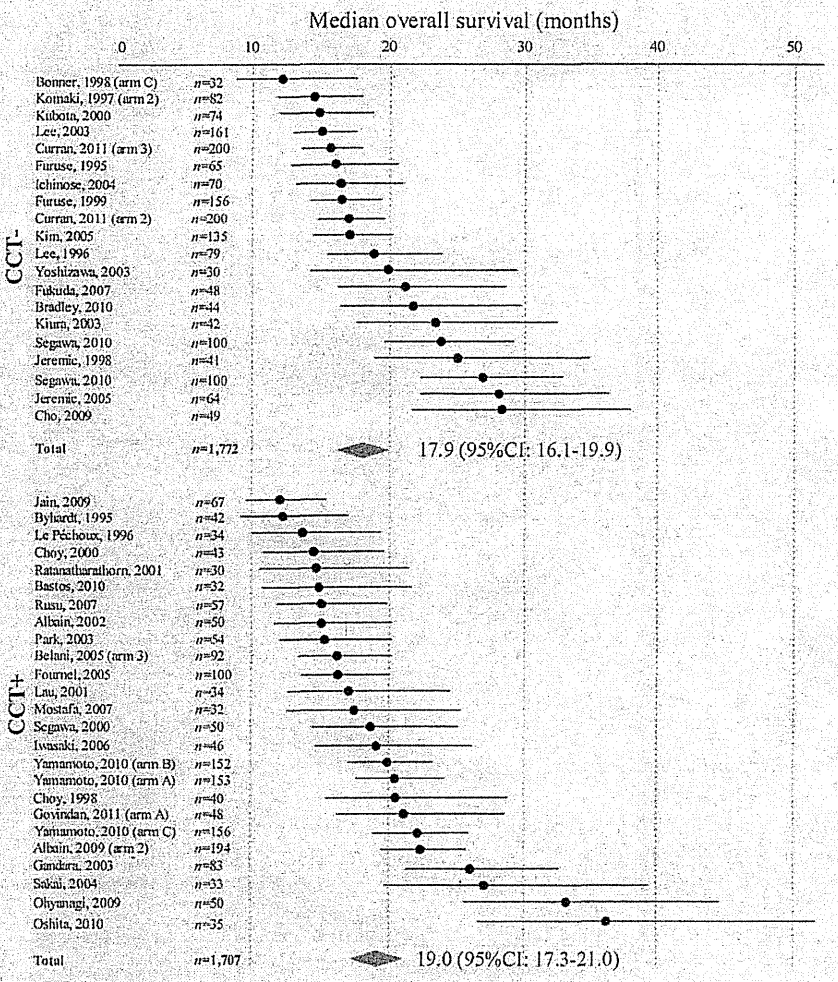

FIGURE 2. Individual and pooled median overall survivals with corresponding 95% CIs in study arms according to the presence of CCT. CCT, consolidated chemotherapy; CI, confidence interval.

models, we estimated that survival follows an exponential distribution. In this assumption, calculated values of 1-, 2-, and 3-year survival rates showed good agreement with actual values of them, with minimal bias and acceptable validity (Supplementary Figure 2, Supplemental Digital Content 4, http://links.lww.com/JTO/A442). In random-effects models, pooled mOS was comparable between CCT+ (19.0 month; 95% CI, 17.3–21.0) and CCT− (17.9 month; 95% CI, 16.1–19.9), and predicted HR of CCT+ to CCT− was 0·94 (95% CI, 0.81–1.09; $p = 0.40$), suggesting that CCT did not significantly improve the mOS of LA-NSCLC patients (Fig. 2). In addition, pooled 1-, 2-, and 3-year survival rates were similar between CCT+ (64.6%, 41.8%, and 27.0%, respectively) and CCT− (62.9%, 39.5%, and 24.8%, respectively), supporting the results of mOS analyses. Similar results were obtained in the additional meta-regression analysis adjusted for four study characteristics that could influence on mOS: proportion of stage IIIA patients, *region* and *period*, and *use of third-generation drugs*, (HR: 0.92; 95% CI, 0.73–1.16; $p = 0.29$). HRs according to study characteristics are shown in Figure 3. CCT did not lead to significant survival benefit in any subgroups analyzed (*period*, *region*, *trial phase*, *proportion of stage IIIA patients*, *use of third-generation drugs*, or *use of taxanes*). Similarly, significant survival advantages were not demonstrated in CCCT or SCCT compared with CCT− (HR: 0.94; 95% CI, 0.81–1.09; $p = 0.424$) and HR: 0.94 (0.71–1.26; $p = 0.694$), respectively, (Supplementary Figure 3, Supplemental Digital Content 5, http://links.lww.com/JTO/A443).

Taken Together, Pooled Analyses on Publication Data Did Not Support Survival Improvement by CCT for Patients with LA-NSCLC

Toxicities

Table 3 summarizes grade 3–5 toxicities reported in the study arms. Toxicities throughout the treatment courses were comparable between CCT− and CCT+ arms. No significant differences were observed in neutropenia, leucopenia, esophagitis, pneumonitis, or treatment-related death.

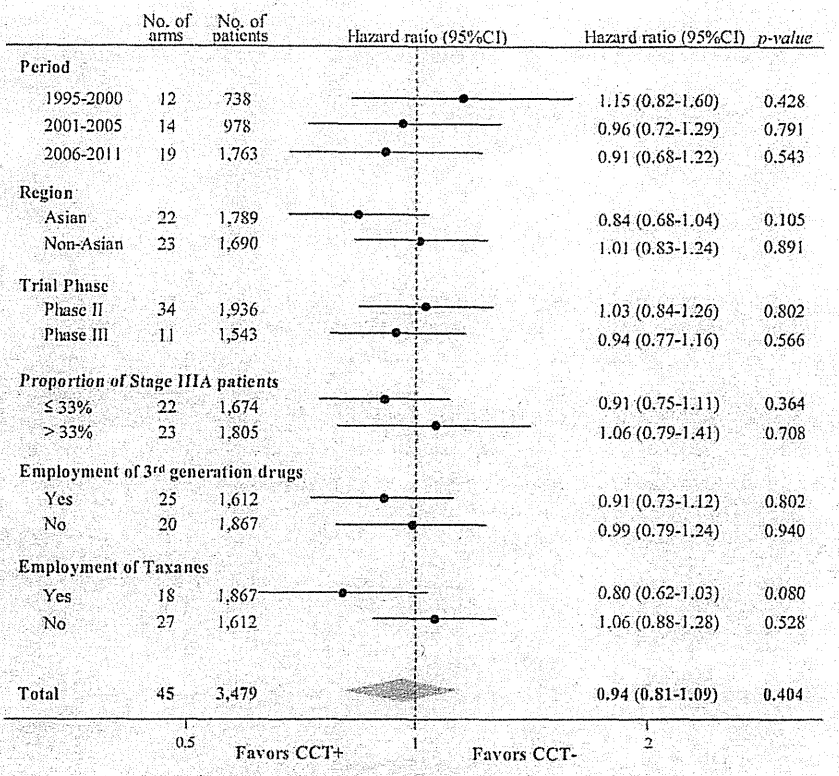

FIGURE 3. Hazard ratios of CCT+ to CCT− in subgroup analysis according to study characteristics. CCT, consolidated chemotherapy; CI, confidence interval.

TABLE 3. Grade 3–5 Toxicities Observed in the Study Arms with and without CCT

	Arms without CCT		Arms with CCT		
Grade 3–5 Toxicities (%)	Mean	SD	Mean	SD	p^a
Neutropenia	50.51	28.42	45.36	24.41	0.63
Leukopenia	58.11	33.11	54.70	22.40	0.74
Esophagitis	14.79	14.68	15.97	12.17	0.78
Pneumonitis	7.97	6.93	7.06	7.30	0.67
Treatment-related death	2.30	2.04	1.96	2.68	0.63

[a]Statistical differences were calculated using Student's *t* test across trial arms.
CCT, consolidation chemotherapy; SD, standard deviation.

DISCUSSION

This pooled analysis on published data did not support the efficacy of CCT in terms of survival prolongation for patients with LA-NSCLC. In this study, the combined mOS of CCT− studies was 17.9 months, which was comparable with that of CCT+ studies, 19.0 months. In addition, the HR of CCT+ to CCT− studies was 0.94. These data suggest that the addition of CCT do not lead to significant survival prolongation or risk reduction in death for LA-NSCLC patients. So far, little is known about the efficacy of CCT after concurrent chemo-RT. Previously, three randomized trials[11,54,55] have been carried out to evaluate the efficacy of CCT for LA-NSCLC (2[54,55] of them have not yet been published as full articles), but all of them failed to show significant survival benefit in CCT arm (Supplementary Table 3, Supplemental Digital Content 6, http://links.lww.com/JTO/A444). Furthermore, we calculated pooled HR using the data of these trials in the same methods described in Materials and Methods, but no significant survival benefit in CCT+ was observed (predicted HR and 95% CI of CCT+ to CCT− were 1.03 and 0.71−1.49, respectively). Combined with these results, our analysis indicates that there is currently no sufficient evidence that supports the benefit of CCT for LA-NSCLC patients. In clinical practice, however, many oncologists still use CCT after concurrent chemo-RT for LA-NSCLC. Moreover, in many ongoing trials, CCT is routinely incorporated, whereas there are few ongoing trials asking the significance of CCT. Further randomized trials will be required to assess the feasibility of using CCT as clinical standard treatment for LA-NSCLC patients. Currently, a phase III study is ongoing in Korea to evaluate the CCT with cisplatin/docetaxel after concurrent chemo-RT with the same agents.[4] The outcome of this study is awaited to assess the significance of CCT for LA-NSCLC patients.

Toxicities induced by CCT are another concern. In previous phase III studies, Hanna and colleagues[11] reported that CCT with docetaxel after concurrent chemo-RT increased toxicities including treatment-related death for LA-NSCLC patients. In this study, however, no difference was observed in toxicities between the two groups. There are several possible explanations regarding this discrepancy. First, our analysis may not able to detect small differences in toxicities because many included studies were not focusing on toxicities in consolidation phase. A second possible explanation is that the number of delivered courses of CCT was lower than planned (Table 1). Third, some chemo-RT regimens used in CCT+ group may have less toxicity. For example, weekly paclitaxel plus carboplatin with TRT followed by two courses of triweekly paclitaxel plus carboplatin has been reported to be less toxic although retaining equivalent efficacy to other full-dose chemo-radiation regimens.[17] Because of less toxic regimens, the toxicities in CCT+ group might have been underestimated. As toxicities mostly depend on the menus and delivered doses/methods of chemotherapy, designs of chemotherapy regimens should be carefully considered for future clinical trials.

This study also highlights two more issues. First, studies conducted in Asian countries, mostly from Japan and Korea, tend to yield longer OS than those in European countries and/or the United States. The finding may be attributable to the ethnic differences between Asian and white patients; an increasing number of publications describe differences in OS and toxicity between Asian and white patients with NSCLC.[56,57] However, why survival of Asian patients is longer than that of white patients has not been clarified, although it may be in part because of the differences among races in tumor behaviors arising from somatic mutations or in sensitivities to drugs/radiation. Of note, the subgroup analyses showed that the HR of Asian studies is 0.84 favoring CCT+, though not statistically significant ($p = 0.105$; Fig. 3). The result may support a possible involvement of ethnicity in the efficacy of CCT. A mechanism underlying these ethnic differences may be a clue to develop a novel treatment strategy for LA-NSCLC. Second, our analyses suggest the improvement in survival outcome of LA-NSCLC patients during the past 15 years. However, this potential survival improvement during this period needs to be assessed with caution, as apparent survival improvement may be influenced by stage migration as a result of advancement in imaging techniques (e.g., positron emission tomography).[58]

This study has several limitations. First, because of the nature of pooled analyses on a publication basis, our analyses included heterogeneous studies with different study designs and various patient populations. Although patient characteristics, trial phase, platinum regimens, study period, and region of the trials did not significantly differ between CCT+ and CCT−, and meta-regression analyses revealed similar results, we cannot exclude the possibility that some other differences might affect our conclusion. In particular, as our analyses were performed on a study basis, they did not cover the heterogeneities in individual patient levels. Second, the impacts of chemotherapy regimens on survival data also remain to be solved. Most studies included in CCT+ were designed for CCCT, and only four studies were designed for SCCT; therefore, the efficacy of SCCT strategy could not be fully evaluated in our analysis, although subset analysis using these four SCCT studies did not show significant survival benefit by CCT. Similarly, we could not clarify the impact of chemotherapy doses on survival, because, in most studies, not full-dose but low-dose/fractionated chemotherapy was offered in the concurrent phase.

Nevertheless, we believe that the findings of this study are relevant because we continue to learn how best to tailor treatment for NSCLC patients. Regarding the treatment of stage IV NSCLC patients, we have experienced a great advance in the last decade; molecular targeted agents and pemetrexed have made a major impact in the selected patients, and molecular profiling has emerged as central to the treatment.[59] In contrast, for LA-NSCLC patients, no significant progress in treatment strategy has been seen during this decade.[60] It seems that we have reached a plateau in survival using current chemotherapy drugs against LA-NSCLC. Therefore, it is urgent to seek new treatment options to improve the prognosis of LA-NSCLC patients. Further clinical studies are vital to establish appropriate CCT regimens, as well as other novel treatment strategies, which lead to survival prolongation and increase in the cure rate of LA-NSCLC patients. Concurrent chemo-RT with no CCT would serve as a reference arm in these trials.

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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

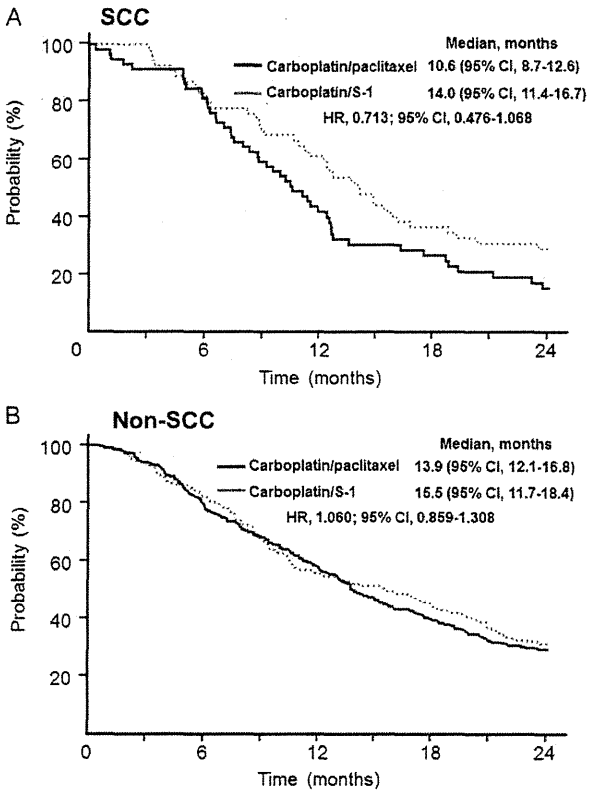

Figure 1. Kaplan–Meier curves for OS according to histological subtype of NSCLC. (A) SCC and (B) Non-SCC.

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