Molecular Cancer Therapeutics

First-in-Human Phase I Study of an Oral HSP90 Inhibitor, TAS-116, in Patients with Advanced Solid Tumors

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Abstract

HSP90 is involved in stability and function of cancer-related proteins. This study was conducted to define the MTD, safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor efficacy of TAS-116, a novel class, orally available, highly selective inhibitor of HSP90. Patients with advanced solid tumors received TAS-116 orally once daily (QD, step 1) or every other day (QOD, step 2) in 21-day cycles. Each step comprised a dose escalation phase to determine MTD and an expansion phase at the MTD. In the dose escalation phase, an accelerated dose-titration design and a "3+3" design were used. Sixty-one patients were enrolled in Japan and the United Kingdom. MTD was determined to be 107.5 mg/m^2/day for QD, and 210.7 mg/m^2/day for QOD. In the expansion phase of step 1, TAS-116 was administered 5 days on/2 days off per week (QD × 5). The most common treatment-related adverse events included gastrointestinal disorders, creatinine increases, AST increases, ALT increases, and eye disorders. Eye disorders have been reported with HSP90 inhibitors; however, those observed with TAS-116 in the expansion phases were limited to grade 1. The systemic exposure of TAS-116 increased dose-proportionally with QD and QOD regimens. Two patients with non–small cell lung cancer and one patient with gastrointestinal stromal tumor (GIST) achieved a confirmed partial response. TAS-116 had an acceptable safety profile with some antitumor activity, supporting further development of this HSP90 inhibitor.

This is a result from a first-in-human study, in which the HSP90 inhibitor TAS-116 demonstrated preliminary antitumor efficacy in patients with advanced solid tumors, including those with heavily pretreated GIST.

Introduction

HSP90 is an ATP-dependent molecular chaperone that is crucial for the stability and function of numerous proteins, referred to as "client" proteins, including receptor tyrosine kinases, signal transducers, cell-cycle regulators, and transcriptional factors (1–5). Most HSP90 clients are cancer-related proteins, such as anaplastic lymphoma kinase (ALK), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), EGFR, ErbB family 2 (ERBB2), insulin-like growth factor-1 receptor (IGF1R), v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), and Met proto-oncogene (MET). They have been observed to have gene amplification, high expression, and increased activity due to mutation in cancer, and mediate key signaling pathways that are involved in tumor development and survival (3). HSP90 itself has also been reported to be overexpressed and exist as activated multichaperone complexes in cancer cells and cancer tissues (6–9).

HSP90 has been regarded as one of targets for cancer treatment, as HSP90 inhibition may block multiple signaling pathways in

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tumor cells, resulting in potent, selective anticancer activity (1, 3, 5). Although many HSP90 inhibitors including ansamycine-, purine-, and resorcinol derivatives have been developed, none of them have been approved for any cancer indication due to their limited single-agent clinical activity and off-target and/or HSP-related toxicities, such as eye disorders (10–13).

TAS-116, 3-ethyl-4-[3-(1-methylethyl)-4-[4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-1-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl]benzamide, is a novel class of orally active inhibitors of HSP90. TAS-116 binds to the N-terminal domain of HSP90, and selectively inhibits cytosolic HSP90α and HSP90β, but does not inhibit HSP90 paralogs such as endoplasmic reticulum GRP94 or mitochondrial TRAP1 (14). TAS-116 demonstrated antitumor activity in human tumor xenograft models including subcutaneous and orthotopic transplantation in nude mice, accompanied by depletion of multiple HSP90 client proteins, without detectable ocular toxicities in rat models. This may be explained by lower TAS-116 distribution to nontarget eye tissues than in target tumor tissues. Even in the 4-week repeated-dose toxicity study of TAS-116 at double dose of the highest nonseverely toxic dose in dogs, TAS-116 did not show ocular toxicity on histopathologic evaluation.

On the basis of preclinical studies, a first-in-human study was designed to evaluate safety, MTD, pharmacokinetics, and antitumor activity when TAS-116 was administered orally in multiple dosing schedules. We also evaluated biological changes in HSP70 protein expression levels in peripheral blood mononuclear cells (PBMC) as a pharmacodynamic marker of TAS-116 (15).

Materials and Methods

Study design and treatment

We conducted a first-in-human, open-label, multicenter, phase I study of TAS-116 in Japan and the United Kingdom. The primary objective was to determine the MTD. Secondary objectives included the safety, efficacy, pharmacokinetics, and pharmacodynamics of TAS-116. At first, two dosing schedules of once daily (QD, step 1) and every other day (QOD, step 2) were planned. Each step comprised two phases: a dose escalation phase to determine MTD and a subsequent expansion phase at the MTD. TAS-116 was administered orally, in 21-day cycles. In step 1, the starting dose of 4.8 mg/m^2/day was chosen based on 1/10 of the severely toxic dose in 10% of rats (STD_{10}), and the dose was escalated according to an accelerated titration design (16), where 1 patient was enrolled at each dose level followed by a "3 + 3″ design. In step 2, QOD dosing was subsequently assessed starting at the MTD in step 1, escalating the dose according to a "3 + 3″ design. Following MTD determination, the expansion phase was conducted to evaluate the safety, tolerability, and efficacy at the MTD of two regimens, modified QD (5 days on/2 days off per week, QD × 5) and QOD. Patients continued treatment with TAS-116 until disease progression, the occurrence of unacceptable adverse events (AE), or withdrawal of informed consent.

Eligibility

Patients with histologically or cytologically confirmed, advanced solid tumors for which standard treatment was no longer effective were enrolled. Key inclusion criteria were as follows: age ≥18 years (≥20 years in Japan); clinically evaluable tumors; an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1; and adequate bone marrow, liver, and renal function [hemoglobin ≥8.5 g/dL; absolute neutrophils ≥1,500/mm^3; platelets (PLT) ≥10 × 10^4 μL; total bilirubin ≤1.5 mg/dL; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <3 times upper limit of normal (ULN); creatinine clearance ≥50 mL/min]. Key exclusion criteria included a serious illness or medical condition, receiving chemotherapy or radiotherapy within 21 days before enrollment, or corrected visual acuity of <0.5 (using the International Visual Acuity Measurement Standard) for both eyes. The study protocol was approved by institutional review boards/independent ethics committees at each institution. The study was conducted in accordance with the study protocol, Good Clinical Practice guidelines, the Declaration of Helsinki, and all applicable regulations. All patients provided written informed consent.

Safety assessment

AEs were graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03. Dose-limiting toxicity (DLT) was defined as any of the following treatment-related AEs occurred during cycle 1: grade 4 neutropenia lasting ≥8 days, febrile neutropenia, ≥grade 3 thrombocytopenia with hemorrhage, grade 4 thrombocytopenia requiring platelet transfusion, ≥grade 3 nonhematologic toxicity in which improvement or recovery was not seen with symptomatic therapy, toxicity requiring drug interruption for ≥8 days, or any toxicity that was considered by investigators and the sponsor to be a DLT. The MTD was defined as the highest dose level at which less than 33% of patients experienced a DLT during cycle 1. To detect eye disorders, one of the class effects of HSP90 inhibitors, ophthalmological examinations including a visual acuity test (corrected), ocular pressure test, ocular fundus examination, slit lamp examination, optical coherence tomography (OCT), and color perception test were performed at screening, on day 21 of cycle 1, and 28 days after the last administration of TAS-116. An ECG was performed at baseline, on days 1, 8, and 21 of cycle 1, and day 8 on cycles 2, 3, and 4, and 28 days after the last administration of TAS-116. The heart rate, RR interval, PR interval, QRS duration, and QT duration in all ECG data were measured by an independent central cardiologist.

Pharmacokinetic assessments

Blood samples for pharmacokinetic analyses were collected at various time points on day 1 and day 8 for QD doses (over a 24-hour period); on day 1 and day 15 for QOD doses (over a 48-hour period); and on day 1, day 8 (only predose), and day 19 or day 1, day 4, day 11 (only predose), and day 22 for QD × 5 doses (over a 24-hour period). Plasma concentrations of TAS-116 were measured using the validated LC/MS-MS method. Standard pharmacokinetic parameters were calculated by noncompartmental analysis with Phoenix WinNonlin 7.0 (Certara LP). The dose proportionality of TAS-116 was evaluated on day 1 (step 1 and step 2), and day 8 (step 1) or day 15 (step 2) using a power regression analysis.

Pharmacodynamic assessments

Blood samples for pharmacodynamic analysis were collected during the 14 days before the start of treatment, on day 3 (QD), and on day 15 (QD and QOD), or on day 12 (QD × 5) in cycle 1. Changes in HSP70 protein expression levels in PBMCs before and after the treatment with TAS-116 were examined as a surrogate

Table 1. Baseline patient demographics and disease characteristics (all treated patients)

Regimen	Step 1 Dose escalation QD	Step 1 Expansion QD × 5	Step 2 Dose escalation QOD	Step 2 Expansion QOD
Dose	4.8–150.5 mg/m^2	160 mg/body	107.5–295.0 mg/m^2	340 mg/body
Number of patients (*n*)	16	19	20	6
Sex, *n* (%)				
Male	10 (62.5)	11 (57.9)	8 (40.0)	4 (66.7)
Female	6 (37.5)	8 (42.1)	12 (60.0)	2 (33.3)
Age, years				
Median	55.5	61.0	54.5	56.0
(Min, Max)	(34, 74)	(40, 73)	(34, 72)	(40, 75)
Race, *n* (%)				
Asian	16 (100.0)	13 (68.4)	20 (100.0)	6 (100.0)
Caucasian	0 (0.0)	6 (31.6)	0 (0.0)	0 (0.0)
ECOG performance status, *n* (%)				
0	12 (75.0)	11 (57.9)	11 (55.0)	3 (50.0)
1	4 (25.0)	8 (42.1)	9 (45.0)	3 (50.0)
Tumor type, *n* (%)				
NSCLC	10 (62.5)	0 (0.0)	11 (55.0)	2 (33,3)
GIST	2 (12.5)	4 (21.1)	1 (5.0)	0 (0.0)
Pancreas cancer	0 (0.0)	3 (15.8)	1 (5.0)	1 (16.7)
Biliary tract cancer	0 (0.0)	3 (15.8)	0 (0.0)	1 (16.7)
Thymic cancer	2 (12.5)	2 (10.5)	0 (0.0)	0 (0.0)
Cancer of unknown primary	0 (0.0)	1 (5.3)	2 (10.0)	0 (0.0)
Other	2 (12.5)	6 (31.6)	5 (25.0)	2 (33.3)

marker of HSP90 inhibition (15). The amount of HSP70 protein in PBMCs was measured using a validated ELISA.

Efficacy assessments

Antitumor activity was assessed by the investigators based on RECIST version 1.1 every 6 weeks up to week 24 and every 8 weeks thereafter via the diagnostic method (CT, MRI, X-ray, etc.) used at enrollment.

Results

Patient characteristics and study drug exposure

Between March 31, 2014 and February 7, 2017, 61 patients were enrolled into the dose escalation ($n = 36$) and expansion ($n = 25$) phases and received at least one dose of TAS-116. Sixty patients were evaluable for efficacy; 1 patient was excluded from the efficacy analysis due to prohibited concomitant medication usage. Six UK patients were enrolled in the step 1 expansion phase. Data cutoff was May 3, 2017, when the last patient completed 4 cycles of treatment. Patient demographics and baseline characteristics are listed in Table 1. The dose of TAS-116 was escalated from 4.8 to 150.5 mg/m^2/day QD in step 1, and from 107.5 to 295.0 mg/m^2/day QOD in step 2 (Fig. 1). The MTDs were 107.5 mg/m^2/day for QD and 210.7 mg/m^2/day for QOD. As there was no correlation between body surface area (BSA) and oral clearance (CL/F; Supplementary Fig. S1), the doses of the expansion phases were determined to be a flat-dose of the MTD, that is, 160 mg/body/day for QD × 5 in step 1 and 340 mg/body/day for QOD in step 2. There were 5 of 6 patients who received TAS-116 QD at the MTD and required drug interruption owing to treatment-related AEs during cycle 1; therefore, the administration schedule was changed from QD to QD × 5 in the expansion phase in step 1. The median treatment duration in step 1 was 3.0 cycles (range, 1–16 cycles) for the dose escalation phase (QD, $n = 16$) and 3.0 cycles (range, 1–22 cycles) for the expansion phase (QD × 5, $n = 19$). In step 2 (QOD), it was 4.0 cycles (range, 1–26 cycles) for the dose escalation phase ($n = 20$) and 2.0 cycles (range, 1–3 cycles) for the expansion phase ($n = 6$).

Safety

The most frequently reported treatment-related AEs (≥25%) were diarrhea (83.6%), creatinine increased (55.7%), anorexia (50.8%), nausea (42.6%), eye disorders (32.8%), AST increased (32.8%), ALT increased (29.5%), and fatigue (29.5%). Treatment-related AEs that occurred in ≥10% of patients are summarized in Table 2. The majority of those were grade 1 or 2.

DLTs are listed in Table 3. In step 1 (QD), DLTs were observed in 3 patients at level 7 (150.5 mg/m^2) with grade 3 night blindness, grade 3 visual impairment, and grade 3 AST/ALT/γ-glutamyltransferase (γ-GTP) increased and in 1 patient at level 6 (107.5 mg/m^2) with grade 3 anorexia. In step 2 (QOD), DLTs were observed in 2 patients at level 4 (295.0 mg/m^2). Grade 3 PLT count decreased was observed in 1 patient. Grade 4 septic shock, grade 4 respiratory failure, grade 4 pneumonia, and grade 3 febrile neutropenia were observed in another patient. As a result, the MTD was determined at 107.5 mg/m^2/day (level 6) for QD and 210.7 mg/m^2/day (level 3) for QOD.

Eye disorders were mainly night blindness ($n = 13$), blurred vision ($n = 3$), and visual impairment ($n = 3$). Eye disorders ≥grade 2, the AE of special interest in this study, occurred in the dose escalation phases at the MTD and maximum administered dose (MAD) on the QD schedule, and MAD on the QOD schedule. However, with QD × 5 and at the MTD in the QOD schedule, eye disorders were limited to grade 1. Except for macular edema found on ophthalmological examination in 1 patient, eye disorders were found on physical examination by the investigators. All eye disorders were reversible with interruption or discontinuation of TAS-116 treatment.

Thirteen treatment-related serious AEs (SAE) were observed in 6 patients (9.8%). Those observed in step 1 were pulmonary embolism and interstitial lung disease at level 5 (76.8 mg/m^2), and AST/ALT/γ-GTP increased ($n = 1$) and visual impairment ($n = 1$) at level 7 (150.5 mg/m^2). Those observed in step 2 were septic

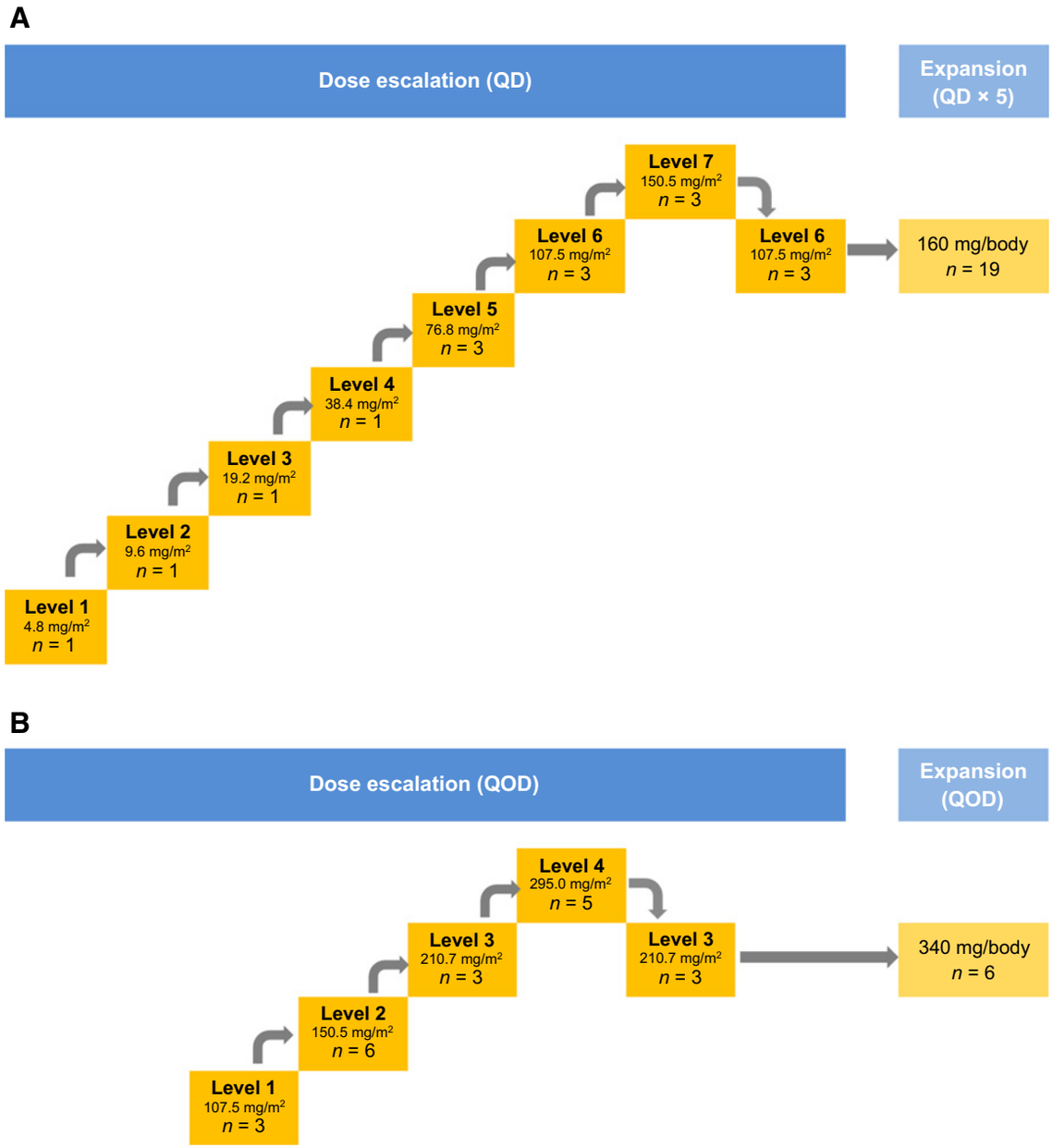

Figure 1.
Study design outline for the dose escalation and expansion phases. **A,** In step 1, the dose of TAS-116 (once daily, QD) was escalated according to an accelerated titration design followed by a "3+3" design, and the MTD was determined to be 107.5 mg/m^2. **B,** In step 2, dose escalation was started from the MTD in step 1 using a "3+3" design, and the MTD was determined to be 210.7 mg/m^2. Both the MTDs were further tested in the expansion phase.

shock, respiratory failure, pneumonia, neutrophil count decrease, and PLT count decrease in 1 patient at level 4 (295.0 mg/m^2), and dehydration and enterocolitis infectious in 1 patient in the expansion phase (340 mg/body). All treatment-related SAEs recovered or resolved after interruption, dose reduction, or discontinuation of TAS-116 treatment. No treatment-related deaths were reported. Seven (11.5%) patients discontinued TAS-116 administration due to the following AE: grade 3 interstitial lung disease (76.8 mg/m^2, QD), grade 2 cystitis (107.5 mg/m^2, QD), grade 2 macular edema (107.5 mg/m^2, QD), grade 3 anorexia (107.5 mg/m^2, QD), grade 3 night blindness (150.5 mg/m^2, QD), grade 3 anemia (295.0 mg/m^2, QOD), and grade 4 septic shock with grade 4 respiratory failure and grade 4 pneumonia (295.0 mg/m^2, QOD).

Local reading of ECGs demonstrated QTc prolongation in 14.8% (9/61) of patients. Upon central review by the independent cardiologist, 8 of these 9 patients did not show increase in QTc > 450 ms; the remaining one was grade 1 and recovered following TAS-116 discontinuation. According to review by the independent central cardiologist, 3 patients showed an increase in QTc >

Table 2. Treatment-related AEs (incidence ≥10%)

	Total			QD Step 1 Dose Escalation									QD × 5 Step 1 Expansion		
				Lv. 1 to 5 (4.8–76.8 mg/m^2)			Lv. 6 (107.5 mg/m^2)			Lv. 7 (150.5 mg/m^2)			(160 mg/body)		
	$n = 61$			$n = 7$			$n = 6$			$n = 3$			$n = 19$		
AEs, *n* (%)	**G1**	**G2**	**≥ G3**	**G1**	**G2**	**≥ G3**	**G1**	**G2**	**≥ G3**	**G1**	**G2**	**≥ G3**	**G1**	**G2**	**≥ G3**
Anorexia	11 (18.0)	17 (27.9)	3 (4.9)	1 (14.3)	—	—	3 (50.0)	1 (16.7)	2 (33.3)	—	2 (66.7)	—	2 (10.5)	7 (36.8)	—
Eye disorder	14 (23.0)	4 (6.6)	2 (3.3)	—	1 (14.3)	—	3 (50.0)	2 (33.3)	—	—	—	2 (66.7)	5 (26.3)	—	—
Diarrhea	31 (50.8)	16 (26.2)	4 (6.6)	3 (42.9)	—	—	2 (33.3)	3 (50.0)	1 (16.7)	2 (66.7)	1 (33.3)	—	8 (42.1)	6 (31.6)	1 (5.3)
Nausea	16 (26.2)	9 (14.8)	1 (1.6)	—	1 (14.3)	—	1 (16.7)	2 (33.3)	1 (16.7)	1 (33.3)	1 (33.3)	—	8 (42.1)	2 (10.5)	—
Vomiting	10 (16.4)	3 (4.9)	—	1 (14.3)	—	—	2 (33.3)	—	—	—	—	—	2 (10.5)	1 (5.3)	—
Stomatitis	7 (11.5)	1 (1.6)	—	—	—	—	2 (33.3)	—	—	—	—	—	—	—	—
Rash	7 (11.5)	3 (4.9)	—	1 (14.3)	—	—	1 (16.7)	2 (33.3)	—	1 (33.3)	—	—	1 (5.3)	—	—
Dermatitis acneiform	9 (14.8)	—	—	—	—	—	2 (33.3)	—	—	—	—	—	3 (15.8)	—	—
Fatigue	12 (19.7)	6 (9.8)	—	1 (14.3)	—	—	2 (33.3)	1 (16.7)	—	—	2 (66.7)	—	3 (15.8)	2 (10.5)	—
Pyrexia	8 (13.1)	—	—	2 (28.6)	—	—	1 (16.7)	—	—	1 (33.3)	—	—	1 (5.3)	—	—
Creatinine increased	13 (21.3)	21 (34.4)	—	2 (28.6)	2 (28.6)	—	—	5 (83.3)	—	1 (33.3)	2 (66.7)	—	3 (15.8)	5 (26.3)	—
AST increased	13 (21.3)	3 (4.9)	4 (6.6)	2 (28.6)	—	—	3 (50.0)	—	—	—	1 (33.3)	1 (33.3)	2 (10.5)	1 (5.3)	1 (5.3)
ALT increased	10 (16.4)	6 (9.8)	2 (3.3)	1 (14.3)	1 (14.3)	—	2 (33.3)	—	—	—	—	1 (33.3)	1 (5.3)	2 (10.5)	1 (5.3)
ALP increased	10 (16.4)	3 (4.9)	1 (1.6)	2 (28.6)	—	—	2 (33.3)	—	—	1 (33.3)	—	—	2 (10.5)	2 (10.5)	—
Protein urine present	2 (3.3)	11 (18.0)	—	1 (14.3)	1 (14.3)	—	—	1 (16.7)	—	—	—	—	—	2 (10.5)	—
Blood phosphorus increased	10 (16.4)	1 (1.6)	—	—	—	—	2 (33.3)	—	—	—	1 (33.3)	—	3 (15.8)	—	—
Electrocardiogram QT prolonged	7 (11.5)	2 (3.3)	—	1 (14.3)	—	—	3 (50.0)	—	—	—	1 (33.3)	—	1 (5.3)	—	—
Hemoglobin urine present	7 (11.5)	1 (1.6)	1 (1.6)	1 (14.3)	1 (14.3)	—	1 (16.7)	—	—	1 (33.3)	—	—	2 (10.5)	—	—
Platelet count decreased	7 (11.5)	—	2 (3.3)	—	—	—	2 (33.3)	—	—	—	—	—	—	—	—

	QOD Step 2 Dose Escalation									QOD Step 2 Expansion					
	Lv. 1 to 2 (107.5–150.5 mg/m^2)			Lv. 3 (210.7 mg/m^2)			Lv. 4 (295.0 mg/m^2)			(340 mg/body)					
	$n = 9$			$n = 6$			$n = 5$			$n = 6$					
AE, *n* (%)	**G1**	**G2**	**> G3**	**G1**	**G2**	**> G3**	**G1**	**G2**	**> G3**	**G1**	**G2**	**> G3**			
Anorexia	2 (22.2)	1 (11.1)	—	2 (33.3)	1 (16.7)	—	1 (20.0)	3 (60.0)	—	—	2 (33.3)	1 (16.7)	—	—	—
Eye disorder	2 (22.2)	—	—	1 (16.7)	—	—	3 (60.0)	1 (20.0)	—	—	—	—	—	—	—
Diarrhea	6 (66.7)	1 (11.1)	—	5 (83.3)	1 (16.7)	—	1 (20.0)	2 (40.0)	2(40.0)	4 (66.7)	2 (33.3)	—	—	—	—
Nausea	2 (22.2)	—	—	3 (50.0)	—	—	1 (20.0)	2 (40.0)	—	—	1 (16.7)	—	—	—	—
Vomiting	2 (22.2)	—	—	2 (33.3)	—	—	—	2 (40.0)	—	1 (16.7)	—	—	—	—	—
Stomatitis	—	—	—	—	—	—	4 (80.0)	—	—	1 (16.7)	1 (16.7)	—	—	—	—
Rash	1 (11.1)	—	—	—	—	—	2 (40.0)	1 (20.0)	—	—	—	—	—	—	—
Dermatitis acneiform	2 (22.2)	—	—	1 (16.7)	—	—	1 (20.0)	—	—	—	—	—	—	—	—
Fatigue	1 (11.1)	—	—	2 (33.3)	1 (16.7)	—	2 (40.0)	—	—	1 (16.7)	—	—	—	—	—
Pyrexia	1 (11.1)	—	—	—	—	—	2 (40.0)	—	—	—	—	—	—	—	—
Creatinine increased	1 (11.1)	1 (11.1)	—	2 (33.3)	2 (33.3)	—	3 (60.0)	2 (40.0)	—	1 (16.7)	2 (33.3)	—	—	—	—
AST increased	2 (22.2)	1(11.1)	—	3 (50.0)	—	—	1 (20.0)	—	1 (20.0)	—	—	1 (16.7)	—	—	—
ALT increased	4 (44.4)	—	—	2 (33.3)	1 (16.7)	—	—	1 (20.0)	—	—	1 (16.7)	—	—	—	—
ALP increased	2 (22.2)	—	—	1 (16.7)	—	—	—	1 (20.0)	—	—	—	1 (16.7)	—	—	—
Protein urine present	1 (11.1)	2 (22.2)	—	—	2 (33.3)	—	—	2 (40.0)	—	—	1 (16.7)	—	—	—	—
Blood phosphorus increased	2 (22.2)	—	—	—	—	—	2 (40.0)	—	—	1 (16.7)	—	—	—	—	—
Electrocardiogram QT prolonged	1 (11.1)	—	—	—	—	—	1 (20.0)	—	—	—	1 (16.7)	—	—	—	—
Hemoglobin urine present	—	—	—	1 (16.7)	—	—	1 (20.0)	—	—	—	—	1 (16.7)	—	—	—
Platelet count decreased	1 (11.1)	—	—	2 (33.3)	—	—	2 (40.0)	—	2 (40.0)	—	—	—	—	—	—

Abbreviation: G, grade.

Table 3. DLTs

Dosage level	Dose (mg/m^2)	Regimen	DLT
Step 1 Level 6	107.5	QD	Anorexia (grade 3)
Step 1 Level 7	150.5	QD	AST, ALT, and γ-GTP increased (grade 3)
Step 1 Level 7	150.5	QD	Night blindness (grade 3)
Step 1 Level 7	150.5	QD	Visual impairment (grade 3)
Step 2 Level 4	295.0	QOD	PLT count decreased (grade 3)
Step 2 Level 4	295.0	QOD	Septic shock, respiratory failure, pneumonia (grade 4), febrile neutropenia (grade 3)

450 ms. In 1 patient, QTc prolongation was reported as a grade 1 AE by the investigator. In the other 2 patients, the QTc changes were confirmed as not clinically significant by the investigator because it was transient or there was little change from baseline. No other clinically significant changes were detected by the independent cardiologist who reviewed all ECG data.

Pharmacokinetics

The plasma concentration–time profiles of TAS-116 in the dose escalation phase of step 1 are shown in Fig. 2. Systemic exposure was dose proportional over the range tested, from 4.8 to 150.5 mg/m^2 on QD and from 107.5 to 295.0 mg/m^2 on QOD. There was no unexpected accumulation in TAS-116 exposure between day 1 and day 8 of cycle 1. The pharmacokinetic parameters for all schedules are presented in Supplementary Table S1. The pharmacokinetic parameters (C_{max} and AUC_{last}) after multiple administrations in QD × 5 were comparable between Japanese and Caucasian patients, although the number of Caucasian patients in this study was small.

Pharmacodynamics

The expression of HSP70 protein in PBMCs was evaluated in 41 patients. After the results from first 15 patients, sampling points were determined to be at baseline and once posttreatment (day 12 or day 15) for the rest of the patients. Induction of HSP 70 protein expression after TAS-116 administration tends to be in a dose-dependent manner from 4.8 to 107.5 mg/m^2 in step 1. In step 2, induction of HSP 70 protein expression after TAS-116 administration occurred at all levels (107.5–295.0 mg/m^2; Fig. 3).

Efficacy

Figure 4 shows the greatest change in tumor size from baseline in patients who had at least one target lesion. Confirmed durable partial responses (PR) by RECIST were observed in 3 patients (Table 4). Disease control rate (DCR) including PR and stable disease (SD) ≥12 weeks were 27% (16/60 patients). Response durations of three patients with PR were 173 days in non–small cell lung cancer (NSCLC) without detectable *EGFR* and *ALK* mutations (107.5 mg/m^2 QD), 463 days (at the time of data cutoff) in NSCLC with an *EGFR* exon 19 deletion mutation (150.5 mg/m^2 QOD), and 239 days in gastrointestinal stromal tumor (GIST) without a detectable *KIT* mutation (150.5 mg/m^2 QD, one dose level higher than the MTD, who continued on TAS-116 treatment for more than 6 months after dose reduction to the MTD on day 42).

A long period of SD was also confirmed in a patient with GIST who had received 5 prior treatments (imatinib, sunitinib, regorafenib, an investigational drug, and imatinib rechallenge), and had secondary *KIT* mutations in exon 17 (D820Y and N822K) at enrollment. Although such *KIT* mutations were associated with resistance to standard treatment for GIST (imatinib and other tyrosine kinase inhibitors), the progression-free duration was as long as 393 days. PET/CT scans 1 and 4 months after the start of TAS-116 treatment (160 mg/body, QD × 5) showed remarkable decreases in fluorodeoxyglucose (FDG) accumulation (Fig. 4).

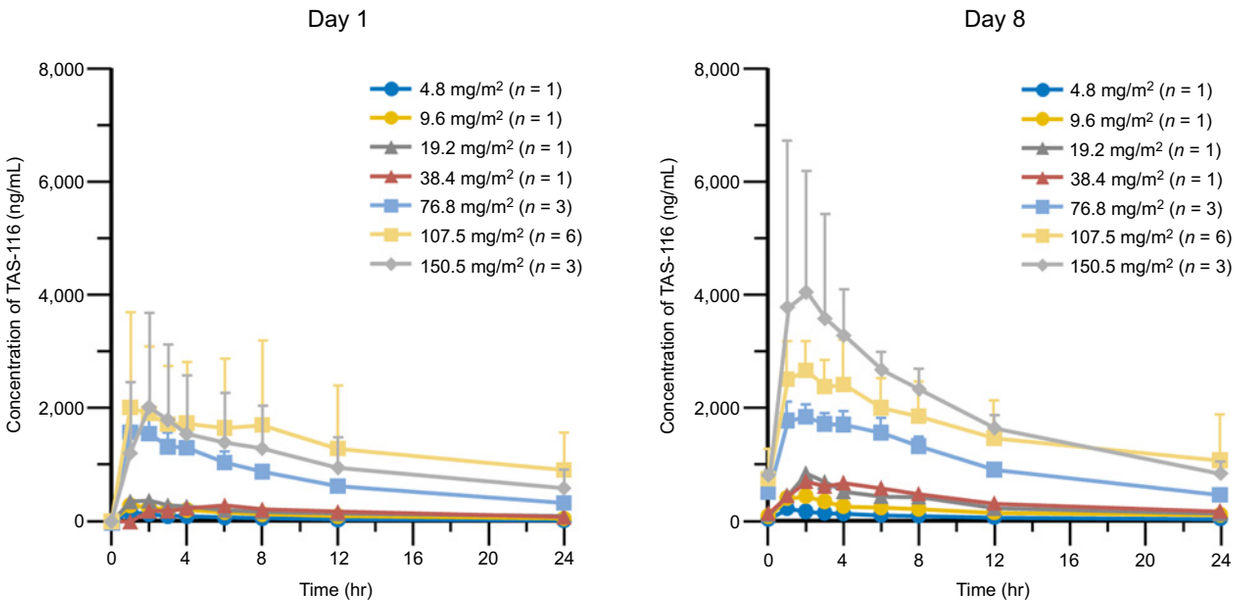

Figure 2.
Plasma concentration–time profile of TAS-116. Each line represents the mean plasma concentration (+SD) in patients in the dose escalation phase of step 1 when TAS-116 was administered once daily (QD) at a given dose.

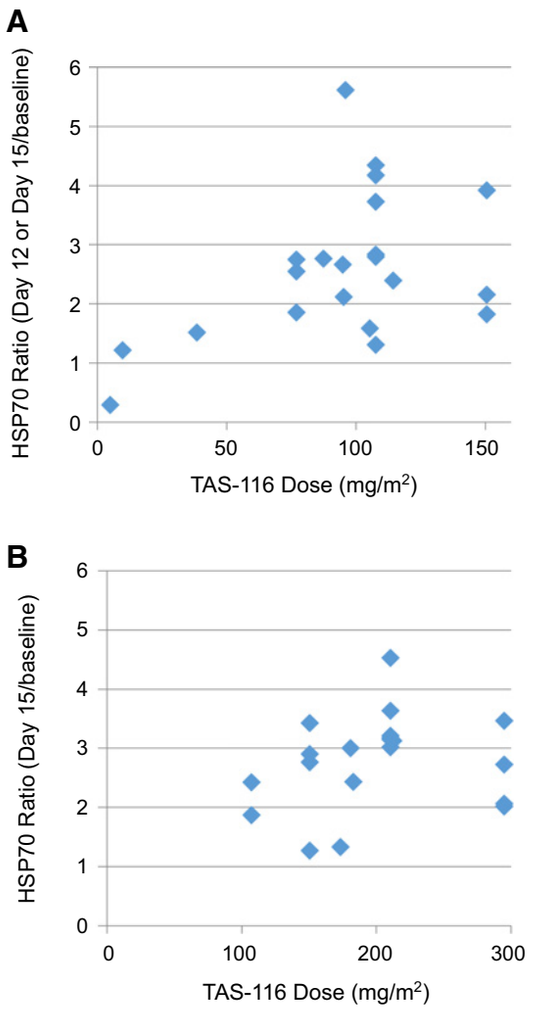

Figure 3.

Change in HSP70 level by TAS-116. TAS-116 was administered QD/QD×5 in step 1 (**A**), and QOD in step 2 (**B**), and expression of HSP70 was analyzed in 41 patients at baseline and during TAS-116 treatment. Every point represents HSP70 ratio (during treatment/at baseline) and TAS-116 dose for each patient.

Discussion

In Japan and the United Kingdom, we conducted the first-in-human phase I study of TAS-116, an orally administered, potent, and highly selective inhibitor of HSP90α and HSP90β. We examined three dosing regimens, QD, QD × 5, and QOD, established MTD, determined a dosing regimen for further development and observed activity in tumors.

We noted that the AEs with TAS-116 were similar to those reported with previous clinical studies of HSP90 inhibitors: gastrointestinal disorders, hepatic enzyme increased, and eye disorders such as night blindness and blurred vison (12, 13, 17, 18).

HSP90 plays a critical role also in retinal function, and sustained HSP90 inhibition may be associated with eye disorders (19–21). Effects of TAS-116 on retina have yet to been examined; it was reported that reduction of rhodopsin kinase (GRK1), one of HSP90 client proteins, by sustained HSP90 inhibition adversely affects visual function (22).

Referring to the monitoring guidelines on the ocular toxicity of targeted therapies (23), we performed intensive ophthalmologic examinations including OCT that is a noninvasive retinal imaging technique and was not mandatory in other previous clinical studies of HSP90 inhibitors (17, 24). Initially, eye disorders ≥grade 2 were observed in this study; however, changing treatment frequency from daily to intermittent dosing greatly improved the safety profile.

Another report may account for differences in the incidence of ocular toxicity among HSP90 inhibitors. Slow elimination of 17-DMAG and AUY922 from the retina compared with 17-AAG and ganetespib could have caused prolonged HSP90 inhibition and photoreceptor cell death in a rat model (21). In rats, TAS-116 is distributed less in the retina than in the plasma, and is more rapidly eliminated from retina than the other HSP90 inhibitors. Consequently, repeated oral administration of TAS-116 did not produce any detectable photoreceptor injury (14). The terminal elimination half-life ($T_{1/2}$) of TAS-116 observed in this study was slightly longer than in animals, which may explain the occurrence of eye disorders observed in this clinical trial. Thus, the effect of TAS-116 on the retina was considered clinically nonsignificant.

Diarrhea has been reported with other HSP90 inhibitors, such as ganetespib and AT13387, and was the most frequent AE observed in this study (all grade; 83.6%, ≥grade 3; 6.6%). The diarrhea with TAS-116 was manageable by dose reduction, interruption, or antidiarrheal agents. Dosing schedule tested in this study is considered feasible. Another common toxicity with HSP90 inhibitors, hepatotoxicity, was not frequent with TAS-116; ≥grade 3 AST increase and ALT increase occurred in 6.6% and 3.3% of patients, respectively, all of which resolved/were resolving after interruption or discontinuation of TAS-116. Hematologic side effects were not frequently seen with TAS-116 as with other HSP90 inhibitors. Overall, TAS-116 had an acceptable safety profile, particularly with QD × 5 and QOD.

This study enrolled 6 patients from the United Kingdom, and the preliminary assessment based on the small number of Caucasian patients dosed is that there seemed to be no ethnic differences in pharmacokinetics between Japanese and Caucasian patients after multiple administrations of TAS-116 in QD × 5. Further information on pharmacokinetics in Caucasians will be obtained from further studies with larger number of Caucasians. From the safety and pharmacokinetic profiles, the recommended doses (RD) and schedule for further study of TAS-116 were established to be a fixed dose of 160 mg/body/day QD × 5 and 340 mg/body/day QOD that are pharmacodynamically relevant.

Durable target inhibition and antitumor activity was seen with weekly administered HSP90 inhibitors in a human NSCLC xenograft mouse model (25, 26). However, suppression of the client proteins in humans could be more transient. In a phase II study of ganetespib in patients with GIST, analysis of client proteins in paired tumor biopsies from 4 patients did not demonstrate prolonged suppression of KIT client protein on weekly infusion, and the conclusion was that an alternative schedule to prolong suppression of KIT may be necessary to increase activity (27, 28). However, excessive exposure to an HSP90 inhibitor has the potential for safety concerns. As for TAS-116, the favorable pharmacokinetic profiles were confirmed in preclinical and these studies. In rats, TAS-116 was distributed more in tumors than in retina or plasma (14). In humans, $t_{1/2}$ was around 8 to 14 hours,

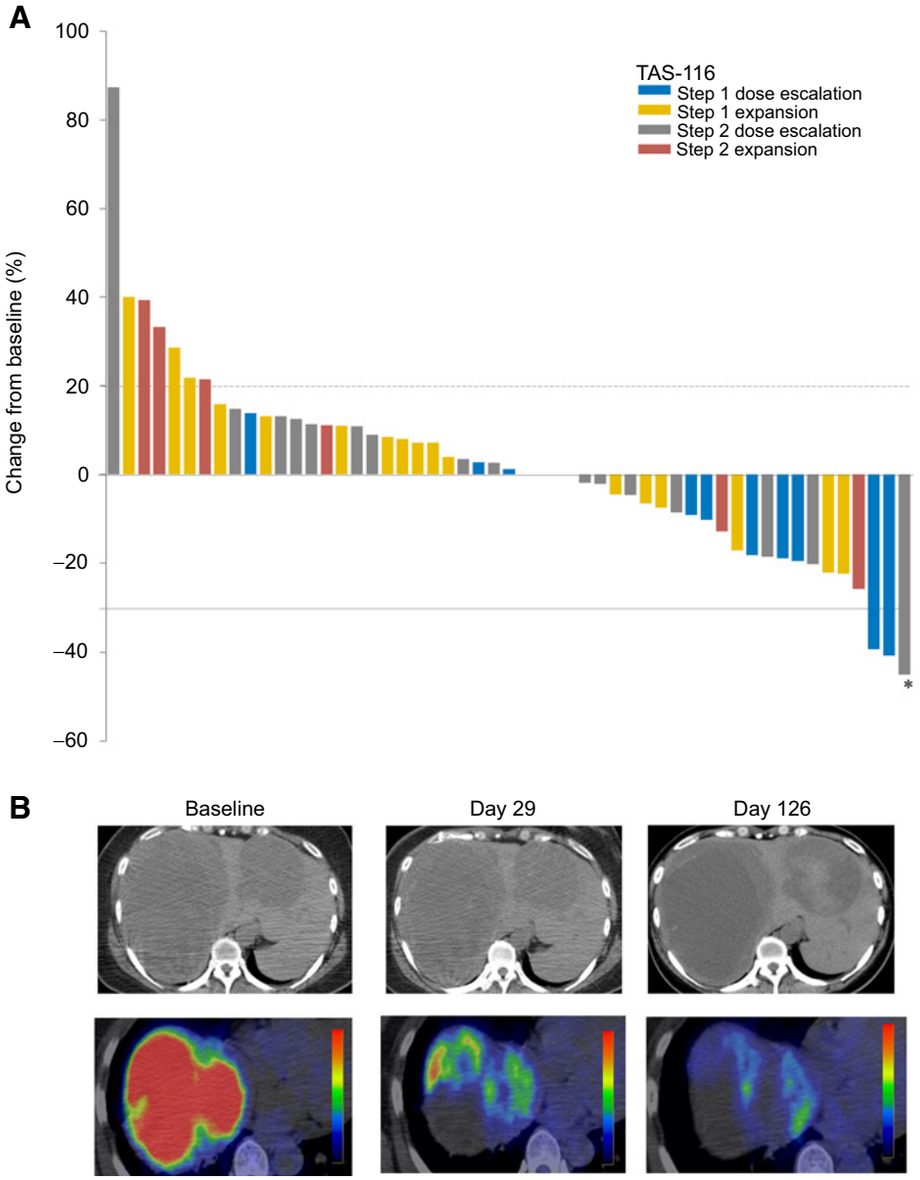

Figure 4.
Preliminary clinical responses of TAS-116. **A,** Best changes in target lesion size from baseline for the 53 patients in the per protocol set. One patient (indicated with *) was on treatment as of data cutoff of May 3, 2017. The solid line indicates PR (at least 30% decrease from baseline), and the dashed line indicates progressive disease (a change of greater than 20% from baseline) according to RECIST. **B,** PET/CT scans of the abdomen of a 43-year-old patient with heavily treated GIST. The patient received 160 mg/body (QD × 5) of TAS-116. Although the tumor response of the patient was SD by RECIST, PET/CT scan showed prolonged regression of the liver metastases and peritoneal dissemination.

which means that TAS-116 would be eliminated during 2 days drug rest. Orally available TAS-116 makes it easy to be administered with more frequent dosing schedules, and to be discontinued or dose adjusted when necessary.

This trial demonstrates that TAS-116 can be administered frequently (QD, QD × 5, and QOD) at doses that increased HSP70 protein expression. HSP70 has been selected as a pharmacodynamic marker also in other clinical studies of HSP90 inhibitors, such as SNX-5422 (29) because it is difficult to measure the activity of HSP90 directly in tissue or blood samples. Inhibition of HSP90 activates heat shock transcription factor-1 (HSF-1), which induces expression of HSP70 (15). Induction of HSP70 was observed at RDs in this study, although the limitation of this study was that induction of HSP70 was not considered in direct relation to antitumor effect, as relationship between client protein reduction and antitumor effect by monitoring client proteins during the study period was not assessed. However, to avoid patients' burdens from multiple biopsies, tumor samples were not required to evaluate the activity of TAS-116.

Treatment with TAS-116 led to three confirmed, durable PRs in 1 patient with advanced GIST and 2 patients with NSCLC. Among 3 patients with PR, 1 patient with NSCLC had an EGFR (one of HSP90 clients) mutation. Another patient with NSCLC (histologic type unknown) did not have any detectable mutation in HSP90 client proteins such as EGFR, ALK, ROS proto-oncogene 1 (ROS1), and rearranged during transfection (RET). The patient with GIST who achieved PR had no detectable KIT mutations. Not only KIT, but also many other proteins found in GIST without KIT mutations, such as platelet-derived growth factor receptor alpha (PDGFRA), hypoxia inducible factor (HIF)-1α, VEGFR, and BRAF are HSP90 clients. GIST without KIT mutations often has other mutations in PDGFRA, BRAF, neurofibromatosis type 1 (NF-1), or those encoding subunits of succinate dehydrogenase (SDH; ref. 30); however, the status of other mutations in this patient

Table 4. Tumor response by the RECIST version 1.1 in the per protocol set

	QD $n = 16$ (%)	QD × 5 $n = 18$ (%)	QOD $n = 26$ (%)
Best overall response, *n* (%)			
PR	2 (12.5)	0 (0.0)	1 (3.8)
SD	7 (43.8)	9 (50.0)	9 (34.6)
PD	5 (31.3)	8 (44.4)	15 (57.7)
Not evaluable (NE)	2 (12.5)	1 (5.6)	1 (3.8)
Response rate (CR + PR), *n* (%)	2 (12.5)	0 (0.0)	1 (3.8)
Disease control rate (CR + PR + SD for ≥12 weeks)	5 (31.3)	7 (38.9)	4 (14.4)

was not known. SDH-deficient GIST has been found in approximately 88% of patients with GIST without *KIT* or *PDGFRA* mutation (31), and it has been reported that HIF-1α accumulation and VEGFR overexpression were involved in disease progression in SDH-deficient GIST (30). Therefore, inhibition of HSP90 might have a positive antitumor effect on GIST regardless of KIT mutations.

The QD × 5 regimen has been chosen for further clinical development, based on safety, tolerability, and pharmacokinetic profiles of TAS-116 in this phase I study. We did not put a high priority on response rates because tumor types and other patient characteristics were different among the three regimens. In the QD × 5 regimen, there were no complete responses (CR) or PRs observed, but a long duration of SD was confirmed in a patient with GIST. Generally, it is known that responses to GIST treatment are not always accompanied by reductions in tumor size (32). Therefore, we considered it to be clinically significant as the PET images of liver metastasis showed a remarkable decrease in FDG accumulation. The TAS-116 dosing regimens investigated in this study have the potential to achieve sustained HSP90 inhibition leading to maximal antitumor activity of this compound.

In conclusion, three oral dosing schedules, QD, QD × 5, and QOD of TAS-116 were evaluated in this first-in-human phase I study, and dosing regimens were identified for further development with promising preliminary clinical activities and safety profiles. Studies of TAS-116 are currently underway in patients with GIST, NSCLC, and $HER2^+$ breast cancer.

Disclosure of Potential Conflicts of Interest

N. Yamamoto reports receiving commercial research grants from IQVIA, Astellas, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, ONO, Janssen Pharma, Chugai, Esai, Taiho, BMS, Pfizer, Novartis, Daiichi-Sankyo, and Bayer; has received speakers bureau honoraria from BMS, Pfizer, AstraZeneca, Eli Lilly, ONO, and Chugai; and is a consultant/advisory board member for Eisai, Takeda, Otsuka, Boehringer Ingelheim, and Cimic. Y. Fujiwara reports receiving commercial research grants from AZD, BMS, Chugai, Daiichi-Sankyo, Eisai, Incyte, Eli Lilly, MerckSerono, MSD, Novartis; has received speakers bureau honoraria from Taiho, BMS, and ONO; and is a consultant/advisory board member for BMS and ONO. S. Suzuki is a consultant/advisory board member for Taiho and Ono. N. Yanagitani has received speakers bureau honoraria from Bristol-Myers Squibb, MSD, and Ono and is a consultant/advisory board member for Chugai. F. Ohyanagi reports receiving commercial research grant from Boehringer Ingelheim and has received speakers bureau honoraria from Boehringer Ingelheim, Chugai, Eli Lilly, Kyorin, MSD, Novartis, Ono, and Taiho. T. Doi is a consultant/advisory board member for Amgen, Chugai, Daiichi-Sankyo, Eli Lilly Japan, Kyowa Hakko Kirinand, and MSD. Y. Kuboki has received speakers bureau honoraria from Taiho, Lilly, Bayer, and Sanofi. K. Shitara reports receiving commercial research grants from Lilly, Ono Pharmaceutical, Dainippon Sumitomo Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharma, and MSD and is a consultant/advisory board member for Astellas Pharma, Lilly, Bristol-Myers Squibb, Takeda, Pfizer, and Ono Pharmaceutical. U. Banerji is an employee at The Institute of Cancer Research and has received commercial research support from AstraZeneca, for an investigator-initiated phase I clinical trial; from Chugai, for an investigator-initiated phase I clinical trial; from Verastem, for an investigator-initiated phase I clinical trial; from Onyx Pharmaceuticals, for an investigator-initiated phase I clinical trial; and from BTG International, for an investigator-initiated phase I clinical trial. He is a consultant/advisory board member for Karus Therapeutics, Clinical Advisory Board; Astex, ERK Workshop; Phoenix Solutions, ACT GI Advisory Board; Novartis, TCO Advisory Board; and Vernalis, AUY922 meeting; and has provided expert testimony for Eli Lilly, European Digestive Oncology Research Forum. R. Sundar has received speakers bureau honoraria from Merck, Bristol-Myers Squibb, and MSD; and is a consultant/advisory board member for Merck and BMS. E.M. Calleja is a senior medical director, clinical development at Taiho Oncology, Inc. M. Nishio has received speakers bureau honoraria from Ono Pharmaceutical, Bristol Myers Squibb, Pfizer, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Boehringer-ingelheim, MSD, and Novartis. No potential conflicts of interest were disclosed by the other authors.

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