

Phase II Study of S-1 and Paclitaxel Combination Therapy in Patients with Previously Treated Non-Small Cell Lung Cancer

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TRIAL INFORMATION

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- **Principal Investigator:** Yoshinobu Iwasaki
- **IRB Approved:** Yes

LESSONS LEARNED

- In terms of efficacy and safety, good results were obtained with S-1 and paclitaxel (PTX) combination therapy.
- The findings suggest that S-1 and PTX combination therapy is a feasible treatment option in patients with previously treated non-small cell lung cancer.

ABSTRACT

Background. Although monotherapy with cytotoxic agents, including docetaxel and pemetrexed, is recommended for patients with previously treated advanced non-small cell lung cancer (NSCLC), its outcomes are unsatisfactory. S-1 is an oral fluoropyrimidine agent that consists of tegafur, 5-chloro-2,4-dihydropyridine, and potassium oxonate. S-1 is approved for patients with gastric cancer in 7 Asian countries and 15 European countries. It is also approved for patients with eight types of cancers, including NSCLC, in Japan. We evaluated the efficacy and toxicity of S-1 and paclitaxel (PTX) combination therapy in patients with previously treated NSCLC.

Methods. Oral S-1 was administered thrice weekly on days 1–14 at 80, 100, and 120 mg/day in patients with body surface areas of <1.25, 1.25–1.5, and >1.5 m², respectively. PTX was administered at 80 mg/m² on days 1 and 8. Primary endpoint

was response rate, and secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety.

Results. Forty patients were enrolled, with response and disease control rates of 27.5% and 75.0%, respectively (Fig. 1). Median PFS and OS were 6.5 and 20.7 months, respectively. Grade 3/4 anemia and thrombocytopenia were seen in five (12%) and one (2%) patients, respectively. Febrile neutropenia occurred in three patients (7%). Common grade 3/4 non-hematological toxicities were stomatitis (5% of patients), diarrhea (7% of patients), and interstitial lung disease (one patient). No treatment-related deaths were observed.

Conclusion. This S-1 and PTX cotherapy dose and schedule showed satisfactory efficacy, with mild toxicities, in patients with previously treated advanced NSCLC. *The Oncologist* 2019;24:1033–e617

DISCUSSION

Lung cancer is the leading cause of cancer deaths in the world. NSCLC accounts for approximately 85% of lung cancer cases. Treatment for advanced NSCLC is dramatically evolving owing to immune checkpoint inhibitors (ICIs) and molecular target drugs. Currently, ICIs are recommended in

the standard initial treatments of advanced or recurrent lung cancer without driver oncogene mutations, as single agents and ICI-platinum based combination chemotherapy [1–3]. When ICIs are used for primary treatment, cytotoxic anticancer drugs are options for second-line treatment

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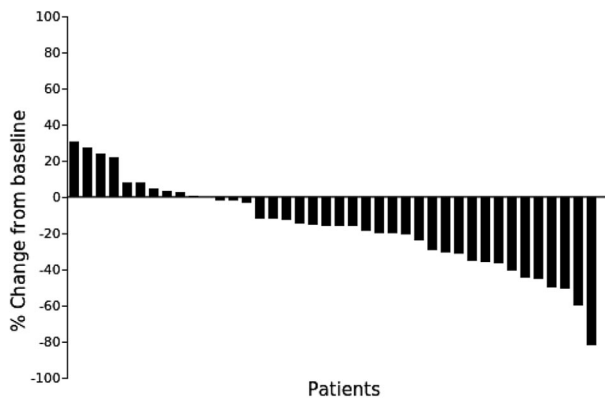


Figure 1. The ORR and disease control rates were 27.5% (95% confidence interval [CI], 14.6-43.9) and 75.0% (95% CI, 58.8-87.3), respectively.

during recurrence. The role of cytotoxic anticancer drugs is still important. Docetaxel (DOC) and pemetrexed (PEM) are used as single agents in previously treated cases; combination treatment with ramucirumab is recommended for younger patients with good performance status (PS).

However, this antiangiogenic agent is not suitable for some patients; the incidence of adverse events is sometimes higher with combination therapy [4]. Single-agent DOC or PEM therapy is an option when angiogenesis inhibitors are unavailable, but the response rates for single-agent therapy are low [5, 6]; therefore, new safe and effective therapies are much needed.

Although nonplatinum combinations provide an alternative strategy, several randomized trials comparing single-agent with doublet chemotherapy had insufficient power to detect potentially relevant differences in survival [7, 8].

We had previously conducted a phase I/II study of S-1 and paclitaxel (PTX) combination therapy in previously untreated non-small cell lung cancers among the elderly (≥ 70 years of age). In the phase II study at the recommended dose (RD; S-1, 80 mg/m²; PTX, 80 mg/m²), the response and disease control rates were 53.3% and 93.3%, respectively, and the toxicities were mild [9, 10]. The present phase II study evaluated the efficacy and safety of S-1 and PTX combination therapy after second-line treatment in patients with previously treated NSCLC. These results warrant further evaluation of this combination in phase III trials.

TRIAL INFORMATION

Disease	Lung cancer – NSCLC
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	1 prior regimen
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Safety

Additional Details of Endpoints or Study Design

Patient eligibility: The patient eligibility criteria were as follows: (a) presence of at least one measurable tumor lesion; (b) cytologically or histologically confirmed NSCLC; (c) presence of confirmed stage IIIB disease without any indications for radiotherapy or stage IV disease in patients who failed at least one prior line of chemotherapy, including platinum-based regimens; (d) more than 4 weeks since the last administration of prior chemotherapy; (e) age ≥ 20 years; (f) Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1; (g) adequate organ function and bone marrow activity (neutrophil count $\geq 3,000/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, and hemoglobin level ≥ 9.5 g/dL), serum bilirubin concentration ≤ 1.5 mg/dL, serum aspartate aminotransferase and alanine aminotransferase concentrations less than or equal to twice the upper limit of the normal range, creatinine level less than or equal to upper limit of normal, and creatinine clearance rate ≥ 60 mL/minute; (h) life expectancy > 2 months; and (i) able to take medications orally. All patients had to provide written informed consent. The patient exclusion criteria were as follows: (a) presence of interstitial pneumonia; (b) severe concomitant disease (e.g., severe cardiac disease, uncontrolled diabetes, or severe infection); (c) active concomitant malignancy; (d) severe hypersensitivity to either the study drugs or alcohol; and (e) receiving treatment with flucytosine.

Treatment plan: The RD of PTX, that is, 80 mg/m², from the results of our phase I study was used. In each 21-day cycle, 80 mg/m² of PTX was administered on days 1 and 8. S-1 was administered twice daily from days 1 to 14. The dose of S-1 was calculated according to the patient's body surface area as follows: 40, 50, and 60 mg S-1 for body surface areas of < 1.25 , 1.25–1.50, and ≥ 1.50 m², respectively. Treatment was continued until disease progression, appearance of unacceptable toxicity, withdrawal of consent by the patient, and termination of treatment by the attending physician. The criteria for initiation of treatment were as follows: white blood cell (WBC) count $\geq 3,000/\text{mm}^3$; neutrophil count $\geq 1,500$ cells/mm³; platelet count $\geq 75,000/\text{mm}^3$; creatinine level less than or equal to upper limit of normal; and peripheral neuropathy or other non-hematological toxicities of grade 1 or lower, excluding pigmentation and alopecia. Criteria for discontinuation of PTX on day 8 and S-1 included WBC count $\geq 2,000/\text{mm}^3$; neutrophil count $\geq 1,000$ cells/mm³; platelet count $\geq 75,000/\text{mm}^3$; creatinine level less than or equal to upper limit of normal; and peripheral neuropathy or other nonhematological toxicities of grade 1 or lower, excluding pigmentation and alopecia. The administration of S-1 and PTX was delayed until the criteria were satisfied up to a maximum of 14 days. Criteria for the reduction of the dose of S-1 and PTX in the next cycle were WBC count $< 1,000/\text{mm}^3$; neutrophil count $< 500/\text{mm}^3$; platelet count $< 25,000/\text{mm}^3$; or occurrence of peripheral neuropathy or toxicities,

excluding pigmentation and alopecia of grade 3 or higher, during the previous cycle. S-1 dose was reduced from 120 to 100 mg/day, 100 to 80 mg/day, or 80 to 50 mg/day, whereas PTX dose was reduced by 10 mg/m².

Evaluation: After the treatment was started as per protocol, computed tomography or magnetic resonance imaging were performed monthly to evaluate the anticancer efficacy of the combination treatment; physical examination and laboratory tests for evaluation of hepatic or renal function and complete blood counts were performed at least once a month. Responses were graded as complete response, partial response (PR), stable disease (SD), and progressive disease (PD) according to RECIST. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis: The primary endpoint of this study was overall response rate (ORR), and the secondary endpoints were PFS, OS, and safety. The sample size was calculated with α and β errors of 0.05 and 0.1, respectively. The threshold and estimated ORRs were 5% and 20%, respectively. The estimated minimum sample size was 38. Considering patient ineligibility, we needed at least 40 patients. OS and PFS were calculated using the Kaplan-Meier method. All analyses were performed using JMP software program version 8.0 for Windows.

Ethics: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The trial was approved by the Ethics Committee of the Kyoto Prefectural University of Medicine, Kyoto, Japan (RBMR-C-974). The trial was supervised and managed by the Ethics Committee. Informed consent was obtained from all individual participants included in the study.

Investigator's Analysis	Active and should be pursued further
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DRUG INFORMATION

Drug 1

Generic/Working Name	S-1
Company Name	Taiho Pharmaceutical Co., Ltd.
Dose	40, 50, and 60 mg/m ²
Route	p.o.
Schedule of Administration	S-1 was administered twice daily from days 1 to 14. The dose of S-1 was calculated according to the patient's body surface area as follows: 40, 50, and 60 mg S-1 for body surface areas of <1.25, 1.25–1.50, and ≥1.50 m ² , respectively.

Drug 2

Generic/Working Name	Paclitaxel
Company Name	Bristol-Myers Squibb
Dose	PTX was fixed as 80 mg/m ²
Route	IV
Schedule of Administration	The RD of PTX, that is, 80 mg/m ² , from the results of our phase I study was used. In each 21-day cycle, 80 mg/m ² of PTX was administered on days 1 and 8.

PATIENT CHARACTERISTICS

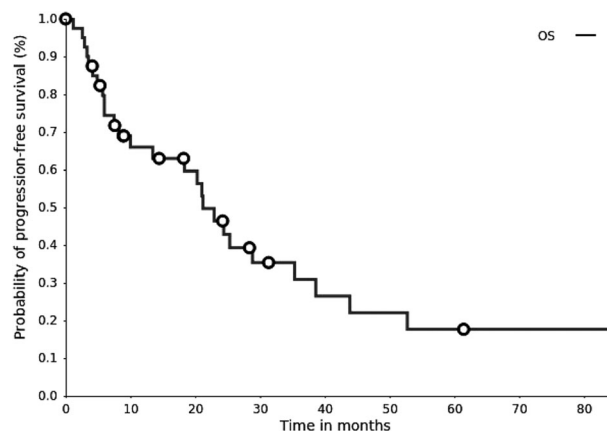
Number of Patients, Male	28
Number of Patients, Female	12
Stage	Presence of confirmed stage IIIB disease without any indications for radiotherapy or stage IV disease in patients who have experienced disease progression on at least one prior line of chemotherapy, including platinum-based regimens
Age	Median (range): 65 (35–83) years
Performance Status: ECOG	0 — 14 1 — 21 2 — 5 3 — Unknown —
Cancer Types or Histologic Subtypes	Adenocarcinoma, 23; squamous cell carcinoma, 15; non-small cell lung carcinoma, 2.

PRIMARY ASSESSMENT METHOD

Title	ORR
Number of Patients Screened	40
Number of Patients Enrolled	40
Number of Patients Evaluable for Toxicity	40
Number of Patients Evaluated for Efficacy	40
Evaluation Method	RECIST 1.1
Response Assessment CR	<i>n</i> = 0 (0%)
Response Assessment PR	<i>n</i> = 11 (27.5%)
Response Assessment SD	<i>n</i> = 19 (47.5%)
Response Assessment PD	<i>n</i> = 10 (25%)
Response Assessment OTHER	<i>n</i> = 0 (0%)
(Median) Duration Assessments PFS	6.5 months, CI: 3.2–8.5
(Median) Duration Assessments OS	20.7 months, CI: 8.1–25.0

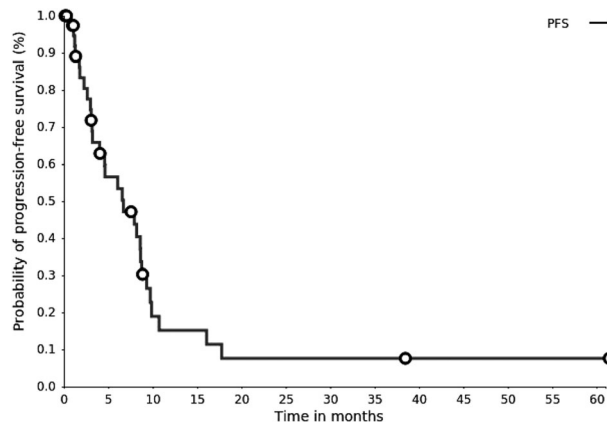
SECONDARY ASSESSMENT METHOD

Title	OS
Number of Patients Screened	40
Number of Patients Enrolled	40
Number of Patients Evaluable for Toxicity	40
Number of Patients Evaluated for Efficacy	40
(Median) Duration Assessments OS	20.7, CI: 8.1



Kaplan-Meier plot. Overall survival (OS). The median survival time was 20.7 months (95% confidence interval, 8.1–25.0 months).

Title	PFS
Number of Patients Screened	40
Number of Patients Enrolled	40
Number of Patients Evaluable for Toxicity	40
Number of Patients Evaluated for Efficacy	40
Evaluation Method	RECIST 1.1
(Median) Duration Assessments PFS	6.5, CI: 3.2



Kaplan-Meier plot. Progression-free survival (PFS). The median PFS survival was 6.5 months (95% confidence interval, 3.2–8.5 months).

ADVERSE EVENTS							
All Cycles							
Name	NC/NA	1	2	3	4	5	All grades
Leukocytes (total WBC)	50%	0%	10%	30%	10%	0%	50%
Neutrophils/granulocytes (ANC/AGC)	47%	0%	5%	28%	20%	0%	53%
Platelets	97%	0%	0%	3%	0%	0%	3%
Hemoglobin	64%	5%	18%	13%	0%	0%	36%
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 × 10e9/L, fever ≥38.5°C)	92%	0%	0%	8%	0%	0%	8%
Nausea	52%	40%	8%	0%	0%	0%	48%
Liver dysfunction/failure (clinical)	95%	0%	5%	0%	0%	0%	5%
Mucositis/stomatitis (clinical exam)	62%	13%	20%	5%	0%	0%	38%
Creatinine	95%	5%	0%	0%	0%	0%	5%
Diarrhea	51%	13%	28%	8%	0%	0%	49%
Constipation	95%	5%	0%	0%	0%	0%	5%
Hair loss/alopecia (scalp or body)	90%	10%	0%	0%	0%	0%	10%
Neuropathy: sensory	95%	5%	0%	0%	0%	0%	5%
Pneumonitis/pulmonary infiltrates	87%	0%	3%	10%	0%	0%	13%

Adverse Events Legend

The median number of completed cycles was 3 (range 1–10). All patients were assessed for toxicity. Grade 3/4 anemia and thrombocytopenia was seen in five (12%) and one (2%) patients, respectively. Febrile neutropenia was seen in three patients (7% of patients). The most common grade 3/4 nonhematological toxicities were stomatitis (5% of patients), diarrhea (7% of patients), and grade 3 interstitial lung disease (one patient). No treatment-related deaths were observed.

Abbreviations: AGC, absolute granulocyte count; ANC, absolute neutrophil count; NC/NA, no change from baseline/no adverse event; WBC, white blood cell.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study completed
Investigator’s Assessment	Active and should be pursued further

Monotherapy with docetaxel (DOC) or pemetrexed (PEM) is recommended for the treatment of previously treated advanced non-small cell lung cancer (NSCLC) cases. The results of the REVEL study demonstrated significantly prolonged progression-free survival (PFS) with ramucirumab (RAM) compared with DOC alone [4]. A combination of DOC + RAM is currently recommended for treating younger patients with good performance status. However, RAM is often unsuitable for many patients, including those with hemoptysis, tumor vascular invasion, and postradiation therapy; adverse events such as neutropenia and febrile neutropenia (FN) may be difficult to manage. In cases unsuited for RAM therapy, single-agent cytotoxic drugs are recommended. Controlled trials with DOC versus PEM [6] and DOC versus S-1 [11] have been conducted to date, but none of the trials showed superiority, with response rates of around 8.3%–9.9%. Currently, there is no treatment that provides superior results to those of single-agent DOC. A meta-analysis of nonplatinum doublets reported that although the overall response rate (ORR) and PFS tended to be superior, overall survival (OS) was not improved; these doublets also demonstrated a higher incidence of adverse events [12].

In the present study combining S-1 with paclitaxel, the ORR was 27.5%, and the primary endpoint was met. This was more favorable than the response rates of single-agent DOC or single-agent S-1, with confirmed noninferiority to single-agent DOC [11]. The results also surpassed the response rate of DOC + RAM (23%) reported in the REVEL study. The study combination demonstrated a PFS of 6.5 months, which was better than the 4.5 months demonstrated by DOC + RAM. The OS was found to be 20.7 months, which possibly surpassed the results of the meta-analysis [12].

In addition, this study found similar response rates in both nonsquamous and squamous cell carcinomas and may be effective in either histology. Angiogenesis inhibitors cannot be used in certain squamous cell carcinoma cases; squamous cell carcinomas had made up only 25% of the population in the REVEL study. We speculate that this study combination could be an effective treatment option, particularly for patients with previously treated squamous cell carcinomas.

In terms of safety, neutropenia above grade 3/4 was the most common with this combination, at 47.5%. In comparison, grade 3/4 neutropenia was reported in 49% of patients receiving DOC + RAM. FN was noted in 7% of this study

cohort. This was less than that reported in the REVEL study (16%). The incidence of FN in the meta-analysis of non-platinum combination therapy was 7%, which was similar to our findings. Among nonhematologic toxicities, stomatitis and diarrhea tended to be more common compared with the results of other concomitant treatments. This could have been due to S-1, but the incidence was higher than that reported with S-1 alone [13] and with DOC + S-1 combination therapy [14]. Conversely, in a report of a phase II study of S-1 + PTX in gastric cancer, stomatitis of grade 3 or higher was reported in 28% [15]; caution should be exercised in interpreting these results as these mucosal lesions may have been increased owing to PTX. In this study, anticancer therapy could be continued with supportive treatment and was considered well tolerated. Also, when compared with our previous phase II study in older adults with similar tumors, neutropenia (47.5% vs. 52.9%), FN (7% vs. 11.8%), and stomatitis (5% vs. 23.5%) were all lower in this study. These results demonstrate that this schedule and dose tailored for older adults was better tolerated by adults of all ages in this cohort, with similar efficacy. As a supplement, S-1 is labelled for use in many European countries, and for head and neck cancer, colorectal cancer, and non-small cell lung, breast, pancreatic, and biliary tract cancers in several countries in Asia [16]. It has not been approved by the U.S. Food and Drug Administration [16].

In conclusion, the results of this study met the criteria for the primary endpoint. Combination chemotherapy with S-1 and PTX was found to be effective and well tolerated in patients with previously treated NSCLC. These results warrant further evaluation of this combination in phase III trials.

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DISCLOSURES

Junji Uchino: Eli Lilly Japan K.K. (RF); **Koichi Takayama:** Chugai-Roche Co. and Ono Pharmaceutical Co. (RF), AstraZeneca, Chugai-Roche Co., MSD-Merck Co., Eli Lilly Co., Boehringer-Ingelheim Co., Daiichi-Sankyo Co. (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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