expression of multiple RTKs. This phenomenon may influence the selection of targeted therapies to prevent the development of drug resistance or primary treatment failure. Our results may be useful for selecting the most suitable patients for each targeted therapy.

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ORIGINAL ARTICLE

Phase I dose-escalation and pharmacokinetic study (TED 11576) of cabazitaxel in Japanese patients with castration-resistant prostate cancer

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Abstract
Purpose The purpose of the study is to analyze the pharmacokinetic (PK) profile of cabazitaxel and evaluate its safety and tolerability as a 1-h IV infusion every 3 weeks in Japanese patients with castration-resistant prostate cancer (CRPC).
Methods Seventeen patients were treated with cabazitaxel at doses of 20 and 25 mg/m^2 for PK analyses. Dose escalation was performed only in the absence of dose-limiting toxicity (DLT). The maximum tolerated dose (MTD) was the highest dose at which less than 33 % of the patients developed DLT.
Results Cabazitaxel exhibited a triphasic elimination profile with a long terminal half-life of 116 ± 29.0 or 113 ± 28.0 h after IV infusion of 20 or 25 mg/m^2 cabazitaxel, respectively. The major differences in the PK parameters of cabazitaxel and docetaxel were cabazitaxel's fairly high clearance rate, representing approximately half the hepatic flow, and its large volume of distribution at steady-state conditions. No DLT was observed during Cycle 1. Mild-to-moderate hematological adverse events (AEs), including neutropenia, and other AEs typically associated with taxanes were observed; all AEs were manageable. Cabazitaxel at 25 mg/m^2 every 3 weeks was selected as the MTD in Japanese patients.
Conclusions The PK parameters of cabazitaxel in Japanese CRPC patients were comparable with those previously determined in Caucasian subjects. The safety and tolerability of cabazitaxel were also comparable in both ethnic populations.

Keywords Cabazitaxel · Chemotherapy · Pharmacokinetics · Castration-resistant prostate cancer · Taxanes

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Introduction

Prostate cancer (PC) is the second most frequently diagnosed male malignancy and the sixth most common cause of cancer death in Japan, and the number of PC patient is estimated to increase further [1]. The therapeutic options for metastatic PC are commonly androgen ablation by bilateral orchiectomy, radiation, anti-prostatic cancer drugs such as luteinizing hormone-releasing hormone (LHRH) receptor agonists and androgen receptor antagonists and the combination of these therapies [2]. However, often,

long-term metastatic PC management cannot be achieved with these therapies, and the disease may eventually recur in most patients, leading to the development of CRPC [3, 4].

Cabazitaxel is a novel semi-synthetic drug of natural taxane that promotes the assembly of tubulin and stabilizes microtubules [5]. Cabazitaxel has a variety of antitumor efficacies in various animal tumor models, including PC and docetaxel-resistant tumors [6]. Cabazitaxel is mainly bound to human serum albumin and lipoproteins [7]. Cabazitaxel is principally metabolized in the liver through the cytochrome P450 3A4/5 isoenzyme [7] and is mainly excreted in feces as numerous metabolites [8].

The results of two previous global phase I studies (TED 6188 [9] and TED 6190 [10]) suggested that exposure to cabazitaxel increased in a dose-dependent manner over the dosing range of 10–30 mg/m^2 when cabazitaxel was administered as a 1-h IV infusion every 3 weeks to Caucasian patients with CRPC. In these studies, cabazitaxel had a triphasic elimination profile, including a long terminal half-life (mean gamma half-life [$t_{1/2}$] = 62–77 h), a high clearance (27.3–44.7 L/h/m^2), and a large volume of distribution at steady state (mean 2,034–2,484 L/m^2).

A phase 3 study indicated that cabazitaxel had a 2.4-month survival benefit in patients with CRPC previously treated with docetaxel, affording survival for 15.1 months, compared with the 12.7-month survival in the mitoxantrone group [11]. In this study, the hazard ratio for death in men treated with cabazitaxel plus prednisone compared with that in men treated with mitoxantrone and prednisone was 0.70 (95 % CI 0.59–0.83, $p < 0.0001$). Cabazitaxel is one of the few drugs that increase the survival time during or after docetaxel therapy. As a first step toward assessing whether it could provide similar benefits in Japanese patients, we examined the PK profile and tolerability of cabazitaxel in Japanese CRPC patients. The primary objective of this study (TED 11576) was to assess the tolerability of cabazitaxel at 20 mg/m^2 and 25 mg/m^2 and to determine the MTD in Japanese CRPC patients treated with a 1-h IV infusion every 3 weeks. The secondary objectives were to evaluate the PK and safety profiles of cabazitaxel in these patients.

Methods

The study protocol was approved by the ethics committee of our institution and was conducted in accordance with the principles of the Declaration of Helsinki (18th World Medical Assembly, Helsinki, 1964) and all applicable amendments laid down by the WMA and the International Conference on Harmonisation guidelines for Good Clinical Practice.

Prior to participation in this clinical trial, written informed consent was obtained from each patient after all medical information was shared and explained in a discussion between the patient and the investigator.

Eligibility criteria

Patients who had not undergone surgery for >4 weeks prior to registration for the study and fulfilled the following eligibility criteria were included: histologically or cytologically proven prostate adenocarcinoma was refractory to hormone therapy (prior castration by orchiectomy and/or chemical castration and documented progression of disease or relapse) or docetaxel, age between 20 and 74 years, a life expectancy of ≥12 weeks, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2. Patients with a serum creatinine level of >1.5 mg/dL, compromised liver function (serum bilirubin/alanine transaminase [ALT]/aspartate transaminase [AST] level of >1.5 times the upper normal limit of the institutional norm), neutrophil count of <2.0 × 10^9/L, platelet count of <100 × 10^9/L, or hemoglobin level of <9.0 g/dL were not eligible. Patients were excluded if they had known brain or leptomeningeal involvement, previously undergone extensive radiotherapy, peripheral neuropathy of ≥grade 2 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [12], other serious diseases including congestive heart failure, angina pectoris, myocardial infarction within 1 year from the time of study registration, uncontrolled hypertension or arrhythmias, significant neurologic or psychiatric disorders such as dementia and seizures, active infections, uncontrolled peptic ulcer, unstable diabetic mellitus, or other contraindications for the use of corticosteroids. Patients with active secondary cancer, those undergoing concurrent treatment with another anticancer chemotherapeutic regimen, or those receiving radiotherapy within 28 days prior to patient registration were also excluded. Patients previously treated with a cumulative docetaxel dose of <225 mg/m^2 were also excluded. Patients with a severe immune deficiency, including an AIDS-related illness or active varicella zoster infection, or who were positive for the anti-HCV antibody were not eligible. Patients with a history of a severe hypersensitivity reaction or intolerance to prednisolone, a severe allergic reaction to a taxane, a severe hypersensitivity reaction (≥grade 3) to drugs containing polysorbate 80, or alcoholic hypersensitivity were ineligible.

Study design

This was a phase I, open-label, dose-escalation, safety, and PK study of cabazitaxel administered as a 1-h IV infusion

every 3 weeks to patients with CRPC. The planned dose levels were 20 and 25 mg/m^2. Three patients were treated with cabazitaxel at the initial dose of 20 mg/m^2 and were assessed for dose-limiting toxicity (DLT, see below) in Cycle 1. If none of the 3 patients developed any DLT in Cycle 1, the dose was escalated to 25 mg/m^2. If one of the 3 patients developed DLT, 3 additional patients were enrolled to receive a dose of 20 mg/m^2, and the safety profiles were evaluated for all 6 patients. If no more than one of 6 patients developed DLT, the dose was escalated to 25 mg/m^2. At a dose of 25 mg/m^2, if none of the 3 patients developed any DLT in Cycle 1, this dose was designated the MTD, and no further dose escalation was conducted in this study. If one of the 3 patients developed DLT, 3 additional patients were enrolled to receive the dose of 25 mg/m^2. If no more than one of the 6 patients developed DLT, this dose was designated as the MTD. If 2 or more of the 6 patients developed any DLT at the dose of 25 mg/m^2 in Cycle 1, 20 mg/m^2 was designated as the MTD, and 25 mg/m^2 was designated as the maximum administered dose (MAD). Then, the safety profile of cabazitaxel was evaluated in more detail in additional patients registered at the MTD, and PK was evaluated only in 10 patients of this expansion cohort.

Definition of DLT

To qualify as DLT, clinical events or laboratory abnormalities had to be cabazitaxel related, as assessed by the investigator. DLT was defined as any of the following events: (1) hematologic toxicity (grade 4) including neutropenia (neutrophil count of <500/μL for >7 days), thrombocytopenia (platelet count of <25,000/μL), and febrile neutropenia (grade 4) and (2) non-hematologic toxicity (grade 3 or 4) excluding the following grade 3 toxicities that are manageable with appropriate treatment: nausea, vomiting, and diarrhea and excluding the following grade 3 toxicities: hypersensitivity, fatigue, and hyponatremia. If a patient was withdrawn from this study during the first cycle because of the following reasons, the patient was not evaluated for DLT and a substitute patient was enrolled to receive the same dose: (1) withdrawal of consent or refusal to undergo any necessary tests defined in this study protocol; (2) judged not to be evaluable for DLT because of protocol deviation(s) and (3) development of adverse events (AEs) that were clearly judged to be unrelated to the study treatments. All dose escalations were conducted in agreement between the investigators and the sponsor.

Safety assessments

The safety profiles were assessed from the findings of physical examinations and laboratory tests and based on incidence severity (as graded by the NCI CTCAE version 4.0) and cumulative treatment-emergent adverse events (TEAEs). For this study, the on-treatment period was defined as the period from the time of the first administration of cabazitaxel up to 30 days after the last administration of cabazitaxel. Performance status (ECOG scale), physical examination findings including weight, height, vital signs (body temperature, blood pressure, and heart rate), electrocardiogram (ECG) data, and the results of hematological tests, biochemical tests, and urinalysis were assessed at predetermined times. AEs were evaluated according to MedDRA version 15.1.

PK sampling and assay

For PK evaluation, blood samples (2 mL each) were collected on Day 1 of Cycle 1 immediately before drug infusion and before the end of infusion and then at the following time points after the end of cabazitaxel infusion: 5 min, 15 min, 30 min, 1 h, 3 h, 5 h, 8 h, on Day 2 (approximately 24 h), on Day 3 (approximately 48 h), on Day 4 (approximately 72 h), on Day 6 (approximately 120 h), on Day 8 (approximately 168 h), and on Day 10 (approximately 216 h). All these samples were taken before starting infusion for Cycle 2. The allowance of the sampling time points was ±2 min for just before the end of the cabazitaxel infusion; 5, 15, and 30 min after the end of infusion; and ±5 min for the subsequent sampling points. Each blood sample was collected into a lithium-heparin Vacutainer™ blood collection tube and kept on ice until plasma preparation within 30 min of the sampling time by centrifugation at 4 °C for approximately 10 min. Each plasma sample was transferred into a polypropylene tube and stored at −20 °C until analysis. Concentrations of cabazitaxel in plasma were determined using a validated liquid chromatography-tandem mass spectrometry method. The limit of quantification was 1 ng/mL.

PK analysis

Non-compartmental PK analysis was performed using the WinNonlin 5.2.1 software (Scientific Consulting, Inc.) for pertinent PK variables. The maximal concentration (C_{max}) of cabazitaxel, total area under the concentration versus time curve (AUC), AUC from 0 to 48 h (AUC_{0-48}), elimination half-life ($t_{1/2\gamma}$), total body clearance (CL), and volume of distribution (V_{ss}) were determined. In addition, compartmental PK analysis (3-compartment open model with a first-order elimination rate and a weighting of $1/\gamma^2_{pred}$) was also carried out to compare the AUC, $t_{1/2\gamma}$, CL and V_{ss} with those of the previous studies.

Table 1 Summary of baseline and demographic characteristics

	Dose level (mg/m^2)		All (N = 17)
	20 (N = 4)	25 (N = 13)	
Age (years)			
Mean (SD)	69.5 (2.4)	62.0 (8.1)	63.8 (7.8)
Median (Min–Max)	70.5 (66–71)	62.0 (50–74)	66.0 (50–74)
Age group (years) [*n* (%)]			
−64	0	8 (61.5 %)	8 (47.1 %)
65–74	4 (100 %)	5 (38.5 %)	9 (52.9 %)
Weight (kg)			
Mean (SD)	64.18 (11.53)	66.52 (10.17)	65.97 (10.17)
Median (Min–Max)	67.70 (48.0–73.3)	63.20 (56.5–96.1)	63.50 (48.0–96.1)
BSA (m^2)			
Mean (SD)	1.684 (0.188)	1.768 (0.158)	1.748 (0.163)
Median (Min–Max)	1.741 (1.42–1.83)	1.737 (1.57–2.15)	1.737 (1.42–2.15)
Performance status (ECOG) [n (%)]			
0	2 (50.0 %)	9 (69.2 %)	11 (64.7 %)
1	2 (50.0 %)	4 (30.8 %)	6 (35.3 %)
Baseline PSA (ng/mL)			
Mean (SD)	217.590 (327.709)	739.375 (1,982.138)	616.602 (1737.481)
Median (Min–Max)	85.220 (2.82–697.10)	144.910 (31.73–7311.00)	144.910 (2.82–7311.00)
Number of lines of chemotherapy[a]			
Median (Min–Max)	1.5 (1–2)	1.0 (1–9)	1.0 (1–9)

[a] Number of prior chemotherapy regimens excluding neoadjuvant and adjuvant therapy

Results

Patient characteristics

A total of 17 patients were included in this phase I trial. In Cycle 1, one patient developed treatment-unrelated AEs and DLT evaluation for this patient was not possible. An additional patient was therefore enrolled. The demographic characteristics of the study participants are presented in Table 1. All 17 patients were assessed for safety (AEs and laboratory tests) and PK parameters. Seven patients were included in the dose-escalation cohort (4 at 20 mg/m^2, 3 at 25 mg/m^2), and 10 patients were included in the expansion cohort. Their ages ranged from 50 to 74 years (median, 66.0 years). All patients were Japanese. Their ECOG performance statuses were 0 and 1. Their base line PSA values ranged from 2.82 to 7311.00 ng/mL (median 144.910 ng/mL). All patients had at least one prior docetaxel regimen.

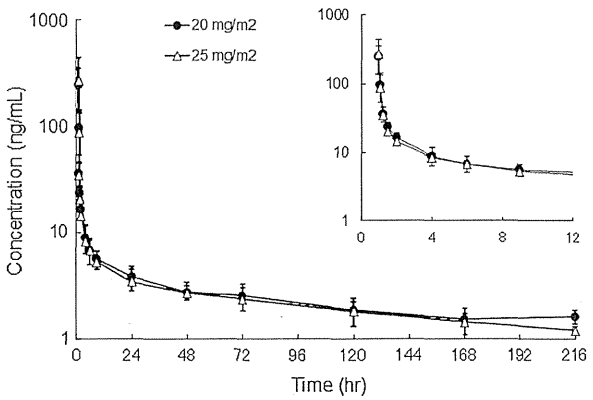

Fig. 1 Plasma concentration versus time curve in Japanese patients with CRPC after 1-h IV infusion of 20 or 25 mg/m^2 cabazitaxel in Cycle 1. Each point and bar represents a mean ± SD. *Filled circle* 20 mg/m^2, *open triangle* 25 mg/m^2. N = 4 for 20 mg/m^2, N = 13 for 25 mg/m^2. *CRPC* castration-resistant prostate cancer

Pharmacokinetics

The plasma concentration–time curve for cabazitaxel is shown in Fig. 1. The decrease in plasma cabazitaxel concentration was best described by a triphasic model. The PK behavior in plasma was characterized by a rapid initial phase with a half-life of 0.0466 ± 0.0149 h and 0.0569 ± 0.0220 h following dosage of 20 and 25 mg/m^2, respectively, followed by an intermediate phase with a half-life of 1.46 ± 0.421 h and 1.70 ± 0.657 h, and a prolonged terminal phase with a half-life of 116 ± 29.0 h and 113 ± 28.0 h.

Pertinent PK parameters are shown in Table 2A. C_{max} values were 247 ± 107 ng/mL for 20 mg/m^2 and 271 ± 170 ng/mL for 25 mg/m^2. AUC_{0-48} values were

Table 2 PK variables of cabazitaxel

Study	Dose (mg/m^2)	N	C_{max}* (ng/mL)	AUC_{0-48}* (ng h/mL)	AUC** (ng h/mL)	$t_{1/2\gamma}$** (h)	CL/BSA** (L/h/m^2)	V_{ss}/BSA** (L/m^2)
			Mean ± SD (Geometric mean) [CV %]					
A. Japanese patients included in the present study								
TED 11576	20	4	247 ± 107 (227) [43.4]	405 ± 73.6 (401) [18.2][a]	1040 ± 272 (1,020) [26.1][a]	116 ± 29.0 (114) [25.0][a]	20.2 ± 6.20 (19.6) [30.7][a]	2,960 ± NC (2,950) [NC][a]
	25	13	271 ± 170 (223) [62.8]	377 ± 129 (357) [34.2]	926 ± 215 (902) [23.3][b]	113 ± 28.0 (110) [24.7][b]	28.0 ± 5.71 (27.7) [25.0][b]	3,450 ± 1,280 (3,240) [37.2][b]
B. Caucasian patients included in previous studies								
TED 6188	20	7	118 [16]	228 [11]	382 [29]	48.5 [41]	55.7 [23]	2,440 [18]
	25	6	242 [65]	354 [39]	678 [41]	66.9 [43]	40.6 [26]	2,570 [45]
TED 6190	20	15	222 [93]	373 [42]	756 [41]	94.3 [58]	30.2 [40]	2,608 [65]
	25	5	535 [57]	642 [50]	1,038 [29]	81.9 [51]	25.0 [22]	1,985 [81]

[a] $n = 3$, [b] $n = 12$; * Non-compartmental analysis; ** Compartmental analysis (3 compartment IV-infusion model with a $1/Y^2_{pred}$ weighting)

TED 11576: present study, *PK* pharmacokinetic

* Non-compartmental analysis; ** Compartmental analysis (3 compartment IV-infusion model with a $1/Y^2_{pred}$ weighting)

TED 6188 [9], TED 6190 [10]

405 ± 73.6 ng h/mL for 20 mg/m^2 and 377 ± 129 ng/mL for 25 mg/m^2. AUC values were 1,040 ± 272 ng h/mL for 20 mg/m^2 and 926 ± 215 ng h/mL for 25 mg/m^2. The V_{ss} values for cabazitaxel were very large, with a mean of 2,960 L/m^2 for 20 mg/m^2 and 3,450 ± 1,280 L/m^2 for 25 mg/m^2. Plasma Clearance (CL) was also high with a mean of 20.2 ± 6.20 L/h/m^2 for 20 mg/m^2 and 28.0 ± 5.71 L/h/m^2 for 25 mg/m^2. Inter-patient variability was moderate and estimated at 43.4 % for C_{max}, 18.2 % for AUC_{-48}, 26.1 % for AUC, 25.0 % for $t_{1/2\gamma}$, and 30.7 % for CL at a dose of 20 mg/m^2. Variability was 62.8 % for C_{max}, 34.2 % of AUC_{0-48}, 19.2 % for AUC, 38.9 % for $t_{1/2Z}$ 20.4 % for CL, and 37.2 % for V_{ss} at the dosage of 25 mg/m^2.

Two previous studies where PK analyses were performed in Caucasian patients adopted essentially the same administration protocol as this study. These data are presented in Table 2B and Fig. 2, showing that the plasma concentration–time curve in Japanese patients was similar to those in Caucasian patients. Other PK variables, including C_{max}, AUC_{0-48}, AUC, $t_{1/2}$, CL, and V_{ss}, were also within similar ranges (Table 2A versus B). For clarity, the C_{max} and AUC data are graphically presented in Fig. 3. Although there is variability in the data obtained from these patient populations, the values obtained from these three studies were within the same range and can be considered to be comparable.

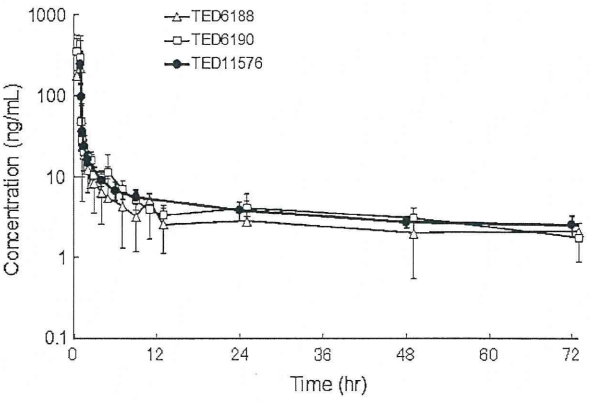

Fig. 2 Plasma concentration versus time curve in Japanese and Caucasian patients with CRPC after 1-h IV infusion of cabazitaxel at 25 mg/m^2. Each point and bar represents a mean ± SD. *Open triangle* Caucasian (TED 6188) [9], *open square* Caucasian (TED 6190) [10], *filled circle* Japanese (TED 11576) [present study]. N = 6 for TED 6188, N = 5 for TED 6190, N = 13 for TED 11576. *CRPC* castration-resistant prostate cancer

Safety and tolerability

One patient treated at the 20 mg/m^2 level was subsequently determined to be ineligible for DLT determination due to a spinal compression fracture, which was unrelated to the drug therapy. This patient was replaced by another patient for DLT determination. No DLT was observed at 20 mg/m^2 or at 25, and 25 mg/m^2 was therefore selected as the MTD in Japanese patients. No DLT was observed in 10 additional patients administered 25 mg/m^2 in the expansion cohort.

All 17 patients developed TEAEs. Table 3 summarizes TEAEs of grade 3 or 4 observed in Cycle 1. All patients had at least one any grade and grade 3–4 TEAEs. Common TEAEs at MTD (25 mg/m^2) were neutropenia in 13 patients (100 %), decreased white blood cell count in 6 patients (46.2 %), nausea in 5 patients (38.5 %),

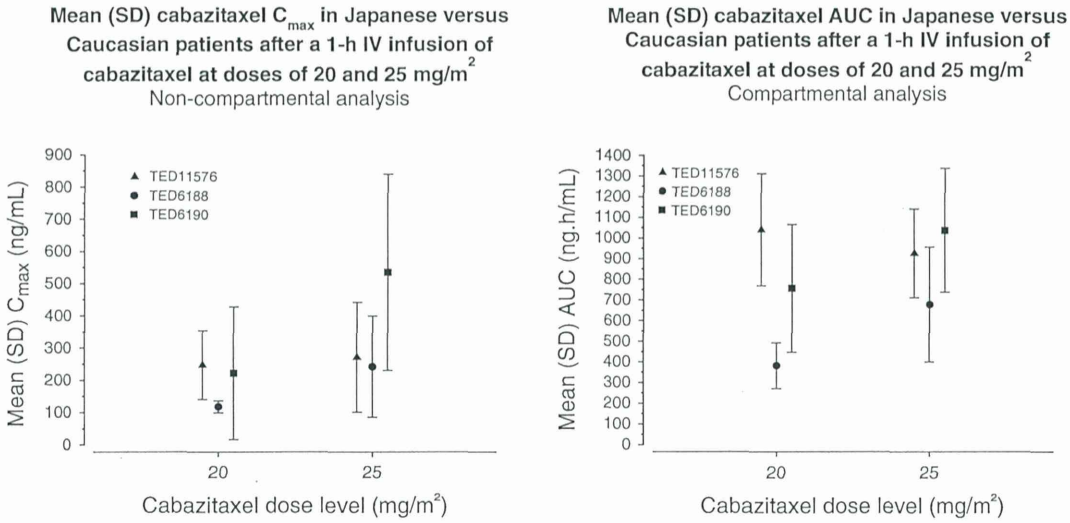

Fig. 3 C_{max} and AUC in Japanese and Caucasian patients with CRPC after 1-h IV infusion of cabazitaxel at 20 and 25 mg/m^2. Each point and bar represents a mean ± SD. *Filled triangle* Japanese (TED 11576) [present study], *filled circle* Caucasian (TED 6188) [9], *filled square* Caucasian (TED 6190) [10]. At 20 mg/m^2: N = 4 for TED 11576, N = 7 for TED 6188, N = 10 for TED 6190. At 25 mg/m^2: N = 13 for TED 11576, N = 6 for TED 6188, N = 5 for TED 6190. *CRPC* castration-resistant prostate cancer

decreased appetite in 4 patients (30.8 %), febrile neutropenia, and anemia, insomnia, and fatigue in 3 patients each (23.1 %).

One serious AE was reported during Cycle 1, where spinal fracture was detected in one patient at the 20 mg/m^2 dosage level. This patient developed lower limb muscle weakness on Day 2 of Cycle 1, and was diagnosed with Grade 3 spinal fracture. The event was considered to be due to bone metastasis of the primary disease. The patient was considered ineligible for DLT evaluation, due to radiation therapy and corticosteroid administration received for this condition. No fatal AEs were observed during Cycle 1.

Laboratory abnormalities observed in Cycle 1 are summarized in the lower part of Table 3. Anemia developed in all patients, most of which were mild to moderate, and severity reached grade 3/4 in 1 patient. Decreased platelet counts were observed in 25 % of patients treated with 20 mg/m^2 and 38.5 % of those treated with 25 mg/m^2, but they were all grade 1/2 low grade. Lymphocyte counts decreased in all patients at 20 mg/m^2 and in 46.2 % of patients at 25 mg/m^2, but only one patient in each treatment group showed grade 3/4 reduction. White blood cell counts decreased in all patients, 75 and 84.6 % of which showed grade 3/4 reduction. Neutrophil counts decreased with grade 3/4 severity in all patients, except for 1 patient at 20 mg/m^2. Alkaline phosphatase levels increased in half the patients, but most were grade 1/2 mild to moderate, except for 1 patient at 20 mg/m^2 and 2 patients at 25 mg/m^2 (both grade 3/4).

Discussion

The present study evaluated the PK profile, safety, and tolerability of cabazitaxel in Japanese patients with CRPC. The PK profile was evaluated at two dose levels, 20 and 25 mg/m^2, after IV infusion of cabazitaxel. The plasma concentration of cabazitaxel was highest immediately after infusion and declined thereafter, as expected for IV-administered drugs. The elimination profile was triphasic, with a rapid initial phase, an intermediate phase, and a long terminal phase. Cabazitaxel exhibited a rather high clearance, representing approximately half of the hepatic flow, and a large V_{ss}. Cabazitaxel is principally metabolized in the liver through the cytochrome P450 3A4/5 isoenzyme [7], suggesting that liver metabolism plays a major role in the rapid clearance of cabazitaxel. The large V_{ss} suggested that a significant portion of cabazitaxel was distributed outside the blood which is consistent with the fact that cabazitaxel is lipophilic. Further data analysis using a Population PK approach (pooling data from Phase 1, 2 and 3 with a 3-compartment structural kinetic model with first-order elimination from the central compartment) showed the presence of a deep peripheral compartment in slow equilibrium with the central compartment which largely contributed to the V_{ss} and was responsible for the long elimination half-life [13].

Our results obtained in Japanese patients were generally consistent with previous reports of cabazitaxel PK in Caucasian patients. The plasma concentration–time curve of cabazitaxel was similar between Japanese and

Table 3 TEAEs and laboratory abnormalities during Cycle 1

Preferred term	20 mg/m^2 (4 patients)		25 mg/m^2 (13 patients)	
	All grades	Grades 3, 4	All grades	Grades 3, 4
	N (%)[a]			
Any class	4 (100)	4 (100)	13 (100)	13 (100)
Neutropenia	3 (75.0)	3 (75.0)	13 (100)	13 (100)
Febrile neutropenia	2 (50.0)	2 (50.0)	3 (23.1)	3 (23.1)
Anemia	1 (25.0)	0	3 (23.1)	1 (7.7)
Decreased appetite	2 (50.0)	0	4 (30.8)	0
Insomnia	0	0	3 (23.1)	0
Nausea	1 (25.0)	0	5 (38.5)	0
Diarrhea	0	0	2 (15.4)	0
Constipation	1 (25.0)	0	2 (15.4)	0
Fatigue	2 (50.0)	0	3 (23.1)	0
White blood cell count decreased	2 (50.0)	2 (50.0)	6 (46.2)	6 (46.2)
Laboratory abnormalities[b]	N/N1 (%)[c]			
Anemia	4/4 (100)	0/4	13/13 (100)	1/13 (7.7)
Platelet count decreased	1/4 (25.0)	0/4	5/13 (38.5)	0/13
White blood cell count decreased	4/4 (100)	3/4 (75.0)	13/13 (100)	11/13 (84.6)
Neutrophil count decreased	4/4 (100)	3/4 (75.0)	13/13 (100)	13/13 (100)
Lymphocyte count decreased	4/4 (100)	1/4 (25.0)	6/13 (46.2)	1/13 (7.7)
ALP increased	2/4 (50.0)	1/4 (25.0)	7/13 (53.8)	2/13 (15.4)
Hyponatremia	2/4 (50.0)	1/4 (25.0)	6/13 (46.2)	0/13

TEAE: Treatment-emergent adverse event

Number (%) of patients with TEAE(s) during Cycle 1 (worst grade by patient) (Grades 3, 4 incidence in any treatment group) and number of patients with on-treatment abnormalities during Cycle 1 (worst grade per patient) are summarized

All-grade TEAEs reported in more than 2 subjects at a dose of 25 mg/m^2 are summarized

[a] Number (%) of patients with at least 1 TEAE

[b] Laboratory abnormalities during the on-treatment period (from the first dose to 30 days after the last dose) were graded using NCI CTC version 4.0

[c] % calculated using the number of patients with at least one event (N) over the number of patients assessed for each parameter (N1) during Cycle 1

Caucasian patients, suggesting similar PK in both groups of patients. Although there was variability between patients, all pertinent PK variables in the Japanese patients were in the same range as those in Caucasian patients (Table 2; Fig. 3). Cabazitaxel PK in Japanese patients were also comparable with the results of population PK of cabazitaxel in patients with advanced solid tumors. In this population PK analysis of 107 patients from five Phase I-III studies receiving 10–30 mg/m^2 of cabazitaxel, terminal half-life was 134 h, clearance was 24.2 L/h/m^2, and volume of distribution was 3,360 L/m^2 [13]. Overall, the pharmacokinetics of cabazitaxel in Japanese patients with hormone-refractory metastatic prostate cancer were consistent with those estimated in patients with advanced solid tumors in previous Phase I-III studies and in Caucasian patients with hormone-refractory metastatic prostate cancer.

The tolerability of 20 and 25 mg/m^2 cabazitaxel in Japanese patients was assessed by examining the occurrence of DLT in Cycle 1. No DLT was observed at either dose in the dose-escalation cohort, and 25 mg/m^2 cabazitaxel as a 1-h IV infusion every 3 weeks was therefore selected as the MTD in Japanese patients. This conclusion was supported by the absence of DLT in the 10 additional patients of the expansion cohort who were treated with 25 mg/m^2 cabazitaxel.

The safety profile of cabazitaxel was evaluated during Cycle 1 in 4 patients who received 20 mg/m^2 and 13 patients who received 25 mg/m^2. The common toxicities observed in Cycle 1 were hematological and gastrointestinal disorders. Frequently reported hematological TEAEs were neutropenia and decreases in white blood cell counts. Prophylactic granulocyte colony-stimulating factor was not allowed during the first cycle likely contributing to the

febrile neutropenia rate observed in 23.1 % of the patients at the 25 mg/m^2 dose, but all patients were able to continue with the study treatment. Other hematological abnormalities such as anemia and decreased platelet and lymphocyte counts were reported, but most were of low grade. Gastrointestinal toxicities such as nausea, diarrhea, and constipation were observed, but no grade 3 or 4 events were reported. The overall safety profile in Japanese patients was consistent with those reported in previous clinical studies [9, 10]. No toxicities specific to Japanese patients were identified in this study.

In summary, cabazitaxel exhibited a triphasic elimination profile with a long terminal half-life in Japanese patients with CRPC. Cabazitaxel showed a rather high clearance representing approximately half of the hepatic blood flow and a large V_{ss}. The PK parameters in Japanese patients were comparable with those in Caucasian patients. Based on DLT frequency and safety data in Cycle 1, the MTD in Japanese patients was determined to be 25 mg/m^2, which is equal to the recommended dose in other approved countries. The PK similarity between Japanese and Caucasian patients supported this conclusion.

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PHASE I STUDIES

Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer

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Summary Onartuzumab is a monovalent, humanized, monoclonal antibody that showed significant survival benefits in combination with erlotinib in MET-positive non-small-cell lung cancer (NSCLC) in pre-specified subgroup analyses of a randomized phase II study. We conducted a two-stage, open-label, multicenter, phase I study of onartuzumab in Japanese patients. Stage 1 investigated the safety, tolerability, pharmacokinetics (PK), and recommended dose of onartuzumab in patients with solid tumors, and Stage 2 determined the safety, tolerability, and PK of onartuzumab plus erlotinib in patients with MET-positive NSCLC. Nine patients received onartuzumab monotherapy (4, 15, or 30 mg/kg on Day 1 of each 21-day cycle) in Stage 1, and six patients received onartuzumab (15 mg/kg) plus erlotinib (150 mg/day) in Stage 2. There were no dose-limiting toxicities in either stage. Serious adverse events (AEs) occurred in one patient in Stage 1 (convulsion), and two patients in Stage 2 (once case each of diarrhea, vomiting, and pulmonary embolism), but there were no grade 4 AEs or AEs leading to death. Onartuzumab PKs were linear in the dose range of 4 to 30 mg/kg, and were not affected by co-administration with erlotinib. PK parameters of onartuzumab were similar to those reported in non-Japanese patients. A partial response was observed in a patient with MET immunohistochemistry 3+ NSCLC without *MET* gene amplification. Based on these results, the recommended dose of onartuzumab in Japanese patients with solid tumors is 15 mg/kg every 21 days. The combination of onartuzumab with erlotinib is feasible in Japanese patients with MET-positive lung cancer.

Keywords MET · Onartuzumab · Japanese patients · Lung cancer · Phase I study · Solid tumors

Introduction

The cell surface receptor tyrosine kinase MET is activated by its only known ligand, the hepatocyte growth factor (HGF). MET/HGF signaling plays a key role in a number of cellular processes, including cell migration and proliferation, invasion, survival, metastasis, and angiogenesis [1–6]. However, dysregulation of this signaling pathway, either by *MET* gene mutation, amplification of the *MET* gene locus, or overexpression of the MET receptor, has been implicated in tumorigenesis in various human cancers [7]. Abnormal MET activation is associated with poor prognosis in many tumor types, including non-small-cell lung cancer (NSCLC) [8, 9]. MET amplification is also a mechanism of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with *EGFR* mutant tumors [10], supporting dual inhibition of MET/EGFR as a therapeutic approach.

Onartuzumab (MetMAb; Genentech, South San Francisco, California), is a monovalent, humanized, monoclonal antibody that prevents binding of HGF to the MET receptor and

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subsequent MET/HGF-mediated signaling. Unlike bivalent anti-MET antibodies, onartuzumab is free of agonistic activity and antibody-dependent cell-mediated cytotoxicity [11]. Outside of Japan, the safety and efficacy of onartuzumab has been investigated in a global phase I dose-escalation study in patients with locally advanced or metastatic solid tumors (OAM4224g) [12] and in a randomized, double-blind, placebo-controlled phase II study in patients with recurrent NSCLC (OAM4558g) [13]. In subgroup analyses of the phase II study, the combination of onartuzumab with erlotinib significantly prolonged progression-free survival (hazard ratio [HR] 0.53, P=0.04) and overall survival (HR 0.37, P= 0.002) in patients with MET-positive tumors [13]. Accordingly, a global phase III study (OAM4971g) was initiated to assess the efficacy of onartuzumab plus erlotinib in a MET-positive population.

Based on the results of the phase II study, we conducted a two-stage phase I study of onartuzumab for Japanese patients. The first stage of the study investigated onartuzumab monotherapy in patients with solid tumors refractory to the current standard treatment, or for which there is no standard treatment, with a view to investigating the safety, tolerability, pharmacokinetics (PK), and recommended dose of onartuzumab in Japanese patients. The second stage of the study assessed the combination of onartuzumab with erlotinib in patients with MET-positive NSCLC who had received at least one prior platinum-based chemotherapy regimen, with the aim of investigating the safety, tolerability, and PK of onartuzumab and erlotinib. This study was conducted in order to enroll Japanese patients into the global phase III study.

Materials and methods

Study design and treatment

This open-label, multicenter, 3+3 design phase I study (JO25725; JapicCTI-111563) was conducted in Japan between August 2011 and April 2013. Stage 1 of the study investigated the safety, tolerability, PK, and recommended dose of onartuzumab monotherapy in patients with solid tumors that were refractory to the standard treatment, or for which there was no standard treatment. Stage 2 determined the safety, tolerability, and PK of onartuzumab in combination with erlotinib in patients with MET-positive NSCLC previously treated with at least one platinum-based chemotherapy regimen. The protocol was approved by the institutional review board of the two participating medical centers and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

In Stage 1, patients received onartuzumab IV 4 mg/kg (cohort 1), 15 mg/kg (cohort 2) or 30 mg/kg (cohort 3) on Day 1 of each 21-day cycle, based on results of the global phase I dose-escalation study [12]. In Stage 2, patients received onartuzumab 15 mg/kg on Day 1 of each 21-day cycle, plus erlotinib 150 mg/day p.o., as per the regimen used in the global phase II NSCLC study [13]. Since there was no established standard treatment for the patients in the study, treatment continued until the withdrawal criteria were met, which were: occurrence of a dose-limiting toxicity (DLT), occurrence of an adverse event (AE) that would make continuation difficult, confirmed disease progression (PD), or the patient or investigator's decision to withdraw.

The feasibility of escalation to the next dose cohort was based on the occurrence of DLTs. In Stage 1, three patients were to be enrolled into each cohort; if no DLTs occurred, the next cohort would be treated. If one of the three patients experienced a DLT, three more patients would be enrolled into the same cohort. If one of these six patients experienced a DLT, the next cohort would be treated, but if more than one of the six patients experienced a DLT, no new patients would be enrolled and no further dose escalations would be permitted. The opinion of the Efficacy and Safety Evaluation Committee was sought as necessary. Stage 2 was conducted regardless of whether treatment was studied in cohort 3 in Stage 1.

The primary endpoints of the study were: occurrence of DLTs and AEs; PK of onartuzumab and erlotinib; and maximum tolerated dose (MTD) and recommended clinical dose of onartuzumab. Secondary endpoints were: the anti-tumor effect of onartuzumab monotherapy and onartuzumab in combination with erlotinib; and the development of anti-therapeutic antibodies (ATAs). The association between efficacy and safety and MET status, *MET* gene copy number, and plasma HGF concentration were investigated as exploratory study endpoints.

Patient eligibility

Key eligibility criteria included: age ≥20 years, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, life expectancy ≥12 weeks, and adequate bone marrow, liver, renal and heart function. For Stage 1 only, patients were required to have histologically or cytologically confirmed solid tumor refractory to the standard treatment or for which there was no standard treatment. For Stage 2 only, patients must have histologically or cytologically confirmed NSCLC and percutaneous oxygen saturation ≥94 % within 2 weeks prior to enrollment. Stage 2 patients were to be previously treated with at least one platinum-based chemotherapy regimen (treatment with one prior EGFR TKI was also permitted). Neoadjuvant or adjuvant chemotherapy was counted as only one prior regimen if the cancer recurred during therapy or within 6 months of completing therapy. Patients in Stage 2 were also required to have MET-positive tumors, defined as ≥50 % of tumor cells showing a moderate or strong staining

intensity, as per the criteria used in the phase II NSCLC trial [13].

Patients were excluded from the study if they met any of the following criteria: primary central nervous system (CNS) malignancy or CNS metastases that were symptomatic or required treatment; angina pectoris, congestive heart failure (New York Heart Association Class ≥ II), or arrhythmia requiring treatment, or myocardial infarction within 6 months prior to enrollment; uncontrollable hypertension or peripheral vascular disease of grade ≥2 (according to Common Terminology Criteria for Adverse Events [CTCAE] v.4.03); persistent grade ≥2 adverse reaction to previous treatment (excluding anemia and alopecia); or previously treated with a drug predominantly inhibiting MET. Additional exclusion criteria in Stage 2 only included: patients who had difficulty taking drugs orally; gastrointestinal disorder or inflammatory bowel disease that might impair drug absorption; previous intolerance to EGFR TKIs; and concurrent or prior radiographically confirmed interstitial lung disease.

Dose-limiting toxicities

The 21-day period following the first infusion of onartuzumab was defined as the DLT evaluation period. DLTs were defined as AEs if they occurred in the DLT evaluation period and met the following criteria: in Stage 1 and Stage 2, grade 4 neutropenia (lasting for ≥3 days) and thrombocytopenia; or grade ≥3 non-hematologic toxicities (excluding controllable nausea, vomiting, or diarrhea, infusion reactions, and transient electrolyte abnormalities). Additionally, in Stage 2, the following DLTs were added: interstitial lung disease and gastrointestinal perforation; events requiring suspension of erlotinib for ≥8 days; and grade ≥3 non-hematologic toxicities (excluding grade 3 skin toxicity, if tolerable, and grade 3 elevated hepatic enzyme levels that resolved to grade ≤1 within 7 days).

Safety

Safety was assessed through AEs, laboratory test data, and medically significant changes in physical measurements, vital signs, and electrocardiogram outputs. AEs were classified according to Medical Dictionary for Regulatory Activities (MedDRA), with events summarized by system organ class and preferred term. Severity of AEs was graded on a scale of 1 to 5 according to CTCAE v4.03. Serum samples for analysis of ATAs to onartuzumab were collected in Stage 1 (Day 1 pre-dose, Day 1 of each treatment cycle, and at withdrawal) and in Stage 2 (Day 1 pre-dose and at withdrawal), and were analyzed centrally.

Pharmacokinetic analysis

Serum samples for onartuzumab PK analysis were collected in Stage 1 during Cycle 1 (Day 1 pre-dose and 0.5, 2, 4, 7, 24, 48, and 72 h post-dose, and Days 8, 11 and 15), Cycle 2 and subsequent cycles (Day 1 pre-dose and 0.5 h post-dose), and at withdrawal. Serum samples for onartuzumab PK analysis in Stage 2 were collected during Cycle 1 (as per Stage 1), Cycles 2 to 4 (Day 1 pre-dose and 1 h post-dose), Cycles 5 to 7 (Day 1 pre-dose), Cycle 8 and subsequent cycles (Day 1 pre-dose) and at withdrawal.

Plasma erlotinib concentrations were determined in samples collected during Cycle 1 (Day 1 pre-dose and 1, 2, 4, 5, 7, and 24 h post-dose), Cycles 2 and 3 (Day 1 pre-dose), and at withdrawal. Plasma HGF concentrations were determined in samples collected during Cycle 1 (Day 1 pre-dose and 24 h post-dose), Cycles 2 and 3 (Day 1 pre-dose), and at withdrawal.

A non-compartmental analysis was used to determine the PK parameters for each patient, including: maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), elimination half-life ($t_{1/2}$), and clearance (CL).

Tumor response

Tumor assessment was performed at baseline, during treatment (Stage 1: Cycles 2, 4, 7, and then every 3 cycles; Stage 2: Cycles 2, 4, 6, and then every 2 cycles), and at withdrawal. Imaging data from within 28 days prior to enrollment were used as baseline measurements. All patients with lesions identifiable on imaging were evaluated, irrespective of whether the lesions were measurable. Tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The best overall response was defined as the best response recorded from the start of treatment until PD or recurrence.

MET expression level and MET gene copy number

MET expression levels were determined at a central laboratory by immunohistochemistry (IHC) using the CONFIRM anti-total cMET (SP44) rabbit monoclonal primary antibody (Ventana Medical Systems, Tucson, AZ). A MET IHC scoring system was used, as described previously [13], with MET positivity defined as a score of 2+ or 3+. *MET* gene copy number was assessed centrally during Stages 1 and 2 using silver in situ hybridization (SISH; Ventana Medical Systems, Tucson, AZ) as previously described [14].

Results

Patient characteristics

In Stage 1, three patients were enrolled into each of the onartuzumab dose cohorts (n=9), with solid tumors consisting of: NSCLC (n=4), colorectal cancer (CRC; n=3), gastric cancer (GC; n=1), and head and neck cancer (HNC; n=1). The median age was 68 years (range: 41–75) and most patients had received ≥3 prior regimens for metastatic disease (Table 1). In Stage 2, six patients with MET-positive NSCLC were enrolled, five with adenocarcinoma and one patient with squamous cell carcinoma. The median age was 69 years (range: 34–74). *EGFR* activating mutations were present in three patients; two patients had received treatment with EGFR TKIs (Table 1). All 15 enrolled patients were eligible for DLT and safety analyses.

Dose-limiting toxicities

The doses evaluated in Stage 1 did not reach the MTD. There were no AEs meeting the definition of DLTs in either Stage 1 (onartuzumab 4, 15, or 30 mg/kg) or Stage 2 (onartuzumab 15 mg/kg plus erlotinib 150 mg/day), suggesting that the combination of onartuzumab 15 mg/kg and erlotinib 150 mg was tolerable.

Table 1 Patient demographics and baseline characteristics

Parameter	Onartuzumab (n=9)	Onartuzumab + erlotinib (n=6)
Age, median (range), years	68.0 (41–75)	69.0 (34–74)
Gender, *n*		
Male	6	1
Female	3	5
ECOG PS, *n*		
0	5	4
1	4	2
No. of prior therapies for metastatic disease, *n*		
1	0	2
2	2	1
≥3	7	3
NSCLC patients	(n=4)	(n=6)
EGFR status, *n*		
Mutant	1	3
Wild type	0	3
Unknown	3	0
EGFR TKI history, *n*		
Yes	4	2
No	0	4

Abbreviations: ECOG PS Eastern Cooperative Oncology Group performance status, *EGFR* Epidermal growth factor receptor, *NSCLC* Non-small-cell lung cancer, *TKI* Tyrosine kinase inhibitor

Safety

The median number of onartuzumab treatment cycles in Stage 1 was 4 in cohort 1, and 2 in each of cohorts 2 and 3; dosing was postponed in one patient in cohort 3. In Stage 2, the median number of onartuzumab treatment cycles was 2.5; dosing was postponed in two patients. The median duration of erlotinib treatment was 57.5 days (range: 36–377).

In Stage 1, AEs occurred in eight patients (Table 2). All AEs were grade 1 or 2 in severity, except for one case of grade 3 hypoalbuminemia. One patient experienced a serious AE (convulsion), which was deemed to be associated with progression of the primary disease, and a causal relationship with onartuzumab was ruled out. There were no grade 4 AEs and no deaths reported during the study period. Onartuzumab treatment was discontinued in one patient in cohort 2 due to peripheral edema, and postponed in one patient in cohort 3 as a result of herpes zoster infection.

In Stage 2, AEs occurred in all six patients (Table 3). There was one case each of grade 3 deep vein thrombosis, pulmonary embolism, rash, hypoxia, dermatitis acneiform, diarrhea, and neutropenia. Two patients experienced serious AEs in Stage 2 and withdrew from the study as a result of these events. One patient had diarrhea and vomiting that required interruption of erlotinib therapy and postponement of onartuzumab. Treatment was restarted following symptomatic improvement, however, the events recurred. The second patient had a pulmonary embolism caused by deep vein

Table 2 Adverse events occurring during onartuzumab monotherapy

Adverse event, no. of patients	Onartuzumab dose cohort									Total G1–G3[a]
	4 mg/kg (n=3)			15 mg/kg (n=3)			30 mg/kg (n=3)			
	G1	G2	G3	G1	G2	G3	G1	G2	G3	
Hypoalbuminemia (Blood albumin decreased)	1	–	–	1	–	1	1	1	–	5
Constipation	1	–	–	–	1	–	1	–	–	3
Somnolence	1	–	–	1	–	–	–	–	–	2
Blood creatinine increased	1	–	–	1	–	–	–	–	–	2
Dry skin	–	–	–	–	1	–	–	1	–	2
Diarrhea	–	–	–	–	–	–	2	–	–	2
Peripheral edema	–	–	–	–	1	–	–	1	–	2

Abbreviation: G, Grade

[a] The table displays total grade 1–3 adverse events occurring in ≥2 patients

Table 3 Adverse events occurring during combined onartuzumab and erlotinib treatment

Adverse event, no. of patients	Onartuzumab + erlotinib (n=6)			Total G1–G3[a]
	G1	G2	G3	
Diarrhea	3	1	1	5
Stomatitis	3	1	–	4
Dry skin	3	1	–	4
Hypoalbuminemia (Blood albumin decreased)	2	2	–	4
Rash	1	1	1	3
Dermatitis acneiform	1	1	1	3
Paronychia	1	2	–	3
Blood bilirubin increased	1	2	–	3
Peripheral edema	3	–	–	3

Abbreviation: G Grade

[a] The table displays total grade 1–3 adverse events occurring in ≥3 patients

thrombosis in the leg. A causal relationship to erlotinib and onartuzumab could not be ruled out for any of these serious AEs. No grade 4 AEs were reported and no deaths occurred. Onartuzumab treatment was discontinued in one patient in Stage 2 due to peripheral edema and deep vein thrombosis, and postponed in two patients as a result of dermatitis acneiform, neutropenia, and leucopenia. Two patients experienced AEs leading to discontinuation of erlotinib, consisting of one case each of diarrhea, pulmonary embolism, and deep vein thrombosis.

None of the patients had a positive response in the ATA assay.

Pharmacokinetics

Dose-dependent increases in C_{max}, AUC_{last}, and AUC_{inf} were observed at onartuzumab doses above 4 mg/kg, suggesting dose linearity (Table 4). Onartuzumab showed biphasic PKs, with an initial rapid elimination phase of approximately 1 day followed by a slower second elimination phase (Fig. 1). The serum onartuzumab concentration-time profile was similar between cohort 2 in Stage 1, receiving 15 mg/kg, and Stage 2 patients receiving 15 mg/kg onartuzumab in combination with erlotinib, showing that the PK parameters of onartuzumab were not affected by erlotinib. PK parameters of onartuzumab in Japanese patients were similar to those reported in non-Japanese patients in the phase I dose-escalation study of onartuzumab administered with or without bevacizumab (Fig. 2) [12]. PK parameters of erlotinib fell within the data range from prior erlotinib studies [15, 16] and the phase II NSCLC study in combination with onartuzumab [13].

Table 4 Pharmacokinetic parameters of onartuzumab (mean ± SD)

PK parameter	Onartuzumab dose cohort		
	4 mg/kg (n=3)	15 mg/kg (n=9)[a]	30 mg/kg (n=3)
C_{max}, μg/mL	119±4.04	473±114	916±239
AUC_{inf}, μg[a]day/mL	542±54.1	3350±726	4930±635
CL, mL/day/kg	7.43±0.722	4.72±1.28	6.15±0.778
$t_{1/2}$, days	5.94±0.277	10.3±4.76	10.4±1.42

[a] Total number in Stage 1 and Stage 2

Abbreviations: AUC_{inf}, Area under the concentration-time curve from zero to infinity, *CL* Clearance, *C_{max}* Maximum plasma concentration, *PK* Pharmacokinetics, *$t_{1/2}$* Elimination half-life, *SD* Standard deviation

Median plasma HGF concentration following administration of onartuzumab was elevated to approximately three-times the baseline level (Fig. 3). Although plasma HGF concentrations varied, similar levels and a dose-dependent increase were observed during onartuzumab monotherapy in Stage 1, and during combined onartuzumab and erlotinib therapy in Stage 2 (data not shown). There was no clear relationship between HGF plasma concentrations and AEs.

Tumor response

All 15 patients were evaluable for tumor response by RECIST v1.1 (Table 5). The best overall response in Stage 1 was stable disease (SD) in two patients with IHC 1+ MET-negative tumors: one patient with CRC had SD after 5 cycles of treatment, and one patient with NSCLC had SD after 4 cycles of therapy. In Stage 2, the best overall response was partial response (PR) in a patient with IHC 3+ MET-positive adenocarcinoma and wild type *EGFR* status. Disease progression did not occur for at least 6 months in two patients in Stage 2 with adenocarcinoma and wild type *EGFR* status: one patient had SD and the other had PR.

MET expression level and MET gene copy number

Since only a small number of patients had data available for analysis, it was difficult to analyze the relationship between MET status and tumor response. *MET* gene copy number was evaluable in eight samples across Stage 1 and 2 (Tables 5 and 6). Gene copy number gain (MET/Ch7 ratio >2) was observed in one patient in Stage 2 with a MET IHC score of 2+. Conversely, another patient with a MET IHC score of 3+, who experienced a PR during Stage 2, did not show *MET* copy number gain (MET/Ch7 ratio <1).

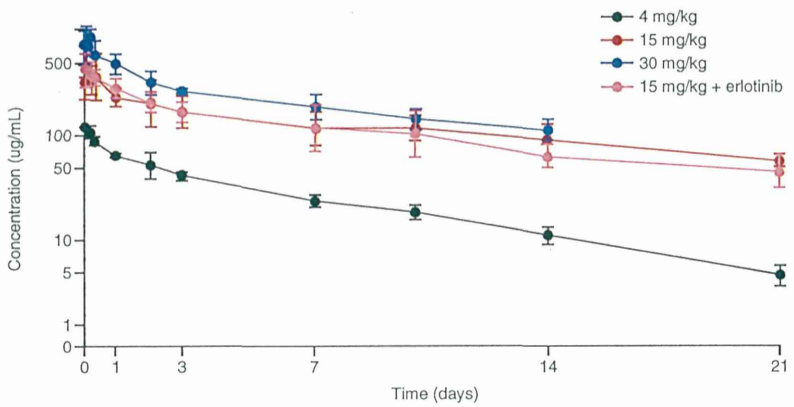

Fig. 1 Serum onartuzumab concentration-time profile (mean ± SD)

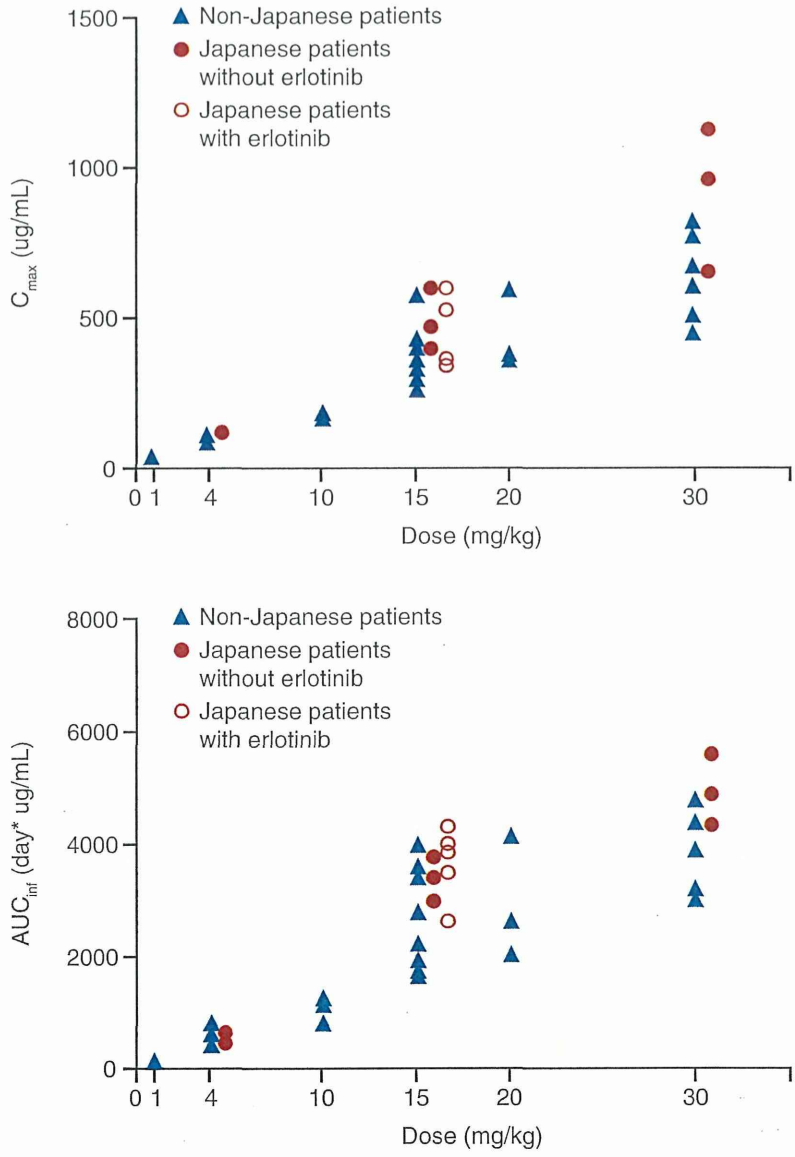

Fig. 2 Pharmacokinetics of onartuzumab in Japanese and non-Japanese patients

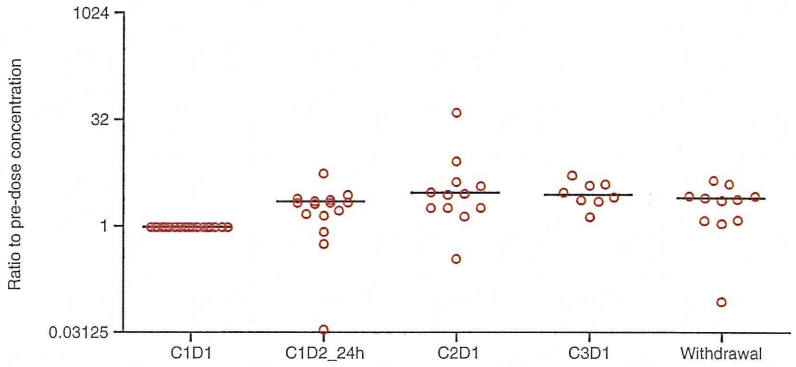

Fig. 3 Median plasma HGF concentration following administration of onartuzumab: plasma HGF concentrations were determined in samples collected during Cycle 1 (Day 1 pre-dose [C1D1] and 24 h post-dose [C1D2_24h]), Cycles 2 and 3 (Day 1 pre-dose [C2D1 and C3D1]), and at withdrawal

Discussion

Single-agent onartuzumab up to 30 mg/kg and at a dose of 15 mg/kg in combination with erlotinib was well tolerated in Japanese patients with diverse solid tumors. There were no DLTs in either Stage 1 (onartuzumab 4, 15, or 30 mg/kg) or Stage 2 (onartuzumab 15 mg/kg plus erlotinib 150 mg/day), and the MTD was not reached at the doses administered in Stage 1. Although serious AEs occurred in one patient in Stage 1 and two patients in Stage 2, there were no grade 4 AEs, and no AEs leading to death in either stage of the study.

The PK parameters of onartuzumab were determined to be linear in the dose range 4 to 30 mg/kg, and were not affected by co-administration with erlotinib. Comparison of the PK results from this study with an earlier phase II study of erlotinib in Japan [17] showed that onartuzumab did not appear to affect the PK profile of erlotinib during combined administration. Thus, no drug-drug interaction in PK between onartuzumab and erlotinib was evident. Of note, the PK profile of onartuzumab was also similar to that reported in non-Japanese patients in the phase I dose-escalation study of onartuzumab dosed as a single agent or in combination with bevacizumab for advanced solid tumors [12]. In the aforementioned phase I study [12], the recommended dose of onartuzumab was determined to be 15 mg/kg based on PK analyses and the minimal tumoricidal concentration (MTC) from preclinical studies. Although no DLT was observed in the 30 mg/kg cohort of the current study, the cohorts receiving onartuzumab doses ≥15 mg/kg provided the trough concentration to be maintained at ≥ MTC. Thus, we concluded that 15 mg/kg onartuzumab was sufficient in terms of efficacy in Japanese patients. Although significant variability in plasma HGF concentrations was observed, concentrations tended to increase following onartuzumab administration. This may have been the result of increased levels of HGF that were unable to bind to MET, since onartuzumab was bound to MET. Similar findings of increased HGF levels after onartuzumab dosing were reported in the phase I dose-escalation study [12], and in the phase II NSCLC study [13], but this was independent of both onartuzumab dose and

Table 5 Tumor response to onartuzumab monotherapy in Stage 1 (n=9)

Onartuzumab dose	Tumor type	MET IHC score	MET SISH (*MET*/Ch7)	No. of cycles	Best overall response
4 mg/kg (n=3)	CRC	1+	0.688	1	PD
	NSCLC	NE	NE	4	PD
	CRC	1+	1.121	5	SD
15 mg/kg (n=3)	NSCLC	—	—	3	PD
	NSCLC	—	—	1	PD
	HNC	1+	NE	2	PD
30 mg/kg (n=3)	CRC	—	—	1	PD
	GC	1+	1	2	PD
	NSCLC	1+	1.093	4	SD

Abbreviations: CRC Colorectal cancer, *GC* Gastric cancer, *HNC* Head and neck cancer, *IHC* Immunohistochemistry, *MET/Ch7* Ratio of MET gene copy number on chromosome 7 to cells, *NE* Not evaluable, *NSCLC* Non-small-cell lung cancer, *PD* Disease progression, *SD* Stable disease, *SISH* Silver in situ hybridization

Table 6 Tumor response to onartuzumab plus erlotinib in Stage 2 (n=6)

Histology	*EGFR* status	MET IHC score	MET SISH (*MET*/Ch7)	No. of cycles	Best overall response
Adenocarcinoma	Wild type	2+	1.081	10	SD
Adenocarcinoma	Wild type	2+	2.406	3	PD
Adenocarcinoma	Wild type	3+	0.985	18	PR
Squamous	Exon 19 deletion	2+	—	2	PD
Adenocarcinoma	Exon 21 L858R	2+	—	2	SD
Adenocarcinoma	Exon 21 L858R	2+	1.272	2	PD

Abbreviations: EGFR Epidermal growth factor receptor, *IHC* Immunohistochemistry, *MET/CH7* ratio of MET gene copy number on chromosome 7 to cells, *PD* Disease progression, *PR* Partial response, *SD* Stable disease, *SISH* Silver in situ hybridization

exposure [18]. The relationship between HGF levels and onartuzumab administration, dose, and exposure requires further investigation.

Due to the small number of available samples the exploratory endpoint of the relationship between *MET* gene copy number and tumor response could not be evaluated. In Stage 1 of the current study, onartuzumab monotherapy showed efficacy in two patients with IHC 1+ MET-negative tumors: one patient with CRC had SD after 5 treatment cycles, and one patient with NSCLC had SD after 4 treatment cycles. Expression levels of MET were assessed using the IHC scoring system validated in the phase II NSCLC study [13]. One patient with IHC 3+ MET-positive NSCLC and wild type *EGFR* status achieved a PR in Stage 2. Of note, three patients with *EGFR* mutant NSCLC in Stage 2 had PD after 2 cycles of therapy, and therefore did not achieve the efficacy expected with even single-agent erlotinib. One of these patients had a history of gefitinib treatment, but the other two patients had not received any prior EGFR TKIs. Further evaluation of the combination of onartuzumab and erlotinib therapy in *EGFR* mutant NSCLC is needed.

In conclusion, onartuzumab was well tolerated in the dose range of 4 to 30 mg/kg in Japanese patients with solid tumors. The observed safety profile did not differ significantly from that seen in previous studies of onartuzumab in patients with advanced solid malignancies [12, 13]. Onartuzumab exhibited a PK profile that allowed the trough concentration to be maintained at ≥15 μg/mL (minimal tumoricidal concentration based on non-clinical findings) in the cohorts receiving doses ≥15 mg/kg. Based on these findings, the recommended dose of onartuzumab in Japanese patients with solid tumors was determined to be 15 mg/kg, administered as a single agent every 21 days. The combination of onartuzumab with erlotinib is feasible in Japanese patients with MET-positive lung cancer.

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Compliance with ethical standards The protocol was approved by the institutional review board of the two participating medical centers. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and all patients provided written informed consent prior to any study-related procedures.

Conflicts of interest Makoto Nishio has received honoraria from Chugai, Pfizer and Eli Lilly. Hiroshi Nokihara has received honoraria from Sanofi, Eli Lilly and Boehringer Ingelheim. Hidehito Horinouchi has received research support from National Cancer Center Research and Development Fund and honoraria from Johnson & Johnson, Taiho and Eli Lilly. Shunji Takahashi has received research support from Chugai, Taiho, Sanofi, Zenyaku and Novartis and honoraria from Astrazeneka, Novartis, Astellas and Daiichisankyo. Noboru Yamamoto has received support from a project sponsor Quintiles, Chugai, BMS, Astellas, Novartis and Taiho. Yasuhide Yamada has received honoraria from Taiho and Chugai. Masaichi Abe and Takashi Tahata are employees of Chugai, and Takashi Tahata holds stock in Chugai. Tomohide Tamura has received honoraria from Chugai, Eli Lilly, Kyowa Kirin, Pfizer and Exelixis.

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ORIGINAL ARTICLE

Observational Study

Prognostic value of *KRAS* and *BRAF* mutations in curatively resected colorectal cancer

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Author contributions: Kadowaki S, Matsuo K and Akagi K designed the study, analyzed the data, interpreted the results and wrote the paper; Kakuta M, Takahashi S, Takahashi A, Arai Y and Akagi K carried out all the laboratory experiments; Kadowaki S, Kakuta M, Ooki A, Nishimura Y, Yatsuoka T and Akagi K collected the data; Yamaguchi K and Muro K supervised this study; and all authors have read and approved the manuscript.
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Abstract

AIM: To investigate the prognostic role of *KRAS* and *BRAF* mutations after adjustment for microsatellite instability (MSI) status in Japanese colorectal cancer (CRC) population.

METHODS: We assessed *KRAS* and *BRAF* mutations and MSI status in 813 Japanese patients with curatively resected, stage Ⅰ-Ⅲ CRC and examined associations of these mutations with disease-free survival (DFS) and overall survival (OS) using uni- and multivariate Cox proportional hazards models.

RESULTS: *KRAS* and *BRAF* mutations were detected in 312 (38%) of 812 and 40 (5%) of 811 tumors, respectively. *KRAS* mutations occurred more frequently in females than in males ($P = 0.02$), while the presence of *BRAF* mutations was significantly associated with the female gender ($P = 0.006$), proximal tumor location ($P < 0.001$), mucinous or poorly differentiated histology ($P < 0.001$), and MSI-high tumors ($P < 0.001$). After adjusting for relevant variables, including MSI status, *KRAS* mutations were associated with poorer DFS (HR = 1.35; 95%CI: 1.03-1.75) and OS (HR = 1.46; 95%CI: 1.09-1.97). *BRAF* mutations were poor prognostic factors for DFS (HR = 2.20; 95%CI: 1.19-4.06) and OS (HR = 2.30; 95%CI: 1.15-4.71). Neither the *BRAF* by MSI interaction test nor the *KRAS* by MSI interaction test yielded statistically significant results for DFS and OS.

CONCLUSION: *KRAS* and *BRAF* mutations are associated with inferior survival, independent of MSI status, in