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Phase I study of YS110, a recombinant humanized monoclonal antibody to CD26, in Japanese patients with advanced malignant pleural mesothelioma

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ABSTRACT

Objectives: CD26 is a transmembrane glycoprotein with dipeptidyl peptidase IV activity that is overexpressed in malignant pleural mesothelioma (MPM). We performed a phase I study to determine the maximum tolerated dose, pharmacokinetics, and antitumor activity of YS110, a monoclonal antibody to CD26, in Japanese patients with MPM intolerant of or refractory to prior standard therapies.

Material and methods: The study was designed as an open-label, 3 + 3 dose-escalation, phase I trial. Patients were sequentially assigned to three dosing cohorts (2, 4, or 6 mg/kg). Each 6-week treatment cycle consisted of YS110 administration weekly for 5 weeks followed by a 1-week rest period. Treatment was continued until disease progression, death, or intolerable toxicity. Corticosteroid, antihistamine, and acetaminophen administration before each infusion was adopted to limit infusion-related reactions (IRRs).

Results: Nine Japanese patients (seven men and two women, mean age of 62.2 years), three in each dosing cohort, were enrolled in the study. No patient developed a dose-limiting toxicity. Adverse events of grade 3 or 4 developed in seven patients, with the most common such event being a decreased lymphocyte count. Two patients had mild or moderate IRRs. The serum concentration of YS110 increased in a dose-dependent manner. Among seven patients evaluable for tumor response, four showed stable disease and one achieved a partial response.

Conclusions: YS110 showed promising antitumor efficacy and was generally well tolerated in Japanese patients with advanced MPM at doses of up to 6 mg/kg. YS110 will be tested at 6 mg/kg in a subsequent phase II study.

1. Introduction

Malignant pleural mesothelioma (MPM) is an aggressive malignancy that arises from the mesothelial lining of the pleura and is generally associated with asbestos exposure. [1] Although the use of asbestos has now been banned in several industrialized countries, the peak incidence of asbestos-related diseases such as MPM will likely occur between 2015 and 2030 [1]. MPM tends to be associated with a poor prognosis [1,2]. A large study of patients with MPM (n > 16,000) in the United States found that overall survival (OS) at 2 years was 26.5% for women and 16.6% for men, with the respective values at 5 years being 9.4% and 4.2%. [2]. Deaths from MPM are also estimated to increase in Japan, with a predicted peak in 2030 [3], consistent with the estimated trend in Europe.

Therapeutic options for MPM include chemotherapy, radiation therapy, surgery, or combinations of these modalities. [4,5] The role of surgery in the management of MPM remains unclear, given that well-conducted trials have been difficult to undertake and there are apparent postoperative complications. Chemotherapy regimens for patients with unresectable tumors usually consist of the combination of pemetrexed

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with a platinum agent (typically, cisplatin), either with or without bevacizumab. [4–6] However, even with multimodal therapy, treatment outcome for patients with MPM is poor, with most individuals dying within 2–3 years of diagnosis [7].

CD26, a 110-kDa type II transmembrane glycoprotein with dipeptidyl peptidase IV (DPPIV) activity, plays an important role in immune regulation. [8] CD26 is co-stimulator and caveolin is its ligand which is expressed on antigen present cell [9]. These are involved in memory T-cell activation and proliferation [9]. CD26 was found to be overexpressed in MPM cells, but not in benign mesothelial tissue [10,11]. CD26 was found in 80% of epithelioid mesothelioma and 78% in epithelioid component of biphasic mesothelioma [10]. While, in sarcomatoid mesothelioma or sarcomatoid component of biphasic mesothelioma, CD26 was not found [10]. CD26 is also expressed in various tumors, and its expression is reported to be a marker of several cancer stem cells including colorectal cancer, chronic myeloid leukemia, gastric adenocarcinoma and MPM [12]. Moreover, preclinical research indicates that blocking CD26 inhibits tumor growth in xenograft models of several human tumor types including non-Hodgkin T cell lymphoma, malignant mesothelioma, and renal cell carcinoma [11,13,14].

YS110 is a recombinant humanized monoclonal antibody that binds with high affinity (dissociation constant, 0.244 nM) to human CD26. Extensive in vitro and in vivo studies have shown that YS110 possesses antitumor activity for malignant mesothelioma cell lines. [11,15] Single or repeated intravenous administration of YS110 has also been found to be safe in nonhuman primates. [16] The first phase I study of YS110 in humans was conducted in France and found that its administration at doses up to 6 mg/kg weekly was generally well tolerated and showed promising efficacy in 33 patients with advanced or refractory CD26-expressing tumors including malignant mesothelioma, renal cell carcinoma, and urothelial carcinoma [16]. The most common adverse events (≥25%) were asthenia, condition aggravated, constipation, dyspnea and hypersensitivity. We have now performed a phase I clinical trial to assess the tolerability, safety, and pharmacokinetics of YS110 in Japanese patients with MPM as well as to determine the recommended dose and preliminary antitumor effects of the antibody. There were no specific regulatory requirements to conduct this phase I trial.

2. Material and methods

2.1. Patients

Patients aged 20 to 74 years with histologically confirmed advanced MPM of any histological subtype were enrolled (ClinicalTrials.gov identifier: NCT03177668). Patients were included if they were intolerant to, or their tumors were refractory to, existing antineoplastic drugs and no standard therapy was suitable. Other key inclusion criteria were the presence of a measurable tumor lesion as defined by modified Response Evaluation Criteria in Solid Tumors (RECIST), an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, a life expectancy of ≥12 weeks, and generally good organ function. Patients were included only if their most recent major surgery, antitumor drug treatment, or radiation therapy was at least 4 weeks ago. Patients were excluded if they had not recovered from toxicity due to previous chemotherapy, had tumor lesions in the central nervous system, had accompanying interstitial pneumonia or pulmonary edema requiring treatment, or had poorly controlled hypertension.

2.2. Study design

This was an open-label, standard 3 + 3 dose-escalation, phase I part of a phase I-II study. Patients were enrolled into three successive cohorts (dose of 2, 4, or 6 mg/kg) and received a 6-week cycle of YS110 treatment consisting of once-weekly infusions for 5 weeks (days 1, 8, 15, 22, and 29) followed by 1 week of rest. Three patients were enrolled in the first cohort and received YS110 at a dose of 2 mg/kg. Each patient was assessed for dose-limiting toxicity (DLT) up to day 18 relative to the first dose (DLT evaluation period). The principal investigators, medical expert, and sponsor determined whether a DLT had developed with reference to the following criteria: febrile neutropenia of grade ≥3, neutrophil count decline of grade 4, platelet count decline of grade 4 or requiring platelet transfusion, or nonhematologic toxicity of grade ≥3 with the exception either of any such toxicity—such as nausea, vomiting, anorexia, diarrhea, pyrexia, or electrolyte abnormalities—that could be controlled by appropriate treatment or of any infusion-related reaction (IRR) of grade 3 that could be controlled by a reduction in the rate or interruption of the infusion or by appropriate treatment. If none of the patients in the first cohort developed a DLT, three patients were assigned to the next dose cohort (YS110 at 4 mg/kg) and the process repeated. The patients in the last cohort were to receive YS110 at a dose of 6 mg/kg. If at any time a patient developed a DLT during treatment, three additional patients were enrolled in that cohort before moving to the next dose level. If two or more patients developed a DLT at any dose level, treatment was maintained at that dose, and no patients were enrolled in the next higher-dose cohort. Treatment was continued until disease progression, the development of unacceptable toxicity including a DLT, or the occurrence of a protocol deviation, or at the request of the patient. The first dose of cycle 2 and any subsequent cycles was administered immediately after evaluation of the patient on day 43 (± 3 days) of the previous cycle. The maximum tolerated dose for the phase II part of the phase I-II study was considered to be the highest dose at which < 33% of evaluated patients developed a DLT.

To minimize IRRs, we administered prophylactic d-chlorpheniramine maleate, methylprednisolone, dexamethasone, acetaminophen, and ranitidine hydrochloride according to a predefined schedule before infusion of YS110. Methylprednisolone could be omitted prior to doses 2–5 of each cycle at the discretion of the investigator.

The study protocol was approved by the Institutional Review Board of the four participating hospitals, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent to participation after being given detailed information about the study.

2.3. Safety assessment

The main safety end point was determination of the recommended dose based on the occurrence of DLT. Patients were monitored for adverse events (AEs) throughout the study. Vital signs were monitored and the electrocardiogram recorded regularly during each drug infusion, and blood samples were collected for hematologic and biochemical assessments. Blood samples were also assayed for antibodies to YS110 including neutralizing activities. Investigators evaluated AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.03), and these events were assessed for a causal relation to YS110. Investigators also evaluated whether or not each AE was an IRR.

2.4. Pharmacokinetics

To assess the pharmacokinetic profile of YS110, we collected serial blood samples during cycle 1. The blood samples were collected before administration of YS110, at 10 min before the end of the infusion, and at 2, 6, 12, 24, 36, 48, and 168 h after the end of drug administration on days 1, 15, and 29. Blood samples were also collected at 72, 96, 120, and 144 h after drug administration on day 1 and at 336 h after drug administration on day 29. The serum concentration of YS110 was measured with a validated electrochemiluminescence assay performed on the Meso QuickPlex SQ120 platform (Meso Scale Diagnostics, Rockville, MD). Pharmacokinetic parameters were calculated by noncompartmental analysis with the use of WinNonlin software v7.0 (Certara USA, Princeton, NJ).

2.5. Efficacy assessment

Tumor response was determined by a central assessment committee using the modified RECIST criteria for the evaluation of response in MPM. [17] RECIST version 1.1 was applied if tumor assessment could not be performed according to the modified RECIST criteria. For observation (imaging) of lesions, contrast medium was used unless there was a specific reason (such as hypersensitivity) not to, and the same imaging method (such as computed tomography) was used under the same conditions (including slice thickness and use of contrast medium) as at baseline. Tumor response was defined in terms of the disease control rate, which is the proportion of patients with a complete response, a partial response (PR), or stable disease for ≥24 weeks. Progression-free survival (PFS) and OS were also assessed, with the former being defined as the time from the first day of treatment until confirmed progressive disease or death and the latter as the time from the first day of treatment to death.

2.6. Pharmacodynamics

Blood samples were also collected before, at the end of, and 24 h after YS110 infusion on days 1, 15, and 29 of cycle 1 for measurement of DPPIV activity, soluble CD26 concentration, and absolute values for lymphocyte subsets including T cell subsets ($CD3^+$/CD56–, $CD3^+$/$CD4^+$, $CD3^+$/$CD4^+$/$CD26^+$, $CD3^+$/$CD8^+$/CD56–, and $CD8^+$/$CD26^+$/CD56–) and natural killer cell subsets (CD3–/$CD56^+$, CD3–/$CD16^+$/$CD56^+$, and CD3–/$CD26^+$/$CD56^+$) as previously described. [18]

2.7. Statistical analysis

An interim evaluation of the phase I data, including results for the last patient up to 6 months after the onset of YS110 administration, was performed. The safety analysis set included all patients who received at least one dose of the study drug, and the pharmacokinetic population included all patients of the safety analysis set who had evaluable drug concentration data. Descriptive statistics were applied to analyze the study results. OS and PFS were evaluated with the Kaplan-Meier method, with censoring at data cutoff. A post hoc analysis examined the number and proportion of patients whose best overall response as determined by central evaluation was a complete response, a PR, or stable disease at the time of data cutoff, with exact 95% confidence intervals (CIs) being calculated with the Clopper-Pearson method.

3. Results

3.1. Patient characteristics

The characteristics of the study patients are shown in Table 1. Nine Japanese individuals (seven men and two women, with a mean age ± SD of 62.2 ± 9.72 years), three in each dose cohort, were enrolled in the study. The histological subtype of MPM was epithelioid in seven patients and biphasic in the other two. MPM was stage III in two patients and stage IV in seven. Five patients had metastatic disease at baseline. All patients had previously received chemotherapy, and one each had also undergone radiotherapy or surgery. All patients discontinued the study (Supplementary Fig. 1), with the most common reason for discontinuation being disease progression (n = 7). In the 2 mg/kg cohort, one patient discontinued treatment during cycle 1, one patient completed cycle 1, and one patient entered cycle 2. In the 4 mg/kg cohort, one patient entered cycle 2, one entered cycle 3, and one entered cycle 4. In the 6 mg/kg cohort, one patient discontinued treatment during cycle 1, one entered cycle 2, and one entered cycle 4.

3.2. Safety

During the DLT evaluation period (days 1–18) for each dose, no patient developed febrile neutropenia of grade ≥3, a neutrophil count decline of grade 4, a platelet count decline of grade 4 or requiring platelet transfusion, or any nonhematologic toxicity of grade ≥3 meeting the criteria for a DLT. Given that no DLTs were observed, the maximum tolerated dose was considered to be 6 mg/kg. All nine patients experienced at least one AE (Table 2). Six patients had treatment-related AEs, the most common of which included fatigue, blood creatinine increase, proteinuria, and rash (each observed in two patients) (Supplementary Table 1). AEs of grade 3 developed in seven patients, and an AE of grade 4 (lymphocyte count decrease) occurred in one patient. The AEs of grade 3 comprised four cases of lymphocyte count decrease and one each of hyponatremia, proteinuria, and nephrotic syndrome. All cases of lymphocyte count decrease were considered by investigators to be unrelated to YS110 but rather related to steroid, and all patients recovered. Hyponatremia, proteinuria, and nephrotic syndrome were considered to be possibly related to YS110, but these events could not be followed up until recovery because of the death of the patients due to disease progression.

There were no deaths associated with AEs. One patient who received YS110 at a dose of 2 mg/kg discontinued treatment after being hospitalized with a serious AE (nephrotic syndrome of grade 3). This was the only AE-related treatment discontinuation. Two patients interrupted treatment because of AEs, including chest pain, malaise, pyrexia, decreased appetite, proteinuria, and rash. Three IRRs (one of grade 2 and two of grade 1) developed in two patients. One patient in the 2 mg/kg cohort developed a rash and pyrexia that were classified as IRRs, and one patient in the 6 mg/kg cohort also had an IRR. None of these IRRs was severe.

3.3. Pharmacokinetics

Pharmacokinetic parameters for YS110 in serum determined after its administration at 2, 4, or 6 mg/kg are shown in Table 3. The maximum serum concentration (C_{max}) and area under the concentration-versus-time curve over the dosing interval (AUC_τ) on days 1 and 29 (fifth and final dose of cycle 1) tended to be proportional to dose level. Exposure to YS110 increased with repeat administration at each dose. The C_{max} and AUC_τ after administration of YS110 at 6 mg/kg on day 29 were thus 1.6 and 2.7 times, respectively, as high as those for day 1.

3.4. Immunogenicity

Antibodies with neutralizing activity to YS110 were detected after treatment in two patients. One patient in the 2 mg/kg cohort had developed antibodies to YS110 by day 29 of cycle 1, and neutralizing activity became apparent on day 43 of cycle 1. Another patient, in the 4 mg/kg cohort, had developed antibodies to YS110 by day 43 of cycle 1 and neutralizing activity on day 50 of cycle 1.

3.5. Efficacy

Seven of the nine study patients were evaluable for tumor response. The best overall response was a PR in one patient and stable disease in four patients (Fig. 1). The patient who achieved a PR was a 70-year-old woman with a baseline ECOG performance status of 1. The total size of her target lesion had decreased relative to baseline (evaluated as a PR) after one treatment cycle (Fig. 2). The patient discontinued treatment after cycle 4 because of progressive disease. Post hoc analysis revealed that 55.6% (95% CI, 21.2%–86.3%) of patients had stable disease or a PR after the first cycle of treatment. The median PFS was 3 months (95% CI, 1.4 months to not evaluable), and the PFS rate at 3 months was 45% (Supplementary Table 2). Median OS was 9.5 months (95% CI, 2.2 months to not evaluable), and the OS rate at 3 months was 78%

Table 1
Baseline Demographics and Clinical Characteristics of the Study Patients.

Characteristic	YS110 Dose			Total (n = 9)
	2 mg/kg (n = 3)	4 mg/kg (n = 3)	6 mg/kg (n = 3)	
Age (years), mean ± SD	61.3 ± 11.59	58.0 ± 13.11	67.3 ± 2.08	62.2 ± 9.72
Sex, n				
Male	2	2	3	7
Female	1	1	0	2
Weight (kg), mean ± SD	59.4 ± 11.02	67.6 ± 20.66	68.0 ± 6.73	65.0 ± 12.89
Tumor stage (IMIG TNM), n				
III	0	1	1	2
IV	3	2	2	7
ECOG performance status, n				
0	2	2	1	5
1	1	1	2	4
Tumor histology, n				
Epithelioid	3	3	1	7
Biphasic	0	0	2	2

IMIG, International Mesothelioma Interest Group; TNM, tumor-node-metastasis; ECOG, Eastern Cooperative Oncology Group.

Table 2
Frequency of Adverse Events in Each Dose Cohort.

Adverse event, number of patients	2 mg/kg		4 mg/kg		6 mg/kg	
	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades
Hematologic						
Lymphocyte count decreased	2	2	2	2	1	2
Neutrophil count increased	0	0	0	0	0	1
White blood cell count increased	0	0	0	0	0	1
Nonhematologic						
Palpitations	0	0	0	0	0	1
Nausea	0	1	0	0	0	1
Vomiting	0	0	0	0	0	1
Toothache	0	0	0	1	0	0
Chest pain	0	0	0	0	0	1
Malaise	0	0	0	0	0	1
Fatigue	0	2	0	0	0	0
Pyrexia	0	1	0	0	0	0
Nasopharyngitis	0	0	0	0	0	1
Lung infection	0	0	0	0	0	1
Upper respiratory tract infection	0	0	0	1	0	0
Infusion related reaction	0	0	0	0	0	1
Hyponatremia	0	0	0	0	1	1
Decreased appetite	0	0	0	0	0	1
Dizziness	0	1	0	0	0	0
Insomnia	0	1	0	0	0	0
Urinary retention	0	0	0	0	0	1
Nephrotic syndrome	1	1	0	0	0	0
Dyspnea	0	0	0	0	0	1
Hiccups	0	1	0	1	0	0
Rash	0	1	0	1	0	0
Hypotension	0	0	0	0	0	1
Electrocardiogram QT prolonged	0	1	0	0	0	0
Laboratory abnormalities						
ALT increased	0	1	0	0	0	1
AST increased	0	1	0	0	0	1
Blood creatinine increased	0	1	0	1	0	0
Blood bilirubin increased	0	0	0	1	0	0
γ-Glutamyltransferase increased	0	1	0	0	0	0
Hypoalbuminemia	0	1	0	2	0	0
Hyperglycemia	0	0	0	1	0	0
Hypophosphatemia	0	1	0	0	0	0
Proteinuria	1	1	0	1	0	0
Hematuria	0	1	0	0	0	0

All adverse events were coded according to the Medical Dictionary for Regulatory, Activities (MedDRA) central coding dictionary, version 19.1 or later.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3
Pharmacokinetic Parameters of YS110 in Cycle 1 for Each Dose Cohort.

Parameter *2 mg/kg*	Day 1 (n = 3)	Day 15 (n = 3)	Day 29 (n = 2)
$t_{½}$ (h)	21.65 ± 7.64	35.22 ± 2.55	32.76 ± 5.23
C_{max} (μg/mL)	38.13 ± 7.14	40.77 ± 3.18	56.95 ± 13.08
$AUC_{τ}$ (h μg mL^{-1})	1793 ± 570	2307 ± 705	3065 ± 1188
CL (mL h^{-1} kg^{-1})	1.19 ± 0.40	0.92 ± 0.25	0.71 ± 0.27
4 mg/kg	(n = 3)	(n = 3)	(n = 3)
$t_{½}$ (h)	55.69 ± 13.48	94.49 ± 42.67	86.72 ± 32.45
C_{max} (μg/mL)	99.47 ± 31.09	129.33 ± 35.73	146.33 ± 36.83
$AUC_{τ}$ (h μg mL^{-1})	6335 ± 1657	10987 ± 3940	13303 ± 5335
CL (mL h^{-1} kg^{-1})	0.57 ± 0.14	0.40 ± 0.15	0.35 ± 0.17
6 mg/kg	(n = 3)	(n = 2)	(n = 2)
$t_{½}$ (h)	68.50 ± 1.79	129.72 ± 28.79	170.25 ± 31.54
C_{max} (μg/mL)	162.67 ± 19.76	241.00 ± 11.31	265.50 ± 48.79
$AUC_{τ}$ (h μg mL^{-1})	10,400 ± 2086	22833 ± 1327	28252 ± 2705
CL (mL h^{-1} kg^{-1})	0.49 ± 0.12	0.26 ± 0.02	0.21 ± 0.02

Data are means ± SD.
$t_{½}$, elimination half-life; C_{max}, maximum serum concentration; $AUC_{τ}$, area under the serum concentration–versus–time curve over the dosing interval; CL, total body clearance.

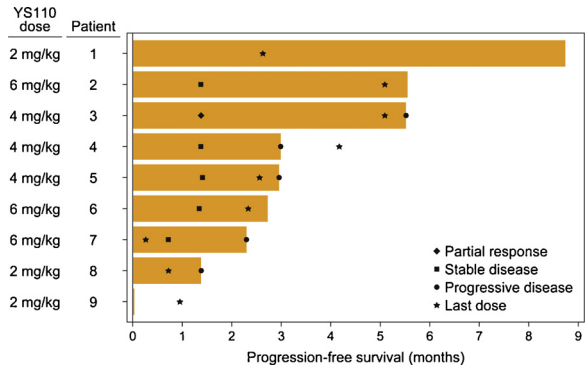

Fig. 1. Swimmer plot of YS110 efficacy at data cutoff. The length of each bar represents time to disease progression or death, whichever came first. Response symbols represent the best response. Patient 9 was censored at the date of first dose administration because of the absence of posttreatment lesion assessment.

(Supplementary Table 2).

3.6. Pharmacodynamics

Soluble CD26 concentration and DPPIV activity were measured in serum of all patients. The mean soluble CD26 concentration decreased from 734.6 μg/L at baseline to 333.4 μg/L after the first dose of YS110 and to 161.4 μg/L after the dose on day 15 and thereafter remained low (range, 122.7–236.3 μg/L) until the end of treatment (Fig. 3A). A similar reduction in DPPIV activity was also apparent (Fig. 3B). The number of $CD3^{+}/CD4^{+}$ T cells decreased from 520.9/μL (42.5% of

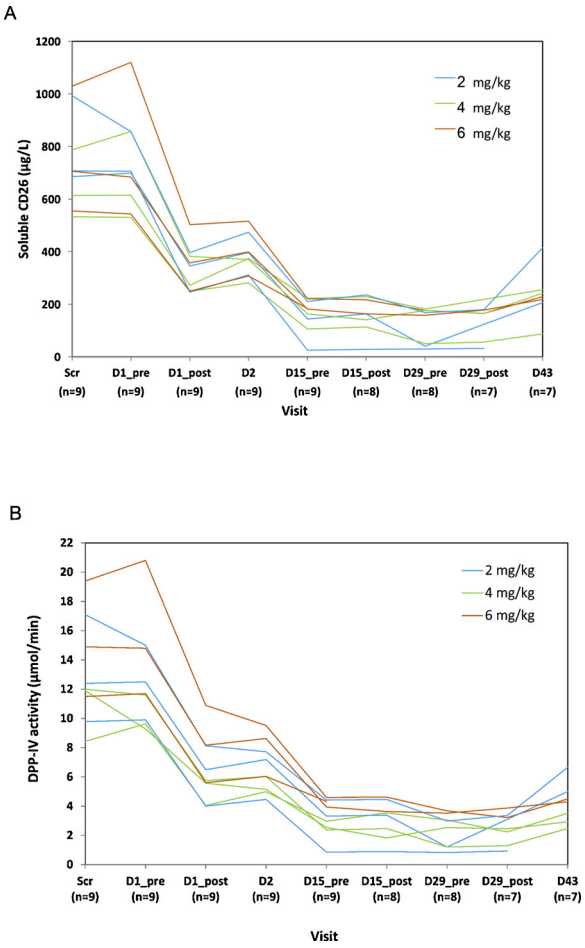

Fig. 3. Levels of soluble CD26 (*A*) and dipeptidyl peptidase IV (DDPIV) activity (*B*) in serum of the study patients at screening (Scr), before (pre) and after (post) YS110 administration on days (D) 1, 15, and 29, as well as on days 2 and 43 of cycle 1.

total lymphocytes) at baseline to 157.7/μL (38.8%) after the first treatment, whereas the number of $CD3^{+}/CD4^{+}/CD26^{+}$ cells decreased from 455.5/μL (37.3%) to 126.3/μL (31.8%). The number of CD3–/$CD56^{+}$ natural killer cells decreased from 243.3/μL (18.0%) to 32.7/μL (7.8%) after the first treatment, and the number of CD3–/$CD26^{+}$/$CD56^{+}$ cells decreased from 18.3/μL (1.9%) to 1.3/μL (0.40%).

4. Discussion

MPM is an aggressive thoracic tumor type with limited treatment options and a poor prognosis. Several novel therapeutic agents for MPM are under investigation, one of which is YS110, a humanized

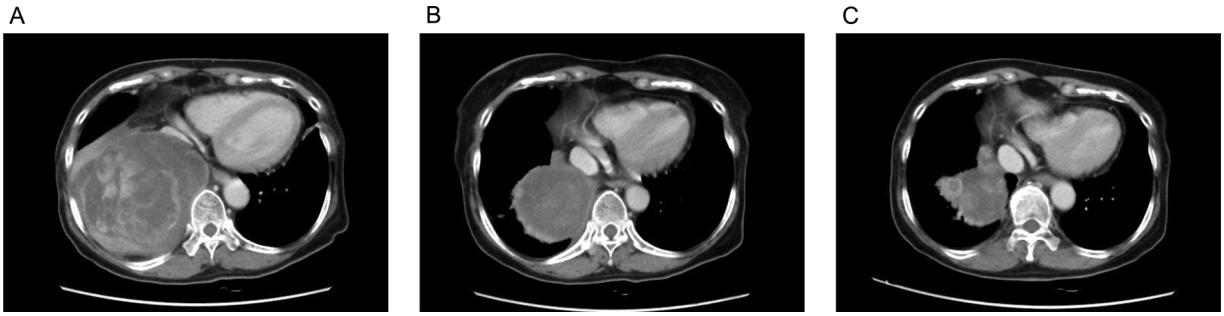

Fig. 2. Computed tomography scans of the lungs of the patient with a partial response performed at screening (*A*), on day 43 of cycle 1 (*B*), and on day 43 of cycle 2 (*C*).

monoclonal antibody that selectively binds with high affinity to the extracellular domain of CD26.

In the present study, YS110 treatment at doses of up to 6 mg/kg did not result in any DLTs in Japanese patients with advanced MPM who were intolerant of or whose tumors were refractory to current anticancer treatments. YS110 was also well tolerated in the first-in-human phase I trial performed with 33 heavily pretreated patients with advanced or refractory CD26-expressing tumors in France. [16] Together, these studies suggest that 6 mg/kg weekly is the recommended dose of YS110, and this dose is now under investigation in the ongoing phase II part of this study. In the French study, seven severe IRRs (six hypersensitivity reactions and one anaphylactic reaction) were observed in six patients (18.2%), with two of these IRRs being designated DLTs. In contrast, no severe IRRs occurred in the present study, and only three mild or moderate such reactions were apparent. This low rate of IRRs and their mild or moderate intensity in our study suggest that the prophylactic treatment to prevent them was efficacious. In the French trial, the first three cohorts of patients received the increasing doses of YS110 administered in the same volume of solution, with the result that patients in the later cohorts received YS110 at a higher concentration. [16] From cohort 4 onward, the volume of the YS110 solution was increased with each increase in dose. On the basis on this experience, the protocol of our trial was modified to include an increase in the volume of infused solution with increasing doses of YS110 for all cohorts, which may also have contributed to the low rate and intensity of IRRs.

Five of the nine patients treated with YS110 in the present study experienced a decrease in lymphocyte count of grade 3 or 4. This reduction in lymphocyte count may have been due to prophylactic corticosteroid administration to limit IRRs. Corticosteroids induce a transient decline in lymphocyte count as a result of the translocation of lymphocytes from blood to tissue. [19] The prompt recovery from the severe reduction in lymphocyte count apparent in the study subjects indicates that YS110 did not destroy lymphocytes. Moreover, a similar trend of a reduction in $CD3^+/CD4^+$ and $CD3^+/CD4^+/CD26^+$ T cell subsets was observed, suggesting that the lymphocyte count decrease was not restricted to cells expressing CD26. The changes in lymphocyte numbers were thus likely not entirely due to YS110 treatment.

The most severe AEs observed in the present study were hyponatremia, nephrotic syndrome, and proteinuria, which were each experienced by one patient and were considered to be related to treatment. One patient discontinued treatment because of serious nephrotic syndrome. The effects of YS110 on the kidneys have not been fully elucidated. [16] DPPIV/CD26 is highly expressed in the proximal tubules of the kidneys [20], and the circulating level of soluble CD26 may be a marker for impaired renal function [21]. We therefore cannot rule out the possibility that YS110 was responsible for the case of nephrotic syndrome. However, this patient had preexisting proteinuria that may have conferred a predisposition to the development of renal toxicity. In addition, no cases of renal toxicity were apparent in the French clinical study or in nonhuman primate toxicity tests [16]. The relation between CD26 inhibition and renal function requires further investigation.

One patient in the present study achieved a PR, which is the first such response reported for YS110, given that no PRs were manifest in the French phase I study. [16] The patient who achieved this response had an epithelioid tumor, and CD26 expression has been shown to be high in epithelioid cells [22]. Although the expression rate of CD26 in tumor tissue had not been determined at the time of data cutoff, it is possible that MPM tumors with an epithelioid histology are more sensitive to CD26 inhibition. We will investigate the relationship between CD26 expression or other biomarkers and clinical outcome of YS110. YS110 has been found to induce MPM cell lysis via antibody-dependent cytotoxicity [12,15,23]. It has also been shown to induce cell cycle arrest in $CD26^+$ malignant mesothelioma cells and to control the growth of MPM cells via up-regulation of the cyclin-dependent kinase inhibitors p21 or p27. [11,15] The antitumor effects of YS110 in vivo are therefore likely mediated by its binding to mesothelioma cells that express CD26.

The serum levels of both soluble CD26 and DPPIV activity decreased after treatment with YS110 according to a similar time course and then remained below baseline values for the duration of the study. Inhibition of DPPIV activity suppresses cleavage of the chemokine CXCL10, which is a ligand for the receptor CXCR3. By reducing the concentration of soluble CD26 and DPPIV activity, YS110 may enhance the migration of CXCR3-expressing effector T cells into the tumor parenchyma. [24,25] Inhibition of DPPIV activity was also recently shown to promote interleukin-33–dependent, eosinophil-mediated control of tumor growth by increasing the concentration of the chemokine CCL11 [23]. Inhibition of DPPIV activity may thus contribute to the antitumor action of YS110.

Our study has some limitations. The study design with the small number of patients in each dose cohort precluded examination of any racial differences in the pharmacokinetics of YS110. In addition, antibodies to YS110 with neutralizing activity were detected in two patients, but the effects of such neutralizing activity on pharmacokinetic parameters were not evaluated given that serial pharmacokinetic data were not obtained after cycle 1. Finally, we did not measure CD26 expression in tumor tissue and so were not able to examine the relation between CD26 expression and tumor response.

In conclusion, YS110 was generally well tolerated at doses up to 6 mg/kg in Japanese patients with advanced MPM. This dose is thus the recommended dose for evaluation in the phase II part of our phase I-II study. YS110 also showed promising antitumor efficacy in patients with MPM.

Author contributions

T.K., I.M., M.Y., Y.K., C.M., and K. Nakagawa contributed to the conception or design of the study. M.T., Y.O., H.H., T.H., J.S., T.S., K. Nosaki, and K. Nakagawa enrolled patients. M.Y. analyzed the study data. All authors contributed to data interpretation and writing of the manuscript and approved the final version of the manuscript.

Conflict of Interest Statement

M.T. received honoraria from Novartis Pharma, ONO Pharmaceutical, and Boehringer Ingelheim. Y.O. reports grants from Kissei during the conduct of the study; grants and personal fees from AstraZeneca, Chugai, Lilly, ONO, BMS, Pfizer, MSD, Kyorin, Takade, Novartis, Taiho, and Abbvie, personal fees from Celltrion, and grants from Amgen, Boehringer Ingelheim, ROXO, and Janssen, outside the submitted work. H.H. reports grants from Kissei Pharmaceutical Co. Ltd during the conduct of the study; grants and personal fees from Eli Lilly, Astra Zeneca, MSD, Ono, BMS, Novartis, Chugai, and Taiho, and grants from Daiichi-Sankyo, Genomic Health, Abbvie, and Meck Serono, outside the submitted work. T.H. reports grants and personal fees from Kissei during the conduct of the study; grants and personal fees from Ono Pharmaceutical Co., Ltd., Bristol-Meyers Squibb, Chugai Pharmaceutical Co., Ltd., AstraZeneca, Nippon Boehringer Ingelheim, Novartis, Eli Lilly, Taiho Pharmaceutical Co., Ltd., Pfizer, Clovis Oncology, MSD, and Ignyta, and grants from Merck Serono, Eisai, Takeda Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma, Abbvie, Kyowa Hakko Kirin, Daiichi Sankyo, Astellas, Servier, and Janssen Pharmaceutical, outside the submitted work. J.S. has nothing to disclose. T.S. reports grants from Kissei Pharmaceutical during the conduct of the study; grants and personal fees from Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Eli Lilly Japan, Kissei Pharmaceutical, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, and Takeda Pharmaceutical, personal fees from Bristol-Myers Squibb, Kyowa Hakko Kirin, Nippon Kayaku, Ono Pharmaceutical, Roche Singapore, Taiho Pharmaceutical, Thermo Fisher Scientific, and Yakult Honsha, and grants from Bayer Yakuhin,

Daiichi Sankyo, Eisai, LOXO Oncology, and Merck Serono, outside the submitted work. K. Nosaki has nothing to disclose. T.K. has nothing to disclose. I.M. and M.Y. are employee of Kissei Pharmaceutical. Y.K. is a members of the board, CEO of Y'sAC Co., Ltd.. Y'sAC Co., Ltd. owns the worldwide Patent of YS110, a humanized monoclonal antibody against CD26 molecule expressed on a surface membrane of cancer cells. C.M. is an inventor of the humanized anti-CD26 mAb YS110 (US Patent #7402698). Y's AC Co.,LTD (Tokyo,Japan) own this patent. C. Morimoto is a founding member and shareholder of this company. K. Nakagawa reports grants and personal fees from MSD K.K., Eli Lilly Japan K.K., Bristol Myers Squibb Company, Taiho Pharmaceutical Co.,Ltd., Ono Pharmaceutical Co.,Ltd., Chugai Pharmaceutical Co.,Ltd., AstraZeneca K.K., Astellas Pharma Inc., Novartis Pharma K.K., Nippon Boehringer Ingelheim Co.,Ltd., and Pfizer Japan Inc., grants from Merck Serono Co., Ltd., during the conduct of the study; grants and personal fees from Takeda Pharmaceutical Co.,Ltd., SymBio Pharmaceuticals Limited., and Daiichi Sankyo Co., Ltd., grants from ICON Japan K.K., PAREXEL International Corp., IQVIA Services JAPAN K.K., A2 Healthcare Corp., AbbVie Inc., EP-CRSU CO., LTD., Linical Co.,Ltd., Otsuka Pharmaceutical Co., Ltd., EPS International Co., Ltd., Quintiles Inc., CMIC Shift Zero K.K., Eisai Co., Ltd., Kissei Pharmaceutical Co.,Ltd., Kyowa Hakko Kirin Co.,Ltd, EPS Corporation., Bayer Yakuhin, Ltd, inVentiv Health Japan, GRITSONE ONCOLOGY.INC, GlaxoSmithKline K.K., Yakult Honsha Co., Ltd., and Covance Inc., and personal fees from KYORIN Pharmaceutical Co.,Ltd., CareNet,Inc, Nichi-Iko Pharmaceutical Co., Ltd., Hisamitsu Pharmaceutical Co.,Inc., YODOSHA CO., LTD., Clinical Trial Co., Ltd., MEDICUS SHUPPAN,Publishers Co., Ltd., AYUMI Pharmaceutical Corporation, Nikkei Business Publications, Inc., Thermo Fisher Scientific K.K., NANZANDO Co.,Ltd, Medical Review Co., Ltd., YOMIURI TELECASTING CORPORATION., and Reno. Medical K.K., outside the submitted work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.09.010.

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