



# Advances in monotherapy and combination therapy of S-1 for patients with advanced non-small cell lung cancer: a narrative review

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**Background and Objective:** Both domestically and worldwide, non-small cell lung cancer (NSCLC) remain the leading cause of cancer-related death. As a fluorouracil derivative, S-1 which shows good efficacy and with few adverse effects have been widely confirmed in many solid tumors that it can provide a glimmer of hope for advanced NSCLC patients. We performed a review to explore the results of previous clinical studies of S-1 monotherapy as well as combined therapy involving S-1 in patients with advanced NSCLC.

**Methods:** A literature search was conducted in Medline and PubMed databases using the keywords “S-1” AND “Advanced lung cancer” OR “Pharmacological mechanism”.

**Key Content and Findings:** A number of phase II clinical studies have reported on the favorable efficacy and excellent safety profiles of S-1 monotherapy in first-line or in posterior-line treatment for advanced NSCLC. In regard to S-1 in combination with chemotherapy, a number of phase II/III clinical studies have found the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) of these regimens are similar to or better than immunological monotherapy with fewer adverse effects. In the case of S-1 combined with anti-vascular therapy, a number of phase II single-arm clinical studies have found that S-1 combined with bevacizumab, anlotinib and apatinib in advanced NSCLC, exhibits higher antitumor activity, less adverse effects for patients with advanced NSCLC. A phase II single-arm clinical study of gefitinib combined with S-1 had the ORR of 85.7% in the first-line treatment of advanced NSCLC. As for the combination of S-1 and immunotherapy, preliminary results of a phase II retrospective clinical trial demonstrated that the ORR was significantly better with S-1 sequential after immune checkpoint inhibitors (ICIs) than with S-1 alone.

**Conclusions:** The findings indicate promising effectiveness and minimal toxicity with S-1 monotherapy and S-1 containing combined therapy in patients with advanced NSCLC to provide a potential treatment option for advanced NSCLC.

**Keywords:** Chemotherapy; immune checkpoint inhibitors (ICIs); non-small cell lung cancer (NSCLC); S-1; platinum combination

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## Introduction

Lung cancer has been expected to cause 127,070 deaths in the United States in 2023, making it the leading cause of cancer-related death worldwide (1). It is estimated that 80% of lung cancer cases are non-small cell lung cancers (NSCLC). A platinum-based doublet chemotherapy regimen combined with a programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitor is the current standard first-line treatment for advanced lung cancer (2-6). However, not all patients can tolerate platinum-based doublet chemotherapy combined with PD-1/PD-L1 inhibitor regimens, such as patients with a performance status (PS)  $\geq 2$ . In addition, subsequent therapy after first-line treatment is limited and with unsatisfactory efficacy (7,8). Therefore, it is necessary to explore efficient regimens with better tolerance.

Fluorinated pyrimidine formulation S-1 contains tegafur, 5-chloro-2,4-dihydropyridine (CDHP), and potassium oxonate, in molar ratios of 1:0.4:1 (9). In the blood, tegafur primarily generates 5-fluorouracil (5-FU). The levels of 5-FU in tumor tissues and plasma are increased by CDHP, a competitive inhibitor of dihydropyrimidine dehydrogenase. By inhibiting the phosphorylation of 5-FU in the gastrointestinal tract, oxonate reduces the gastrointestinal toxicity of 5-FU. The S-1 drug is approved for treating locally advanced or metastatic stomach cancer that cannot be surgically removed. Other solid tumors, including NSCLC, have also been shown to benefit from S-1 (10-16). S-1 was approved in Japan in 2004 for the treatment of non-small cell lung cancer. S-1 monotherapy or combination therapy has also shown good anti-tumor activity in advanced NSCLC as first-line, second-line, or later-line treatments (17-21). In late-stage NSCLC patients with no driver gene mutations, weakened physical functions (22), multiple underlying diseases, and high PS scores, which have resulted in limited treatment options, S-1 could fill the gap.

This review summarized and described the results of previous clinical studies involving S-1 monotherapy and S-1 containing combined therapy in advanced NSCLC. We present this article in accordance with the Narrative Review reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-2019/rc>).

## Methods

A literature search was conducted in Medline and PubMed

databases using the keywords “S-1” AND “Advanced lung cancer” OR “Pharmacological mechanism”. The secondary references cited in articles obtained from the Medline and PubMed search were also retrieved. Methodology of the search is summarized in the *Table 1*. In this study, 25 studies on the S-1 monotherapy as well as on the S-1 containing combined therapy were included by searching the databases of PubMed and Medline. S-1 monotherapy and S-1 containing combined therapy were concluded to exhibit promising effectiveness and minimal toxicity (*Tables 2-5*).

## Monotherapy of S-1

### *S-1 monotherapy as front-line treatment in advanced NSCLC*

Two phase II studies evaluated single-agent S-1 as a first-line treatment for advanced NSCLC (*Table 2*). During the study, 32 elderly patients (age >70 years) with advanced NSCLC without chemotherapy were enrolled (23). According to the results, the objective response rate (ORR) was 22.6% [95% confidence interval (CI), 11–38%]. A median progression-free survival (mPFS) of 5.5 months was observed (95% CI, 2.5–10.0). There was 12.4 months median overall survival (mOS) (95% CI, 8.7–27.9). It was reported that grade 3 and 4 thrombocytopenia, neutropenia, anemia, leukopenia, and febrile neutropenia occurred in 9.4%, 6.3%, 6.3%, 3.1%, and 3.1% of patients, respectively. There were also few severe gastrointestinal adverse events (AEs), such as grade 3 nausea, vomiting, and diarrhea, occurring to 9.4%, 6.3%, and 3.1% of the patients, respectively. In a multicenter phase II study conducted by Goto *et al.*, 40 elderly patients (age  $\geq 75$  years) with advanced NSCLC who had not previously received chemotherapy were enrolled (24). There was an ORR of 7.9% (95% CI, 0.0–16.4%). Among all patients, the mPFS was 4.4 months (95% CI, 4.2–8.5) and the mOS was 17 months (95% CI, 11.2–18.7). The mPFS and mOS of patients with adenocarcinoma were 4.2 and 21.2 months, while those for patients with squamous cell carcinoma were 4.5 and 15.6 months, respectively. There were no significant differences of the mPFS and mOS between different histological subtypes. Severe hematologic AEs were minimal, i.e., among the hematologic AEs, grade 3 or 4 events only occurred in two patients with neutropenia (5.0%). Among the non-hematologic AEs, the incidence rates of grade 3 or 4 hyponatremia, hypokalemia, and anorexia were observed in 2 (5.0%), 1 (2.5%), and 3 (7.5%) patients, respectively.

**Table 1** Methodology of the search for the review

Items	Specification
Date of search	December 1st 2022 to March 31st 2023
Databases and other sources searched	Medline and PubMed databases
Search terms used	“S-1” AND “Advanced lung cancer” OR “Pharmacological mechanism”
Time frame	2015–2023
Inclusion criteria	Restricted to articles published in English; without predefined restriction as to the study type
Selection process	All articles were screened by two authors (F.C. and C.G.) independently, with any disagreements resolved by a third author (W.H.). Eligibility of studies was based on the assessment of title, abstract and full-text

**Table 2** Monotherapy of S-1

Regimen	Phase	No. of lines of therapy	No. of patients	ORR (%)	mPFS (months)	mOS (months)	Region	Conclusion	References
S-1	Phase 2	First-line	32	22.6	5.5	12.4	Japan	In elderly patients with previously untreated advanced NSCLC, S-1 appears to be well tolerated and demonstrates encouraging activity	Kasai <i>et al.</i> , 2016 (23)
S-1	Phase 2	First-line	40	7.9	4.4	17	Japan	In elderly patients with previously untreated advanced NSCLC, a 2-week S-1 monotherapy treatment, with a 1-week interval was well tolerated and demonstrated promising efficacy	Goto <i>et al.</i> , 2018 (24)
S-1	Phase 2	Second- or later-line	8	7.1	1.5	7.6	Japan	Alternate-day S-1 administration can be a safe treatment regimen for elderly patients with NSCLC	Masuda <i>et al.</i> , 2018 (25)
S-1	Phase 2	Second- or later-line	96	8.3	3.1	9.6	Japan	S-1 monotherapy is effective and feasible as a subsequent-line treatment in elderly patients who were previously treated for NSCLC	Imai <i>et al.</i> , 2020 (26)
S-1 versus DTX	Phase 3	Second- or later-line	577	8.3	2.9	12.8	Japan	S-1 is equally as efficacious as docetaxel and offers a treatment option for patients with previously treated advanced NSCLC	Nokihara <i>et al.</i> , 2017 (27)
			577	9.9	2.9	12.5			
S-1 versus DTX	Phase 3	Second- or later-line	361	ND	2.9	13.4	Japan	S-1 had similar efficacy to docetaxel in patients with previously treated advanced NSCLC	Sugawara <i>et al.</i> , 2019 (28)
			359	ND	3.0	12.6			

ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NSCLC, non-small cell lung cancer; DTX, docetaxel; ND, not described.

**Table 3** S-1 in combination with chemotherapy

Regimen	Phase	No. of lines of therapy	No. of patients	ORR (%)	mPFS (months)	mOS (months)	Region	Conclusion	References
S-1 + CDDP	Phase 2	First-line	55	19.6	5.7	15.1	China	Oral S-1 plus cisplatin is an effective and safe first-line regimen for patients with advanced NSCLC	Lai <i>et al.</i> , 2020 (29)
S-1 + CDDP vs. DTX + CDDP	Phase 3	First-line	301 vs. 297	26.9 vs. 31.3	4.9 vs. 5.2	16.1 vs. 17.1	Japan	Oral S-1 plus cisplatin is not inferior to docetaxel plus cisplatin and is better tolerated in patients with advanced NSCLC	Kubota <i>et al.</i> , 2015 (30)
S-1 + CBDCA	Phase 2	First-line	33	30.3	4.4	15.7	Japan	The oral S-1 plus carboplatin regimen seems to be a favorable treatment option	Kuyama <i>et al.</i> , 2017 (31)
S-1 + Gem	Phase 2	First-line	20	40	6.4	17.8	Japan	The combination of gemcitabine and S-1 may be a promising and feasible regimen in the first-line setting for elderly patients with advanced NSCLC	Kaira <i>et al.</i> , 2017 (32)
S-1 + PTX	Phase 2	First-line	17	47.1	4.5	35	Japan	S-1 and paclitaxel showed satisfactory efficacy with mild toxicities in elderly patients with advanced NSCLC	Yoshimura <i>et al.</i> , 2019 (33)
S-1 + DTX	Phase 1, 2	Second- or later-line	39	7.7	4.5	13.3	Japan	Docetaxel plus oral S-1 had a lower response rate than anticipated; however, the survival data were encouraging	Takayama <i>et al.</i> , 2019 (34)
S-1 + PTX	Phase 2	Second- or later-line	40	27.5	6.5	20.7	Japan	S-1 and PTX co-therapy dose and schedule showed satisfactory efficacy, with mild toxicities, in patients with previously treated advanced NSCLC	Chihara <i>et al.</i> , 2019 (35)

ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NSCLC, non-small cell lung cancer; CDDP, cisplatin; CBDCA, carboplatin; Gem, gemcitabine; PTX, paclitaxel; DTX, docetaxel.

**Table 4** S-1 in combination with anti-angiogenic therapy and EGFR-TKI

Regimen	Phase	No. of lines of therapy	No. of patients	ORR (%)	mPFS (months)	mOS (months)	Region	Conclusion	References
S-1 + CDDP + Bev followed by Bev	Phase 2	First-line	39	64.1	7.3	21.4	Japan	S-1 plus cisplatin in combination with bevacizumab met the primary endpoint in patients with advanced non-squamous NSCLC. The response rate was anticipated to be high with acceptable toxicities	Miyanaga <i>et al.</i> , 2019 (36)
S-1 + CDDP + Bev followed by Bev vs. MTA + CDDP + Bev followed by Bev	Phase 2	First-line	24 vs. 24	83.3 vs. 54.2	11.5 vs. 13.3	39.0 vs. 22.2	Japan	The combination regimen of SCB was identified as having a similar activity and tolerability to that of PCB in patients with advanced non-squamous NSCLC	Kaira <i>et al.</i> , 2019 (37)
DTX + Bev vs. S-1 + Bev	Phase 2	Second- or later-line	45	20	3.9	16	Japan	DB and SB produced modest PFS benefits in the second-line treatment of patients with advanced non-squamous NSCLC	Nishino <i>et al.</i> , 2015 (38)
S-1 + Bev	Phase 2	Second- or later-line	28	14.3	3.2	11.4	Japan	Although SB was well tolerated, this combination did not provide any additional benefit in terms of PFS for patients with non-squamous NSCLC after failure of platinum-based chemotherapy	Yamada <i>et al.</i> , 2016 (39)
S-1 + Bev	Phase 2	Second- or later-line	30	6.7	4.8	13.8	Japan	The addition of bevacizumab to S-1 was tolerable, but not beneficial for patients with previously treated non-squamous NSCLC	Nishijima-Futami <i>et al.</i> , 2017 (40)
S-1 + anlotinib vs. anlotinib	Phase 2	Second- or later-line	40 vs. 30	20 vs. 10	3.9 vs. 3	8.1 vs. 6.2	China	Advanced squamous NSCLC patients with higher PS scores still benefit from anlotinib and S-1 combination regimen, even after they failed second-line or later-line systemic treatment	Xie <i>et al.</i> , 2020 (41)
S-1 + anlotinib	Phase 2	Second- or later-line	29	37.9	5.8	16.7	China	The combination of anlotinib with S-1 in the third- or later-line treatment of stage IV NSCLC shows promising antitumor activity and manageable toxicity in patients with NSCLC	Xiang <i>et al.</i> , 2021 (42)

Table 4 (continued)

Table 4 (continued)

Regimen	Phase	No. of lines of therapy	No. of patients	ORR (%)	mPFS (months)	mOS (months)	Region	Conclusion	References
S-1 + apatinib	Phase 2	Second- or later-line	31	22.6	3.3	13.8	China	Combination of low-dose apatinib and S-1 could be an effective and tolerable choice for advanced NSCLC patients who are unable to benefit from standard treatment	Zhou <i>et al.</i> , 2019 (43)
S-1 + apatinib	Phase 2	Second- or later-line	13	ND	4.7	9.8	China	Apatinib plus S-1 for advanced solid tumor patients as palliative treatment have a certain efficacy and was relatively safe	Chen <i>et al.</i> , 2021 (44)
S-1 + CBDCA + gefitinib	Phase 2	First-line	35	85.7	17.6	Not reached	Japan	Combination chemotherapy with carboplatin, S-1, and gefitinib is efficacious and well tolerated as a first-line treatment in advanced NSCLC patients with activating EGFR mutations	Tamiya <i>et al.</i> , 2015 (45)
S-1 + erlotinib	Phase 2	Second- or later-line	10	10	ND	ND	Japan	The combination therapy of erlotinib plus S-1 was not feasible in the EGFR wild-type NSCLC at least and early stopped	Nakahara <i>et al.</i> , 2021 (46)

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NSCLC, non-small cell lung cancer; CDDP, cisplatin; Bev, bevacizumab; MTA, pemetrexed; DTX, docetaxel; CBDCA, carboplatin; EGFR, epidermal growth factor receptor; ND, not described; SCB, S-1 + cisplatin + bevacizumab; PCB, pemetrexed + cisplatin + bevacizumab; DB, docetaxel plus bevacizumab; SB, S-1 plus bevacizumab.

Table 5 S-1 in combination with immunotherapy

Items	S-1			DTX		
	S-1 immediately after Nivo	S-1 in any line after Nivo	S-1 without ICIs	DTX-based CT immediately after Nivo	DTX-based CT in any line after Nivo	DTX without ICIs
N	15	21	23	24	30	66
ORR (%)	30	20	17.6	27.8	27.3	16
mPFS (months)	3.88	3.06	2.63	5.98	4.67	2.87

Conclusion: subsequent cytotoxic chemotherapy, especially immediately after nivolumab, has better treatment efficacy than that of regimens without ICI pretreatment [Tamura *et al.*, 2019, Japan (47)]. Nivo, nivolumab; ICIs, immune checkpoint inhibitors; CT, chemotherapy; DTX, docetaxel; ORR, objective response rate; mPFS, median progression-free survival.

The age of the patient plays an important role in determining the right chemotherapy regimen for them. Due to their compromised organ systems and comorbid conditions, older patients are more likely to experience

chemotherapy-related AEs than younger patients. For this reason, elderly patients should select drugs with low toxicity. The efficacy and excellent safety profiles of S-1 monotherapy make it a promising first-line treatment for

advanced NSCLC, particularly in elderly patients.

### ***S-1 monotherapy as second- or later-line treatment in advanced NSCLC***

Four trials were conducted to assess the effectiveness of S-1 monotherapy in patients with previously treated NSCLC (Table 2). In a phase II prospective trial, Masuda *et al.* enrolled eight senior patients (age 75 years or older) and administered S-1 monotherapy to them (25). An ORR of 7.1% was reported (95% CI, 2–17.3%). A median PFS of 1.5 months was observed (95% CI, 0.9–1.8), as well as a median OS of 7.6 months (95% CI, 3–17.1). There were no AEs of grade 3 or higher. According to a phase II study published by Imai, single-agent S-1 exhibited anticancer activity in 96 elderly patients (aged 75 years or older) with platinum-resistant advanced NSCLC (26). An ORR of 8.3% (95% CI: 2.8–13.8%) was obtained. Second-line therapy had a median PFS of 3.1 months (95% CI: 1.7–5.4) compared with third- or later-line therapy at 3.4 months (95% CI: 2.5–4.2). The median OS for the second-line therapy group was 9.6 months (95% CI: 5.3–14.4) while that of the third- or later-line therapy group was 11.0 months (95% CI: 6.8–14.2). Grade 3 hematological toxicities included anemia (3.1%) and decreased platelet count (2.1%). Grade 3/4 non-hematologic toxicity consisted of anorexia (9.4%), nausea (3.1%), mucositis oral (2.1%), fatigue (1%), diarrhea (1%). Two randomized phase III studies were conducted to examine the non-inferiority of S-1 monotherapy in comparison to the docetaxel regimen as a result of these encouraging results. A total of 1,154 treated NSCLC patients were enrolled and randomly assigned to each group in Nokihara's study (27). In the S-1 arm, the ORR was 8.3% and in the docetaxel arm, it was 9.9%. In the S-1 arm, median PFS was 2.86 months (95% CI: 2.73–3.12), while in the docetaxel arm it was 2.89 months (95% CI: 2.79–3.09), respectively [hazard ratio (HR) =1.03; 95% CI: 0.91–1.17]. In the S-1 arm, median OS was 12.75 months (95% CI: 11.53–14.00), while in the docetaxel arm, it was 12.52 months (95% CI: 11.14–14.36) (HR =0.945; 95% CI: 0.833–1.073). There was no difference in PFS and OS between oral S-1 and docetaxel regimen, indicating non-inferiority of S-1 to docetaxel. Grade 3–4 hematologic toxicity included neutropenia (5.4% *vs.* 47.7%), anemia (2.6% *vs.* 1.4%), leukocytopenia (1.2% *vs.* 29.1%), thrombocytopenia (1.2% *vs.* 0.2%) and febrile neutropenia (0.9% *vs.* 13.4%) in the S-1 arm and docetaxel arm. Grade 3–4 major gastrointestinal toxicity

included decreased appetite (6.5% *vs.* 2.7%), diarrhea (6.3% *vs.* 1.1%) in the S-1 arm and docetaxel arm. Sugawara enrolled 720 patients with treated NSCLC and randomly assigned them to each group in his study (28). In the S-1 group, median PFS was 2.9 months (95% CI: 2.8–3.9) and in the docetaxel group, median PFS was 3.0 months (95% CI: 2.8–3.6) (HR =1.04; 95% CI: 0.89–1.22). In the S-1 group, median OS was 13.4 months (95% CI: 12.1–15.2) and in the docetaxel group, median OS was 12.6 months (95% CI: 11–15) (HR =0.92; 95% CI: 0.79–1.08). PFS and OS for oral S-1 were not different from the docetaxel regimen. Grade  $\geq 3$  hematologic toxicity included neutropenia (6.7% *vs.* 54%), anemia (2.8% *vs.* 1.1%), thrombocytopenia (1.7% *vs.* 0%) in the S-1 arm and docetaxel arm. Grade  $\geq 3$  nonhematologic toxicity included stomatitis (3.4% *vs.* 1.1%), nausea (1.4% *vs.* 1.7%), vomiting (2% *vs.* 0.9%), decreased appetite (9.8% *vs.* 3.4%), diarrhea (8.4% *vs.* 0.9%), constipation (0.8% *vs.* 0.3%) and maculopapular rash (1.4% *vs.* 0.3%) in the S-1 arm and docetaxel arm.

In conclusion, a comparison of S-1 monotherapy to second-line and later-line treatments found similar response rates and better tolerability for patients with advanced or recurrent NSCLC who had previously received platinum-based therapy.

### **S-1 in combination with chemotherapy**

#### ***S-1 combined with chemotherapy as front-line treatment in advanced NSCLC***

Based on S-1's effectiveness as a single drug in NSCLC and 5-FU plus cisplatin's synergistic anticancer effects, 55 previously untreated patients with advanced NSCLC were treated with S-1 plus cisplatin in a phase II trial (Table 3) (29). The ORR was 19.6%. There were 5.7 months (95% CI: 3.3–8.4) of mPFS and 15.1 months (95% CI: 11.5–25.6) of mOS, respectively. A total of 11 patients (20%) experienced treatment-related AEs of grade 3 or above. Grade 3/4 hematological AEs included decreased neutropenia/neutrophil count in 3 patients (5.5%), platelet count in 1 patient (1.8%), and white blood cell count (WBC) in 1 patient (1.8%). Most commonly, diarrhea (7.3%) and neutropenia (3.6%) were reported as grade 3 non-hematological AEs. To compare the noninferiority of S-1 plus cisplatin with docetaxel plus cisplatin in patients with stage IIIB or IV NSCLC who had not previously received treatment, Kubota *et al.* conducted

the TCOG0701CATS study, a randomized phase III trial (30). There were 608 patients enrolled and assigned randomly to each group. In the cisplatin-S-1 arm, median PFS was 4.9 months, whereas in the cisplatin-docetaxel arm, it was 5.2 months (HR =1.113; 95% CI: 0.945–1.311). In the cisplatin-S-1 arm, median OS was 16.1 months, whereas in the cisplatin-docetaxel arm, it was 17.1 months (HR =1.013; 96.4% CI: 0.837–1.227). PFS and OS for oral S-1 plus cisplatin were not different from docetaxel plus cisplatin. Grade  $\geq 3$  hematologic toxicity included, neutropenia (22.9% *vs.* 73.4%,  $P < 0.001$ ), leukopenia (8.0% *vs.* 55.2%,  $P < 0.001$ ), anemia (13.6% *vs.* 17.8%,  $P = 0.178$ ), thrombocytopenia (5.6% *vs.* 1.3%,  $P = 0.006$ ) in the carboplatin-S-1 arm and carboplatin-paclitaxel arm. Grade  $\geq 3$  nonhematologic toxicity included anorexia (17.6% *vs.* 27.3%,  $P = 0.001$ ), nausea (9.6% *vs.* 19.9%,  $P < 0.001$ ), diarrhea (6% *vs.* 3.7%,  $P = 0.930$ ), vomiting (4% *vs.* 8.1%,  $P < 0.001$ ) and febrile neutropenia (3% *vs.* 7.4%,  $P < 0.001$ ) between the cisplatin-S-1 arm and in the cisplatin-docetaxel arm. A combination of carboplatin and S-1 was investigated as first-line therapy in 33 older patients with advanced NSCLC (aged 70 years or more) who had previously not been treated (31). The ORR was 30.3% (95% CI, 14.6–46%). The mPFS was 134 days (95% CI: 79–173). mOS was 479 days (95% CI: 250–571). Thrombocytopenia (42.4%), neutropenia (33.3%), and anemia (27.3%) were the most common grade 3 or higher hematological AEs. Grade 3 or 4 nonhematologic toxicity included febrile neutropenia (12.1%) and pneumothorax (3.03%) and erythema multiforme (3.03%). Even for older NSCLC patients (aged 70 years or more), the carboplatin + S-1 regimen proved viable and tolerated because of its excellent survival result and moderate toxicities. In chemotherapy-naïve NSCLC patients, the combination of S-1 with cisplatin or carboplatin resulted in similar effectiveness results and reduced toxicity than those platinum-based doublet chemotherapy regimens.

According to a recent meta-analysis, these newer non-platinum regimens are effective for the treatment of advanced NSCLC due to their demonstrated activity and tolerable side effects (17). A combination of S-1 and other active agents with different mechanisms of action is being studied in order to achieve greater clinical benefits. Gemcitabine is a deoxycytidine analog with high anti-tumor activity and a favorable toxicity profile. A notable synergistic cytotoxic impact of Gemcitabine and 5-FU is seen, and it is sequence-dependent (18). Kaira *et al.* conducted a phase II study of gemcitabine combined with S-1 in 20

untreated elderly advanced NSCLC patients who were older than 70 years of age (32). The ORR was 40% (95% CI, 18.5–61.5%). In terms of PFS and OS, the median was 6.4 months (95% CI, 4.0–17.0) and 17.8 months (95% CI, 6.0–46.0). Neutropenia (25%), leukocytopenia (30%), anemia (0%), and thrombocytopenia (0%) were the hematological AEs reaching grades 3–4. The only non-hematological AE was a grade 3 skin rash, which occurred in 10% of cases. Paclitaxel is a taxane drug with favorable efficacy and safety as monotherapy for elderly patients (aged of  $\geq 70$  years) with advanced NSCLC. Yoshimura *et al.* conducted a phase II study, 17 untreated elderly patients (age of  $\geq 70$  years) received paclitaxel (PTX) plus S-1 (33). There was a 47.1% ORR, a PFS of 4.5 months (95% CI, 1.6–6.8) and an OS of 35 months (95% CI, 9.1– not reached), respectively. As for hematological AEs, there were 58.9% of leukopenia, 52.9% of neutropenia and 11.8% of anemia reaching grade 3 or more, respectively. Non-hematological toxicities reaching grade 3 or more were stomatitis (23.5%), febrile neutropenia (12%), pneumonitis (12%), diarrhea (6%), diarrhea (5.9%).

Combination regimens based on S-1 are similar to or better than platinum-based regimens in terms of ORR, PFS, and OS. As far as toxicity is concerned, S-1-based combinations are also superior to platinum-based combinations.

### ***S-1 combined with chemotherapy in second-line or later line treatment for advanced NSCLC***

Single agent chemotherapy is the standard second-line therapy for individuals with advanced NSCLC after first-line immunotherapy combined with chemotherapy. However, by the efficacy of second-line therapy's continued unsatisfactory performance and the patients' dismal prognosis, researches for new chemotherapeutic drugs and combination regimens as second-line treatment for advanced NSCLC were prompted. A study was performed by Takayama *et al.* to explore the efficacy of S-1 plus docetaxel against 39 previously treated NSCLC patients (Table 3) (34). The ORR was 7.7% (95% CI, 1.6–20.9%). The median PFS and mOS were 18.0 weeks (95% CI, 11.3–22.9) and 53.0 weeks (95% CI, 40.9–134.6), respectively. Leukocytopenia, neutropenia of grade 3 to 4 hematological toxicities were observed in 17 (43.6%) and 26 (66.7%). The most common non-hematologic toxicity was loss of appetite (7.7%), fever (5.1%), and interstitial pneumonia (5.1%). An evaluation of S-1 and PTX combined therapy in 40 patients



with advanced NSCLC following second-line treatment failure was conducted by Chihara *et al.* in a phase II clinical trial (Table 3) (35). The ORR was 27.5%. There were 6.5 months (95% CI, 3.2–8.5) and 20.7 months (95% CI, 8.1–25.0) of mPFS and mOS, respectively. Anemia (13%), neutropenia (48%), and thrombocytopenia (3%) were the most common hematologic toxicity grades 3 or 4. Non-hematologic toxicity grade 3/4 is composed of pneumonitis (10%), febrile neutropenia (8%), diarrhea (8%), and mucositis (5%).

A recent meta-analysis found that combination chemotherapy is more harmful than single-agent chemotherapy in the second-line setting (48). Even though monotherapy is currently recommended for recurrent NSCLC, combination chemotherapy for S-1 can easily be repeated for a longer period than monotherapy, likely equal to or longer than what is currently recommended. For patients who prefer outpatient or oral pharmaceutical treatment, S-1 may be an alternative option.

### **S-1 in combination with anti-angiogenic therapy**

#### *S-1 combined with bevacizumab as front-line treatment in advanced NSCLC*

Humanized monoclonal antibody, Bevacizumab, targets vascular endothelial growth factors. A meta-analysis found that Bevacizumab significantly improved PFS and OS in patients with advanced NSCLC when combined with platinum-based chemotherapy (49). Additionally, two preclinical studies indicate that bevacizumab combined with 5-FU derivatives enhanced antitumor activity (50,51). In two phase II studies, platinum, S-1, and Bevacizumab combination chemotherapy was used as first-line therapy in patients with advanced NSCLC who had not previously received treatment (Table 4). In a phase II trial, 39 untreated NSCLC patients received oral S-1 plus Cisplatin and Bevacizumab (36). The ORR was 64.1% (95% CI, 47.2–78.8%). There were 7.3 months (95% CI, 5.9–8.7 months) of mPFS and 21.4 months (95% CI, 14.7–not reached) of mOS. Leukopenia (12.8%) and neutropenia (23%) were the two most common Grade 3 or 4 hematological AEs. As regards the most common non-hematological AEs (grade 3 or above), hypertension accounted for 28.2%, and pulmonary infection for 7.8%. Based on these encouraging results, an exploratory randomized phase II study was conducted to test if cisplatin + S-1 + bevacizumab (SCB) is non-inferior to

cisplatin + pemetrexed + bevacizumab (PCB) (37). Forty-eight untreated patients were enrolled and randomly assigned to each group. PCB and SCB had ORRs of 54.2% and 83.3%, respectively (P=0.06). In both PCB and SCB administrations, the median PFS was 406 and 351 days, respectively (P=0.96), whereas the median OS was 678 and 1190 days (P=0.23). The results demonstrated that SCB regimen was non-inferior to carboplatin–paclitaxel arm concerning the ORR, OS, and PFS. Grade 3 or 4 toxicity included neutropenia (12.5% *vs.* 12.5%), anorexia (1.1% *vs.* 7.2%), infection (0.4% *vs.* 2.9%), skin rash (4.1% *vs.* 8.3%), hypertension (12.5% *vs.* 4.1%), urinary protein (8.3% *vs.* 4.1%) between the PCB regimen and SCB regimen. In individuals with untreated advanced NSCLC, bevacizumab combined with S-1 and platinum resulted in significant improvements in ORR, PFS, and OS compared with S-1 and cisplatin alone. It is possible to combine bevacizumab with platinum regimens as a first-line therapy for advanced NSCLC.

#### *S-1 combined with anti-angiogenic therapy in second-line or later line treatment for advanced NSCLC*

For the first time, Herbst *et al.* showed in 2007 that bevacizumab added to single-agent chemotherapy tended to increase PFS in the second-line situation (52). Three studies of S-1 plus bevacizumab have been conducted against previously treated NSCLC patients (Table 4). During a randomized phase II study, S-1 plus bevacizumab (SB) versus docetaxel plus bevacizumab (DB) were compared for non-inferiority (38). Each group received 45 patients who had previously received platinum-based chemotherapy through random assignment. There was a significant difference in ORR between the DB and SB arms (20.0% *vs.* 2.2%; P=0.015). In the DB arm, median PFS was 3.9 months (95% CI, 3.0–6.5) and in the SB arm, 3.5 months (95% CI, 2.9–5.9) (P=0.451). In the DB arm, median OS was 16.0 months (95% CI, 3.0–21.8) and in the SB arm, 21.7 months (95% CI, 11.6–31.5), respectively (P=0.406). There was noninferior to the DB arm with the SB arm concerning the PFS and OS. Grade 3 or 4 hematological toxicity included neutropenia (93.3% *vs.* 4.4%), anemia (2.2% *vs.* 0%), and febrile neutropenia (33.3% *vs.* 0%). Grade 3 or 4 non-hematological toxicity included infection (6.7% *vs.* 8.9%), fatigue (0% *vs.* 8.9%), hyponatremia (4.4% *vs.* 8.9%), proteinuria (2.2% *vs.* 6.7%), nausea (0% *vs.* 4.4%), mucositis oral (4.4% *vs.* 4.4%), diarrhea (0% *vs.* 4.4%), vomiting (0% *vs.* 2.2%), constipation (0% *vs.*

2.2%), increased alanine aminotransferase (ALT) (0% vs. 2.2%), increased aspartate aminotransferase (AST) (2.2% vs. 0%), bilirubin increased (0% vs. 2.2%), hyperkalemia (0% vs. 2.2%). With advanced non-squamous NSCLC, Yamada conducted a multicenter phase II study combining S-1 and Bevacizumab (39). Among the 28 treated NSCLC patients enrolled in the study, 14.3% had an ORR (95% CI, 1.3–27.3%). There were 3.2 months of median PFS (95% CI, 2.2–4.0) and 11.4 months of median mOS (95% CI, 8.9–13.9). There were 14.3% neutropenia, 3.6% leukopenia, 3.6% anemia, and 3.6% thrombocytopenia of grade 3 or 4 hematologic toxicity. Nonhematologic toxicity grade 3/4 included anorexia (10.7%), nausea (3.6%), stomatitis (3.6%), and diarrhea (3.6%). A multi-center phase II study was conducted by Nishijima-Futami *et al.* to assess the safety and effectiveness of S-1 + bevacizumab in 30 patients with recurrent non-squamous NSCLC (40). The ORR was 6.7% (95% CI, 1.8–21.3%). There was a median PFS of 4.8 months (95% CI, 2.7–6.4) and a median OS of 13.8 months (95% CI, 8.4– not available). Anemia (3.3%) was the only grade 3 hematologic toxicity. The most common grade 3 non-hematologic toxicities were diarrhea (10%), anorexia (10%), and infection (10%). No deaths or severe toxicity were associated with treatment.

The oral tyrosine kinase inhibitor anlotinib inhibits tumor growth and angiogenesis. Two studies of S-1 plus anlotinib have been performed against previously treated NSCLC patients (Table 4). An evaluation of S-1 plus anlotinib in 70 Chinese patients with EGFR mutation-negative advanced squamous cell lung cancer (SqCLC) with poor performance status (PS, 2–3) following progression of second- or later-line chemotherapy was conducted by Xie *et al.* (41). In terms of the short-term efficacy, there were no significant differences in ORR (20.0% vs. 10.0%,  $P=0.464$ ) between the anlotinib+S1 group and the anlotinib group. As for the long-term efficacy, there was no significant difference in PFS between the anlotinib + S1 group and anlotinib group ( $3.87\pm 0.29$  vs.  $3.00\pm 0.24$  months,  $P=0.11$ ). mOS of patients in the anlotinib + S-1 group was longer than anlotinib group ( $8.07\pm 0.56$  vs.  $6.17\pm 0.42$  months,  $P=0.022$ ). No AE of grade 3 or higher requiring discontinuation was observed. In a phase II study, Xiang *et al.* evaluated S-1 plus anlotinib in 29 previously treated advanced NSCLC patients (42). There was an ORR of 37.9% (95% CI: 20.7–57.7%). A median PFS of 5.8 months (95% CI: 2.9–8.7) and a median mOS of 16.7 months (95% CI: 14.9–18.6) were obtained. Grade 3 AEs were consisted of nausea (11%), fatigue (7%), hypertension (7%), rash (7%) and hemorrhage

(3%). Anlotinib and S-1 are both given orally without the requirement for an infusion pump or hospital stay, which may increase patient compliance and save expenses.

Inhibiting proliferation, migration, and neovascularization of endothelial cells, apatinib was a novel tyrosine kinase inhibitor (TKI) targeting VEGFR-2. The efficacy of apatinib for patients with advanced NSCLC who had failed second-line treatment has been demonstrated in a previous study. There have been two studies performed on NSCLC patients who had previously been treated with S-1 plus apatinib (Table 4). The combination of apatinib and S-1 was studied in 31 advanced NSCLC patients by Zhou in a retrospective study (43). There was an ORR of 22.6% (95% CI: 11.1–38.2%). There was 102 days mPFS (95% CI: 57–147) and 422 days mOS (95% CI: 148–696) during the study period. Treatment-related grade III toxicity were myelosuppression (10%), hand-foot-skin reaction (6%), hypertension (3%), fatigue (3%). In a phase II study conducted by Chen, 13 patients with treated advanced NSCLC were enrolled in the study to evaluate S-1 plus apatinib's efficacy and toxicity (44). The mOS was 9.8 months and the mPFS was 4.7 months. Grade 3 or above AEs were consisted of thrombocytopenia (12.1%), anemia (6.1%), leucopenia (6.1%), hypertension (15.2%), proteinuria (9.1%), hemorrhagic tendency (6.1%), hand-foot syndrome (3.0%) and diarrhea (3%).

### S-1 in combination with EGFR-TKI

An epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) is the preferred treatment for patients with advanced NSCLC with the EGFR mutation. To compare the efficacy and safety of S-1 monotherapy and S-1 containing combined chemotherapy for NSCLC, a population-based observational study was conducted. As a result of the clinical trial, it was confirmed that S-1 chemotherapy is effective and tolerable against wild and mutated types of EGFR NSCLC (53). In NSCLC patients regardless of their EGFR mutation status, the combination of S-1 and gefitinib has a synergistic antiproliferative effect and is well tolerated (54). A total of 35 patients with untreated EGFR mutations received oral S-1 plus carboplatin and gefitinib (Table 4) (45). There was an ORR of 85.7%. All patients had a median PFS of 17.6 months [95% CI: 15.5– not described (ND)]. The mOS was not reached (95% CI: 27.9–ND). Neutropenia (17.1%), thrombocytopenia (14.3%), and anemia (5.7%) were among the hematologic toxicity grades 3 or 4. In grades 3 nonhematologic toxicity, elevated aminotransferase was

20.0%, diarrhea was 14.3%, febrile neutropenia was 2.9%, anorexia was 2.9%, and nausea was 2.9%. According to the findings, triplet chemotherapy using carboplatin, S-1, and gefitinib is an effective first-line treatment option for advanced NSCLC.

Erlotinib showed a positive survival benefit in previously treated advanced NSCLC, regardless of EGFR mutation status. Nakahara *et al.* conducted a phase I/II study of erlotinib combined with S-1 in treated advanced NSCLC (Table 4) (46). Phase II enrollment included 10 patients with PS 0, 1, or 2 EGFR-wild type NSCLC. The ORR in phase II was 10.0%, and the disease control rate (DCR) was 40.0%. On the basis of two treatment-related deaths, enrolment was halted after the enrollment of 10 participants. A combination of erlotinib and S-1 failed to work in patients with EGFR wild-type NSCLC and was stopped early.

### S-1 in combination with immunotherapy

Immune checkpoint inhibitors (ICIs) and molecular target drugs have revolutionized lung cancer treatment over the past decade. Due to their significant benefit in treating metastatic disease and recurrent lung cancer without causing oncogene alterations, ICIs are now employed as first- and second-line treatments. A retrospective analysis of immunotherapy combined with S-1 in patients with advanced NSCLC was carried out by Tamura *et al.* (Table 5) (47). The outcomes were compared between patients with advanced NSCLC who received docetaxel-based chemotherapy or S-1 following nivolumab and those who received S-1 or docetaxel but not ICIs. S-1 without ICIs had an ORR of 17.6%, S-1 immediately after nivolumab had an ORR of 30.0% (OR =2.0, P=0.46), and in any lines after nivolumab had an ORR of 20.0% (OR =1.17, P=0.86). While docetaxel without ICIs had an ORR of 16.0%, docetaxel-based chemotherapy immediately after nivolumab had an ORR of 27.8% (OR =2.02, P=0.28), and in any lines after nivolumab had an ORR of 27.3% (OR =1.97, P=0.27). The median PFS to S-1 without ICIs was 2.63 months, S-1 immediately after nivolumab was 3.88 months (HR =1.00, P>0.99), and in any lines after nivolumab was 3.06 months (HR =0.81, P=0.60), respectively. While the median PFS for docetaxel without ICIs was 2.87 months, docetaxel-based chemotherapy immediately after nivolumab was 5.98 months (HR =0.69, P=0.23), and in any lines after nivolumab was 4.67 months (HR =0.76, P=0.34), respectively. The results showed

that compared with regimens without ICI pretreatment, cytotoxic chemotherapy followed by nivolumab was more effective at treating advanced NSCLC. It is urgent to investigate the efficacy of S-1 in the treatment of NSCLC with ICIs.

### Conclusions

S-1 is a novel oral anticancer agent that combines potassium oxonate, tegafur, and CDHP. The findings indicate a promising effectiveness and minimal toxicity with S-1 as monotherapy or in combinations with chemotherapy, anti-angiogenic therapy, targeted treatment and immunotherapy for patients with solid tumors as well as advanced NSCLC. In patients with advanced NSCLC with no driver gene mutation, age-related functional decline, multiple underlying diseases, and poor treatment tolerance have resulted in limited treatment options. S-1 has good clinical efficacy and a low incidence of adverse reactions, not only prolonging life but also improving the quality of life for patients, making it a new choice.

New researches have explored the S-1 in more detail. A preliminary clinical study conducted by Tanaka *et al.* explored the efficacy of combination of immunotherapy with S-1 and radiotherapy (55). This study of durvalumab after cisplatin plus S-1 (SP)-based chemoradiotherapy (CRT) found a 1-year PFS of 73%. A phase II clinical study conducted by Yamamoto *et al.* explored the frequency of S-1 administration. They found that both alternate-day and daily oral administrations of S-1 were demonstrated to be feasible in elderly patients with NSCLC (56). S-1's role as a therapeutic approach to advanced NSCLC will be further defined by results of ongoing and future trials.

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