Annals of Oncology

Annals of Oncology 24: 1326–1331, 2013
doi:10.1093/annonc/mds629
Published online 30 December 2012

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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Received 20 August 2012; revised 29 October 2012; accepted 2 November 2012

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

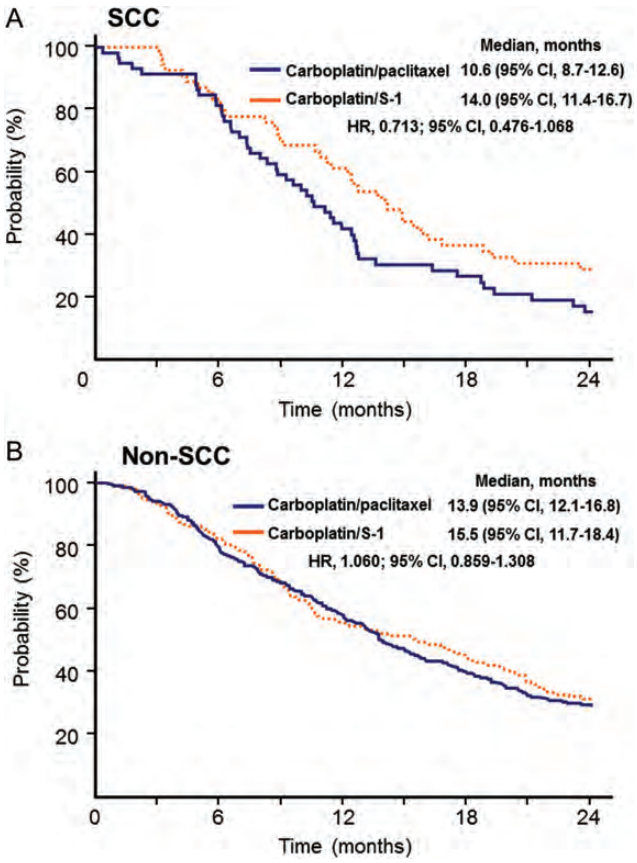

Figure 1. Kaplan–Meier curves for OS according to histological subtype of NSCLC. (A) SCC and (B) Non-SCC.

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

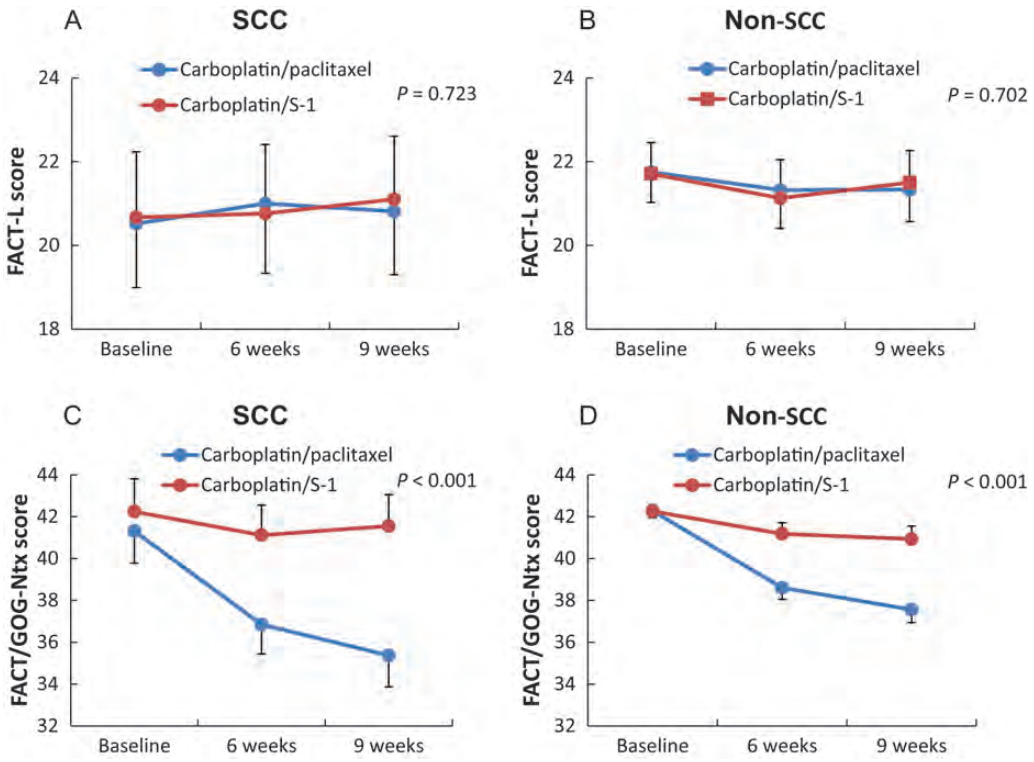

Figure 2. QOL assessments according to histological subtype of NSCLC. Assessments were carried out with the seven-item FACT-L (A and B) and 11-item FACT/GOG-Ntx (C and D) subscales for patients with SCC (A and C) or with non-SCC (B and D). Data are presented as least-square means and 95% CIs. Higher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

acknowledgements

We thank all participating sites and investigators for their support with the clinical study.

funding

This work was supported by West Japan Oncology Group.

disclosure

The authors have declared no conflicts of interest.

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