



Original Research

Randomised phase III study of S-1 alone versus S-1 plus lentinan for unresectable or recurrent gastric cancer (JFMC36-0701)[☆]



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KEYWORDS

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Abstract Background: Lentinan (LNT) is a purified β -1, 3-glucan that augments immune responses. The present study was conducted to assess the efficacy of LNT in combination with S-1 as a first-line treatment for unresectable or recurrent gastric cancer.

Patients and methods: Eligible patients were randomly assigned to receive S-1 alone or S-1 plus LNT. The primary end-point was overall survival (OS). Secondary end-points were time-to-treatment failure (TTF), overall response rate (ORR), safety, quality of life (QOL), and biomarker. The percentages of LNT-binding monocytes in peripheral blood prior to treatment were analysed for the biomarker assessment.

Results: One hundred and fifty-four and 155 patients were randomly assigned to receive S-1 alone or S-1 plus LNT, respectively. The median OS was 13.8 and 9.9 months ($P = 0.208$), the median TTF was 4.3 and 2.6 months ($P < 0.001$), the ORR was 22.3% and 18.7% for the S-1 and S-1 plus LNT groups, respectively. The incidences of haematologic and non-haematologic adverse events were similar, and no significant changes in QOL scores were observed during the treatment in both groups. In a subpopulation of patients with LNT-binding monocytes $\geq 2\%$, patients who received more than two cycles of chemotherapy showed a longer survival time in the S-1 plus LNT group.

Conclusions: OS did not improve and TTF was significantly worse in the S-1 plus LNT group as compared with the S-1-only group. This study showed no efficacy of LNT when combined with S-1 treatment in patients with unresectable or recurrent gastric cancer.

Clinical trial registration ID number: UMIN 000000574.

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1. Introduction

Lentinan (LNT) is a purified β -1, 3-glucan with β -1, six branches obtained from *Lentinus edodes*, an edible mushroom cultivated in Japan [1]. LNT augments immune responses and increases host resistance against murine and human tumours [2]. LNT promotes T cell-dependent immunopotentiality and functions as a maturation factor for lymphoid cells [3]. We previously determined that the initial step of immunomodulation by LNT may be its binding to monocytes [4]. In cancer patients, LNT-bound macrophages may produce IL-12 followed by the induction of a T helper (Th) 1 response, which mediates cellular immunity, and may induce downregulation of Th2 responses [5]. In patients with advanced gastric cancer, cellular immunity is decreased and Th2-dominant status develops [6]; so, it is important to enhance the cellular immunity and alleviate the Th2-dominant condition. Ochiai *et al.* [7] reported that an increase in the number of cytotoxic T cells in peripheral blood was found in the chemotherapy plus LNT group as compared with chemotherapy-alone group in a controlled randomised study in advanced gastric cancer.

A cooperative clinical study group in Japan has performed a phase III clinical trial of LNT that revealed that LNT prolonged survival when patients with advanced gastric cancer were treated in combination with tegafur

[8]. Recently, an individual patient data meta-analysis of chemoimmunotherapy using LNT was performed in 650 patients with unresectable or recurrent gastric cancer in five trials. This meta-analysis revealed that LNT significantly prolonged the overall survival (OS) in advanced gastric cancer patients who were treated in combination with tegafur or other fluoropyrimidines [9]. However, all five clinical studies included in the analysis were performed in the 1980s, and S-1, which was developed in the 1990s, was not used in these trials.

S-1 was designed to enhance the anti-cancer activity of tegafur by combining it with two modulating substances: gimeracil to inhibit dihydropyrimidine dehydrogenase and potassium oxonate to reduce gastrointestinal toxicities [10]. The JCOG9912 trial, which was designed to assess whether S-1 alone was as good as 5-fluorouracil alone, revealed that S-1 was not inferior to 5-fluorouracil [11]. S-1 is the most widely used drug for the treatment of unresectable or recurrent gastric cancer in Japan. It is reported that the median survival time (MST) of 400 d was in a pilot study of S-1 combined with LNT in advanced gastric cancer [12]. It is of great interest that LNT may also have a synergistic effect with this new type of fluoropyrimidine S-1. Therefore, we conducted a randomised phase III study of S-1 alone versus S-1 plus LNT in advanced or recurrent gastric cancer to assess the

efficacy of LNT (JFMC36-0701, UMIN Clinical Trial ID 000000574).

2. Patients and methods

2.1. Patients

Eligibility criteria included histologically proven, unresectable or recurrent gastric cancer; measurable lesion if gastrectomy was performed; age ≥ 20 years (no upper age limit); an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; no previous chemotherapy or immunotherapy; no adjuvant chemotherapy with S-1; oral intake capability, adequate haematologic, renal, and hepatic function; and an expected survival of at least 3 months. Exclusion criteria were as follows: pregnant or breast-feeding women, clinically significant cardiovascular disease, gastrointestinal bleeding, central nervous system metastases, and ascites and thoracic effusions necessitating paracentesis. This study was performed in accordance with the principles of Good Clinical Practice and the ethical standards laid down in the Declaration of Helsinki. The study protocol was approved by each site's ethics committee, and written informed consent was obtained from each patient.

2.2. Study design

This study was a prospective, multicentre, randomised, open-label phase III clinical trial conducted at 97 centres in Japan. S-1 monotherapy was selected for the control arm because the SPIRITS trial had not finished yet when this study started [13]. Patients were centrally randomised to receive treatment with S-1 alone or S-1 plus LNT at a 1:1 ratio, stratified by ECOG PS (0/1 versus 2), disease status (unresectable versus recurrent), and the institution.

2.3. Treatment

S-1 was given orally twice daily for the first 4 weeks of a 6-week cycle. The dose of S-1 administered was calculated according to the patient's body surface area as follows: less than 1.25 m^2 , 40 mg; $1.25\text{--}1.5 \text{ m}^2$, 50 mg; and greater than 1.5 m^2 , 60 mg. LNT was given as an intravenous infusion of 2 mg/body every week. Treatment for both groups was continued until one of the following occurred: progressive disease, unacceptable toxicity, withdrawal of consent by the patient, or termination of treatment by the attending physician.

2.4. Efficacy and safety assessments

The primary end-point was OS, defined as time from date of randomization to date of death from any cause. Secondary end-points were time-to-treatment failure (TTF), overall response rate (ORR), safety, quality of

life (QOL) score, and biomarker level. TTF was defined as the time from randomization to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, physician's decision, or death. Measurable lesions were assessed every month during initial four cycles by computed tomography scan according to RECIST version 1.0 [14] by principal investigators at each participating centre until onset of progressive disease. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Clinical and laboratory assessments were performed at screening and on days 1, 15, and 29 of each cycle. S-1 was withheld at grade 3 haematological toxicities or grade 2 non-haematological toxicities and reintroduced after recovery of toxicities at grade 1. S-1 was reduced at any grade 3 toxicities. Treatment could be withheld for up to 4 weeks.

2.5. QOL assessment

The self-administered, 40-item Functional Assessment of Cancer Therapy-Biological Response Modifier [15] was used to assess participants' overall QOL. Patients were asked to complete the QOL assessment at five time points: baseline (before treatment), at 4 and 6 weeks after treatment (during the first chemotherapy cycle) and at 10 and 12 weeks after treatment (during the second chemotherapy cycle). The QOL assessment was not obligatory in this study; so, the data were collected from the patients who agreed to participate in the QOL assessment.

2.6. Biomarker assessment

LNT-binding monocytes were assessed by using fluorescein-labelled LNT [16]. Briefly, peripheral blood obtained from patients prior to the treatment was incubated with fluorescein-labelled LNT at 37°C for 75 min, and phycoerythrin-labelled anti-CD14 antibody (CALTAG) was added during the last 30 min. The percentage of LNT-binding CD14^+ monocytes was measured with a fluorescence-activated cell sorter (FACS Calibur, Becton Dickinson).

2.7. Statistical analysis

In the phase II study of S-1 treatment in patients with advanced gastric cancer who had not received previous chemotherapy, the MST was 244 d [17]. In a pilot study of S-1 combined with LNT, the MST was 400 d [12]. On the basis of these findings, we assumed MST would be 8 months in the S-1 group and 12 months in the S-1 plus LNT group. The required number of events was estimated as 284 with a 2-sided α value of 0.05 and a power of 90% to detect differences in survival on completion of follow-up between the S-1 and the S-1 plus LNT group.

Baseline patient characteristics were compared by using Pearson's chi-square test, except for age, which was compared by using Mann–Whitney's U test. OS and TTF were compared by using log-rank tests stratified by randomization factors and Kaplan–Meier estimates. Cox proportional hazards models stratified by the randomization factors estimated hazard ratios (HRs) and 95% confidence intervals (CIs). For the biomarker assessment, we performed the weighted log-rank test with the Harrington–Fleming class of weights [18]. *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed by using SAS version 9.2 and version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patients and treatment exposure

Between February 2007 and June 2010, 309 patients were enrolled (Fig. 1). Fourteen patients were excluded from the analysis; so, the full analysis set comprised 295 patients, and OS was analysed in these patients. Six patients were excluded from the full analysis set population. The safety population comprised 289 patients, and the safety, response, TTF, and QOL were analysed in this safety population. Table 1 shows baseline patient characteristics, which were well balanced between the treatment groups. However, the proportion of patients with serum albumin less than 3.0 g/dl was significantly higher in the S-1 plus LNT group as compared to the S-1 group,

Table 1
Patient characteristics.

	S-1 (n = 146) n (%)	S-1 + LNT (n = 149) n (%)	<i>P</i>
Sex			
Men	107 (73.3)	101 (67.8)	0.31
Women	39 (26.7)	48 (32.2)	
Age (years)			
Median (range)	74 (32–94)	73 (44–93)	0.97
ECOG PS			
0	102 (69.9)	107 (71.8)	0.57
1	39 (26.7)	34 (22.8)	
2	5 (3.4)	8 (5.4)	
Serum albumin (g/dl)			
3.0≤	108 (74.0)	104 (69.8)	0.04
3.0>	17 (11.6)	32 (21.5)	
Unknown	21 (14.4)	13 (8.7)	
Disease status			
Unresectable	126 (86.3)	126 (84.6)	0.74
Recurrent	20 (13.7)	23 (15.4)	
Primary lesion			
Present	96 (65.8)	94 (63.1)	0.72
Resected	50 (34.2)	55 (36.9)	
Measurable lesions			
Yes	94 (64.4)	96 (64.4)	0.99
No	52 (35.6)	53 (35.6)	
Histology			
Intestinal type	57 (39.0)	76 (51.0)	0.10
Diffuse type	77 (52.8)	65 (43.6)	
Unknown	12 (8.2)	8 (5.4)	

LNT, lentinan; ECOG PS, Eastern Cooperative Oncology Group performance status.

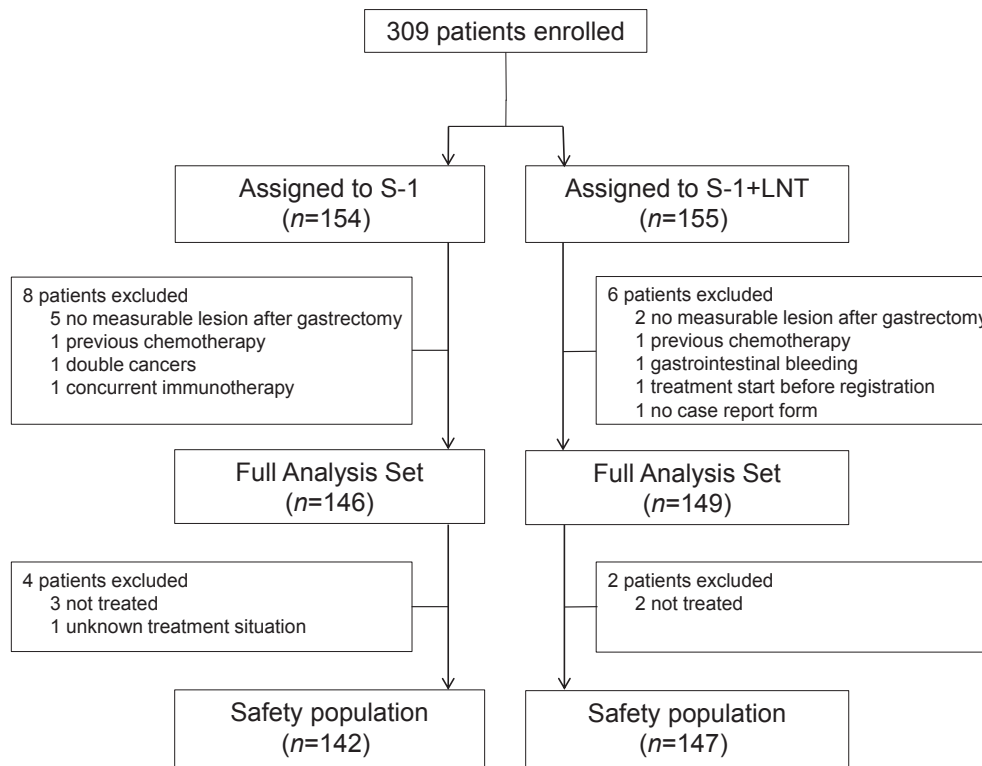


Fig. 1. CONSORT diagram.

whereas an ECOG PS was well balanced between the two groups.

Patients in the S-1 group received a median of three cycles of S-1 (range, 1–38), and patients in the S-1 plus LNT group received a median of two cycles of S-1 (range, 1–19) and 22 treatments with LNT (range, 1–104). In the S-1 group, the S-1 doses were reduced in 17.8% of patients. In the S-1 plus LNT group, 19.5% of patients had dose reductions.

3.2. Efficacy

All follow-up assessments were completed by 30th June 2012, which was 48 months after the enrolment of the last patient. The median OS was 13.8 months (95% CI, 11.8–15.8) and 9.9 months (95% CI, 7.9–12.0) for the S-1 group and S-1 plus LNT group, respectively, with an HR of 1.169 (95% CI, 0.916–1.493, $P = 0.208$) (Fig. 2).

The reasons for treatment discontinuation are progressive disease in 79 and 74 patients, clinical non-efficacy in 8 and 15 patients, adverse events in 18 and 29 patients, withdrew consent in 15 and 13 patients, indications for surgery in 2 and 3 patients, death in 2 and 4 patients, and others in 16 and 10 patients in the S-1 group and the S-1 plus LNT group, respectively. Median TTF was 4.3 months (95% CI, 3.8–4.7) and 2.6 months (95% CI, 2.2–3.0) for the S-1 group and S-1 plus LNT group, respectively, with an HR of 1.540 (95% CI, 1.210–1.961, $P < 0.001$) (Fig. 2).

Objective response was evaluable by the investigators in the 190 patients (65.7%) with measurable disease at baseline. The ORR was 22.3% in the S-1 group including complete response (CR) in one patient and partial response (PR) in 19 patients. The ORR was 18.7% in the S-1 plus LNT group including CR in one

patient and PR in 17 patients. There was no statistical difference in the ORR between the two groups.

3.3. Safety

The incidence of adverse events during treatment is summarised in Table 2. The incidences of haematologic and non-haematologic adverse events were similar in both groups. Only one patient died as a result of neutropenia related to protocol treatment in the S-1 plus LNT group. The proportions of patients who terminated treatment because of intolerable adverse events

Table 2
Haematologic and non-haematologic adverse events.

	S-1 (n = 142)		S-1 + LNT (n = 147)	
	All grades, n (%)	Grade 3 or 4, n (%)	All grades, n (%)	Grade 3 or 4, n (%)
Leucopenia	65 (45.8)	6 (4.2)	69 (46.9)	12 (8.2)
Neutropenia	73 (51.4)	17 (12.0)	68 (46.3)	16 (10.9)
Anaemia	72 (50.7)	7 (4.9)	75 (51.0)	12 (8.2)
Thrombocytopenia	63 (44.4)	1 (0.7)	64 (46.3)	6 (4.1)
Febrile neutropenia	1 (0.7)	1 (0.7)	0	0
Anorexia	52 (36.6)	12 (8.5)	75 (51.0)	19 (12.9)
Nausea	22 (15.5)	0	35 (23.8)	5 (3.4)
Vomiting	14 (9.9)	1 (0.7)	19 (12.9)	2 (1.4)
Diarrhoea	24 (16.9)	1 (0.7)	28 (19.0)	6 (4.1)
Fatigue	43 (30.3)	5 (3.5)	52 (35.4)	13 (8.8)
Stomatitis	24 (16.9)	1 (0.7)	28 (19.0)	3 (2.0)
Pigmentation	36 (25.4)	0	38 (25.9)	0
Rash	0	0	3 (2.0)	1 (0.7)
Lacrimation	18 (12.7)	4 (2.8)	14 (9.5)	0
Hand–foot syndrome	12 (8.5)	1 (0.7)	11 (7.5)	0
Creatinine elevation	17 (12.0)	0	14 (9.5)	1 (0.7)
Hyponatremia	31 (21.8)	7 (4.9)	27 (18.4)	7 (4.8)

LNT, lentinan.

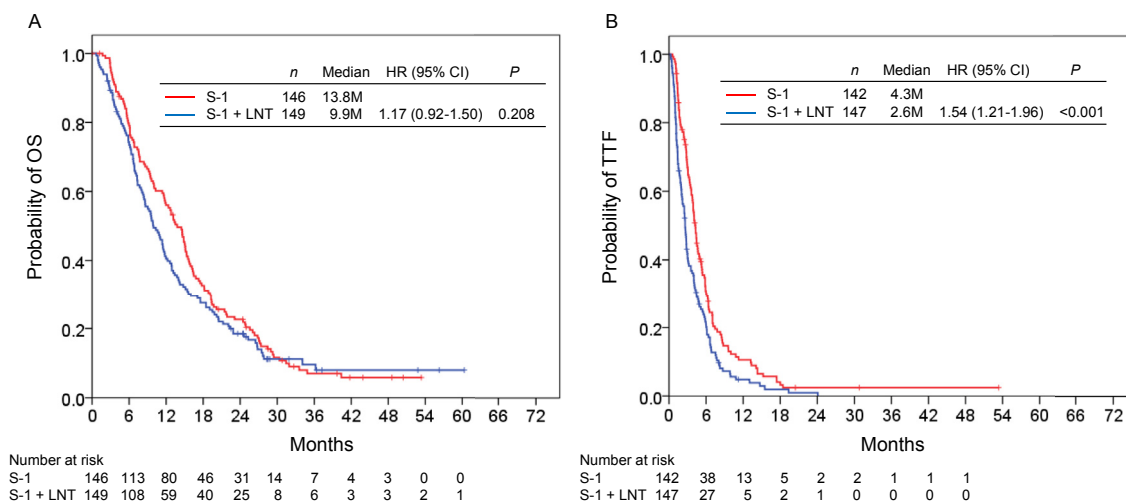


Fig. 2. Kaplan–Meier curves for OS in the full analysis set population (A) and TTF in safety population (B). OS, overall survival; TTF, time-to-treatment failure; LNT, lentinan; HR, hazard ratio; CI, confidence interval.

were similar: 13.1% in the S-1 group and 19.9% in the S-1 plus LNT group.

3.4. QOL analysis

One hundred and nine (76.8%) patients in the S-1 group and 117 (79.6%) patients in the S-1 plus LNT group completed a baseline QOL assessment. Fig. 3 shows the baseline scores and changes in the mean scores for the overall QOL scale of each group. No significant changes were observed at 4, 6, 10, and 12 weeks after chemotherapy as compared with baseline in both the S-1 and S-1 plus LNT groups.

3.5. Biomarker assessment

The percentages of LNT-binding cells in total CD14⁺ monocytes showed individual variations ranging from 0.03% to 38.7% (median, 2.0%) among 309 patients. Patients were divided into an LNT high-binding population with at least 2.0% of monocytes bound to LNT and an LNT low-binding population with less than 2.0% of monocytes bound to LNT.

In patients who received more than two cycles of chemotherapy, OS was similar in both the S-1 and S-1 plus LNT groups in the LNT low-binding population. However, in the LNT high-binding population, some patients showed a longer survival time in the S-1 plus LNT group as compared to the S-1 group. The 3-year survival rate of the S-1 group was 3.1%, whereas that of the S-1 plus LNT group was 24.1%. A longer OS was observed in the S-1 plus LNT group as compared to the

S-1 group (Harrington–Fleming method, $\rho_1 = 0$ and $\rho_2 = 0.5$, $P = 0.0491$; $\rho_1 = 0$ and $\rho_2 = 1$, $P = 0.0171$) (Fig. 4).

4. Discussion

This study showed no efficacy of LNT administration combined with S-1 treatment in patients with unresectable or recurrent gastric cancer. OS did not improve in the S-1 plus LNT group as compared with the S-1-only group. However, TTF was significantly worse in the S-1 plus LNT group. Although the patient characteristics were well balanced between the groups, the proportion of patients with low serum albumin was significantly higher in the S-1 plus LNT group. Hypoalbuminemia is an independent prognostic factor for OS in patients with advanced gastric cancer who receive chemotherapy [19,20]. Therefore, it is speculated that the unexpected high proportion of enrolment of patients with hypoalbuminemia in the S-1 plus LNT group caused the worse TTF as compared to the S-1 group.

In the present study, MST was 13.5 months in the S-1 group and 10.9 months in the S-1 plus LNT group, respectively. In previous phase III clinical trials in patients with advanced gastric cancer, the median survival of 10.5, 11.0, and 11.4 months was reported for S-1 treatment by Narahara *et al.* [21], Koizumi *et al.* [13], and Boku *et al.* [11], respectively. The MST for S-1 treatment in our study was almost the same as those in these three previous studies. However, patients analysed in these three studies were 75 years of age or younger. According to the Surveillance, Epidemiology, and End

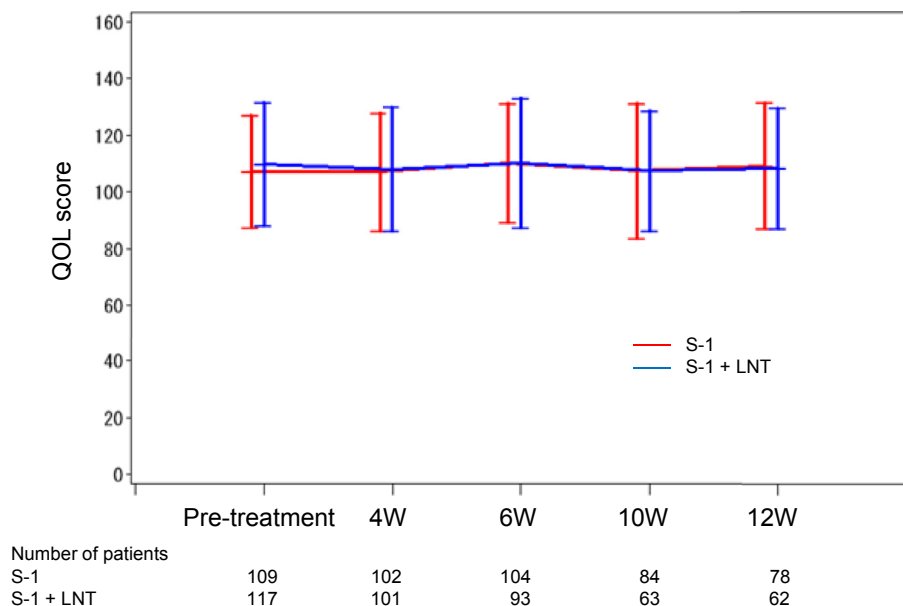


Fig. 3. Changes in QOL score during treatment. QOL was assessed by FACT-BRM. Maximum score is 160 points, and values are expressed as mean \pm standard deviation. QOL, quality of life; FACT-BRM, Functional Assessment of Cancer Therapy-Biological Response Modifier; LNT, lentinan.

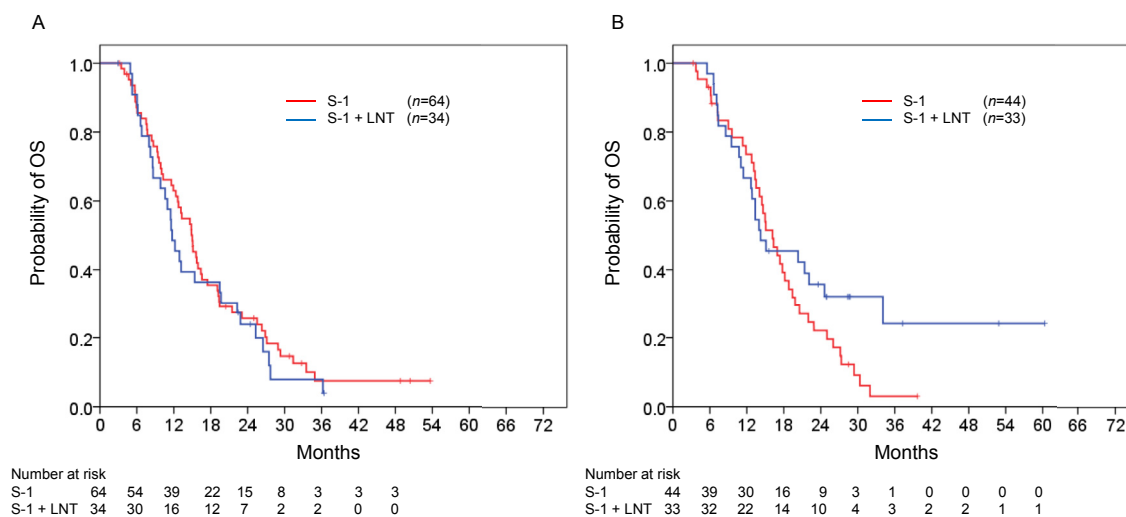


Fig. 4. Kaplan–Meier curves of OS according to the percentages of LNT-binding monocytes in patients who received more than two cycles of treatment. OS in LNT low-binding population (A) and LNT high-binding population (B). The weighted log-rank test with the Harrington–Fleming class of weights were performed in LNT high-binding population and resulted in, $\rho_1 = 0$ and $\rho_2 = 0.5$, $P = 0.0491$; $\rho_1 = 0$ and $\rho_2 = 1$, $P = 0.0171$. OS, overall survival; LNT, lentinan.

Results data from the United States of America [22], 35.7% of patients with gastric cancer were diagnosed over 75 years of age. Half of the patients enrolled in this study were over the age of 73; so, the efficacy of S-1 treatment for elderly patients with gastric cancer could be suggested in this study.

QOL is impaired in patients with advanced gastric cancer [23]; so, it is important to maintain the QOL during the cancer treatment. An improvement of QOL was showed in patients with gastric cancer who received chemotherapy [24]. However, some authors reported no improvement of QOL during cancer treatment [25,26]. No significant changes were observed during treatment with either S-1 alone or S-1 plus LNT as compared with before treatment. LNT had no efficacy to improve the QOL in patients with advanced gastric cancer.

LNT-binding monocytes were analysed for the biomarker assessment. In the LNT high-binding population, patients who received more than two cycles of chemotherapy showed a longer survival time in the S-1 plus LNT group as compared with in the S-1 group. In chemotherapy, it is important to select patients who are promising candidates for responding to treatment. Hazama *et al.* [27] reported the importance of biomarker exploration for selecting patients with a better treatment outcome in chemotherapy with vaccine treatment for advanced colorectal cancer. The percentages of LNT-binding monocytes could be one of the biomarker for predicting the long survivors in patients with advanced gastric cancer who received S-1 treatment with LNT.

In conclusion, the present study showed no efficacy of LNT administration combined with S-1 treatment in patients with unresectable or recurrent gastric cancer.

Disclosure

S. Yoshino has received personal fees from MSD, Taiho and Chugai, outside the submitted work. K. Nishikawa has received personal fees from Taiho, Ajinomoto, Yakult and Chugai, outside the submitted work. S. Morita has received personal fees from Taiho, outside the submitted work. T. Takahashi has received grants from SBI pharma, outside the submitted work. T. Yoshikawa has received personal fees from Taiho, outside the submitted work. The other authors have declared no conflicts of interest.

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