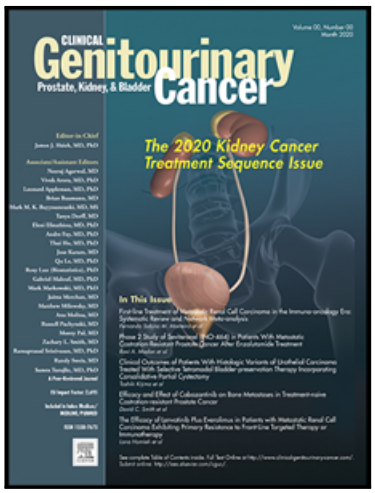

A Phase 2, Randomized, Open-Label, Multi-arm Study of TAS-115 for Castration-Resistant Prostate Cancer Patients With Bone Metastases

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Highlights

- Castration-resistant prostate cancer often metastasizes to bone
- TAS-115 is an oral multikinase inhibitor with activity against bone metastases
- TAS-115 300 mg achieved a bone scan index of ≤ 66.7% in docetaxel-naïve patients
- TAS-115 300 mg reduced serum bone alkaline phosphatase by > 30% in > 50% of patients
- TAS-115 showed acceptable safety and tolerability, even combined with abiraterone

Original study

A Phase 2, Randomized, Open-Label, Multi-arm Study of TAS-115 for Castration-Resistant Prostate Cancer Patients With Bone Metastases

Short Title: TAS-115 for CRPC With Bone Metastases

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Disclosure

Nobuaki Matsubara reports honoraria from Janssen, Taiho, and MSD; consulting or advisory fees from Janssen, Bayer, MSD, Roche, and Sanofi; payment for participation in a speakers' bureau from Janssen, Sanofi, MSD, and AstraZeneca; and research funding from Janssen, MSD, Bayer, Roche, and Taiho. Hirotsugu Uemura reports grant support, consultant fees, lecture fees, and fees for serving as a meeting chairman from Sanofi, Janssen, and Ono/Bristol-Myers Squibb; grant support from AstraZeneca, Takeda, Astellas, and Taiho; and lecture fees and fees for serving as a meeting chairman from Pfizer, Bayer, Merck Sharp and Dohme, and Novartis. Hiroyoshi Suzuki reports grants from Taiho during the conduct of the study; grants and personal fees from Chugai, Pfizer, Novartis, Asahi Kasei, Takeda, Astellas, Bayer, Daiichi-Sankyo, Sanofi, Ono, Nihon Kayaku, Nihon Shinyaku, Kissei, and Kyorin; and personal fees from AstraZeneca, Fuji Film, and Janssen outside the submitted work. Satoshi Nagamori, Go Kimura, and Hiroji Uemura have nothing to disclose.

MicroAbstract

New treatments to improve quality of life and survival for castration-resistant prostate cancer patients with bone metastases are needed. We evaluated the safety and efficacy of the oral multikinase inhibitor TAS-115 in 50 patients. Overall, we observed improvements in bone metastasis and pain measures, and acceptable safety profiles with TAS-115. TAS-115 may be a useful treatment for these patients.

Abstract

Introduction: TAS-115 is an oral multikinase inhibitor targeting the MET proto-oncogene, vascular endothelial growth factor receptor, and colony-stimulating factor 1 receptor. We evaluated the efficacy and safety of TAS-115 in castration-resistant prostate cancer (CRPC) patients with bone

metastases. **Patients and Methods:** This phase 2 study, conducted in Japan, comprised 2 cohorts of CRPC patients. Cohort A included patients with bone metastasis and no history of docetaxel; TAS-115 200–400 mg/day was administered with abiraterone and prednisone. Cohort B included patients with symptomatic multiple bone metastases, post- or unfit for docetaxel, randomized 1:1 to receive TAS-115 400 or 600 mg/day orally, once daily, in a repeated weekly schedule of 5 days on/2 days off. The primary endpoint was bone scan index (BSI) response rate at Week 12 in each dose group. **Results:** Cohorts A and B included 24 and 26 patients, respectively. The 12-week BSI response rates for 200, 300, and 400 mg were 0%, 33.3%, and 16.7% in Cohort A, and for 400 and 600 mg were 7.1% and 25.0% in Cohort B. The best BSI response rates for 200, 300, and 400 mg were 0%, 66.7%, and 16.7% in Cohort A, and for 400 and 600 mg were 7.1% and 33.3% in Cohort B. A ≥30% reduction in BPI-SF score was shown in 57.7% of patients in Cohort B. The most frequent Grade ≥3 adverse drug reactions were hypophosphatemia (20.8%) in Cohort A and anemia (23.1%) in Cohort B. **Conclusion:** TAS-115 appears to demonstrate anti-tumor activity and acceptable tolerability in CRPC patients with bone metastases.

Japan Pharmaceutical Information Center number: JapicCTI-163448

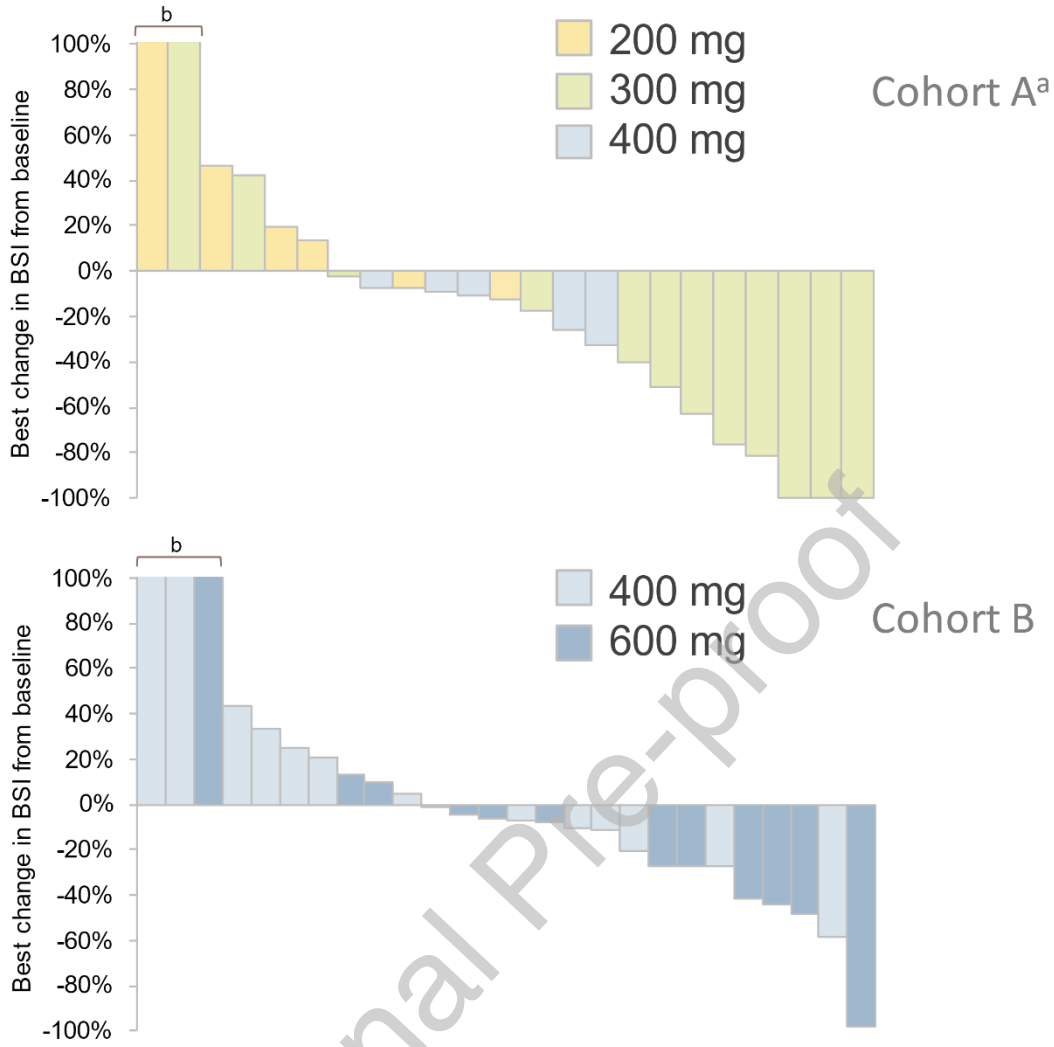
Keywords: Bone scan index, Brief Pain Inventory; Multikinase inhibitor; MET proto-oncogene, Vascular endothelial growth factor receptor

Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase

AST	aspartate aminotransferase
BAP	bone-specific alkaline phosphatase
BMA	bone-modifying agent
BPI-SF	Brief Pain Inventory-Short Form
BSI	bone scan index
CI	confidence interval
cPD	clinical progressive disease
CRPC	castration-resistant prostate cancer
FMS	McDonough feline sarcoma
Hs	hotspot
IC	informed consent
MET	MET proto-oncogene
PSA	prostate-specific antigen
QOL	quality of life
rPD	radiological progressive disease
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization

Graphical abstract



Best response in bone scan index (BSI) with TAS-115 200, 300 or 400 mg/day (Cohort A) and 400 or 600 mg/day (Cohort B). In Cohort A, more patients treated with TAS-115 300 mg/day had a BSI reduction. In Cohort B, more patients treated with TAS-115 600 mg had a BSI reduction.
[a]One patient who only had baseline data was excluded from the analysis.
[b]Values higher than 100% are represented as 100% because of y-axis truncation at 100%.

Clinical Practice Points

• What is already known about this subject?

Prostate cancer is a common disease that can progress to castration-resistant prostate cancer (CRPC). This may lead to bone metastases, which negatively affect patients' quality and duration of life. Current treatments are limited, particularly in terms of increasing survival, so there is a need for new therapies. Previous studies have shown that the oral multikinase inhibitor TAS-155 targets factors involved in the modulation of bone metastases – namely, colony-stimulating factor 1 receptor, MET proto-oncogene, and vascular endothelial growth factor receptor – and thus, shows promise as a treatment.

• What are the new findings?

In 50 patients with CRPC, 200, 300, 400 mg TAS-155, administered in combination with abiraterone and prednisone, or alone (400 or 600 mg), showed effective preliminary anti-tumor activity on bone lesions and improvement in pain. The greatest responses were seen in the 300 mg TAS-155-combined and 600 mg TAS-155-alone groups. It also had an acceptable safety profile, with most adverse drug reactions being Grade 1 or 2 in severity. The proportions of patients who discontinued due to adverse events were 20.8% and 15.4% in the combined and alone groups, respectively.

• How might it impact on clinical practice in the foreseeable future?

TAS-115 appears to be safe and effective for the treatment of CRPC with bone metastases. Further studies are required, but TAS-115 may prove useful, possibly combined with other agents, as a much-needed treatment that could improve quality of life and survival times for patients with CRPC and bone metastasis.

Introduction

Prostate cancer is the second most prevalent cancer in males worldwide, with approximately 1,300,000 new cases reported in 2018.[1] Most prostate cancer patients with locally advanced, metastatic, or biochemically recurrent disease progress to castration-resistant disease within 2-3 years.[2] Such patients frequently develop bone metastasis, which can profoundly impair quality of life (QOL).[3]

Docetaxel, abiraterone, enzalutamide, cabazitaxel, and radium-223 chloride (Ra-223) are recommended for the treatment of metastatic castration-resistant prostate cancer (CRPC),[4] while medical and local treatment of CRPC with bone metastases generally aims to relieve pain and improve QOL. Medical treatment comprises zoledronate and denosumab, which target osteoclasts.[4] These agents significantly control the occurrence of skeletal-related events and relieve pain, but there is no evidence they improve survival. For patients with symptomatic bone metastases without visceral metastases, guidelines recommend Ra-223.[5,6] Ra-223 significantly controlled the occurrence of symptomatic skeletal events, and extended survival versus placebo in a phase 3 study.[7] However, the use of Ra-223 is limited to a treatment period of 6 months and is occasionally associated with a major fall in serum prostate-specific antigen (PSA). There is therefore a clear unmet medical need for new medications for CRPC with bone metastases.

Bone metastasis occurs via interactions between tumor and bone cells, with cancer cells simultaneously increasing osteoclast activity and inhibiting osteoblasts.[3,8,9] Osteoclasts are modulated by the colony-stimulating factor 1 receptor (formerly known as McDonough feline sarcoma; FMS),[10] and are involved in promotion of bone resorption and formation. Additionally, MET proto-oncogene (MET) and vascular endothelial growth factor receptor (VEGFR) have been reported to act on bone,[11,12] both being expressed in osteoclasts and osteoblasts.[13] Tumor growth suppression by MET and VEGFR inhibition may also suppress bone metastasis.[14]

TAS-115 has been developed as an oral multikinase inhibitor targeting MET, VEGFR, and FMS in an adenosine triphosphate-competitive manner, inhibiting FMS-mediated osteoclast differentiation at the site of tumor cell implantation. In an in vivo study, TAS-115 led to significant inhibition of tumor growth and bone destruction in a mouse bone metastasis model.[15] A phase 1 study demonstrated the tolerability of TAS-115 dosages of 200-650 mg/day and its efficacy in various solid tumors, whereby 8/17 (47.1%) patients with bone metastases or osteosarcoma, including CRPC patients, showed a response assessed by bone scan index (BSI). That study found the maximum tolerated dosage of TAS-115 to be 650 mg/day.[16]

Given its potential inhibitory effects on bone metastasis, TAS-115 is expected to contribute to improving QOL and overall survival of CRPC patients with bone metastases. This phase 2 study evaluated the efficacy and safety of TAS-115 in CRPC patients with bone metastases.

Patients and Methods

Ethics

This study adhered to the Declaration of Helsinki, Pharmaceutical Affairs Law, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, and associated Japanese regulations. The institutional review board at each participating center reviewed and approved the study protocol and associated documents. All patients provided written informed consent.

Study design

This was a phase 2, open-label, multi-arm, and multi-dose study (Supplemental Figure 1), comprising 2 cohorts: A and B.

In Cohort A, TAS-115 200, 300 and 400 mg/day was administered with standard dose of abiraterone acetate to patients prior to docetaxel, with 6 patients enrolled in each dosage group (Supplemental Methods).

In Cohort B, CRPC patients with symptomatic multiple bone metastases who had received prior treatment with docetaxel, or were unsuitable for treatment with docetaxel, were randomized 1:1 to receive either TAS-115 400 or 600 mg/day based on the non-deterministic minimization algorithm. Presence or absence of treatment history with docetaxel was used as an allocation adjustment factor.

Patients

Patients aged ≥ 20 years, diagnosed with CRPC, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate bone marrow, hepatic, and renal function were enrolled. Patients were eligible if they had a lymph node diameter ≥ 5 mm in absolute value in the sum of short-axis diameters at the lymph node lesion or the emergence of a new lymph node lesion (≥ 15 mm in the short-axis diameter). Additional inclusion criteria for Cohort A were bone metastasis lesion, no history of chemotherapy, including docetaxel, and no more than 1 prior treatment regimen with a novel androgen receptor inhibitor (abiraterone, enzalutamide, or investigational agents). Additional inclusion criteria for Cohort B were symptomatic bone metastasis; history of docetaxel treatment or not being scheduled to receive docetaxel treatment; or 2 or 3 prior treatment regimens with a novel androgen receptor inhibitor, docetaxel, or cabazitaxel. The key exclusion criterion for both cohorts was history of visceral metastasis (including brain metastasis and meningeal metastasis) or current visceral metastasis in imaging studies within 28 days of enrollment. Additionally, patients with a lymph node metastasis diameter ≥ 3 cm were excluded. Patients who had Ra-223 within 12 weeks prior to enrollment or who had previously received Ra-223 but did not show a progression of bone metastasis (defined as the emergence of > 2 new bone lesions, or an

observed increase in BSI value when comparing the data between imaging before or after treatment with Ra-223 and imaging performed during the baseline period in this study) were also excluded from this study.

Treatments

TAS-115 was administered orally once daily under fasting conditions, with 1 cycle defined as 21 days and Day 1 in Cycle 1 as the reference date. TAS-115 was administered for 5 consecutive days/week with 2 days of rest. The dosage interruption and reduction criteria are shown in the Supplemental Methods. TAS-115 was administered with standard doses of abiraterone acetate plus prednisone in Cohort A.

Endpoints

The primary endpoint was BSI response rate at Week 12, defined as the percentage of patients whose BSI change rate was ≤ −30% at Week 12 (rationale provided in the Supplemental Methods). Best BSI response rate was defined as the percentage of patients whose BSI change rate was ≤ −30%. Bone scintigraphy was performed at each evaluation time point and analyzed by BONE NAVI® (FUJIFILM RI Pharma, Tokyo, Japan), which allowed centrally assessed scintigraphy results. The BSI change rate at Week 12 was calculated as follows (BONE NAVI®): BSI change rate (%) at Week 12 = 100 × (BSI at Week 12 − BSI at baseline) / BSI at baseline.

The key secondary endpoints were changes in the Brief Pain Inventory-Short Form (BPI-SF) score (Cohort B only), PSA, bone metabolism markers (bone-specific alkaline phosphatase [BAP]), and safety. The grade of adverse events (AEs) was assessed using the Common Terminology Criteria for Adverse Events version 4.03.

Statistical analysis

For the 12-week BSI response rate, which is the primary endpoint, the threshold percentage was supposed to be 25% for both Cohort A and Cohort B, and the expected rate to be 60% and 50% for Cohort A and Cohort B, respectively. The significance level of the entire study was set at a 1-sided 10% and that of each test for Cohort A and Cohort B was set at a 1-sided 5% using the Bonferroni method. Thus, the sample size was determined as the number of patients required to demonstrate the significance by testing for the population rate using binomial distribution with a power of 80% for each cohort. More details of the sample size calculation and analysis set definitions are provided in the Supplemental Methods.

Patients without evaluable BSI data at Week 12 were handled as non-responders. In the full analysis set, the 12-week BSI response rate and its 90% confidence interval (CI) were calculated for each cohort. Summary statistics for change in BPI-SF scores were calculated (Cohort B only). The statistical package used for statistical analyses was SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Disposition and Baseline Characteristics

Fifty patients were enrolled between January 23, 2017, and May 17, 2018. Figure 1 shows the patient disposition and main reasons for discontinuation. Cohort A included 24 patients and Cohort B included 26 patients. In Cohort A, BSI response was observed in the first 6 patients registered in the 300 mg/day group, so 6 additional patients were enrolled in this group.

In Cohorts A and B, the median age was 70.5 and 70.0 years, respectively, and most patients had a performance status of 0. Most patients (88.5%) in Cohort B had previously received docetaxel treatment (Table 1). Dose intensities and treatment durations, by cohort and dosage group, are shown in Supplemental Table 1.

Table 1. Baseline Patient Demographic and Disease Characteristics

	Cohort A				Cohort B		
	200 mg (n = 6)	300 mg (n = 12)	400 mg (n = 6)	All (N = 24)	400 mg (n = 14)	600 mg (n = 12)	All (N = 26)
Age, median (range), years	70.5 (63.0-76.0)	70.5 (49.0-82.0)	71.0 (63.0-77.0)	70.5 (49-82)	71.5 (59.0-82.0)	68.5 (58.0-80.0)	70.0 (58-82)
Performance status, *n* (%)							
0	6 (100.0)	12 (100.0)	3 (50.0)	21 (87.5)	9 (64.3)	9 (75.0)	18 (69.2)
1	0 (0.0)	0 (0.0)	3 (50.0)	3 (12.5)	5 (35.7)	3 (25.0)	8 (30.8)
Time from CRPC diagnosis, median (range)[a], days	933 (252-1815)	393 (29-4563)	532 (309-2554)	503 (29-4563)	897 (608-2352)	681 (252-1733)	896 (252-2352)
Prior docetaxel use, *n* (%)	-	-	-	-	12 (85.7)	11 (91.7)	23 (88.5)
Prior Radium-223 use, *n* (%)	0 (0.0)	4 (33.3)	2 (33.3)	6 (25.0)	7 (50.0)	3 (25.0)	10 (38.5)
Novel AR targeting agent							
Yes, *n* (%)	6 (100.0)	12 (100.0)	6 (100.0)	24 (100.0)	14 (100.0)	10 (83.3)	24 (92.3)
No, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	2 (7.7)
Current use of BMA, *n* (%)	3 (50.0)	6 (50.0)	3 (50.0)	12 (50.0)	10 (71.4)	5 (41.7)	15 (57.7)
PSA, median (range), ng/mL	11.1 (2.2-162.5)	6.5 (0.4-110.3)	8.6 (2.2-441.7)	7.7 (0.4-441.7)	77.7 (2.2-1633.0)	58.1 (0.1-630.7)	58.1 (0.1-1633.0)
Total ALP, median (range), IU/L	454.5 (186.0-883.0)	281.0 (116.0-425.0)	277.5 (218.0-535.0)	289.5 (116.0-883.0)	372.5 (155.0-907.0)	280.0 (171.0-1458.0)	297.0 (155.0-1458.0)
BAP, median (range), U/L	38.6 (8.9-98.3)	18.6 (7.5-32.2)	19.9 (12.8-44.2)	20.6 (7.5-98.3)	28.9 (7.7-79.2)	19.0 (10.4-138.0)	20.8 (7.7-138.0)

WHO ladder for cancer pain, *n* (%)							
1	3 (50.0)	3 (25.0)	1 (16.7)	7 (29.2)	12 (85.7)	6 (50.0)	18(69.2)
2	1 (16.7)	0 (0.0)	0 (0.0)	1 (4.2)	1 (7.1)	2 (16.7)	3(11.5)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)	1 (7.1)	4 (33.3)	5(19.2)
No pain	2 (33.3)	9 (75.0)	5 (83.3)	16 (66.7)	0 (0.0)	0 (0.0)	0 (0)
Extent of disease, *n* (%)							
< 5	0 (0.0)	6 (50.0)	1 (16.7)	2 (8.3)	0 (0.0)	1 (8.3)	1 (3.8)
5-9	2 (33.3)	1 (8.3)	3 (50.0)	6 (25.0)	2 (14.3)	2 (16.7)	4 (15.4)
10-20	1 (16.7)	3 (25.0)	1 (16.7)	5 (20.8)	4 (28.6)	3 (25.0)	7 (26.9)
> 20	3 (50.0)	2 (16.7)	1 (16.7)	6 (25.0)	8 (57.1)	6 (50.0)	14 (53.8)
Bone Scan Index, median (range), %[b]	0.63 (0.05- 6.51)	0.38 (0.15- 2.47)	1.49 (0.20-7.00)	0.71 (0.05-7.00)	4.01 (0.49-10.35)	3.40 (0.90-9.80)	3.40 (0.49-10.35)

[a]Cohort A, 200 mg (n = 6), 300 mg (n = 11), 400 mg (n = 6); Cohort B, 400 mg (n = 10), 600 mg (n = 11)
[b]Based on the independent review committee
Abbreviations: ALP = alkaline phosphatase; AR = androgen receptor; BAP = bone-specific alkaline phosphatase; BMA = bone-modifying agent; CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen; WHO = World Health Organization.

Efficacy

Based on the BSI, patients in Cohort A receiving 200, 300, and 400 mg had a response rate (90% CI) of 0% (0.0, 39.3), 33.3% (12.3, 60.9), and 16.7% (0.9, 58.2), respectively, at 12 weeks. Patients in Cohort B receiving 400 mg and 600 mg had a response rate of 7.1% (0.4, 29.7) and 25.0% (7.2, 52.7) at 12 weeks (Table 2). The best BSI response rates for 200, 300, and 400 mg were 0%, 66.7%, and 16.7% in Cohort A, and for 400 and 600 mg were 7.1% and 33.3% in Cohort B.

In Cohorts A and B, 12.5% and 0% of patients, respectively, achieved ≥ 50% reductions in PSA from baseline and 50.0% and 11.5% achieved ≥ 30% decreases in BAP from baseline (Table 2). Figure 2A shows the best response in BSI. In Cohort A, more patients treated with TAS-115 300 mg had a BSI reduction. In Cohort B, more patients treated with TAS-115 600 mg had a BSI reduction. Figure 2B shows the best response in pain reduction by dose. The ≥ 30% reduction from baseline in the BPI-SF score was shown in 57.7% of patients (Table 2).

Table 2. Key Efficacy Outcomes in Cohorts A and B

	Cohort A								Cohort B					
	200 mg		300 mg		400 mg		All		400 mg		600 mg		All	
	n	%	n	%	n	%	N	%	n	%	n	%	N	%
Bone scan														
No. of evaluable patients	6		12		6		24		14		12		26	
Response at 12 weeks		0.0		33.3		16.7		20.8		7.1		25.0		15.4
Response at 6 weeks or later		0.0		66.7		16.7		37.5		7.1		33.3		19.2
Pain (BPI-SF)														
No. of evaluable patients	-	-	-	-	-	-	-	-	14		12		26	
≥ 30% decrease, best change from baseline	-	-	-	-	-	-	-	-		57.1		58.3		57.7
PSA														
No. of evaluable patients	6		12		6		24		14		12		26	
≥ 50% reduction, best change from baseline		0.0		16.7		16.7		12.5		0.0		0.0		0.0
BAP														
No. of evaluable patients	6		12		6		24		14		12		26	
≥ 30% decrease, best change from baseline		50.0		58.3		33.3		50.0		7.1		16.7		11.5

Abbreviations: BAP = bone-specific alkaline phosphatase; BPI-SF = Brief Pain Inventory-Short Form; PSA = prostate-specific antigen.

Figure 3 shows the bone scan assessment of 2 patients who demonstrated a remarkable reduction in BSI: 1 patient (Figure 3A) in Cohort A and 1 (Figure 3B) in Cohort B. BSI and hotspot decreases were observed in both patients. Supplemental Figure 2 shows a remarkable reduction in the bone scan assessment of 1 patient in Cohort A who had a history of treatment with Ra-223.

Safety

Adverse drug reactions (ADRs) occurring at a frequency of ≥ 20% in Cohorts A and B are shown in Table 3, and ADRs occurring at a frequency of ≥ 20% by dose group are shown in Supplemental Table 2. The most common ADRs of any grade in Cohort A were decreased appetite; aspartate aminotransferase (AST) increased; face edema, edema peripheral, and hypophosphatemia; and alanine aminotransferase (ALT) increased, diarrhea, and rash. Most ADRs were either Grade 1/2 in severity, with hypophosphatemia being the most common Grade ≥ 3 ADR. In Cohort B, the most common ADRs of any grade were decreased appetite, face edema, anemia, malaise, and AST increased. The most common Grade ≥ 3 ADR was anemia.

In Cohorts A and B, 20.8% and 15.4% of patients, respectively, discontinued treatment because of AEs. In Cohort A, reasons for discontinuation were deafness neurosensory, decreased appetite, pleural effusion, erythema multiforme, and rash, all occurring in 1 patient each (4.2% each). The reasons for discontinuation in Cohort B were decreased appetite (7.7%, 2 patients) and osteonecrosis of the jaw and spinal cord compression in 1 patient each (3.8% each).

Serious AEs occurred in 33.3% and 46.2%, and serious ADRs occurred in 25.0% and 3.8% of patients in Cohorts A and B, respectively. Serious ADRs were deafness neurosensory, macular fibrosis, duodenal ulcer, diverticular perforation, pleural effusion (1 patient [4.2% of patients] each), and erythema multiforme (2 patients [8.3%]) in Cohort A and decreased appetite in 1 patient (3.8%) in Cohort B. Serious

AEs/ADRs, and any AEs leading to dose reduction, study drug withdrawal, and discontinuation are shown in Supplemental Table 3. There were no deaths related to ADRs in this study.

Table 3. Adverse Drug Reactions Occurring in ≥ 20% of Patients

	Cohort A (N = 24)		Cohort B (N = 26)	
N (%)	All	Grade ≥ 3	All	Grade ≥ 3
Decreased appetite	10 (41.7)	1 (4.2)	16 (61.5)	2 (7.7)
Face edema	7 (29.2)	0 (0.0)	11 (42.3)	0 (0.0)
Anemia	5 (20.8)	1 (4.2)	10 (38.5)	6 (23.1)
Malaise	4 (16.7)	0 (0.0)	8 (30.8)	0 (0.0)
AST increased	8 (33.3)	0 (0.0)	8 (30.8)	2 (7.7)
Nausea	5 (20.8)	0 (0.0)	6 (23.1)	0 (0.0)
Edema peripheral	7 (29.2)	0 (0.0)	6 (23.1)	0 (0.0)
ALT increased	6 (25.0)	0 (0.0)	6 (23.1)	1 (3.8)
Dysgeusia	4 (16.7)	0 (0.0)	6 (23.1)	0 (0.0)
Rash maculo-papular	3 (12.5)	1 (4.2)	6 (23.1)	1 (3.8)
Hypophosphatemia	7 (29.2)	5 (20.8)	5 (19.2)	3 (11.5)
Diarrhea	6 (25.0)	0 (0.0)	2 (7.7)	0 (0.0)
Rash	6 (25.0)	0 (0.0)	1 (3.8)	0 (0.0)

Adverse drug reactions are categorized according to the Medical Dictionary for Regulatory Activities (version 21.1) preferred term.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Discussion

This study evaluated the efficacy and safety of TAS-115 in CRPC patients with bone metastases, and response based on BSI was observed in patients in both Cohorts. However, the effect of treatment on the reduction of PSA from baseline values was low at 12.5% in Cohort A and 0% in Cohort B, while a reduction in bone metabolism markers was observed. This tendency (low PSA response and high response in bone metabolism markers) was similar to that reported with Ra-223 and cabozantinib,[17,18] suggesting that bone metabolism markers (e.g., BAP) may be more appropriate indicators of TAS-115 effects than PSA. Further, in Cohort B, 61.5% of patients presented pain reduction/improvement of pain according to BPI-SF. Extracellular protons accompanying bone destruction by osteoclasts are known as 1 of the causes of pain from bone metastasis,[19] and TAS-115 may reduce bone pain by reducing osteoclast activity. Such pain relief can lead to QOL improvements for these patients.

The threshold percentage for BSI response at 12 weeks, the primary endpoint, was set at 25%, but this threshold was not exceeded in either Cohort A or B. However, the best BSI response was 66.7% in the TAS-115 300 mg/day dosage group of Cohort A, showing anti-tumor activity on bone lesions. In prostate cancer, the progression of bone metastasis by the vicious cycle of tumor and bone metastasis is well described.[9,20] Osteoclasts are activated by FMS and promote bone resorption and formation. Furthermore, MET and VEGFR are reportedly involved in bone metastasis, so suppression of tumor growth by inhibiting MET and VEGFR may also suppress the progression of bone metastasis.[9] TAS-115 inhibits the differentiation of osteoclasts by inhibiting FMS and tumor growth by inhibition of VEGFR and MET.[15] We hypothesize that TAS-115 inhibits the cycle of bone metastasis, which may explain its efficacy in bone lesions, and that the efficacy results of this study further validate the inhibition of FMS, VEGFRs, and MET previously reported with TAS-115.

Ra-223 reduced skeletal-related events and improved overall survival for CRPC patients with bone metastases,[7,17] but the administration period for Ra-223 is limited to 6 doses over a 6-month

period. A novel finding of our study was that TAS-115 showed a favorable response in some patients after Ra-223 administration and exacerbation of bone metastasis, meaning that TAS-115 may benefit patients after Ra-223 treatment.

The most commonly reported ADRs (decreased appetite, malaise, and anemia) were similar to those reported for other multiple tyrosine-kinase inhibitors such as cabozantinib.[21] TAS-115-specific events such as facial/eyelid edema, AST/ALT increase, hypophosphatemia, and rash were also reported. Notably, most ADRs were either Grade 1 or 2 in severity. Discontinuation rates due to AEs were 20.8% and 15.4% in Cohorts A and B, respectively. In the overall population, 3 patients discontinued due to an ADR of decreased appetite, and 6 other ADRs resulted in discontinuations in 1 patient each. In contrast, the AE discontinuation rate in the cabozantinib trial (COMET-1) was higher at 33%.[22] In terms of AE discontinuation rate and AE type, TAS-115 tended to have acceptable drug safety**.** Patients in Cohort A received abiraterone in combination with TAS-115, but the tendency of increasing toxicity reported with abiraterone monotherapy[23] was not confirmed.

While we investigated safety and efficacy with several different doses, the sample size in each dose group was too small to confirm a dose-dependent toxicity increase with TAS-115. Other limitations were sources of potential bias introduced by the open-label design, and lack of a comparator. The study design did not allow us to confirm any potential synergistic anti-tumor activity of TAS-115 and abiraterone coadministration, nor could we ascertain the optimal dose of TAS-115.

Conclusion

The set threshold for BSI response at 12 weeks was not exceeded in this study. However, TAS-115 exerted preliminary anti-tumor activity on bone lesions, evidenced by BSI responses and improvement in pain, and has acceptable safety, including in combination with abiraterone.

Combined with other agents, TAS-115 could be a new treatment method for CRPC patients with bone metastasis, but further study is necessary to validate its benefits in this patient population.

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Data Statement

The data sets used during the present study will not be made available.

CRediT authorship contribution statement

Nobuaki Matsubara: Study conceptualization and design; data acquisition; quality control of data and algorithms; data analysis and interpretation; statistical analysis; manuscript preparation; manuscript editing; and manuscript review. **Hirotsugu Uemura:** Study conceptualization and design; data acquisition; quality control of data and algorithms; data analysis and interpretation; statistical analysis; manuscript preparation; manuscript editing; and manuscript review. **Satoshi Nagamori:** Data acquisition; quality control of data and algorithms; data analysis and interpretation;

statistical analysis; manuscript preparation; manuscript editing; and manuscript review. **Hiroyoshi Suzuki:** Data acquisition; quality control of data and algorithms; data analysis and interpretation; statistical analysis; manuscript preparation; manuscript editing; and manuscript review. **Hiroji Uemura:** Study conceptualization and design; data acquisition; quality control of data and algorithms; data analysis and interpretation; statistical analysis; manuscript preparation; manuscript editing; and manuscript review. **Go Kimura:** Data acquisition; quality control of data and algorithms; data analysis and interpretation; statistical analysis; manuscript preparation; manuscript editing; and manuscript review.

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Figure Legends

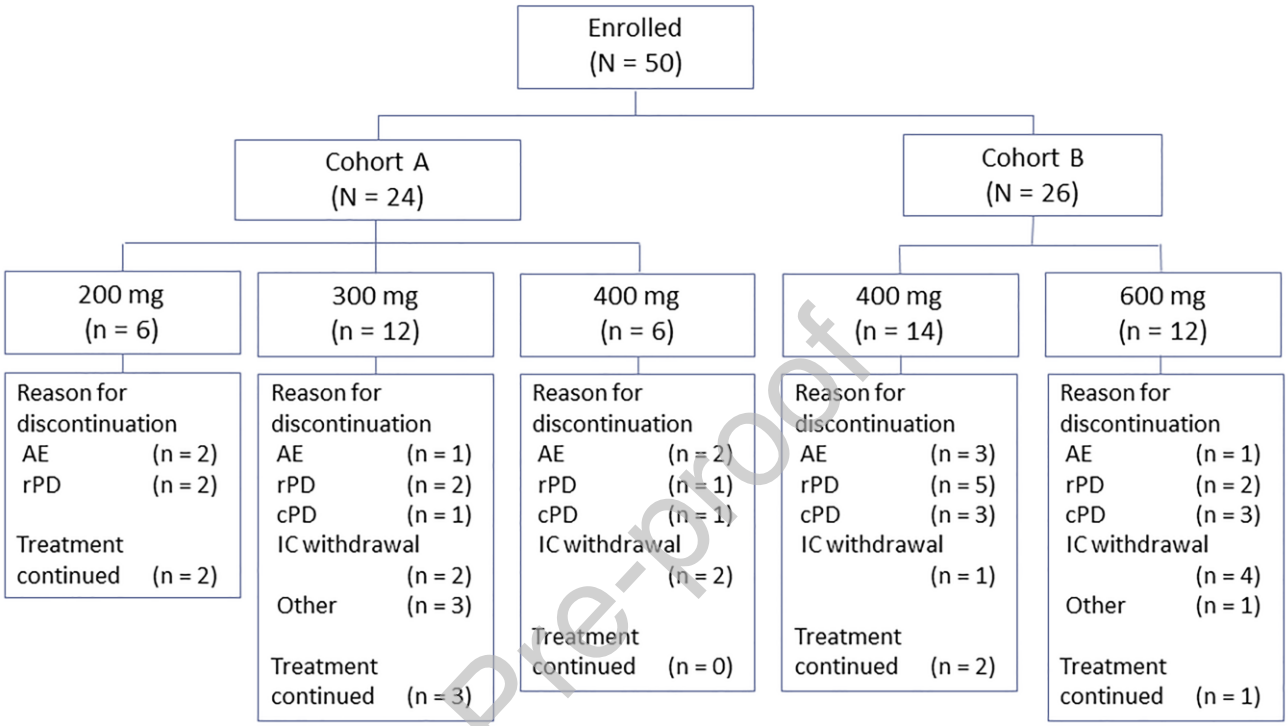


Figure 1. Patient disposition, indicating cohorts, TAS-115 dosages, and reasons for discontinuation. Data cut-off for this study was July 27, 2018.

Abbreviations: AE = adverse event; rPD = radiological progressive disease; cPD = clinical progressive disease; IC = informed consent.

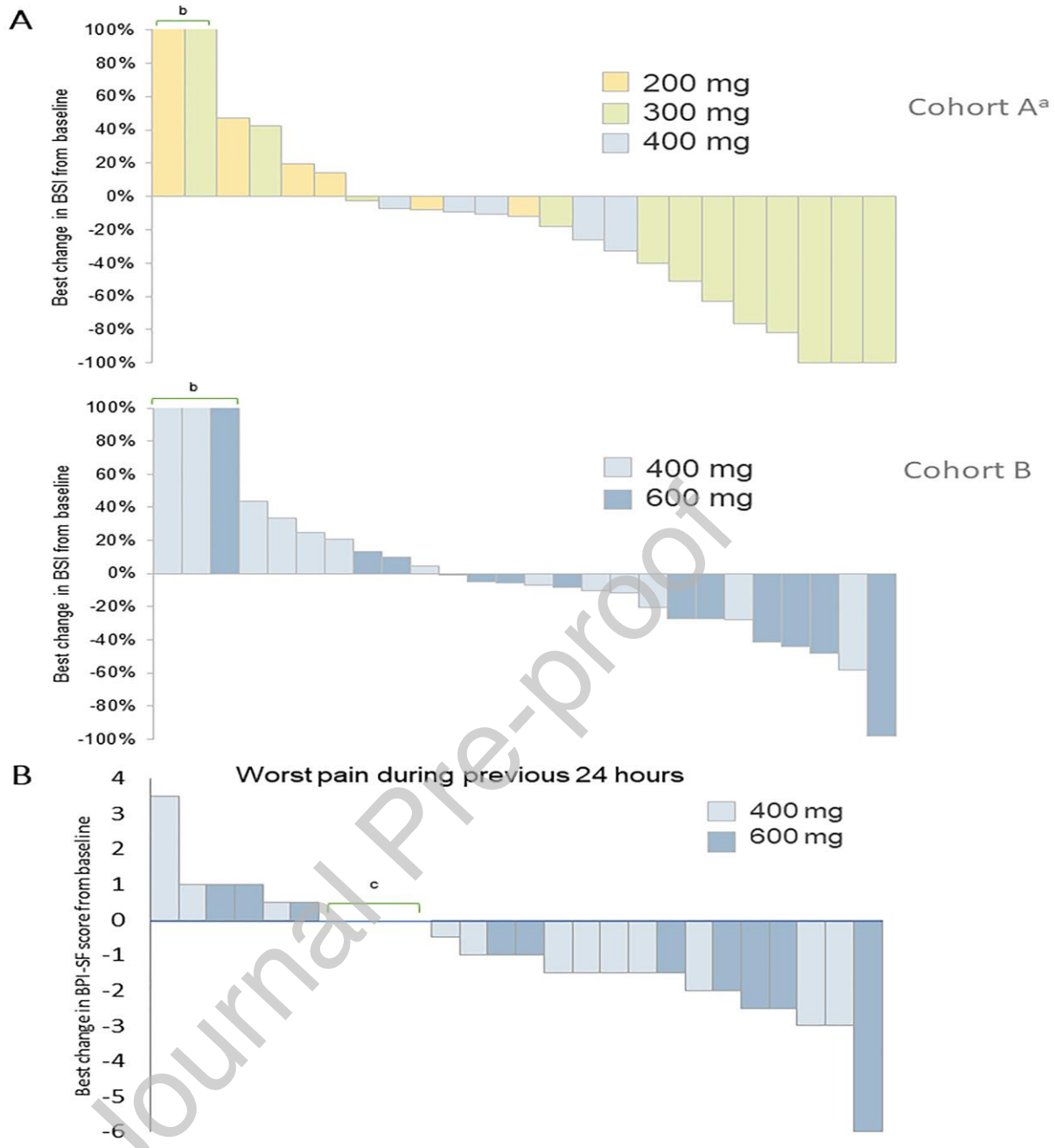


Figure 2. Best response in the bone scan index (A; values were centrally assessed as of July 27, 2018) and in the Brief Pain Inventory-Short Form (B; data current as of July 27, 2018).

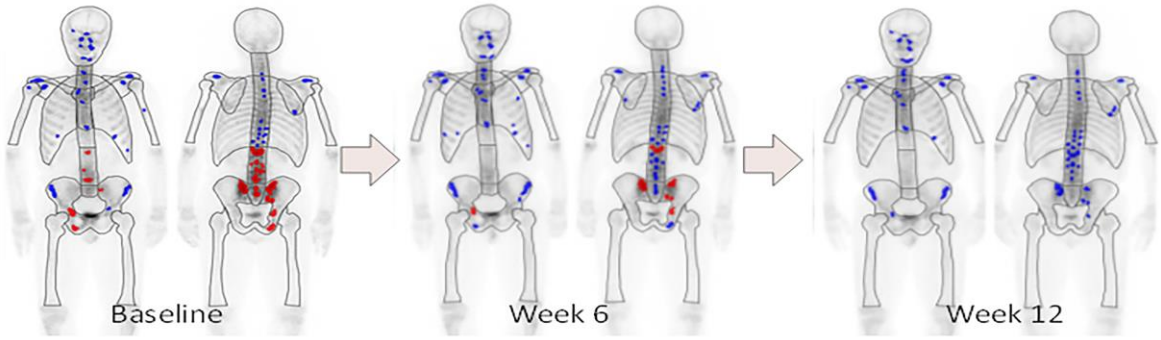
[a]One patient who only had baseline data was excluded from the analysis.

[b]Values higher than 100% are represented as 100% because of y-axis truncation at 100%.

[c]Indicates 0 points in 4 patients (600 mg/day: 2 patients, 400 mg/day: 2 patients). Any reduction in BPI-SF score was observed in 61.5% (16/26 patients) of patients

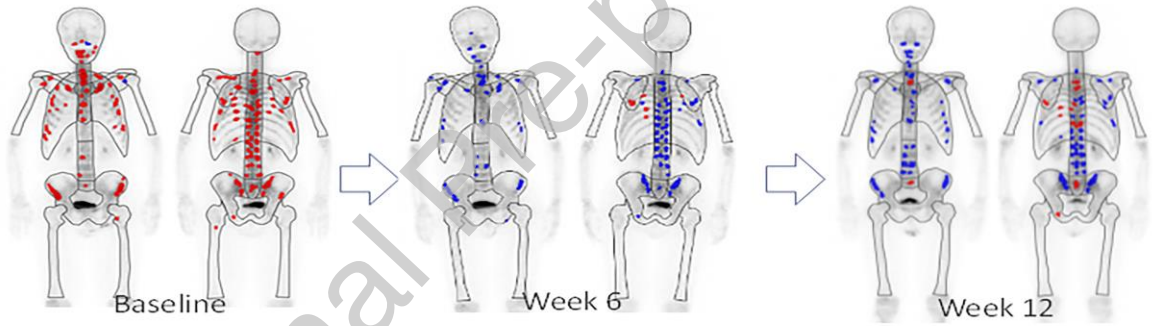
Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; BSI = bone scan index.

A



	Baseline	Week 6	Week 12	Week 24
BSI, % (change)	2.47	1.09 (-55.9%)	0.00 (-100%)	0.33 (-86.6%)
Hs, n	12	6	0	4

B



	Baseline	Week 6	Week 12
BSI, % (change)	5.21	0.19 (-96.3%)	0.61 (-88.3%)
Hs, n	87	5	11

Figure 3. Bone scan assessments of 2 patients who demonstrated a reduction in bone scan index. Start date: 2018/2/2; dose: 300 mg; treatment duration: 230 days (7.6 months) (A). Start date: 2017/9/1; dose: 600 mg; treatment duration: 106 days (3.5 months) (B).

Abbreviations: BSI = bone scan index; Hs = hotspot.