Phase II Trial of S-1 as Second-Line Therapy in Patients with Advanced Non-small Cell Lung Cancer

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Purpose: Currently available agents for the treatment of advanced stage non-small cell lung cancer (NSCLC) have limited efficacy. S-1 is a novel formulation of oral fluoropyrimidine shown to be tolerable and active in patients with NSCLC in Japan. We conducted a multicenter phase II study in previously treated patients with NSCLC to evaluate the efficacy of single-agent S-1 in a predominantly non-Asian population.

Patients and Methods: Patients with advanced NSCLC and previously treated with only one line of chemotherapy received oral S-1 at 30 mg/m^2 every 12 hours for 14 consecutive days followed by a 7-day rest until meeting discontinuation criteria. The primary end point was to evaluate the overall response rate.

Results: Fifty-seven patients were accrued from 21 centers across the United States. Overall response rates and stable disease according to independent review were 7.1% and 48.2%, respectively, with a disease control rate of 55.3%. Progression-free survival was 2.9 months, median overall survival 7.3 months, and 1-year survival 31.6%. There were no significant differences in survival according to histologic subtype. The treatment was well tolerated, with the most common treatment-related side effects being nausea (54%) and diarrhea (49%).

Conclusion: Single-agent S-1 is well tolerated and has activity comparable with the other agents approved for use in recurrent/relapsed NSCLC.

Key Words: NSCLC, S1, Phase II.

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Lung cancer is the most common cause of cancer-related death in the United States, with 159,390 deaths estimated by the American Cancer Society for the year 2009.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 87% of lung cancer cases,[2] with at least two thirds of patients presenting with locally advanced or advanced disease at diagnosis.[3] Even among patients with early-stage disease, distant relapses are common despite the use optimal surgery and adjuvant chemotherapy.[4]

Although first-line chemotherapy is associated with improved survival and quality of life in patients with advanced NSCLC, virtually all patients eventually develop progressive disease (PD) requiring additional treatment. There are currently three agents (docetaxel, pemetrexed, and erlotinib) approved for the use in patients with metastatic NSCLC progressing after a platinum-based doublet therapy in the United States. In other countries such as Japan, gefitinib and tegafur/uracil have also been approved. The outcomes for second-line therapy remain suboptimal, with overall response rates (ORRs) in this setting of less than 10%, progression-free survival (PFS) less than 3 months, median overall survival (OS) between 5.7 and 8.3 months, and 1-year OS between 30% and 37%.[5–8] Therefore, there is a great need for the development of new agents or combination regimens in this patient population.

Since the first description by Heidelberger et al.[9] in 1957, 5-fluorouracil (5-FU) has been successfully used in a variety of solid tumors, particularly colorectal cancer, and upper gastrointestinal malignancies. In patients with advanced NSCLC, however, 5-FU has demonstrated minimal activity.[10] One of the possible explanations for this lack of benefit from 5-FU might be the presence of higher dihydropyrimidine dehydrogenase (DPD) activity in NSCLC compared with other solid tumors.[11,12] On entering the cell, 5-FU may be metabolized into the anabolic or catabolic pathways, with the former represented by phosphorylation into active metabolites and the latter through the action of DPD into inactive metabolites.[13] The rapid degradation of approximately 90% of administered 5-FU by DPD significantly limits its activity, with decreased amounts of the drug available for the anabolic pathway. Oral 5-FU is associated with erratic absorption, mainly due to the high DPD activity in the liver and gastrointestinal walls. One attractive option to circumvent this rapid DPD metabolism, while avoiding the

inconvenient use of costly implantable access devices and portable infusion pumps, has been the use of oral fluoropyrimidine prodrugs in combination with DPD inhibitors. Oral fluoropyrimidines may be broadly divided into 5-FU prodrugs, 5-FU combined with a DPD inhibitor, and 5-FU prodrugs combined with a DPD inhibitor. The 5-FU prodrugs, such as capecitabine and tegafur, were designed to undergo intact absorption through the gastrointestinal tract with posterior enzymatic activation to 5-FU in the liver or within the tumor. The most commonly used irreversible DPD inhibitor is eniluracil, whereas reversible inhibitors include uracil and 5-chloro-2,4-dihydropyrimidine.[14] Orotate phosphoribosyltransferase (OPRT) is the enzyme that activates 5-FU in the gastrointestinal tract.[15] As gastrointestinal toxicity is common in patients treated with fluoropyrimidines and OPRT is not present in the tumor, inhibition of this enzyme may decrease toxicity without affecting the antitumor efficacy. S-1 is the combination of the prodrug tegafur, the reversible DPD inhibitor 5-chloro-2,4-dihydropyrimidine, and the OPRT inhibitor oxo. S-1 is currently marketed in Japan for the treatment of head and neck cancer, colorectal cancer, breast cancer, pancreatic cancer, biliary cancer, gastric cancer, and NSCLC.

The recommended doses for single-agent S-1 based on phase I studies conducted in western countries were 50 mg/m^2 daily for 21 days every 4 weeks,[16] 40 to 50 mg/m^2 daily for 28 days every 5 weeks,[17,18] or 30 mg/m^2 twice daily for 28 days every 5 weeks.[19] An alternative approach, used in Japanese studies, was to administer the dose according to the body surface area, where patients with body surface area less than 1.25 m^2, 1.25 to 1.5 m^2, and more than 1.5 m^2 receiving 40 mg twice daily, 50 mg twice daily, or 60 mg twice daily, respectively, for 28 consecutive days.[20] The toxicity profile from these phase I trials differed significantly based on the geographic region of study, with predominant hematological toxicities observed in Japanese studies[19] and gastrointestinal toxicities in studies from North America or Europe.[16,17,19]

We performed a phase II study to evaluate the efficacy of single-agent S-1 in a predominantly non-Asian population of pretreated patients.

PATIENTS AND METHODS

Study Population

Patients with histologically and/or cytologically proven NSCLC who have had PD after a platinum-based doublet therapy, Eastern Cooperative Oncology Group performance status 0 or 1, and adequate organ functions were eligible to participate in the study.

Patients were excluded if they had mixed small cell and non-small cell histology, received investigational therapy within the past 30 days, systemic therapy for NSCLC within the previous 3 weeks, radiation therapy to a target lesion within the previous 3 months unless there was disease progression in that lesion and there were additional target lesions, radiation therapy within the last 2 weeks, and serious medical conditions including other malignancies, symptomatic brain metastases not controlled by corticosteroids, leptomeningeal metastases, psychiatric disorder, known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, myocardial infarction within the last 6 months, severe or unstable angina, and congestive heart failure with New York Heart Association class III or IV.

The following medications were prohibited during the study due to their potential interaction with S-1: sorivudine, uracil, cimetidine, folinic acid, flucytosine and dipyridamole due to enhanced S-1 activity, allopurinol, which may decrease S-1 activity, and phenytoin, which may have its activity enhanced by S-1.

The protocol, protocol amendments, informed consent, and other documents pertaining to the study were approved by the institutional review board of each participating center. This trial is registered on the clinical trials site of the US National Cancer Institute web site (trial registration NCT00227552).[21]

Treatment Plan

S-1 was supplied by Taiho Pharma USA, Inc. (NJ) and was administered orally, under fasting condition (defined as 1 hour prior or 1 hour after a meal) at 30 mg/m^2 every 12 hours for 14 days followed by a 7-day rest, with each cycle of therapy lasting 21 days. S-1 was supplied as 15-mg or 20-mg capsules. Treatment was continued until evidence of disease progression, development of intolerable side effects, or withdrawal of consent.

In case of grade ≥ 3 drug-related adverse events (AEs), the treatment was interrupted and restarted at a lower dose after improvement to baseline or grade ≤ 1. Patients who developed renal failure during therapy required an estimated creatinine clearance of at least 30 ml/min to restart S-1. Patients requiring more than a 3-week recovery period from the scheduled starting date of the next cycle were removed from the study. The two dose reductions allowed for S-1 were 25 mg/m^2 (first dose reduction) and 20 mg/m^2 (second dose reduction).

Study Assessments

Tumor response was evaluated by the RECIST criteria. Imaging studies with CT scans were performed within 21 days before day 1 and repeated at the end of every even cycle until disease progression. Nevertheless, if a patient responded, response confirmation was to be obtained through tumor assessments at least 4 weeks after the first documentation of response. Patients then returned to their original even-cycle schedule of assessments. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Physical examination and laboratory chemistry were performed at baseline and on day 1 of each cycle, whereas hematology was performed also on days 8 and 15.

Statistical Analysis

This was an open-labeled, multicenter, single-arm, phase II study divided into three stages including futility stage (stage 1), decision stage (stage 2), and precision improvement stage (stage 3). The primary end point of the study was to evaluate the antitumor activity of S-1, assessed by ORR including complete response (CR) and partial response

(PR). The secondary objectives included duration of response and PFS, OS, and safety profile. Based on the exact binomial probability distribution Simon two-stage Minimax design with acceptable ORR (p1) of 20%, unacceptable ORR (p0) of 8%, type I error (α) of 0.05, and type II error (β) of 0.2, the initial sample size was 50 patients. The patient sample for the first stage was 30, and the study would go to the second phase only if 10% or more patients achieved a confirmed response. For the study to be considered sufficiently efficacious to warrant further evaluation, the criteria to proceed to the third stage was an ORR in 16% or more patients. The sample for stage 3 would be estimated based on the ORR for the first two stages to achieve a lower 95% one-sided confidence bound of 10% or more, ranging from 35 additional patients in case of ORR of 16% to no additional patients in case of ORR of 20%. Assuming a 10% rate for loss to follow-up or nonevaluability for ORR assessment, the projected accrual for all stages combined was between 55 and 95 patients.

The primary statistical assessment of ORR at the end of the study was based on the Independent Reader assessment of the images, whereas the decision to proceed to stages 2 and 3 were based on ORR assessment by the on-site Investigators.

RESULTS

Patient Demographics

A total of 57 patients from 21 US centers were enrolled into the study. Demographics and baseline characteristics are described in Table 1. Median age was 62 years (range: 44–85). Most patients were men (61%), whites (88%), and former smokers (72%). Adenocarcinoma was the most common histology (46%) followed by squamous cell carcinoma (32%). Four patients (7%) received prior systemic therapy in addition to the first-line therapy including one patient treated with second-line erlotinib and three patients who had received adjuvant chemotherapy. Prior radiotherapy was administered in 58% of the patients.

Efficacy

The best ORR by Investigator and Independent Reader assessments were 8.8% (95% confidence interval [CI]: 2.9–19.3%) and 7.1% (95% CI: 2.0–17.3%), respectively. According to the Independent Reader, 27 (48.2%) patients had stable disease (SD), 19 (33.9%) had PD, and six (10.7%) were considered not evaluable (Table 2). Among the responding patients, the median duration of response was 6 months (95% CI: 3.8–18.8 months).

The PFS was 2.9 months (95% CI: 1.7–4.1 months), with 15.5% (95% CI: 6.5–28.1%) of patients without progression at 6 months (Figure 1). The median OS for all patients was 7.3 months (95% CI: 6.0–9.7 months) with survival rates at 6, 12, and 18 months of 59.6%, 31.6%, and 17.5%, respectively (Figure 2). PR and SD were 0% and 44.4%, respectively, for squamous cell carcinoma, and 10.5% and 50%, respectively, for nonsquamous histology. Median OS for patients with squamous and nonsquamous histologies were 7.0 months (95% CI: 3.4–9.3) and 9.1 months (95% CI: 5.7–10.3), respectively. The demographics of patients achieving PR or PFS ≥6 months are described in Table 3.

TABLE 1. Patient Characteristics at Baseline

Characteristics	*n*	Percentage
Age		
Mean	62	
Range	44–85	
Sex		
Male	35	61
Female	22	39
Ethnicity		
White	50	88
Smoking status		
Current smoker	12	21
Former smoker	41	72
Never smoker	4	7
Histology		
Adenocarcinoma	26	46
Squamous cell	18	32
Large cell	7	12
Other	6	10
ECOG performance status		
0	13	23
1	44	77
Disease stage		
IIIB	1	3
IIIB with pleural effusion	2	2
IV	54	95
Previous radiotherapy		
Yes	33	58
No	24	42
Previous systemic therapy		
Yes	4	7
No	53	93
Best response to previous treatment		
CR	4	7
PR	8	14
SD	22	39
PD	15	26
Unknown	8	14

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; ECOG, Eastern Cooperative Oncology Group.

TABLE 2. Response Rate by Independent Assessment ($n = 56$)

	Total ($n = 56$)	Squamous Cell ($n = 18$)	Nonsquamous Cell ($n = 38$)
Response			
Complete response	0 (0%)	0 (0%)	0 (0%)
Partial response	4 (7.1%)	0 (0%)	4 (10.5%)
Stable disease	27 (48.2%)	8 (44.4%)	19 (50%)
Progressive disease	19 (33.9%)	7 (38.9%)	12 (31.6%)
Not available	6 (10.7%)	3 (16.7%)	3 (7.9%)
Overall response rate, *n* (%)	4 (7.1%)	0%	10.5%
Disease control rate, *n* (%)	31 (55.3%)	44.4%	60.5%

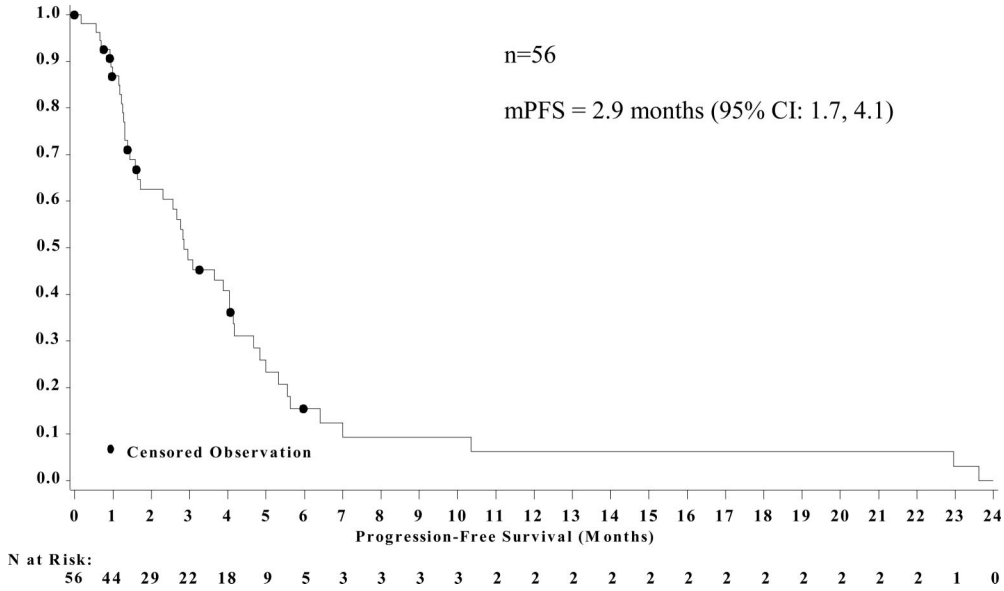

FIGURE 1. Progression-free survival.

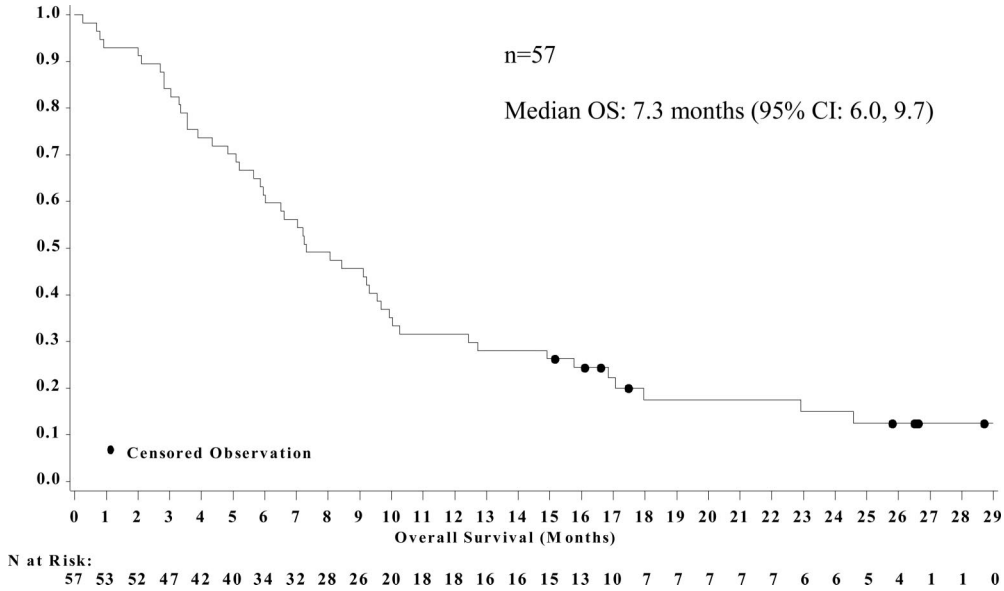

FIGURE 2. Overall survival.

Safety

All 57 patients received at least one dose of S-1 and were included in the safety analysis. The total number of cycles administered was 257, with a median number of three cycles (range: 1–38). Cycle 4 was initiated in 46% of patients and cycle 8 in 25% of patients. Seven percent of patients received more than 10 cycles.

The most common treatment-related AEs were nausea (54%), diarrhea (49%), fatigue (40%), vomiting (39%), and anorexia (32%) (Table 4). Anemia occurred in 10 patients (17%) and was the most common hematologic AE, followed by thrombocytopenia (5%), and neutropenia (3%). There were no cases of neutropenic fever. Treatment-related grade 3 toxicities occurred in 24 patients (42%) and grade 4 in three patients (5%). Diarrhea occurred in 12 patients (21%) and represented the most frequent grade 3/4 toxicity. Other common grade 3/4 AEs included fatigue (12%), dehydration (9%), and anorexia (7%).

Eight patients (14%) died during the treatment, including one death due to acute myocardial infarction considered possibly related to the study medication, one death due to unknown cause, and six patients with tumor progression.

DISCUSSION

The Japanese Lung Cancer Working Group[22] reported the first phase II study on single-agent S-1 in previously

TABLE 3. Demographics of Patients Achieving Partial Response or Progression-Free Survival ≥6 mo

Age (yr)	Sex	ECOG PS	Smoking Status	Histology	Best ORR	PFS (mo)	OS (mo)
52	Male	0	Former	Adenocarcinoma	PR	23.9	26.9
58	Female	0	Former	Other	SD	23.2	29.1
47	Male	1	Current	Adenocarcinoma	PR	10.5	26.9
55	Female	1	Former	Large cell	SD	7.1	10.4
58	Female	0	Current	Other	SD	6.5	27
74	Male	0	Former	Squamous	SD	6.1	16.3
70	Male	1	Former	Other	PR	5.7	7.3
62	Male	1	Current	Large cell	PR	5.1	7.4

ORR, overall response rate; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PFS, progression-free survival; OS, overall survival.

TABLE 4. Treatment-Related Adverse Events Reported in At Least 10% of Patients

	Any Grade		Grade ≥3	
Adverse Events	**No.**	**Percentage**	**No.**	**Percentage**
Nonhematologic				
Nausea	31	54	3	5
Diarrhea	28	49	12	21
Fatigue	23	40	7	12
Vomiting	22	39	1	2
Anorexia	18	32	4	7
Rash	13	23	1	2
Weight decrease	9	16	0	0
Stomatitis	9	16	2	3
Dysgeusia	8	14	0	0
Dehydration	7	12	5	9
Pruritus	6	10	0	0
Headaches	6	10	0	0
Hematologic				
Anemia	10	17	1	2

untreated patients with advanced stage NSCLC administered according to the previously described earlier phase I[20] for 28 consecutive days every 6 weeks. Among the 59 assessable patients, 13 achieved PR (22%), including 10 of 38 patients with adenocarcinoma (26.3%) and 2 of 20 patients with squamous cell carcinoma (10%). The median and 1-year OS were 10.2 months and 41%, respectively. Both gastrointestinal and hematological toxicities were mild and did not require dose interruption.

Several studies showed the feasibility of first-line S-1 combinations in patients with advanced NSCLC, with good efficacy and tolerability. The combination of S-1 and cisplatin showed acceptable toxicity and was associated with response rates of 47%, median OS of 11 months, and 1-year OS of 45% in 55 evaluable patients.[23] The combination of S-1 and carboplatin was well tolerated and resulted in response rate, PFS, and OS in 29 evaluable patients of 31%, 4.5 months, and 16 months, respectively.[24] The West Japan Thoracic Oncology Group 3505[25] showed response rate of 28.6%, disease control rate of 71.4%, median PFS of 4.9 months, and median OS of 15 months in patients with advanced NSCLC treated with S-1 and irinotecan. The response rate, PFS, and OS for the combination of S-1 and docetaxel in 60 patients with previously untreated advanced NSCLC were 30%, 4.9 months, and 15.2 months, respectively.[26]

In pretreated patients with NSCLC, a phase II study evaluated S-1 at the dose of 80 mg/m^2 twice daily for 28 days every 6 weeks.[27] Among the 27 enrolled patients, five achieved PR (19%). Median PFS and OS were 3.4 months and 10.2 months, respectively. The treatment was overall well tolerated, with less than 10% grade 3 or 4 toxicities. Although both response rate and survival were lower in our study compared with the Japanese phase II trial in pretreated patients, the median OS at 12 and 18 months (31.6% and 17.5%) was encouraging. These differences are not surprising, as it is now well known that Asians with advanced NSCLC have better outcomes than whites with NSCLC. The treatment schedule in the United States was established based on a phase I study, which demonstrated that S-1 dosed at 30 mg/m^2 twice daily for 14 days with a 7-day recovery period was safe and well tolerated.[28] This dosage of S-1 was repeated every 3 weeks, which is the standard treatment schedule for NSCLC. Furthermore, similar to the large phase III trial on S-1 plus carboplatin,[29] there were no large differences in outcomes according to histological subtype. Therefore, unlike pemetrexed,[30] which has selective activity in patients with nonsquamous histology, S-1 does not seem to have differential activity based on histology.

S-1 was well tolerated especially for hematological toxicities compared with other agents, although diarrhea was higher in this study. It is, therefore, important to provide patients with loperamide and instruct the patient on how to use it at the first sign of diarrhea. The primary dose-limiting toxicity in the US/European clinical trials was diarrhea, whereas hematological toxicities were observed in the Japanese studies. Differences in toxicity, particularly gastrointestinal toxicity, of 5-FU in patients of different regions have been described in the literature,[31] although the reasons for regional differences in toxicity caused by fluoropyrimidines are not completely defined.

In summary, S-1 is a convenient oral medication for patients with previously treated advanced stage NSCLC, with similar response rates, when compared with the available second-line therapies, acceptable toxicity, and clinical benefit in all histological subtypes. Although S-1 was well tolerated and achieved efficacy similar to other agents tested in this setting, this study failed to meet its objectives. Lower tissue

levels of thymidylate synthase were correlated with better response to S-1 in patients with stomach and renal cell cancer.[32,33] It is possible that S-1 may be more active in such a defined molecular subset of patients with NSCLC.

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