

[ORIGINAL ARTICLE]

A Phase II Study of Tailored-dose S-1 Plus Carboplatin Followed by Maintenance S-1 for Advanced Squamous Cell Lung Cancer: OSAKA-LCSG 1102

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Abstract:

Objective A subset analysis of the LETS study suggested that S-1 plus carboplatin was more beneficial than paclitaxel plus carboplatin in terms of the overall survival (OS) in squamous cell lung cancer. However, the benefit of maintenance therapy for squamous cell non-small cell lung cancer (NSCLC) patients is still unknown. We herein report a phase II study to evaluate the efficacy and safety of a tailored dose of S-1 plus carboplatin followed by maintenance S-1 in chemotherapy-naïve advanced squamous cell NSCLC.

Methods Patients received carboplatin on day 1 plus S-1 on days 1 to 14 every 21 days. The dose of S-1 was determined by the body surface area and creatinine clearance. After four cycles of induction, non-progressive patients continued to receive S-1 until disease progression or unacceptable toxicity occurred. The primary endpoint was an objective response rate (RR) with a threshold value of 15%. The secondary endpoints were the progression-free survival (PFS) and OS from enrollment, the PFS in the maintenance phase, and safety.

Results In the 33 patients analyzed, the rate of patients who met the primary endpoint was 30.3% (95% confidence interval: 15.6-48.7%), and the disease control rate was 75.8%. The median PFS and OS were 3.5 and 11.3 months, respectively. Ten patients received maintenance S-1, and the median PFS from the beginning of induction treatment was 5.3 months. Grade 3/4 toxicities with a frequency of more than 5% were all controllable.

Conclusion Tailored-dose S-1 plus carboplatin followed by maintenance S-1 is an effective and feasible treatment for advanced squamous cell NSCLC.

Key words: tailored-dose S-1, carboplatin, maintenance, squamous cell lung cancer, creatinine clearance, body surface area

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Introduction

Lung cancer is the leading cause of cancer-related death

worldwide. Approximately 85% of patients with lung cancer have non-small cell lung cancer (NSCLC), with most being diagnosed with advanced (stage IIIB/IV) disease. As first-line chemotherapy for advanced NSCLC, “platinum-doublet”

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chemotherapy, a combination of platinum plus third-generation anti-cancer drugs, such as paclitaxel, docetaxel, vinorelbine, gemcitabine, or irinotecan, is the recommended therapy and is widely used in daily clinical practice. However, the median overall survival (OS) with platinum-doublet chemotherapy is only 11 to 14 months (1), so the development of new therapeutic strategies and drugs is essential.

S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) is an oral fluoropyrimidine agent that consists of tegafur, 5-chloro-2,4-dihydropyridine, and potassium oxonate (2, 3). In a randomized phase III study (West Japan Oncology Group 3605; LETS study), carboplatin plus S-1 demonstrated comparable efficacy to standard chemotherapy of carboplatin plus paclitaxel for chemotherapy-naïve advanced NSCLC (4). In a subset analysis of this study, patients with squamous cell carcinoma experienced a longer median OS in the carboplatin/S-1 group than in the carboplatin/paclitaxel group (14.0 versus 10.6 months, respectively) (5), suggesting that S-1 may be a viable standard treatment for squamous cell carcinoma. However, 32% of the patients experienced grade ≥ 3 thrombocytopenia, and the treatment delay rate was 70% in the carboplatin plus S-1 arm, suggesting that a better-tolerated regimen is required.

We previously reported that a tailored dose of S-1, adjusted based on the individual creatinine clearance (Ccr) and body surface area (BSA), showed pharmacokinetics similar to a standard unadjusted dose of S-1 (80 mg/m²/day) and was safe and therapeutically useful for chemotherapy-naïve elderly patients with advanced and recurrent NSCLC (OSAKA-LCSG0702) (6).

However, maintenance therapy for non-squamous NSCLC is already established. A randomized phase III trial (PARAMOUNT) found that maintenance therapy with pemetrexed was effective and well tolerated in patients with advanced non-squamous NSCLC who did not progress after induction therapy with pemetrexed plus cisplatin (7). However, the clinical benefits of maintenance therapy have been limited to non-squamous NSCLC. Although therapy with S-1 following induction therapy with carboplatin and S-1 showed a median progression-free survival (PFS) of 3.0 months from the start of maintenance therapy (8), the value of maintenance therapy for squamous cell NSCLC patients is still unknown.

We therefore conducted a multicenter, single-arm, phase II trial of tailored-dose S-1 plus carboplatin combination therapy followed by maintenance S-1 in chemotherapy-naïve patients with squamous cell lung cancer (OSAKA-LCSG1102, UMIN000008083)

Mateials and Methods

Eligibility criteria

The inclusion criteria for patients were a diagnosis of NSCLC confirmed either histologically or cytologically, stage IIIB or IV squamous cell lung cancer or recurrence of

this condition after surgery, existence of measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, no prior chemotherapy, age over 20 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a projected life expectancy of at least 3 months. Patients also had to demonstrate an adequate bone marrow reserve and organ function, including a serum creatinine level of <1.5 mg/dL. Radiation therapy for metastatic disease was permitted if it had been completed at least two weeks before informed consent was given. The main exclusion criteria included active concomitant malignancy, symptomatic brain metastasis, interstitial pneumonia, watery diarrhea, heart failure, uncontrolled diabetes mellitus, active infection, and a history of drug allergies.

Written informed consent was obtained from all patients, and the study protocol was approved by the institutional ethics committee of each of the participating institutions.

Study treatment

Induction therapy

Eligible patients received carboplatin (AUC, 5) on day 1 plus oral S-1 on days 1 to 14 of each cycle. Chemotherapy was repeated every three weeks for a maximum of four cycles unless there was earlier evidence of disease progression or intolerance of the study treatment.

S-1 was given orally twice daily (after breakfast and dinner). The initial dose of S-1 was determined by the BSA and a calculated Ccr, based on the standard Cockcroft and Gault formula. In patients with BSA ≥ 1.5 m², the starting dose of S-1 was 60, 50, and 40 mg twice daily if the Ccr was ≥ 60 mL/min, 40 to <60 mL/min, and 30 to <40 mL/min, respectively. In patients with a BSA 1.25 to <1.5 m², the starting dose of S-1 was 50, 40, and 30 mg twice daily if the Ccr was ≥ 60 mL/min, 40 to <60 mL/min, and 30 to <40 mL/min, respectively. In patients with a BSA <1.25 m², the starting dose of S-1 was 40, 30, and 20 mg twice daily if the Ccr was ≥ 60 mL/min, 40 to <60 mL/min, and 30 to <40 mL/min, respectively. A one-level dose reduction was recommended if grade ≥ 3 hematologic toxicity had occurred in the previous cycle, but a dose re-escalation was not permitted.

Maintenance therapy

Patients achieving a complete response (CR), partial response (PR), or stable disease (SD) after induction were eligible for the maintenance phase. These patients received oral S-1 on days 1 to 14 every 3 weeks. Maintenance treatment was continued until progression of disease (PD), death, or withdrawal of consent.

Statistical analyses

The response rate (RR) was set as the primary endpoint of this study. The RR for carboplatin plus S-1 in chemotherapy-naïve advanced NSCLC patients was reported to be 30.8% [95% confidence interval (CI): 17.1-58.3%] in a phase I/II study (9), 31.0% (95% CI: 15.3-50.8%) in phase II study,

Table 1. Patient Characteristics.

Age	
Median (range)	72 (44-82)
Sex	
Male	32 (97%)
Female	1 (3%)
ECOG performance status	
0	4 (12%)
1	29 (88%)
Stage	
IIIB	8 (24%)
IV	23 (70%)
postoperative recurrence	2 (6%)
Estimated Ccr (mL/min)	
≥60	23 (70%)
40≤Ccr<60	9 (27%)
30≤Ccr<40	1 (3%)

and 20.4% in a Japanese phase III study (LETS study) (4).

Using the SWOG statistical tool (<http://www.swogstat.org/statoolsout.html>), we estimated that 28 patients would be sufficient to explain the hypothesis to disregard an RR of 15% and to provide a two-sided significance level of 0.05 with a statistical power of 80% in assessing the expected RR of the regimen as 35%. A target sample size of 35 patients was chosen after factoring in the proportion of patients who would be ineligible for the study.

Results

Patient characteristics

From February 2011 to January 2013, 35 patients were enrolled. Two patients were excluded due to protocol violations. In both cases, they failed to satisfy the Ccr outlined in the eligibility criteria. The median age of the remaining 33 patients was 72 years (range: 44-82). Of these patients, 32 (97%) were men, 25 (76%) had stage IV disease, 2 (6%) had post-operative recurrences, and 29 (88%) had an ECOG performance status of 1. The calculated Ccr, based on the standard Cockcroft and Gault formula at baseline, was ≥60 mL/min in 23 patients (70%), 40 to <60 mL/min in 9 patients (27%), and 30 to <40 mL/min in 1 patient (3%) (Table 1).

Treatment

Thirty-three patients received a median of 4 cycles (range: 1-4 cycles) of induction chemotherapy. Of these, 16 patients (48.5%) had treatment delay, and 11 (33.3%) had dose reduction in the induction phase. The causes of treatment delay were thrombocytopenia in eight, neutropenia in five, diarrhea in one, renal dysfunction in one, and liver damage in one. The causes of dose reduction were thrombocytopenia in six, neutropenia in two, diarrhea in one, and nausea in one.

Ten patients (30.3%) received maintenance S-1 chemo-

therapy with a median number of 3 cycles (range: 1 to 9). Of the 23 patients who did not receive maintenance chemotherapy, 16 had PD during or after the induction chemotherapy. Protocol therapy was discontinued in 5 patients due to adverse events (AEs) and in 2 due to refusal of treatment (Fig. 1).

The response and survival

Of the 33 patients, 10 (30.3%) achieved PR, 15 (45.5%) maintained SD, and 6 (18.2%) showed PD as their best overall response to therapy. Thus, the RR was 30.3% (95% CI: 15.6-48.7%), and the disease control rate (DCR) was 75.8% (95% CI: 57.7-88.9) (Table 2). When the results were analyzed according to individual Ccr values, the 23 (70%) patients in the Ccr ≥60 mL/min category had an RR of 30.4% (95% CI: 13.2-52.9), the 9 (27%) patients with a Ccr of 40 to <60 mL/min had an RR of 33.3% (95% CI: 7.5-70.1), and the 1 (3%) patient with a Ccr of 30 to <40 mL/min had SD (Table 2).

Regarding the induction and maintenance populations, while the median PFS values (secondary endpoint) were 3.5 months (95% CI: 2.8-4.2) and 5.3 months (95% CI: 3.9-8.6), respectively, the median OS values were 11.3 months (95% CI: 8.1-17.3) and 17.1 months (95% CI: 6.3-NE), respectively (Fig. 2, 3).

Safety

The AEs noted during the treatment are listed in Tables 3 and 4. AEs of grade 3 and 4 were observed in 10 patients (30.3%). During four cycles of induction chemotherapy, grade 3 and 4 hematologic AEs included thrombocytopenia (21.3%), neutropenia (12.1%), and leukopenia (10.0%), and grade 3 and 4 nonhematologic AEs included appetite loss (12.1%), nausea (6.1%), and fatigue (6.1%) (Table 3). Toxicity during the maintenance phase was minimal; the grade 3 and 4 hematological AEs included thrombocytopenia (10.0%), neutropenia (10.0%), and leukopenia (10.0%), and no grade 3 or 4 nonhematologic AEs were observed (Table 4).

Further treatment

Twenty-two patients (66.7%) received second-line chemotherapy, and 45.5% of these patients were treated with docetaxel.

Discussion

In this study, tailored-dose S-1 plus carboplatin combination therapy in a phase II setting showed an RR of 30.3% (95% CI: 15.6-48.7%) and a DCR of 75.8%, and the primary endpoint was met. In the LETS study, S-1 plus carboplatin showed an RR of 27.5% and a DCR of 80.0% in squamous cell carcinoma, but 32% of the patients experienced grade 3 and 4 thrombocytopenia, and the treatment delay rate was 70% in the S-1 plus carboplatin arm (4). These findings suggest that thrombocytopenia is a contrain-

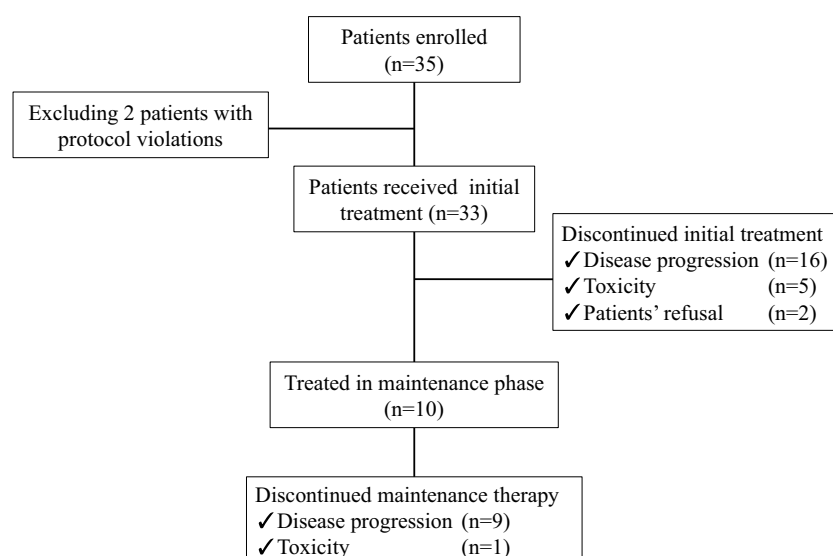


Figure 1. Consort diagram of OSALA-LCSG1102. Thirty-five patients were enrolled. Two patients with protocol violations were excluded, so 33 received the initial treatment. Sixteen patients showed disease progression during initial treatment, five discontinued treatment due to toxicity, and two discontinued due to refusal. Ten patients were treated with continuation maintenance with S-1, and nine showed disease progression during maintenance therapy while one discontinued maintenance therapy due to toxicity.

Table 2. Tumor Response (n=33).

Response	Total	Ccr \geq 60 (n=23)	40 \leq Ccr<60 (n=9)	30 \leq Ccr<40 (n=1)
CR	0	0	0	0
PR	10	7	3	-
SD	15	10	4	1
PD	6	5	1	-
NE	2	1	1	-
Response rate (CR+PR)	30.3 (95% CI: 15.6-48.7)	30.4% (95% CI: 13.2-52.9)	33.3% (95% CI: 7.5-70.1)	0% (95% CI: 0.0-97.5)
Disease control rate (CR+PR+SD)	75.8 (95% CI: 57.7-88.9%)	73.9% (95% CI: 51.6-89.8)	77.8% (95% CI: 40.0-97.2)	100% (95% CI: 2.5-100.0)

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable

dication for S-1 plus carboplatin, which is widely used in practice as a standard regimen for NSCLC. In contrast, in our study, a regimen involving a tailored dose of S-1 adjusted based on the individual Ccr and BSA plus carboplatin resulted in an incidence of 21.3% for grade 3 and 4 thrombocytopenia, and a treatment delay in the induction phase in 48.5% of patients. The median duration of treatment delay was only 1 week (range: 1-3 weeks). Compared with the LETS study, lower rates of grade 3 and 4 thrombocytopenia and treatment delay were observed, findings considered to support the efficacy of the tailored-dose S-1 plus carboplatin regimen. However, grade 3 anorexia appeared in 12.1% of patients, which is more frequent than in the previous study. This is considered because the median age in this study was 72 years old, which was higher than that in the LETS study (64 years old).

Thus, the efficacy of the tailored-dose S-1 plus carboplatin regimen was similar to the standard-dose regimen

of S-1 plus carboplatin, while the rate of AEs was the same or less and the tolerance seemed better. We previously reported that a tailored dose of S-1 was safe and therapeutically useful (6). In the present study, we demonstrated the validity of a tailored-dose regimen of S-1 plus carboplatin.

S-1 is an oral anticancer agent with a low cumulative toxicity compared to other anticancer agents, which may make it a suitable agent for maintenance therapy. Indeed, in a previous phase II study of S-1, carboplatin plus bevacizumab followed by maintenance S-1 plus bevacizumab for advanced non-squamous NSCLC showed good feasibility as a maintenance therapy; 60% of patients received maintenance therapy with a median number of 4 cycles (10). In a phase II study of S-1 maintenance therapy for squamous NSCLC, the median PFS was 4.4 months (95% CI: 3.8-5.1), and the median OS was 10.3 months (95% CI: 7.6-12.9). Maintenance therapy was given to 35.3% (95% CI: 22.3-48.3) of patients with a median of 3 cycles (range: 1-8 cycles) (8).

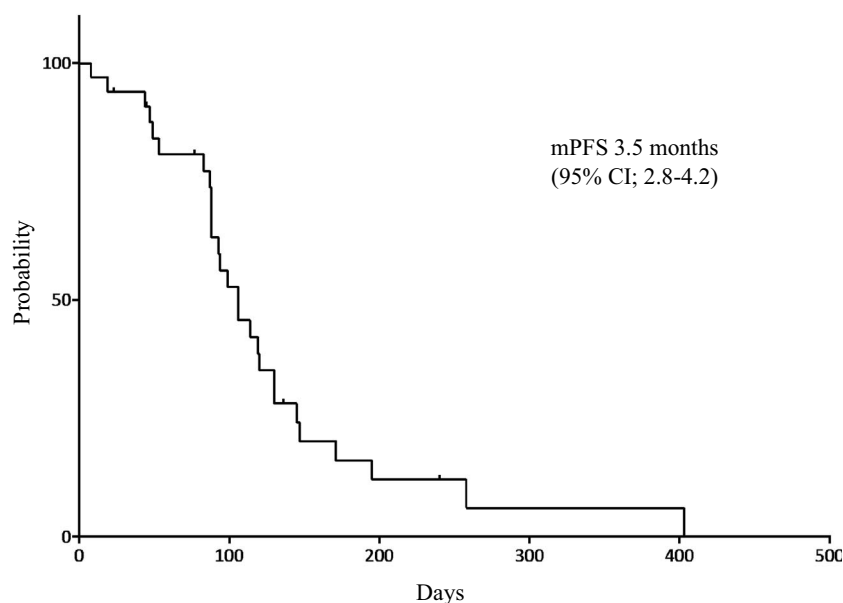


Figure 2. The progression-free survival (PFS) from induction therapy. The Kaplan-Meier survival curve of the PFS from induction therapy. The median PFS was 3.5 months (95% CI: 2.8-4.2).

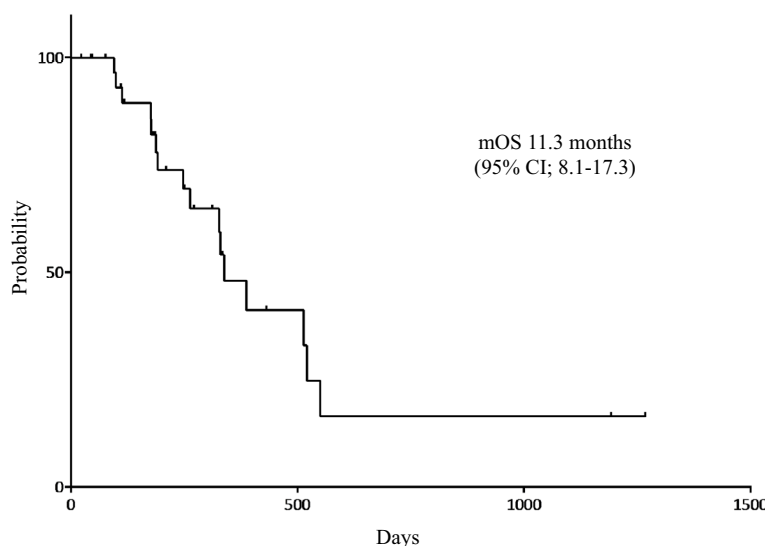


Figure 3. The overall survival (OS) from induction therapy. The Kaplan-Meier survival curve of the OS from induction therapy. The median OS was 11.3 months (95% CI: 8.1-17.3).

Our OSAKA-LCSG1102 study was also designed to evaluate the efficacy and safety of maintenance therapy with S-1 for squamous NSCLC. In this study, the DCR was 75.8%, and the median number of treatment cycles including the maintenance phase was 4 (1 to 13). Ten patients (30.3%) were eligible for and received maintenance therapy with S-1, and the transition rate to the maintenance phase was 30.3%. This rate is less than the 57.4% in the PARAMOUNT study and 66.1% in the POINTBREAK study, which targeted non-squamous NSCLC population (11), but was almost equal to that seen in the phase II study of S-1 maintenance therapy for squamous NSCLC. The reasons for not having shifted to maintenance treatment were PD in 16 patients (69.6%) and AEs in 7 patients (21.7%). These find-

ings are consistent with those of a previous report (64.7% in PD and 13.7% in AEs) (8). Given that the median number of treatment courses for a standard dose of S-1 plus carboplatin is four (4), the low rate of transitioning to maintenance phase may be attributed to the squamous cell histology.

Regarding the S-1 maintenance population, the median number of treatment cycles was 3 (range: 1 to 9). The median PFS and OS were 6.0 and 14.6 months, respectively, suggesting an improvement over previous reports with a tolerable toxicity profile. Maintenance S-1 therapy may therefore be recommended, given the low cumulative toxicity and preservation of the quality of life. Furthermore, S-1 is less expensive than most anticancer drugs, which will reduce the

Table 3. Adverse Events (Induction Phase, n=33).

Adverse events	G1	G2	G3	G4	G3/4 (%)
Hematologic					
Leukopenia	4	3	1	0	3.0
Neutropenia	0	4	4	0	12.1
Anemia	14	9	2	0	6.1
Thrombocytopenia	16	2	5	2	21.3
Nonhematologic					
Diarrhea	6	2	1	0	3.0
Anorexia	7	9	4	0	12.1
Nausea	8	8	2	0	6.1
Vomiting	3	4	0	0	0.0
Fatigue	7	6	2	0	6.1
Liver damage	0	1	0	0	0.0
Renal dysfunction	1	0	0	0	0.0

Table 4. Adverse Events (Maintenance Phase, n=10).

Adverse events	G1	G2	G3	G4	G3/4 (%)
Hematologic					
Leukopenia	0	1	1	0	10.0
Neutropenia	0	1	1	0	10.0
Anemia	8	0	1	0	10.0
Thrombocytopenia	4	0	0	0	0.0
Nonhematologic					
Diarrhea	0	0	0	0	0.0
Anorexia	3	2	0	0	0.0
Nausea	2	1	0	0	0.0
Vomiting	0	0	0	0	0.0
Fatigue	2	1	0	0	0.0
Stomatitis	1	0	0	0	0.0

financial burden for patients in the long term. However, our study is a single-arm study, and only 10 patients (30.3%) received maintenance therapy. In addition, we did not determine the effectiveness of maintenance therapy with S-1. At present, a phase III trial comparing the best supportive care and maintenance therapy with S-1, after induction with four cycles of carboplatin plus S-1, for advanced squamous cell lung cancer (WJOG7512 L) is in progress (UMIN 000010396).

In conclusion, a tailored dose of S-1 plus carboplatin followed by maintenance S-1 is an effective and feasible treatment for advanced squamous cell lung cancer. This regimen is a potential treatment option for patients with advanced squamous cell NSCLC.

The authors state that they have no Conflict of Interest (COI).

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References

- Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* **18**: 317-323, 2007.
- Shirasaka T, Nakano K, Takechi T, et al. Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2,4-dihydropyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res* **56**: 2602-2606, 1996.
- Okamoto I, Fukuoka M. S-1: a new oral fluoropyrimidine in the treatment of patients with advanced non-small-cell lung cancer. *Clin Lung Cancer* **10**: 290-294, 2009.
- Okamoto I, Yoshioka H, Morita S, et al. Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer: results of a west Japan oncology group study. *J Clin Oncol* **28**: 5240-5246, 2010.
- Yoshioka H, Okamoto I, Morita S, et al. 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. *Ann Oncol* **24**: 1326-1331, 2013.
- Shiroyama T, Kijima T, Komuta K, et al. Phase II tailored S-1 regimen study of first-line chemotherapy in elderly patients with advanced and recurrent non-small cell lung cancer. *Cancer Chemother Pharmacol* **70**: 783-789, 2012.
- Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* **13**: 247-255, 2012.
- Suzuki S, Karayama M, Inui N, et al. Continuation maintenance therapy with S-1 in chemotherapy-naïve patients with advanced squamous cell lung cancer. *Invest New Drugs* **34**: 490-496, 2016.
- Tamura K, Okamoto I, Ozaki T, et al. Phase I/II study of S-1 plus carboplatin in patients with advanced non-small cell lung cancer. *Eur J Cancer* **45**: 2132-2137, 2009.
- Urata Y, Okamoto I, Takeda M, et al. Phase 2 study of S-1 and carboplatin plus bevacizumab followed by maintenance S-1 and bevacizumab for chemotherapy-naïve patients with advanced nonsquamous-small cell lung cancer. *Cancer* **119**: 2275-2281, 2013.
- Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous-small-cell lung cancer. *J Clin Oncol* **31**: 4349-4357, 2013.

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