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Phase I study of the HER3-targeted antibody patritumab (U3-1287) combined with erlotinib in Japanese patients with non-small cell lung cancer☆

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ABSTRACT

Objectives: Human epidermal growth factor receptor 3 (HER3) is a key dimerization partner for HER family members and is associated with resistance to other HER family receptor-targeted therapeutics. This study evaluated the safety, tolerability, pharmacokinetics and efficacy of patritumab (U3-1287), a fully human anti-HER3 monoclonal antibody, in combination with erlotinib, an epidermal growth factor receptor-tyrosine kinase inhibitor in patients with previously treated advanced non-small cell lung cancer (NSCLC).

Patients and methods: This study enrolled patients with stage IIIB/IV NSCLC with Eastern Cooperative Oncology Group performance status 0–1, life expectancy >3 months and who had progressed after at least one prior course of chemotherapy (excluding erlotinib). This open-label study included two parts: dose escalation (Part 1) and dose expansion (Part 2). In Part 1, patients received intravenous patritumab 9 or 18 mg/kg every 3 weeks in addition to per-oral erlotinib 150 mg/day daily. In Part 2, patients received the recommended dose of patritumab as determined in Part 1. Adverse event rates, pharmacokinetics and tumor responses were determined.

Results: Twenty-four Japanese patients received patritumab at 9 mg/kg ($n = 3$) or 18 mg/kg ($n = 21$), and erlotinib. No dose-limiting toxicities were reported, indicating the maximum-tolerated dose was not reached. The most frequent adverse events were gastrointestinal or skin toxicities, which were generally mild and manageable. Patritumab pharmacokinetics were similar to those reported in previous studies. The median progression-free survival (95% confidence interval) was 44.0 (22.0–133.0) days for the *EGFR* wild-type group ($n = 9$) and 107.0 (74.0–224.0) days for the *EGFR*-activating mutation group ($n = 13$). Evaluation of biomarkers by immunohistochemical analysis did not indicate a relationship between efficacy and HER3 expression in tumor tissues.

Conclusion: Patritumab in combination with erlotinib was well tolerated and the efficacy of the combination was encouraging, especially in patients where prior gefitinib treatment failed.

Abbreviations: HER, human epidermal growth factor receptor; NSCLC, non-small cell lung cancer; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; RECIST, response evaluation criteria in solid tumors; ECOG, Eastern Cooperative Oncology Group; CTCAE, Common Terminology Criteria for Adverse Events; AE, adverse events; ELISA, enzyme-linked immunosorbent assay; AUC, area under the curve; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease; PD, progressive disease.

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1. Introduction

The human epidermal growth factor receptor (HER) family consists of four structurally related cellular receptors (Her1, Her2, Her3, Her4) that are expressed on the surface of cells and contain extracellular, transmembrane, and tyrosine kinase domains. Each of these domains is responsible for a different aspect of HER signaling pathways. Ligand binding to HERs results in the formation of homo- or heterodimers that activate receptor tyrosine kinases and subsequently downstream PI3K and AKT pathway signaling to mediate various cellular processes including morphogenesis, proliferation, angiogenesis, and survival [1]. Thus, inappropriate activation of HER signaling pathways might cause the growth and spread of cancer cells.

HER3 is the only HER family member that lacks tyrosine kinase activity because of an amino acid substitution in the conserved kinase domain. Thus, interactions of HER3 with binding partners are essential for its biological activity [2]. In particular, HER3 potently activates downstream PI3K and AKT pathway signaling by directly binding to PI3K through six consensus phosphotyrosine sites [3]. HER3 is overexpressed in various solid tumors including non-small cell lung cancer (NSCLC) [4–7], and is a poor prognostic factor as patients with these cancers have shorter survival [8–11]. *In vitro* studies have confirmed the direct involvement of HER3 in cancer cell growth [12–14]. Moreover, a recent study suggested that HER3 was involved in the development of resistance to other HER family receptor(s)-targeted therapeutics [12]. Therefore, HER3 is considered an important target for cancer chemotherapy.

Patritumab is a fully human monoclonal immunoglobulin G1 (IgG1) antibody [15] that specifically binds to the extracellular domains of HER3, thereby inhibiting downstream signal transduction and reducing HER3 expression [15]. A more recent study indicated that patritumab abrogated cetuximab resistance in colorectal cancer cells by inhibiting the phosphorylation of EGFR, HER2, HER3, ERK, and AKT [16]. In a mouse model of human NSCLC using a Calu-3 (a cell line) xenograft, administration of patritumab alone inhibited tumor proliferation. In addition, the combined use of patritumab with erlotinib, an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), led to increased inhibition of tumor proliferation, compared with patritumab alone [17].

In a phase I study (ClinicalTrials.gov Identifier: NCT00730470), the tolerability and safety of patritumab in patients with advanced solid tumors were evaluated. No dose-limiting toxicity (DLT) was observed at doses of 0.3–20 mg/kg, the maximum tolerated dose (MTD) was not reached, and the safety of doses up to 20 mg/kg was confirmed [18]. In another phase I study (ClinicalTrials.jp Identifier: JapicCTI-101262), the tolerability and safety of patritumab at doses of 9 mg/kg and 18 mg/kg were evaluated in Japanese patients with advanced solid tumors. No DLTs were observed at the dose levels studied and the MTD was not reached [19].

Based on an *in vivo* study showing that combined patritumab and erlotinib enhanced inhibition of tumor proliferation, compared with patritumab alone [20], the current study evaluated the safety and pharmacokinetics of patritumab combined with erlotinib and determined the recommended dose for subsequent clinical studies. Anti-patritumab antibody formation, tumor responses and potential biomarkers related to patritumab were also evaluated.

2. Patients and methods

2.1. Patients

This study enrolled stage IIIB/IV NSCLC patients who had progressed after at least one prior course of chemotherapy. Patients were 20–75 years old at the time of provision of informed consent, had measurable disease as per the response evaluation criteria in solid tumors (RECIST v.1.1, Japanese version) [21], had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 [22], and a life expectancy of more than 3 months. Additional inclusion criteria required for patients were adequate hematologic, hepatic and renal function. Eligible patients must have recovered from any toxicity related to prior therapy, except for alopecia. Exclusion criteria included a history of erlotinib or anti-HER3 therapy (prior gefitinib therapy allowed); other active malignancies; history or presence of interstitial lung disease; history (within 6 months before enrollment) or presence of severe cardiovascular or cerebrovascular disease, pulmonary thrombosis, deep vein thrombosis, or other clinically severe pulmonary disease; any of the following complications including clinically severe infections requiring systemic administration of an antimicrobial agent, antiviral agent or other agents; presence of chronic diarrhea, inflammatory bowel disease or partial ileus; presence of peptic ulcer; fluid retention requiring treatment; corneal disease; uncontrolled diabetes mellitus; hypertension; psychiatric symptoms; a positive test for hepatitis B virus surface antigen, hepatitis C virus antibody or human immunodeficiency virus antibody; history of a bleeding diathesis; and history of serious hypersensitivity to drugs containing polysorbate 20.

The study protocol was approved by each participating Institutional Review Board and each patient provided written informed consent.

2.2. Study design

This was a multicenter open-label trial conducted in two parts: dose escalation (Part 1) and dose expansion (Part 2). In Part 1, evaluation of the DLT for the combined treatment with patritumab and erlotinib was conducted at two dose levels: 9 mg/kg and 18 mg/kg patritumab where dose escalation followed a modified 3 + 3 design. The recommended dose of 18 mg/kg patritumab alone was previously determined in a phase I study [19]. Patients were initially enrolled in a cohort to receive patritumab 9 mg/kg (Level 1) every 3 weeks in combination with an oral daily dose of erlotinib 150 mg. Patritumab was administered as an intravenous infusion over 60 minutes. The first cycle (Day 1–21, with Day 1 defined as the first day of patritumab administration) served as the DLT evaluation period. If DLTs were observed in less than 33% of patients, the dose was escalated to 18 mg/kg (Level 2).

DLTs were defined as toxicities graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0) [21] and assessed as related to either patritumab or erlotinib: (1) grade 3 or higher febrile neutropenia, or persistent (7 days or longer) grade 4 neutropenia, (2) grade 4 thrombocytopenia, or grade 3 thrombocytopenia requiring blood transfusion, (3) uncontrollable grade 3 or higher fatigue, anorexia, nausea, vomiting, skin disorder (*e.g.*, skin eruption, urticaria), and diarrhea despite maximal supportive therapy, (4) grade 3 or higher toxicity, with the exception of (1)–(3) as well as pyrexia without neutropenia, transient electrolyte abnormality, and transient laboratory abnormality not requiring treatment and without clinical symptoms, and (5) toxicity requiring suspension of erlotinib therapy for more than 7 days during the DLT evaluation period. The MTD was defined as the highest dose level in the first cycle at which the frequency of DLT was below 33%.

Part 2 was designed to assess further the safety of the combined treatment in 18 patients using the recommended dose that was determined in Part 1. The target sample size for the U3-1287 + erlotinib combination therapy arm in the phase II study (ClinicalTrials.gov Identifier: NCT01211483) was 130 subjects. We selected 21 patients for the phase II study (3 for Part 1 and 18 for Part 2) based on that being approximately 15% of the target sample size.

In addition, the incidences of anti-patritumab antibodies, tumor response and related biomarkers were assessed.

2.3. Safety evaluation

Adverse events (AEs) were evaluated according to CTCAE v4.0 throughout the treatment period until 30 days after administration of the last dose (patritumab or erlotinib). Safety evaluations were based on a medical review of AEs and the results of clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms, physical examination, ECOG PS, and X-ray/computed tomography scans. The presence of anti-patritumab antibodies was assessed before each treatment cycle and measured by electrochemiluminescence immunoassay.

2.4. Pharmacokinetics

Pharmacokinetics were evaluated in 3 patients in the 9 mg/kg dose group and in 11 patients in the 18 mg/kg dose group. Blood samples were collected at pre-dose and 1 (end of infusion), 4, 7, 24 and 72 h after the start of first dose infusion, on Days 8 and 15 of Cycle 1, and on Day 1 of Cycles 2, 3 and 4. Serum patritumab concentrations were measured by enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic parameters after the first dose were calculated by non-compartmental analysis using WinNonlin (Ver 5.2.1, Pharsight Corp., CA, USA). Pharmacokinetic statistical analyses were performed using SAS System Release 9.2 (SAS Institute Japan Ltd., Tokyo, Japan).

2.5. Tumor response

Tumor responses were evaluated using RECIST v 1.1, Japanese version [22]. Disease responses were assessed at screening and at the end of Cycle 2 and every 6 weeks thereafter.

2.6. Biomarkers

Analysis of biomarkers using tumor tissues was performed only for patients who had provided written informed consent to participate in biomarker research. Paraffin-embedded samples of archived tumor tissues were used to evaluate HER3 protein expression level by immunohistochemistry. The frequency of HER3 gene amplification was assessed by fluorescence *in situ* hybridization at Mosaic Laboratories (Lake Forest, CA, USA).

Serum HER3 levels were also evaluated in all patients. Blood for serum biomarkers was collected on Day 1 (before administration), 8, 15 and 21 of Cycle 1, and Day 21 of Cycle 2 and every 6 weeks thereafter, and changes in soluble HER3 serum levels were evaluated. Soluble HER3 levels were measured by ELISA.

2.7. Statistical methods

All patients who received study medication were included in the analysis of safety and efficacy. Safety and efficacy data were summarized as descriptive statistics using SAS System Release 8.2 (SAS Institute Japan Ltd., Tokyo, Japan). In this study, no significance level was established because no hypothesis test was performed.

3. Results

3.1. Patient characteristics

Of the 25 patients enrolled in this study, 1 was ineligible because of suspected radiation pneumonitis after registration and withdrew before receiving any study treatment. Therefore, the study drug was administered to 24 patients. In Part 1, 3 patients received patritumab 9 mg/kg (Level 1) and 3 patients received patritumab 18 mg/kg (Level 2); in Part 2, 18 patients received patritumab 18 mg/kg.

Table 1
Demographics and baseline characteristics.

	Patritumab 9 mg/kg $N=3$ (%)	Patritumab 18 mg/kg $N=21$ (%)	Overall $N=24$ (%)
Sex			
Male	3 (100)	13 (61.9)	16 (66.7)
Female	0	8 (38.1)	8 (33.3)
Age (years)			
Median (range)	60.0 (53–69)	67.0 (36–73)	66.5 (36–73)
ECOG PS[a]			
0	2 (66.7)	7 (33.3)	9 (37.5)
1	1 (33.3)	14 (66.7)	15 (62.5)
Histology			
Adenocarcinoma	2 (66.7)	17 (81.0)	19 (79.2)
Squamous cell	0	3 (14.3)	3 (12.5)
Large cell	0	1 (4.8)	1 (4.2)
Other	1 (33.3)	0	1 (4.2)
Stage			
IIIB	0	0	0
IV	3 (100)	21 (100)	24 (100)
EGFR genotype			
Wild-type	1 (33.3)	8 (38.1)	9 (37.5)
Mutations	1 (33.3)	12 (57.1)	13[b] (54.2)
Exon 19	1 (33.3)	6 (28.6)	7 (29.2)
L858R	0	5 (23.8)	5 (20.8)
Exon 18 and 21	0	1 (4.8)	1 (4.2)
T790M	0	0	0
Unknown	1 (33.3)	1 (4.8)	2 (8.3)
Number of prior chemotherapy lines			
Median (range)	4.0 (2–4)	2.0 (1–4)	2.5 (1–4)

[a] Eastern Cooperative Oncology Group performance status.
[b] 12 of 13 patients received prior gefitinib therapy.
EGFR, epidermal growth factor.

Patient characteristics are summarized in Table 1. Eight patients were female and 16 patients were male. The median age (range) was 66.5 (36–73) years. Tumor genotyping of *EGFR* showed wild-type *EGFR* in 9 patients (37.5%), deletion of exon 19 (Exon 19 del) in 7 patients (29.2%), substitution of amino acid arginine with leucine at 858 (L858R) in 5 patients (20.8%), deletion of exon 18 and 21 (exon 18 and 21 del) in 1 patient (4.2%), and was unknown in 2 patients (8.3%). The median (range) number of lines of prior chemotherapy was 2.5 (1–4).

3.2. Safety

Throughout the study, adverse events (AEs) were reported in all 24 patients as summarized in Table 2. The most common overall AEs (≥50%) were diarrhea, stomatitis, paronychia, dermatitis acneiform, dry skin, decreased weight, and decreased appetite, which were generally mild and manageable. Most of the AEs were related to both patritumab and erlotinib, and were generally mild and manageable. No grade 5 AEs were reported. One patient receiving patritumab 18 mg/kg had a decreased lymphocyte count, which was a grade 4 AE. Serious adverse events (SAEs) including bacterial pneumonia, abnormal hepatic function, bacterial infection, cancer pain, and acneiform rash were reported in 4 patients, and these events required hospitalization. No DLT was reported during the DLT observation window and the tested doses did not reach the MTD. No patients developed anti-patritumab antibodies after the administration of patritumab in this study.

3.3. Pharmacokinetics

Serum patritumab pharmacokinetic parameters are summarized in Table 3. For the 9 and 18 mg/kg dose groups, the mean area under the curve (AUC) values were 1190 and 2480 μg/day/mL; the

Table 2
Treatment-emergent adverse events in more than 10% of patients.

Preferred term	Patritumab 9 mg/kg (N = 3)		Patritumab 18 mg/kg (N = 21)		Overall (N = 24)
	≥3 N	Any grades N (%)	≥3 N	Any grades N (%)	Any grades N (%)
Diarrhea	0	3(100.0)	4	20(95.2)	23(95.8)
Stomatitis	0	2(66.7)	1	20(95.2)	22(91.7)
Paronychia	0	2(66.7)	1	18(85.7)	20(83.3)
Dermatitis acneiform	0	2(66.7)	3	15(71.4)	17(70.8)
Dry skin	0	2(66.7)	0	13(61.9)	15(62.5)
Weight decreased	0	3(100.0)	0	10(47.6)	13(54.2)
Decreased appetite	0	3(100.0)	0	9(42.9)	12(50.0)
Rash maculo-papular	0	3(100.0)	1	8(38.1)	11(45.8)
Nausea	0	2(66.7)	0	8(38.1)	10(41.7)
Dysgeusia	0	1(33.3)	0	8(38.1)	9(37.5)
Cheilitis	0	0(0.0)	0	7(33.3)	7(29.2)
Vomiting	0	2(66.7)	0	5(23.8)	7(29.2)
Malaise	0	3(100.0)	0	4(19.0)	7(29.2)
Blood bilirubin increased	1	1(33.3)	0	6(28.6)	7(29.2)
Alanine aminotransferase increased	0	0(0.0)	1	6(28.6)	6(25.0)
Hypoalbuminemia	0	0(0.0)	0	5(23.8)	5(20.8)
Pruritus	0	0(0.0)	0	5(23.8)	5(20.8)
Fatigue	0	0(0.0)	0	5(23.8)	5(20.8)
Aspartate aminotransferase increased	0	0(0.0)	0	5(23.8)	5(20.8)
Lymphocyte count decreased	0	0(0.0)	1	4(19.0)	4(16.7)
Anemia	0	0(0.0)	0	3(14.3)	3(12.5)
Hypertriglyceridemia	0	1(33.3)	0	2(9.5)	3(12.5)
Headache	0	0(0.0)	0	3(14.3)	3(12.5)
Dry eye	0	1(33.3)	0	2(9.5)	3(12.5)
Cough	0	1(33.3)	0	2(9.5)	3(12.5)
Abdominal pain upper	0	1(33.3)	0	2(9.5)	3(12.5)
Constipation	0	1(33.3)	0	2(9.5)	3(12.5)
Proteinuria	0	0(0.0)	0	3(14.3)	3(12.5)
Blood alkaline phosphatase increased	0	0(0.0)	0	3(14.3)	3(12.5)
Blood uric acid decreased	0	0(0.0)	0	3(14.3)	3(12.5)

Table 3
Pharmacokinetic parameters after intravenous infusion of patritumab.

Parameters	Unit	Patritumab 9 mg/kg (N = 3) mean ± SD	Patritumab 18 mg/kg (N = 11) mean ± SD
$AUC_{0\text{-}21day}$	μg day/mL	1190 ± 87.6	2480 ± 420
C_{max}	μg/mL	242 ± 29.4	400 ± 46.7
CL	mL/day/kg	6.94 ± 0.72	6.61 ± 1.08
V_{ss}	mL/kg	51.4 ± 2.97	58.0 ± 14.8
$T_{1/2}$	day	6.44 ± 1.20	7.12 ± 2.30

AUC, area under the curve; C_{max}, maximum concentration; CL, total body clearance; V_{ss}, apparent volume of distribution at steady state; $T_{1/2}$; half-life.

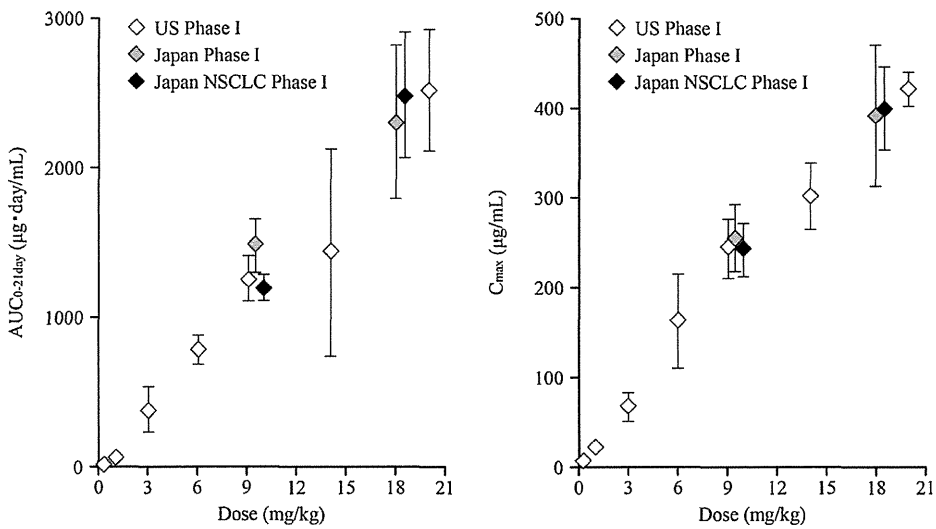

Fig. 1. C_{max} and AUC for patritumab in Phase I studies in Japan and the US. NSCLC: non-small cell lung cancer.

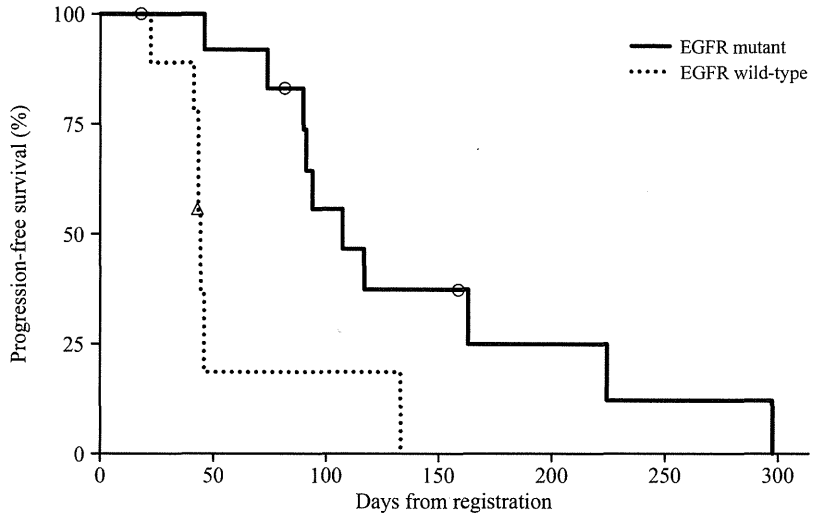

Fig. 2. Kaplan–Meier analysis of progression-free survival: subgroup analysis by *EGFR* status. EGFR: epidermal growth factor receptor.

Table 4
HER3 levels in tumor samples, *EGFR* status and tumor responses in NSCLC patients.

HER3 expression (IHC: membrane)	Total $N=11$	*EGFR* status		Best response		
		Mutant $N=7$	Wild-type $N=4$	PR $N=1$	SD $N=5$	PD $N=5$
3+	0	0	0	0	0	0
2+	6	5	1	1	3	2
1+	1	1	0	0	1	0
0	4	1	3	0	1	3

IHC, immunohistochemistry; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease; PD, progressive disease.

C_{max} values were 242 and 400 μg/mL; and the terminal half-lives were 6.44 and 7.12 days, respectively. The AUC and C_{max} values for patritumab are shown in Fig. 1. The AUC and C_{max} values in this study were within a similar range to those from phase I studies in Japan and the US (Fig. 1) [18,19].

3.4. Efficacy

One partial response (PR) and 14 cases with stable disease (SD) (1 SD at level 1, and 1 PR and 13 SD at level 2) were observed at 6 weeks. The overall response rate (ORR) was 4.2% and the disease control rate (DCR = CR + PR + SD) was 62.5%.

The PR was observed in a patient who had a tumor with an *EGFR*-activating mutation (L858R) but who had received no prior EGFR-TKI. Among the 14 SD patients, 10 patients had tumors with an *EGFR*-activating mutation and received prior gefitinib treatment (exon 19 del, $n=5$; L858R, $n=4$; exon 18 and 21 del, $n=1$), 3 patients had a tumor with wild-type *EGFR* and 1 patient had a tumor with an unknown *EGFR* status without a history of prior gefitinib treatment.

The progression-free survival (PFS) is shown in Fig. 2. The median PFS (95% confidence interval) was 44.0 (22.0–133.0) days for the *EGFR* wild-type group ($n=9$) and 107.0 (74.0–224.0) days for the *EGFR*-activating mutation group ($n=13$). The median PFS (95% confidence interval) in patients who had a tumor with an *EGFR*-activating mutation and who had received prior gefitinib treatment ($n=12$) was 107.0 (74.0–224.0) days.

3.5. Biomarker analysis

Tumor tissues for biomarker identification analysis were obtained from 11 patients. HER3 protein levels, *EGFR* mutation status, and tumor responses of these patients are summarized in Table 4. A correlation between tumor response and HER3 expression was not found. Serum soluble HER3 concentrations during treatment with patritumab and erlotinib significantly increased from baseline in all patients. Soluble HER3 concentrations (mean ± SD) at baseline were 6.88 ± 0.48 ng/mL for 9 mg/kg ($n=3$) and 7.35 ± 2.48 ng/mL for 18 mg/kg ($n=21$) groups. Soluble HER3 concentrations (mean ± SD) on cycle 1 day 21 were 29.72 ± 1.14 ng/mL for the 9 mg/kg ($n=3$) group and 27.53 ± 6.17 ng/mL for the 18 mg/kg ($n=21$) group. There was no statistically significant difference in soluble HER3 concentrations between dose groups. A correlation between serum soluble HER3 concentrations during the treatment and tumor response was not found.

4. Discussion

We completed the first phase I study of patritumab in combination with erlotinib that evaluated the safety, pharmacokinetics and potential biomarkers in patients with previously treated advanced NSCLC. We found that the combination therapy had good efficacy in advanced NSCLC patients, especially for those who had tumors with *EGFR*-activating mutations and had developed resistance to gefitinib treatment.

The findings in the current study (the median PFS of patients with *EGFR*-activating mutations who received prior gefitinib treatment ($n=12$) was 3.56 months, and there were 13 patients (92.9%) with SD at level 2) compared favorably to the findings of recent studies investigating third-generation EGFR-TKIs. Early phase I results with CO-1686, a third-generation EGFR-TKI, indicated that, of 9 patients with EGFR-activating mutations and failed EGFR-TKI therapy, 2 (22.2%) had SD [23]. A study investigating another third-generation EGFR-TKI, AZD9291, demonstrated that 15 patients

(43%) had confirmed or unconfirmed PR [24]. A phase Ib study of patients with EGFR-TKI resistance treated with combined afatinib and cetuximab showed that 35% of patients responded and 95% had SD [25], demonstrating a better response than was shown in a trial using afatinib alone (response rate of 8.2%, median PFS of 4.4 months with a median overall survival of 19.0 months) [26].

A study investigating the use of cetuximab in EGFR-positive NSCLC demonstrated a small benefit when it was used in combination with chemotherapy (median OS of 11.3) compared with chemotherapy alone (10.1 months, $P=0.044$) [27]. However, the median PFS was 4.8 months in both groups.

The most common AEs in this study were gastrointestinal and skin toxicities, which were generally mild and manageable. No deaths due to adverse events were reported. Some SAEs were reported including grade 2 cancer pain, which was attributable to the primary disease and was unrelated to either patritumab or erlotinib treatment. No DLTs were reported at either dosage levels (patritumab 9 or 18 mg/kg with oral daily dose of erlotinib 150 mg) and the doses tested did not reach MTD. Although most AEs in this study were similar to the well-known side effects of erlotinib, patritumab might have caused an incremental increase in the incidence of diarrhea compared with the incidence in a previous Japanese phase II study of erlotinib alone (95.8% *vs.* 74%) [28]. The incidence and rates of other grade 3 or 4 AEs including skin toxicities were similar to those in a previous erlotinib study [29]. Therefore, patritumab at a dose of 18 mg/kg in combination with an oral daily dose of erlotinib 150 mg was determined as the recommended dose for future studies in Japanese patients with NSCLC. The levels of pharmacokinetic parameters or patritumab in this study were similar to those observed in previous phase I studies of patritumab [18,19]. Furthermore, no neutralizing antibodies were detected in patients in this study after patritumab administration, as assessed by an anti-patritumab antibody and cell-based bioassay, similar to findings in previous studies [18,19].

In terms of efficacy of the combined treatment, 1 PR and 14 cases with SD were observed. The ORR was 4.2% and the DCR was 62.5%. The PR patient had a tumor with an *EGFR*-activating mutation and did not receive prior gefitinib treatment. The low ORR might be explained by the patient characteristics including the presence of wild-type *EGFR* and prior gefitinib treatment.

For the exploratory analysis, we separately evaluated the efficacy of this combination in patients with wild-type *EGFR* and those with *EGFR* mutations who developed resistance to gefitinib treatment. Of 9 patients with wild-type *EGFR*, 3 had SD (DCR 33%) and the median PFS for all 9 patients was 44.0 days. These results were not encouraging because they were similar to those obtained with the use of erlotinib alone in recent phase III studies in patients with previously treated NSCLC and wild-type *EGFR* (DCR 26% with a median PFS of 2.4 months [30], and DCR 52.8% with a median PFS of 1.3 months [31]). However, 10 SDs were observed in 12 patients with *EGFR* mutations who received prior gefitinib treatment. In the current study, the cohort DCR was 83.3% and the median PFS was 107 days. Although the results were limited because of the small number of patients, the DCR and median PFS are encouraging and suggest that patritumab might enhance the activity of erlotinib in patients with *EGFR*-activating mutations who develop resistance to gefitinib treatment, because the DCR and median PFS in a previous phase II study of erlotinib alone in patients after failure of gefitinib were only 28.6% and 60 days, respectively [32].

With respect to biomarkers, we investigated the correlation between HER3 expression in tumor tissues and the efficacy of combined patritumab and erlotinib treatment. Although recent studies suggested that HER3 was involved in the resistance to other HER receptor-targeted therapies [12], we observed no correlation between tumor response and HER3 expression in tumor tissues or serum soluble HER3 levels before treatment. An explanation for the lack of correlation between HER3 and efficacy might be the type of tumor tissues used in this study or the relatively low numbers of patients studied. Because we tested HER3 expression from tissue archived at the initial diagnosis, we could not examine HER3 expression just prior to this study. To confirm that hypothesis, it would be necessary to examine these biomarkers in larger numbers of patients in future studies.

In addition, serum soluble HER3 levels were significantly increased in all patients during treatment and serum soluble biomarkers were similar to those observed in previous studies of patritumab [19]. The mechanisms underlying these phenomena are unclear and require further study.

In conclusion, patritumab in combination with erlotinib was well tolerated up to 18 mg/kg without DLTs in previously treated Japanese NSCLC patients. This preliminary demonstration of the efficacy of the combined treatment was encouraging, especially in NSCLC patients with *EGFR*-activating mutations where prior gefitinib treatment failed.

Conflicts of interest

M. Nagashima and M. Sekiguchi are employed by Daiichi Sankyo. No potential conflicts of interest are disclosed by the other authors.

Role of the funding source

This study was funded by Daiichi Sankyo. The study sponsor contributed to the design of the study, was involved in the collection, analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

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References

[1] Yarden Y, Sliwkowski MX. Untangling the ErbB signaling network. Nat Rev Mol Cell Biol 2001;2:127–37.
[2] Pinkas-Kramarski R, Soussan L, Waterman H, Levkowitz G, Alroy I, Klapper L, et al. Diversification of Neu differentiation factor and epidermal growth factor signaling by combinatorial receptor interactions. EMBO J 1996;15:2452–67.
[3] Campbell MR, Amin D, Moasser MM. HER3 comes of age: new insights into its functions and role in signaling, tumor biology, and cancer therapy. Clin Cancer Res 2010;16:1373–83.
[4] Wheeler DL, Huang S, Kruser TJ, Nechrebecki MM, Armstrong EA, Benavente S, et al. Mechanisms of acquired resistance to cetuximab: role of HER (ErbB) family members. Oncogene 2008;27:3944–56.
[5] Naidu R, Yadav M, Nair S, Kutty MK. Expression of c-erbB3 protein in primary breast carcinomas. Br J Cancer 1998;78:1385–90.
[6] Narayan M, Wilken JA, Harris LN, Baron AT, Kimbler KD, Maihle NJ. Trastuzumab-induced her reprogramming in "resistant" breast carcinoma cells. Cancer Res 2009;69:2191–4.
[7] Friess H, Yamanaka Y, Kobrin MS, Do DA, Buchler MW, Korc M. Enhanced erbB-3 expression in human pancreatic cancer correlates with tumor progression. Clin Cancer Res 1995;1:1413–20.
[8] Müller-Tidow C, Diederichs S, Bulk E, Pohle T, Steffen B, Schwäble J, et al. Identification of metastasis-associated receptor tyrosine kinases in non-small cell lung cancer. Cancer Res 2005;65:1778–82.
[9] Bieche I, Onody P, Tozlu S, Driouch K, Vidaud M, Lidereau R. Prognostic value of ERBB family mRNA expression in breast carcinomas. Int J Cancer 2003;106:758–65.
[10] Yi ES, Harclerode D, Gondo M, Stephenson M, Brown RW, Younes M, et al. High c-erbB-3 protein expression is associated with shorter survival in advanced non-small cell lung carcinomas. Mod Pathol 1997;10:142–8.
[11] Tanner B, Hasenclever D, Stern K, Schormann W, Bezler M, Hermes M, et al. ErbB-3 predicts survival in ovarian cancer. J Clin Oncol 2006;24:4317–23.
[12] Sergina NV, Rausch M, Wang D, Blair J, Hann B, Shokat KM, et al. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. Nature 2007;445:437–41.

[13] Zhou BB, Peyton M, He B, Liu C, Girard L, Caudler E, et al. Targeting ADAM-mediated ligand cleavage to inhibit HER3 and EGFR pathways in non-small cell lung cancer. Cancer Cell 2006;10:39–50.
[14] van der Horst EH, Murgia M, Treder M, Ullrich A. Anti-HER-3 MAbs inhibit HER-3-mediated signaling in breast cancer cell lines resistant to anti-HER-2 antibodies. Int J Cancer 2005;115:519–27.
[15] Treder M, Hartmann S, Ogbagabriel S, Borges E, Green L, Kang J, et al. Fully human anti-HER3 monoclonal antibodies (mAbs) inhibit oncogenic signaling and tumor cell growth in vitro and in vivo. In: AACR meeting abstracts; 2008. p. LB-20.
[16] Kawakami H, Okamoto I, Yonesaka K, Okamoto K, Shibata K, Shinkai Y, et al. The anti-HER3 antibody patritumab abrogates cetuximab resistance mediated by heregulin in colorectal cancer cells. Oncotarget 2014;5:11847–56.
[17] Treder M, Moor R, Scultze-Horsel U, Hettman T, Rothe M, Radinsky R, et al. Fully human anti-HER3 mAb U3-1287 (AMG 888) demonstrates unique in vitro and in vivo activities versus other HER family inhibitors in NSCLC models. Eur J Cancer 2008;6(Suppl.):99 [abstract 309].
[18] LoRusso P, Jänne PA, Oliveira M, Rizvi N, Malburg L, Keedy V, et al. Phase I study of U3-1287, a fully human anti-HER3 monoclonal antibody, in patients with advanced solid tumors. Clin Cancer Res 2013;19:3078–87.
[19] Wakui H, Yamamoto N, Nakamichi S, Tamura Y, Nokihara H, Yamada Y, et al. Phase 1 and dose-finding study of patritumab (U3-1287), a human monoclonal antibody targeting HER3, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 2014;73:511–6.
[20] Freeman D, Ogbagabriel S, Treder M, Schneider M, Radinsky R, Hettmann T. U3-1287 (AMG 888), a fully human anti-HER3 mAb, demonstrates in vitro and in vivo efficacy in NSCLC models. In: AACR-EORTC meeting abstracts. 2009.
[21] National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.0 2010; 2014. Accessed from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (last accessed on 10 October).
[22] Eisenhauer EA, Therasse P, Roberts J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) [Internet]. In: Japanese version 1.0 by JCOG. Translated by the JCOG Steering committee. 2014, 27 p. Available from: http://www.jcog.jp/doctor/tool/RECISTv11J_20100810.pdf [last accessed on 10 October].
[23] Soria JC, Sequist LV, Gadgeel S. First-in-human evaluation of CO-1686, an irreversible, highly, selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M). J Thorac Oncol 2013;8 [abstr O03.06].
[24] Ranson M, Pao W, Kim DW. AZD9291: an irreversible, potent and selective tyrosine kinase inhibitor (TKI) of activating (EGFRm) and resistance (T790M) mutations in advanced NSCLC. J Thorac Oncol 2013;8 [abstr MO21.12].
[25] Janjigian YY, Groen HJ, Horn L, Smit EF, Fu F, Wang F, et al. Activity and tolerability of combined EGFR targeting with afatinib (BIBW 2992) and cetuximab in T790M non-small cell lung cancer patients. In: 14th world conference on lung cancer, 2011. 2011.
[26] Katakami N, Atagi S, Goto K, Hida T, Horai T, Inoue A, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol 2013;31:3335–41.
[27] Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525–31.
[28] Kubota K, Nishiwaki Y, Tamura T, Nakagawa K, Matsui K, Watanabe K, et al. Efficacy and safety of erlotinib monotherapy for Japanese patients with advanced non-small cell lung cancer: a phase II study. J Thorac Oncol 2008;3:1439–45.
[29] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 1982;5:649–55.
[30] Garassino MC, Martelli O, Broggini M, Farina G, Veronese S, Rulli E, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013;14:981–8.
[31] Kawaguchi T, Ando M, Asami K, Okano Y, Fukuda M, Nakagawa H, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2014;32:1902–8.
[32] Cho BC, Im CK, Park MS, Kim SK, Chang J, Park JP, et al. Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. J Clin Oncol 2007;25:2528–33.

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Phase I study of weekly *nab*-paclitaxel combined with S-1 in patients with human epidermal growth factor receptor type 2-negative metastatic breast cancer

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Key words
Combination chemotherapy, metastatic breast cancer, *nab*-paclitaxel, phase I study, S-1

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We conducted a phase I study of a weekly *nab*-paclitaxel and S-1 combination therapy in patients with human epidermal growth factor receptor type 2-negative metastatic breast cancer. The primary objective was to estimate the maximum tolerated and recommended doses. Each treatment was repeated every 21 days. Levels 1, 2a, 2b, and 3 were set depending on the S-1 dose (65 or 80 mg/m^2) and *nab*-paclitaxel infusion schedule (days 1 and 8 or days 1, 8, and 15). Fifteen patients were enrolled. Dose-limiting toxicity was observed in one patient at Level 3 (100 mg/m^2 *nab*-paclitaxel on days 1, 8, and 15 with 80 mg/m^2 S-1 daily for 14 days, followed by 7 days of rest). Although the maximum tolerated dose was not reached, the recommended dose was determined to be Level 3. Neutropenia was the most frequent grade 3–4 treatment-related adverse event. For patients with measurable lesions, the response rate was 50.0% and the median time to treatment failure and median progression-free survival was 13.2 and 21.0 months, respectively. The present results show the feasibility and potential for long-term administration of this combination therapy.

Chemotherapies for breast cancer, including molecular targeted therapies, have undergone remarkable development in recent years; conventional anthracycline and taxane-containing regimens continue to play a key role in this treatment. For cases of human epidermal growth factor receptor type 2 (HER2)-negative breast cancer, the treatment options are limited compare to those for HER2-positive cases and the development of highly efficacious therapy is warranted.

Combination chemotherapy represents a treatment choice that has been prescribed for increased efficacy. The selection of a combination of cytotoxic chemotherapies versus sequential single-agent treatment is controversial.[1] In phase III clinical trials involving metastatic breast cancer (MBC), O'Shaughnessy *et al.* evaluated a combination therapy with docetaxel and capecitabine, whereas Albain *et al.* prescribed a combination therapy with paclitaxel and gemcitabine; both research groups reported the superiority of the combined regimens over monotherapies.[2,3] Combination therapies have also been reported to correlate with a high incidence of toxicity and high efficacies, therefore, the development of a well-tolerated, highly efficacious therapy is anticipated.

Nab-paclitaxel is a 130-nm nanoparticulate drug preparation comprising paclitaxel bound to human serum albumin particles and is widely used as a key drug for the treatment of breast cancer.[4] In a pivotal phase III clinical study, treatment with *nab*-paclitaxel showed a significantly better response rate (RR; a primary endpoint) of 24.0%, as compared with an RR of 11.1% for treatment with the standard solvent-based paclitaxel.[5] Furthermore, in a randomized phase II clinical study, the median progression-free survival (PFS) and RR of weekly *nab*-paclitaxel was 12.9 months and 49%, respectively, which suggested that weekly *nab*-paclitaxel might be superior to triweekly administration.[6,7] In that study, the major toxicities associated with weekly *nab*-paclitaxel were myelosuppression and peripheral neuropathy.

The oral, fixed-dose combination agent S-1 comprises tegafur (FT), a fluoropyrimidine prodrug of 5-fluorouracil (5-FU), and the 5-FU metabolism modulating agents 5-chloro-2.4-dihydrooxypyridine (CDHP) and oteracil potassium (Oxo). S-1 is designed to orally deliver 5-FU, a pyrimidine analog antimetabolite and antineoplastic agent while reducing the rate of 5-FU degradation and conversion in the gastrointestinal tract

to a toxic phosphorylated metabolite.[8] The results of a phase II clinical study revealed an RR of 41.7% for patients with MBC who received S-1 monotherapy, indicating the efficacy of this regimen.[9] The major adverse events associated with S-1 treatment in that study were myelosuppression and gastrointestinal toxicity. A phase III study (SELECT BC) carried out in chemotherapy-naïve patients with HER2-negative MBC, which investigated overall survival as a primary endpoint, confirmed the non-inferiority of S-1 to taxanes.[10,11]

Thymidine phosphorylase is an enzyme that converts 5-FU to its active form, fluorodeoxyuridylate, and taxanes have been reported to induce the upregulation of thymidine phosphorylase in tumor tissues.[12] Nukatsuka *et al.*[13] reported a synergistic reduction in tumor size following treatment with paclitaxel combined with S-1 in a mouse model of human breast cancer.

The mechanisms of cytotoxic action differ between *nab*-paclitaxel and S-1. A major toxicity of both *nab*-paclitaxel and S-1 is myelosuppression; otherwise, these two drugs have no other overlapping toxicity profiles that would affect the continuation of treatment. Given this information and the assumption from the results of basic studies that the combined use of these two drugs might yield synergistically enhanced efficacy, we carried out a phase I study of weekly *nab*-paclitaxel in combination with S-1 in patients with HER2-negative MBC.

Materials and Methods

This phase I dose-escalation study to evaluate treatment with weekly *nab*-paclitaxel in combination with S-1 in patients with HER2-negative MBC was carried out in conformance with the Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of each participating medical institution prior to initiation of the study. Written informed consent was obtained from every patient prior to participation in the study.

Patient population. Patients who met the following major criteria were considered eligible to participate in the study: women with cytologically or histologically confirmed breast cancer who were aged 20–74 years; patients with clinically confirmed MBC; patients with demonstrated HER2-negativity through immunohistochemical analysis or FISH; patients previously treated with single-regimen or no chemotherapy for MBC; a survival expectancy of ≥60 days; an Eastern Cooperative Oncology Group performance status of 0 or 1; and an absolute neutrophil count (ANC) of ≥2000/mm^3, hemoglobin concentration of ≥9.0 g/dL, platelet count of ≥10.0 × 10^4/mm^3, total bilirubin concentration of ≤1.5 mg/dL, albumin concentration of ≥3.5 g/dL, serum aspartate aminotransferase concentration of <100 IU/L, serum alanine aminotransferase concentration of <100 IU/L, and creatinine clearance of ≥60 mL/min as determined from a 24-h urine collection or predicted creatinine clearance calculated using the Cockcroft–Gault formula.[14]

However, patients with tumor progression during or within 12 months after the last dose of pre- or post-operative taxane chemotherapy were excluded from the study. Patients with a history of taxane or S-1 chemotherapy for MBC and those who had experienced grade ≥2 peripheral neuropathy before or since enrolment were also excluded. Measurable disease using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was not required.

Study design and treatment. The dosage schedules at each dose level are shown in Figure 1. *Nab*-paclitaxel (100 mg/m^2) was given by i.v. drip infusion over a 30-min period in doses

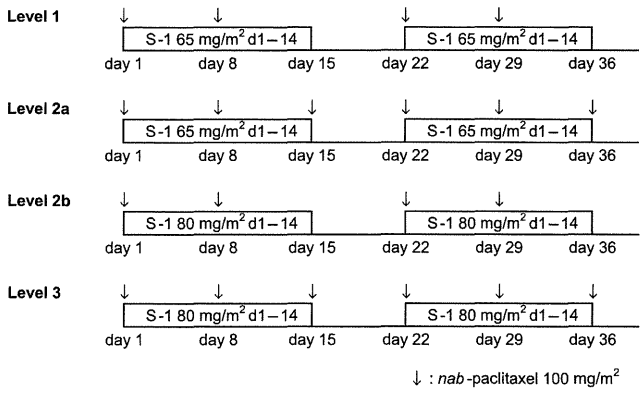

Fig. 1. Therapeutic experimental regimens for *nab*-paclitaxel and S-1 combination therapy in patients with human epidermal growth factor receptor type 2-negative metastatic breast cancer.

based on the body surface area (BSA) and calculated using the Mosteller formula; doses were given on days 1 and 8 for Levels 1 and 2b, and on days 1, 8, and 15 for Levels 2a and 3.[15] S-1 was given orally twice daily for 14 consecutive days, followed by a 7-day rest. The S-1 dosage was set at 65 mg/m^2 for Levels 1 and 2a, and at 80 mg/m^2 for Levels 2b and 3. The following daily S-1 dose levels were based on the BSA and calculated using the Fujimoto formula:[16] Level 1 and 2a cohorts (65 mg/m^2), the dose was 50, 80, or 100 mg at a BSA of <1.25, 1.25–1.5, or ≥1.5 m^2, respectively; Level 2b and 3 cohorts (80 mg/m^2), the dose was 80, 100, or 120 mg at a BSA of <1.25, 1.25–1.5, or ≥1.5 m^2, respectively. Administration of the combination chemotherapy was repeated in 21-day cycles until the occurrence of disease progression or development of intolerable toxicities. Although the rule was to avoid corticosteroid or anti-allergic pretreatments, such treatments were allowed in cases with signs of hypersensitivity.

Dose modification was carried out in accordance with the protocol. Before commencement each cycle, patients were required to have an ANC ≥1500/mm^3, platelet count ≥75 000/mm^3, total bilirubin ≤1.5 mg/dL, liver transaminase <100 IU/L, serum creatinine ≤1.5 mg/dL, ≤grade 2 peripheral sensory neuropathy, ≤grade 2 eye disorders, ≤grade 3 diarrhea, and ≤grade 3 stomatitis. If any toxicity applicable to Table S1 occurred during the administration period in a cycle, the study treatment was to be interrupted. If any toxicity applicable to Table S2 occurred, the dose of each drug in the next administration was to be decreased according to Table S3.

Level escalation plan. This study was carried out with a unique 3 + 3 design in a sequential order of Levels 1, 2a, 2b, and 3. Whether to proceed to the next Level was determined by deliberation between the investigator, medical officer, and study sponsor by considering the dose-limiting toxicity (DLT) and administration conditions during the first and second cycles. For cases in which DLT was observed in one or two of three patients at any Level, three additional patients were to be recruited for the same Level. When DLT was observed in three or more of six patients at any Level, that Level was considered a maximum tolerated dose (MTD) and the dose level immediately below that Level was defined as a recommended dose (RD). In the case that the DLT incidence was <50% at Level 3, the study sponsor was entrusted with the final judgment of an RD after deliberation with the medical officer and at the suggestion of the Data and Safety Monitoring Committee. Dose-limiting toxicity was defined as the occurrence of any of the following during cycle 1:

grade 4 platelet count decrease; grade 3 platelet count decrease requiring blood transfusion; febrile neutropenia with a neutrophil count of <500/mm^3 and pyrexia at ≥38.5°C; grade 4 neutrophil count decrease persisting for ≥8 days; grade ≥3 nausea, vomiting, and diarrhea refractory to symptomatic treatment; and the postponement of cycle 2 initiation for ≥15 days from the scheduled time point because of adverse reaction(s). For ≥grade 3 non-hematological toxicities, cases of all other abnormal clinical laboratory test values, and/or transient non-hematological toxicities, the principle investigators, medical officer, and sponsor would confer to determine the presence or absence of a DLT.

Study objectives. The primary objective of this study was to estimate the MTD and RD of the combination therapy including weekly *nab*-paclitaxel and S-1 in patients with MBC. The secondary objective comprised evaluations of safety, antitumor responses, administration conditions, and pharmacokinetic profiles.

Safety and efficacy assessments. Adverse events were evaluated for severity in accordance with the Common Terminology Criteria for Adverse Events version 4.0. Antitumor response evaluations were carried out every two cycles according to RECIST version 1.1.

Pharmacokinetics. The paclitaxel and S-1 component plasma pharmacokinetics were investigated in this study. Blood samples were collected at 0, 0.5, 1, 2, 4, 10, 24, 48, and 72 h after *nab*-paclitaxel dosing and at 0, 0.5, 1, 2, 4, 6, 8, and 10 h after S-1 dosing during the first cycle only. The plasma concentrations of paclitaxel, FT, 5-FU, CDHP, and Oxo were determined through validated analytical procedures that incorporated HPLC with tandem mass spectrometry at the Shin Nippon Biochemical Laboratories (Wakayama, Japan). The lower limit of quantitation for paclitaxel in human plasma was 1 ng/mL, and the reliable response range was 1–1000 ng/mL. The lower limit of quantitation values for FT, 5-FU, CDHP, and Oxo in human plasma were 20, 2, 4, and 4 ng/mL, respectively, and the reliable response ranges were 20–4000, 2–400, 4–800, and 4–400 ng/mL, respectively.

The pharmacokinetic parameters were calculated according to non-compartmental techniques using the WinNonlin software program (Pharsight, Mountain View, CA, USA). The maximum observed concentration (C_{max}) and the time to C_{max} (t_{max}) were determined directly from the observed plasma concentration–time profiles over the 72-h sampling interval. The apparent terminal elimination rate constant (λz) was estimated by linear regression of the individual plasma concentration–time data. The terminal elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = \ln(2)/\lambda z$ for each individual. Individual areas under the concentration–time curves (AUCs) from time 0 to the last measurable time point (AUC_{0-t}) were calculated according to the trapezoidal rule. Individual AUCs extrapolated to infinity (AUC_{inf}) were calculated using the last measurable concentration (C_{last}) according to the formula $AUC_{inf} = AUC_{0-t} + C_{last}/\lambda z$.

Results

Fifteen patients were enrolled at two medical institutions in Japan between July 2010 and December 2012. A follow-up to the study treatment continued until December 2013.

Patient characteristics. The patient characteristics are summarized in Table 1. All 15 patients were subjected to the safety analysis. Eleven and four patients had histologically positive and negative hormone receptor statuses, respectively. Nine patients had chemotherapy-naïve MBC and the other six had undergone chemotherapy for MBC with anthracycline-containing regimens.

Table 1. Characteristics of patients with human epidermal growth factor receptor type 2-negative metastatic breast cancer (MBC) treated with *nab*-paclitaxel and S-1 combination therapy (n = 15)

Characteristic	No. of patients (%)
Age, years	
Median (range)	63.0 (41–67)
ECOG PS	
0	9 (60.0)
1	6 (40.0)
Hormonal status	
ER-positive and/or PgR-positive	11 (73.3)
ER-negative and PgR-negative	4 (26.7)
Metastatic site	
Lung	6 (40.0)
Bone	9 (60.0)
Liver	4 (26.7)
Distant lymph nodes	6 (40.0)
Other	3 (20.0)
Prior chemotherapy for MBC	
0	9 (60.0)
1	6 (40.0)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor; PS, performance status.

Dose-limiting toxicity, MTD, and RD. The dosage level was escalated up to Level 3, the highest level specified in the protocol; however, no DLT was observed in three patients per group through Levels 1 to 3. Three additional patients were enrolled for Level 3 treatment with the intent to evaluate tolerability at that dosage level in six patients. As a result, a DLT (neutropenia leading to a delay in the start of cycle 2 for ≥15 days beyond the scheduled day) occurred in one patient, so MTD was not reached. However, at Level 3 dose reductions were required in three of the six patients in cycle 2 (grade 1 diarrhea in one patient, grade 2 diarrhea and grade 1 vomiting in one patient, and a prolonged neutropenia in one patient); therefore, it was determined that the dosage should not be increased further, and the RD was determined to be Level 3.

Drug administration and safety profile. Fifteen patients received a total of 206 cycles of combination chemotherapy. The median number of cycles administered per patient was 14.0 (range, 1–35). The overall relative dose intensity (RDI) was 62.5% for *nab*-paclitaxel and 70.5% for S-1. The overall RDIs up to cycle 2, as required to determine whether to proceed to the next Level, were 84.0% and 81.0% for *nab*-paclitaxel and S-1, respectively. The RDIs up to cycle 2 at Level 3 were 68.5% and 76.3% for *nab*-paclitaxel and S-1, respectively. The major reasons for requiring a *nab*-paclitaxel dose reduction were peripheral sensory neuropathy (33.3%; n = 5) and fatigue (20.0%; n = 3); S-1 dose reductions were mainly because of fatigue (26.7%; n = 4) or diarrhea (20.0%; n = 3). Skipping of *nab*-paclitaxel administration was most often because of fatigue (33.3%; n = 5) or peripheral sensory neuropathy (20.0%; n = 3), whereas neutropenia (26.7%; n = 4), decreased appetite (13.3%; n = 2), and diarrhea (13.3%; n = 2) were the main reasons for skipping S-1 treatment. Neutropenia was a major reason for delaying the initiation of the next cycle (86.7%; n = 13). The following factors accounted for the discontinuation of treatment: disease progression in six patients; adverse events (psoriasis, ker-

atitis, cheilitis, and diarrhea) in four patients; refusal of further treatment in three patients; and end of study in two patients.

The treatment-related adverse events that occurred in ≥30% (≥5 patients) of all patients are listed in Table 2. The hematological toxicities with high incidence were neutropenia (100%; n = 15), leukopenia (100%; n = 15), and anemia (80%; n = 12). The non-hematological toxicities with high incidence included alopecia (93%; n = 14), peripheral sensory neuropathy (87%; n = 13), diarrhea (80%; n = 12), and decreased appetite (80%; n = 12). Most of the treatment-related adverse events, although high in incidence, were grade ≤2 and clinically manageable. Grade ≥3 treatment-related adverse events that occurred in two or more patients included neutropenia (93%; n = 14), leukopenia (67%; n = 10), lymphopenia (20%; n = 3), fatigue (20%; n = 3), and peripheral sensory neuropathy (13%; n = 2). Grade 3 peripheral sensory neuropathy improved to grade 2 rapidly after skipping the administration.

Efficacy. The RRs and disease control rates (complete response [CR] + partial response [PR] + stable disease [SD] for ≥16 weeks) are shown in Table 3. Twelve of the 15 patients had measurable lesion(s) as defined by RECIST version 1.1. The responses in the 12 patients included CR in one patient, PR in five patients, SD in five patients, progressive disease in one patient, and not evaluable in one patient, with a RR of 50.0% (95% confidence interval [CI], 21.1–78.9). Among the triple-negative cases, the responses were CR in one patient, PR in one patient, and progressive disease in one patient. Among patients with hepatic metastasis, the responses were PR in three patients and SD in one patient. The disease control rate was 83.3% (95% CI, 51.6–97.9), and the median time to treatment failure (TTF) and median PFS were 13.2 months (95% CI, 6.9–16.2) and 21.0 months (95% CI, 14.9–not reached), respectively.

Pharmacokinetics. Twelve patients (six patients at Levels 1 and 2a, and six patients at Levels 2b and 3) underwent pharmacokinetic evaluations. The pharmacokinetic parameters for the S-1 components and paclitaxel are summarized in Table 4. The plasma concentrations of FT, 5-FU, CDHP, and Oxo increased in a dose-dependent manner at a dose of 65 or 80 mg/m^2 S-1 with the co-administration of 100 mg/m^2 *nab*-paclitaxel. The pharmacokinetic parameters of paclitaxel following the concomitant administration of *nab*-paclitaxel and S-1 were similar regardless of the S-1 dose level.

Discussion

To our knowledge, this phase I study represents the first clinical trial carried out to evaluate a combination treatment of weekly *nab*-paclitaxel and S-1 in patients with HER2-negative MBC.

Because the attempt to estimated MTD failed under the 3 + 3 design in this study, we explored the possibility of further *nab*-paclitaxel dose escalation in order to estimate MTD. However, this dose escalation was determined inappropriate upon deliberation with the medical officer and the Data and Safety Monitoring Committee on the grounds of the RDI at Level 3 as well as the adverse reaction occurrence status, which included <grade 3 adverse reactions. Therefore, Level 3 was determined as the RD (100 mg/m^2 *nab*-paclitaxel on days 1, 8, and 15 with an 80 mg/m^2 S-1 dose for 14 days, followed by 7 days of rest).

One of the most important factors for evaluating combination chemotherapies is the balance of efficacy and toxicity. In previously reported phase III clinical studies of docetaxel in combination with capecitabine and of paclitaxel in combination with gemcitabine, the median time to disease progression was 6.1 months for both combination therapy groups, a signifi-

Table 2. Treatment-related adverse events at each level

Adverse Events / CTCAE Grade	Level 1				Level 2a				Level 2b				Level 3				Total			
	n = 3				n = 3				n = 3				n = 6				n = 15			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Neutropenia	0	0	2	1	0	1	1	1	0	0	2	1	0	0	4	2	0	1	9	5
Leukopenia	0	0	3	0	0	1	2	0	0	2	1	0	1	1	3	1	1	4	9	1
Alopecia	3	0	NA	NA	1	2	NA	NA	0	2	NA	NA	2	4	NA	NA	6	8	NA	NA
Peripheral sensory neuropathy	1	0	1	0	0	2	1	0	0	2	0	0	3	3	0	0	4	7	2	0
Anemia	1	1	0	0	0	1	1	0	0	2	0	0	2	4	0	0	3	8	1	0
Diarrhea	1	1	0	0	2	0	1	0	1	1	0	0	3	2	0	0	7	4	1	0
Decreased appetite	2	0	0	0	1	1	0	0	1	1	1	0	4	1	0	0	8	3	1	0
Nausea	2	0	0	NA	2	0	0	NA	2	1	0	0	2	1	0	0	8	2	0	0
Stomatitis	2	0	0	0	2	0	0	0	0	2	0	0	4	0	0	0	8	2	0	0
Fatigue	1	0	0	NA	0	2	0	NA	1	1	1	NA	1	1	2	NA	3	4	3	NA
Dysgeusia	1	0	NA	NA	3	0	NA	NA	0	1	NA	NA	4	0	NA	NA	8	1	NA	NA
Skin hyperpigmentation	1	0	NA	NA	1	0	NA	NA	2	0	NA	NA	4	1	NA	NA	8	1	NA	NA
Dry skin	0	1	0	NA	0	1	0	NA	1	1	0	NA	4	0	0	NA	5	3	0	NA
ALT level increased	2	0	0	0	0	0	0	0	0	0	0	0	3	0	1	0	5	0	1	0
AST level increased	1	0	0	0	1	0	0	0	0	0	0	0	3	0	1	0	5	0	1	0
Myalgia	1	1	0	NA	1	0	0	NA	2	0	0	NA	1	0	0	NA	5	1	0	NA
Abdominal pain	0	0	0	NA	1	1	0	NA	0	2	0	NA	2	0	0	NA	3	3	0	NA
Peripheral edema	0	0	0	NA	1	1	0	NA	0	0	0	NA	2	2	0	NA	3	3	0	NA
Lymphopenia	0	0	0	0	0	0	2	0	0	1	0	0	0	2	1	0	0	3	3	0
Constipation	1	0	0	0	1	0	0	0	1	0	0	0	2	0	0	0	5	0	0	0
Thrombocytopenia	2	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	5	0	0	0
Watering of eyes increased	0	0	0	NA	0	0	0	NA	1	0	0	NA	4	0	0	NA	5	0	0	NA

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable

Table 3. Efficacy of combination therapy according to RECIST

Response	Level 1 (n = 2)	Level 2a (n = 3)	Level 2b (n = 3)	Level 3 (n = 4)	Total (n = 12)
CR	1	0	0	0	1
PR	0	2	0	3	5
SD	0	1	2	1	4
PD	1	0	0	0	1
NE	0	0	1	0	1
Response rate (CR+PR)	50.0%	66.7%	0.0%	75.0%	50.0% (95% CI, 21.1–78.9)
Disease control rate (CR+PR+SD for ≥16 weeks)	50.0%	100.0%	66.7%	100.0%	83.3% (95% CI, 51.6–97.9)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

Table 4. Plasma pharmacokinetic parameters for S-1 components and paclitaxel

Dose level	FT		5-FU		CDHP		Oxo		Paclitaxel	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Level 1 and 2a (n = 6)										
t_{max}, h	1.3	0.5	2.3	0.8	1.5	0.5	1.7	0.5	0.5	0.0
C_{max}, ng/mL	1901	310	148.9	65.0	417.0	69.9	53.51	77.41	4778	343
AUC_{0-t}, ng/h/mL	12 201	3119	695.4	276.3	1463	360	230.5	409.8	4583	479
AUC_{inf}, ng/h/mL	21 998	8800	718.6	271.7	1567	422	1217	NA	4806	490
$t_{1/2}$, h	8	1.8	1.6	0.5	2.5	0.2	3.4	NA	26.2	3.9
Level 2b and 3 (n = 6)										
t_{max}, h	1.3	0.5	2.3	0.8	1.2	0.4	1.7	0.5	0.5	0.0
C_{max}, ng/mL	2768	432	193.9	83.1	452.6	97.5	80.19	63.11	5689	1056
AUC_{0-t}, ng/h/mL	16 057	3697	903.5	310.4	1648	175	275.8	201.7	4876	1007
AUC_{inf}, ng/h/mL	29 732	12 675	933.7	300.9	1772	119	411.5	258.6	5087	1066
$t_{1/2}$, h	8.3	2.4	1.7	0.4	2.7	0.7	2.7	2.0	25.2	2.6

AUC, area under the curve; AUC_{inf}, AUC from time zero extrapolated to infinity; AUC_{0-t}, AUC from time zero to t; CDHP, 5-chloro-2.4-dihydrooxypyridine; C_{max}, maximum plasma concentration; FT, tegafur; 5-FU, 5-fluorouracil; NA, not applicable; Oxo, oteracil potassium; $t_{1/2}$, half-life time; t_{max}, maximum concentration time.

cantly longer duration than those in the corresponding monotherapy groups.[2,3] The incidence of hand–foot syndrome, oral mucositis, and diarrhea in the docetaxel–capecitabine combination therapy group and of neutropenia and febrile neutropenia in the paclitaxel–gemcitabine combination therapy group, nevertheless, tended to be higher when compared with the corresponding monotherapy groups.

Regarding the efficacy and safety in our clinical trial, the PFS of the *nab*-paclitaxel with S-1 combination therapy was longer than the *nab*-paclitaxel monotherapy (21.0 and 12.9 months, respectively), and the therapy was feasible, with manageable toxicities. Neutropenia was seen as a notable adverse event with the present combination therapy when compared with *nab*-paclitaxel or S-1 monotherapy.[6,9] Grade 4 neutropenia occurred in 33.3% (n = 5) of patients in the present study. Delayed initiation of the next cycle because of neutropenia was rather common; however, no patients were discontinued from the study because of neutropenia, none developed febrile neutropenia, and only two patients required granulocyte colony-stimulating factor administration. Therefore, the adverse reactions were clinically controllable. None of the other noted toxicities constituted any noticeable add-on when compared with the toxicities in either corresponding monotherapy group, although grade 1 or 2 mild toxicities occurred relatively frequently. Grade ≥3 toxicities were uncommon and the TTF and PFS were also longer when compared with those in either corresponding historical monotherapy group, thus allowing the continuation of long-term treatment. Discrepancy between PFS and TTF was seen in this study; one of the reasons is considered to be that nine patients were censored in PFS because post-discontinuation treatment was initiated before disease progression had occurred.

The appropriateness of combination versus sequential monotherapy was discussed in the 1st International Consensus Guidelines for Advanced Breast Cancer and developed at the Consensus Conference on Metastatic/Recurrent Breast Cancer.[17] Although sequential single-agent chemotherapy was recommended for the treatment of MBC, it was agreed that combination chemotherapy might also be included among the options in cases requiring the urgent control of disease progression, such as a life-threatening case of visceral metastasis. Likewise, combination chemotherapy should be considered as an option when a rapid and significant response is required, according to the European Society for Medical Oncology guidelines.[18] Inasmuch as gratifying results were obtained with the combination chemotherapy in our present study in a case with multiple hepatic metastases and another with triple-negative disease and an otherwise poor prognosis, the applicability of this regimen in similar subpopulations would be anticipated. It is also important to identify populations in which this combination therapy is effective. Regarding *nab*-paclitaxel, SPARC (secreted protein, acidic and rich in cysteine, also known as osteonectin, BM40) is expected to be a valuable biomarker, and further investigation into this protein as a therapeutic response-predicting factor is needed.[19]

Although Level 3 was set as the RD in this study based on the importance of the patients' quality of life during chemotherapy for MBC, it may be appropriate to adjust the medicinal dosage and administration schedule according to each patient's

condition in the clinical practice setting. As the non-inferiority of S-1 to taxanes in terms of overall survival was verified in the SELECT BC study, a flexible approach that begins with combined *nab*-paclitaxel and S-1 therapy and then shifts to maintenance therapy with S-1 monotherapy after attaining control of the tumor size and symptoms might be proven valid.[11]

We also evaluated the pharmacokinetics of combination therapy with *nab*-paclitaxel and S-1. To compare our findings with previously reported data, we reanalyzed the $AUC_{0-10\ h}$ from a phase I study.[20] There was no significant difference between the administration of S-1 alone and in combination with 100 mg /m^2 *nab*-paclitaxel in terms of the C_{max} and $AUC_{0-10\ h}$ of 5-FU, which is considered a relevant compound with respect to the efficacy and safety of S-1. However, the C_{max} of FT or CDHP was significantly increased in comparison with data from a previous report.[20] An additional pharmacokinetic study should be carried out to evaluate the pharmacokinetic parameters of combination therapy with *nab*-paclitaxel and S-1. When compared with the mean total clearance (18.6–24.8 L/h/m^2) and mean volume of the terminal phase (527–935 L/m^2) for paclitaxel in Japanese patients following the administration of *nab*-paclitaxel alone (80–300 mg/m^2), there were no obvious differences between those results and the results of this study.[21,22]

In conclusion, the present data shows the feasibility of a combination therapy with weekly *nab*-paclitaxel and S-1 and the possibility of long-term administration of this regimen, suggesting that this combination may be a promising therapy for HER2-negative MBC. Further investigation regarding the long-term safety and efficacy in phase II and ensuing studies is needed.

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Disclosure Statement

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References

1 Cardoso F, Bedard PL, Winer EP *et al.* International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. *J Natl Cancer Inst* 2009; **101**: 1174–81.
2 O'Shaughnessy J, Miles D, Vukelja S *et al.* Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002; **20**: 2812–23.
3 Albain KS, Nag SM, Calderillo-Ruiz G *et al.* Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol* 2008; **26**: 3950–7.
4 Gradishar WJ. Albumin-bound paclitaxel: a next-generation taxane. *Expert Opin Pharmacother* 2006; **7**: 1041–53.
5 Gradishar WJ, Tjulandin S, Davidson N *et al.* Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil–based paclitaxel in women with breast cancer. *J Clin Oncol* 2005; **23**: 7794–803.
6 Gradishar WJ, Krasnojon D, Cheporov S *et al.* Significantly longer progression-free survival with *nab*-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol* 2009; **27**: 3611–9.
7 Gradishar WJ, Krasnojon D, Cheporov S *et al.* Phase II trial of *nab*-paclitaxel compared with docetaxel as first-line chemotherapy in patients with metastatic breast cancer: final analysis of overall survival. *Clin Breast Cancer* 2012; **12**: 313–21.
8 Shirasaka T, Shimamato Y, Ohshimo H *et al.* Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 1996; **7**: 548–57.
9 Saeki T, Takashima S, Sano M *et al.* A phase II study of S-1 in patients with metastatic breast cancer–a Japanese trial by the S-1 Cooperative Study Group, Breast Cancer Working Group. *Breast Cancer* 2004; **11**: 194–202.
10 Mukai H, Takashima T, Hozumi Y *et al.* Randomized study of taxane versus TS-1 in women with metastatic or recurrent breast cancer (SELECT BC). *Jpn J Clin Oncol* 2010; **40**: 811–4.
11 Hara F, Matsubara N, Saito T *et al.* Randomized phase III study of taxane versus TS-1 as first-line treatment for metastatic breast cancer (SELECT BC). *J Clin Oncol* 2014; **32**: 1012.
12 Puglisi F, Andreetta C, Valent F *et al.* Anthracyclines and taxanes induce the upregulation of thymidine phosphorylase in breast cancer cells. *Anticancer Drugs* 2007; **18**: 883–8.
13 Nukatsuka M, Fujioka A, Nakagawa F *et al.* Antimetastatic and anticancer activity of S-1, a new oraldihydropyrimidine-dehydrogenase-inhibiting fluoropyrimidine, alone and in combination with paclitaxel in an orthotopically implanted human breast cancer model. *Int J Oncol* 2004; **25**: 1531–6.
14 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
15 Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; **317**: 1098.
16 Fujimoto S, Watanabe T, Sakamoto A, Yukawa K, Morimoto K. Studies on the physical surface area of Japanese. 18. Calculation formulae in three stages over all ages. *Nippon Eiseigaku Zasshi* 1968; **23**: 443–50.
17 Cardoso F, Costa A, Norton L *et al.* 1st International consensus guidelines for advanced breast cancer (ABC 1). *Breast* 2012; **21**: 242–52.
18 Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23**: vii11–9.
19 Desai N, Trieu V, Yao Z *et al.* Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of Cremophor-free, albumin-bound paclitaxel, ABI-007, compared with Cremophor-based paclitaxel. *Clin Cancer Res* 2006; **12**: 1317–24.
20 Hirata K, Horikoshi N, Aiba K *et al.* Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. *Clin Cancer Res* 1999; **5**: 2000–5.
21 Yamada K, Yamamoto N, Yamada Y, Mukohara T, Minami H, Tamura T. Phase I and pharmacokinetic study of ABI-007, albumin-bound paclitaxel, administered every 3 weeks in Japanese patients with solid tumors. *Jpn J Clin Oncol* 2010; **40**: 404–11.
22 Ando M, Yonemori K, Katsumata N *et al.* Phase I and pharmacokinetic study of *nab*-paclitaxel, nanoparticle albumin-bound paclitaxel, administered weekly to Japanese patients with solid tumors and metastatic breast cancer. *Cancer Chemother Pharmacol* 2012; **69**: 457–65.

Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Dose interruption criteria within treatment cycle.

Table S2. Dose reduction criteria for *nab*-paclitaxel and S-1.

Table S3. Dose reduction schema for *nab*-paclitaxel and S-1.