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Clinical Trial

Efficacy and safety of TAS-116, an oral inhibitor of heat shock protein 90, in patients with metastatic or unresectable gastrointestinal stromal tumour refractory to imatinib, sunitinib and regorafenib: a phase II, single-arm trial

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TAS-116;
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Phase II;
Pharmacogenomics

Abstract ***Aim:*** We evaluated the efficacy and safety of TAS-116, a novel class of an orally active selective inhibitor of heat shock protein 90, in patients with advanced gastrointestinal stromal tumour (GIST) after failure of three or more lines of standard treatment with imatinib, sunitinib and regorafenib.
Methods: In this single-arm phase II study, patients received 160 mg/day oral TAS-116 for five consecutive days, followed by a 2-day rest. The primary end-point was centrally assessed progression-free survival (PFS). The secondary end-points were objective response rate, disease control rate, overall survival (OS), metabolic response rate, safety, pharmacokinetics and pharmacogenomics.
Results: Forty-one patients were enrolled in Japan, and 40 patients underwent efficacy and safety evaluation. At the cut-off date, the median PFS was 4.4 months (95% confidence

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interval [CI], 2.8–6.0) and 12-week progression-free rate was 73.4% (95% CI, 58.1–88.7). Thirty-four patients (85.0%) had stable disease for ≥ 6 weeks. The median OS was 11.5 months (95% CI, 7.0–not reached). All patients experienced at least one treatment-related adverse event (AE), including diarrhoea (80.0%), decreased appetite (45.0%) and increase in blood creatinine level (42.5%). Grade ≥3 AEs and treatment-related grade ≥3 AEs occurred in 23 (57.5%) and 21 (52.5%) patients, respectively. All AEs resolved after dose modification, and no TAS-116–related AEs led to treatment discontinuation.

Conclusion: TAS-116 showed significant activity in advanced GIST refractory to standard treatment. Further development of TAS-116 is warranted.

Trial registration: JapicCTI-163182.

1. Introduction

Gastrointestinal stromal tumour (GIST) is the most frequent gastrointestinal sarcoma, with an annual incidence of 11.0–19.6 cases per million [1]. Approximately 75–80% and 5–10% of GISTs harbour mutations in *KIT* and in the platelet-derived growth factor receptor alpha (*PDGFRA*) gene, respectively [2].

Imatinib [3], sunitinib [4] and regorafenib [5], tyrosine kinase inhibitors (TKIs) that inhibit KIT/PDGFRA tyrosine kinase, proved effective as first-, second- and third-line treatments for unresectable and/or metastatic GIST, respectively. They are the current standard treatments [6–8]. Imatinib exerts significant clinical activity; however, 10–15% of patients have imatinib-resistant GIST, and imatinib-sensitive GIST develops secondary resistance, with a median time to progression of 24 months [3]. The efficacy of TKIs depends on *KIT* or *PDGFRA* mutation status, and secondary resistance is caused by acquired mutations. Other resistance mechanisms include KIT overexpression, increased copy number of mutated *KIT* and activation of alternative pathways [2,9]. GIST with mutations in *BRAF*, succinate dehydrogenase and neurofibromatosis type I does not respond to imatinib [9]. There is still a large unmet medical need for treatments against advanced GIST with these resistances as there is no fourth-line or later treatment for GIST available [10].

KIT, PDGFRA and BRAF are client proteins of the molecular chaperone heat shock protein 90 (HSP90). Their activation, particularly that of mutated forms, depends on stabilisation by HSP90 [11–13]. Hence, inhibition of HSP90 represents a rational target in GIST treatment with the potential to overcome TKI resistance. AT13387, an HSP90 inhibitor, showed antitumour activity in both imatinib-sensitive and imatinib-resistance GIST xenograft models [14].

Although clinical trials have been conducted for several HSP90 inhibitors in patients with advanced GIST, they have not shown clinical benefits owing to their limited single-agent activity and off-target and/or HSP-related toxicities, such as hepatotoxicity and visual and gastrointestinal disorders.

TAS-116 is an orally active, novel, selective inhibitor of HSP90α and HSP90β [15]. Oral administration allows for a more flexible dosing schedule compared with intravenous administration. TAS-116 has a different structure from other HSP90 inhibitors: geldanamycin derivatives (e.g. 17-AAG and 17-DMAG) that showed excess hepatotoxicity, likely due to their quinone structure [16–18], or brain penetrable HSP90 inhibitors (e.g. BIIB021 and HSP990) that have neurological toxicities [19–21]. In a phase I study [22], TAS-116 was well tolerated, three confirmed partial responses were observed in patients with solid tumours including GIST and the inhibition of HSP90 was confirmed by the induction of HSP70 expression. The recommended dose for phase II was determined to be 160 mg/body/day with dosing 5 days on/2 days off per week.

We conducted this study to evaluate the efficacy, safety, pharmacokinetics (PKs) and pharmacogenomics (PGx) of TAS-116 in patients with advanced GIST refractory to imatinib, sunitinib and regorafenib.

2. Methods

2.1. Study design and participants

This was an open-label, single-arm, phase II study conducted in Japan. The eligibility criteria included the following: histologically confirmed GIST, age ≥20 years, refractory to imatinib, sunitinib and regorafenib, at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, Eastern Cooperative Oncology Group Performance Status of 0 or 1 and adequate bone marrow, renal and liver function. The exclusion criteria included a corrected visual acuity of <0.5 for both eyes and severe concurrent disease. The study protocol and the informed consent form were approved by the institutional review board at each study site. All patients provided written

informed consent before enrolment. The study complied with the Declaration of Helsinki, Good Clinical Practice guidelines and all applicable regulations.

2.2. Procedures

The patients received 160 mg/day of TAS-116 orally under fasting conditions, with dosing 5 days on/2 days off per week in 21-day cycles until disease progression, unacceptable adverse events (AEs) or consent withdrawal. Tumour assessments were performed at the following time points: at baseline, every three weeks for the first six weeks of TAS-116 administration, every six weeks for the next three months and every eight weeks thereafter. Positron emission tomography (PET) scans were performed at baseline and on day 21 of cycle 1. The tumour responses were evaluated according to RECIST, the criteria used by Choi et al [23], and the European Organisation for Research and Treatment of Cancer (EORTC) criteria for PET [24]. AEs were graded according to the Common Terminology Criteria for Adverse Events version 4.03. Regular ophthalmological examinations were conducted to detect ocular toxicity. Blood samples for PKs were collected at before dosing and after dosing on day 5 of cycle 1 to assess the influence of gastrectomy on exposure to TAS-116. The mutation status of *KIT*, *PDGFRA* and *BRAF* at baseline was assessed on blood samples using BEAMing assay [25] and next-generation sequencing (NGS) assay (AVENIO circulating tumour DNA [ctDNA] analysis kit for the blood samples) and on baseline or archival tissues using NGS assay (Oncomine Focus Assay for the tumour tissue).

2.3. Outcomes

The primary end-point was centrally assessed progression-free survival (PFS) based on RECIST. The secondary end-points were as follows: overall survival (OS); objective response rate (ORR), proportion of patients who achieved complete or partial response; disease control rate (DCR) and proportion of patients who continued complete response, partial response or stable disease for six weeks or longer, metabolic response rate (MRR) based on the EORTC criteria; safety; PKs and PGx.

2.4. Statistical analysis

We assumed the PFS curve followed an exponential distribution with a median PFS of 0.7 months. The sample size was 40, and the lower and upper time points corresponding to the 95% confidence interval (CI) for the median PFS was 0.5 and 1.0 months, respectively.

Efficacy was analysed in the full analysis set, defined as the population of patients evaluated for at least one efficacy end-point after TAS-116 administration. The primary analysis was conducted when the 6-week imaging evaluation of the last patient was complete. The Kaplan–Meier method was used to calculate the median PFS with 95% CI. Safety was assessed in all treated patients. The PK parameters were calculated by non-compartmental analysis. The log-transformed PK parameters (C_{max}, C_{trough} and $AUC_{0\text{-}t}$) and t_{max} were compared between patients who underwent no gastrectomy and patients who underwent partial gastrectomy using the unpaired t-test and Wilcoxon rank-sum test, each at a 5% significance level (2-sided). Data analyses were conducted using SAS and Phoenix WinNonlin.

3. Results

Between May 12, 2016, and April 26, 2017, 41 Japanese patients were enrolled (Supplementary Table S1) and 40 patients received TAS-116. Thirteen patients (32.5%) remained on treatment as of the cut-off date of June 9, 2017. The reasons for treatment discontinuation of the 27 patients were progressive diseases (n = 24, 88.9%), AEs with no causal relationship to TAS-116 (n = 2, 7.4%) and withdrawal of consent (n = 1, 3.7%). No patient received TAS-116 after radiological progressive disease. Table 1 presents the baseline patient characteristics. Half of the patients had received at least four previous therapy lines. The median duration of TAS-116 treatment was 77.5 days (interquartile range [IQR]: 42–126). The median relative dose intensity was 71.9% (IQR: 55.9–89.4).

According to RECIST, the centrally assessed median PFS was 4.4 months (95% CI, 2.8–6.0) and the progression-free rate at 12 weeks was 73.4% (95% CI, 58.1–88.7) (Fig. 1A). The ORR was 0%, and the DCR was 85.0% (95% CI, 70.2–94.3). In one patient, 37.2% of tumour shrinkage was observed, which was classified as a partial response after the cut-off date. Fig. 2A shows the greatest change in tumour size from the baseline. Based on the investigator assessment, the median PFS was 3.4 months (95% CI, 2.8–4.4) (Supplementary Fig.), the ORR was 5.0% (95% CI, 0.6–16.9) and the DCR was 77.5% (95% CI, 61.5–89.2) (Supplementary Table S2). There was a slight discrepancy between the central and investigator assessments of the median PFS (4.4 vs 3.4 months, respectively). Eight of 40 patients (20.0%) had first been assessed as progressive disease by investigators but were centrally determined to be other than progressive disease. Increases in tumour size of non-target lesions were assessed as progressive disease by investigators in five patients. According to the criteria used by Choi et al [23], the median PFS, ORR and DCR were 2.8 months (95% CI, 1.4–4.2), 18.4% (95% CI, 8.0–35.2) and 47.4% (95% CI, 31.9–65.6), respectively (Supplementary Table S3). The MRR was 17.5% (95% CI, 7.3–32.8) (Fig. 2B). The median OS was 11.5 months

Table 1
Patient demographics and other baseline characteristics (full analysis set).

	Patients, no. (%)
Age, median (range), year	62 (51–70)
Sex	
Male	26 (65)
ECOG performance status	
0	28 (70)
1	12 (30)
Treatment history	
3 previous treatments	19 (48)
Imatinib > sunitinib > regorafenib	15 (38)
Other (the different order of imatinib, sunitinib and regorafenib)	4 (10)
4 previous treatments	13 (33)
Imatinib > sunitinib > regorafenib > imatinib	6 (15)
Imatinib > sunitinib > imatinib > regorafenib	4 (10)
Other	3 (8)
≥5 previous treatments	8 (20)
Imatinib > sunitinib > regorafenib > imatinib > sunitinib	2 (5)
Imatinib > sunitinib > regorafenib > sunitinib > regorafenib	1 (3)
Imatinib > sunitinib > regorafenib > sunitinib > ID	1 (3)
Imatinib > sunitinib > regorafenib > ID > ID > ID > ID	1 (3)
Imatinib > sunitinib > regorafenib > pazopanib > gemcitabine + DTX > imatinib > sunitinib	1 (3)
Imatinib > sunitinib > imatinib > regorafenib > imatinib > regorafenib	1 (3)
Imatinib > sunitinib > imatinib > sunitinib > regorafenib	1 (3)
Primary tumour site	
Small intestine	21 (53)
Stomach	15 (38)
Colon	2 (5)
Other	1 (3)
Unknown	1 (3)

DTX, docetaxel; ECOG, Eastern Cooperative Oncology Group; Gem, gemcitabine; ID, investigational drug.

(95% CI, 7.0—not reached) (Fig. 1B). Thirty patients were alive at the data cut-off, and further follow-up is required.

All patients experienced at least one TAS-116—related AE. Fig. 3 shows treatment-related AEs occurring in ≥10% of patients. AEs of grade ≥3 and treatment-related AEs of grade ≥3 occurred in 23 (57.5%) and 21 (52.5%) patients, respectively. Serious AEs (SAEs) and treatment-related SAEs were observed in 12 (30.0%) and 6 (15.0%) patients, respectively. No treatment-related deaths were reported. Eye disorders were reported in eight (20%) patients: night blindness (n = 4, 10%), blurred vision (n = 3, 7.5%) and visual impairment (n = 1, 2.5%). All eye and gastrointestinal disorders, including grade 3 diarrhoea, resolved after dose interruption. Dose reduction or interruption due to treatment-related AEs was required in 20 (50.0%) and 32 (80.0%) patients, respectively. No differences were found in the centrally assessed PFS between patients with and without dose reduction (5.6 vs 4.4 months, respectively).

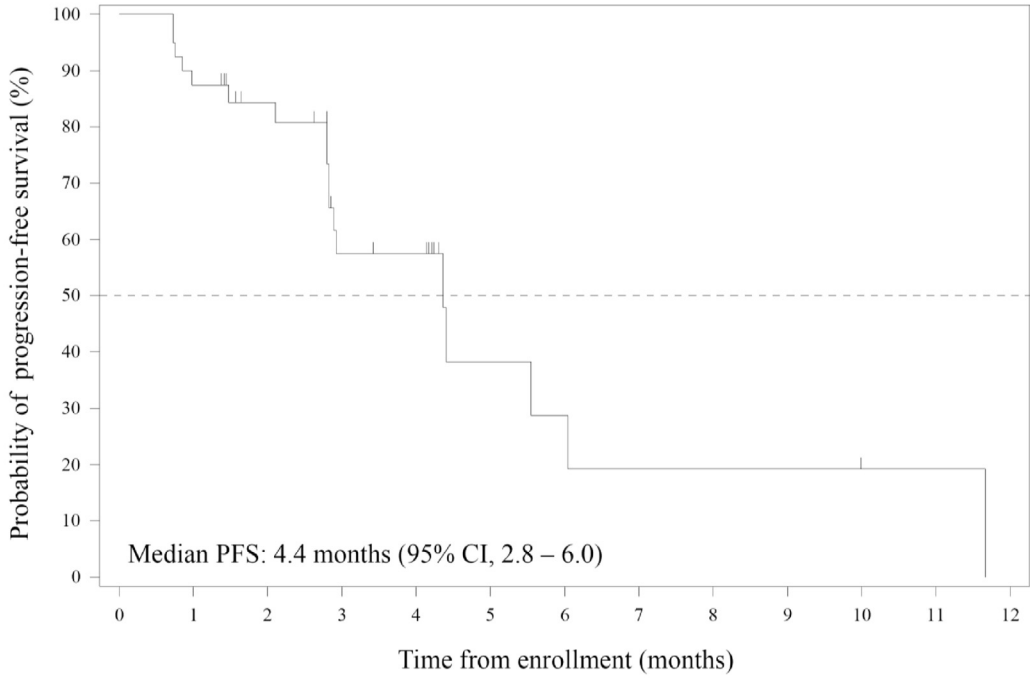
Blood samples of 30 patients (75.0%) were available for PK evaluation. TAS-116 was rapidly absorbed, with the median t_{max} of 2.48 h (Table 2). Although the exposure of TAS-116 was not significantly impacted by prior partial gastrectomy, it tended to be lower in patients who underwent total gastrectomy (n = 2) than in patients who did not undergo gastrectomy (n = 19).

Mutations in *KIT*, *PDGFRA* and *BRAF* were detected in 30 (75.0%) patients using BEAMing or NGS of ctDNA (Supplementary Table S4). *KIT*, *PDGFRA* and *BRAF* mutations were detected using an NGS assay in ctDNA in 23, 6 and 2 patients, respectively (Fig. 4). Secondary *KIT* mutations were detected in 17 patients. Among patients without *KIT* mutation, one patient with *PDGFRA* mutation (D842V) had stable disease for 4.1 months and remains on treatment. In addition, a stable disease period of 10 months was observed in a patient with *BRAF* mutation (A728T), who remains on treatment.

4. Discussion

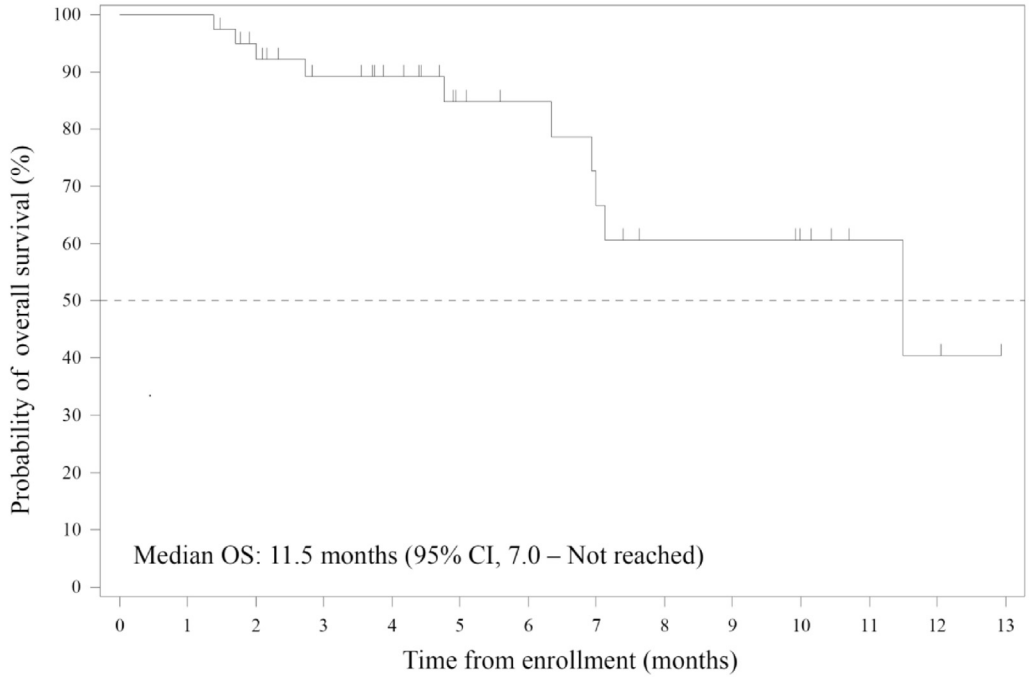
TKIs dramatically improved survival of patients with advanced GIST. However, secondary mutations in *KIT* and *PDGFRA* genes frequently occur during imatinib, sunitinib and regorafenib treatment, resulting in efficacy attenuation of TKIs [2]. Limited clinical effectiveness for patients with secondary mutations in *KIT* exon 13/14 was also reported with new TKIs, such as avapritinib [26] and ripretinib [27]. In addition, treatment duration and efficacy tend to become shorter and lower in

(A)



Number at risk	40	35	24	14	13	4	3	2	2	2	1	1	0
(number censored)	(0)	(0)	(10)	(13)	(14)	(21)	(21)	(21)	(21)	(21)	(22)	(22)	(22)

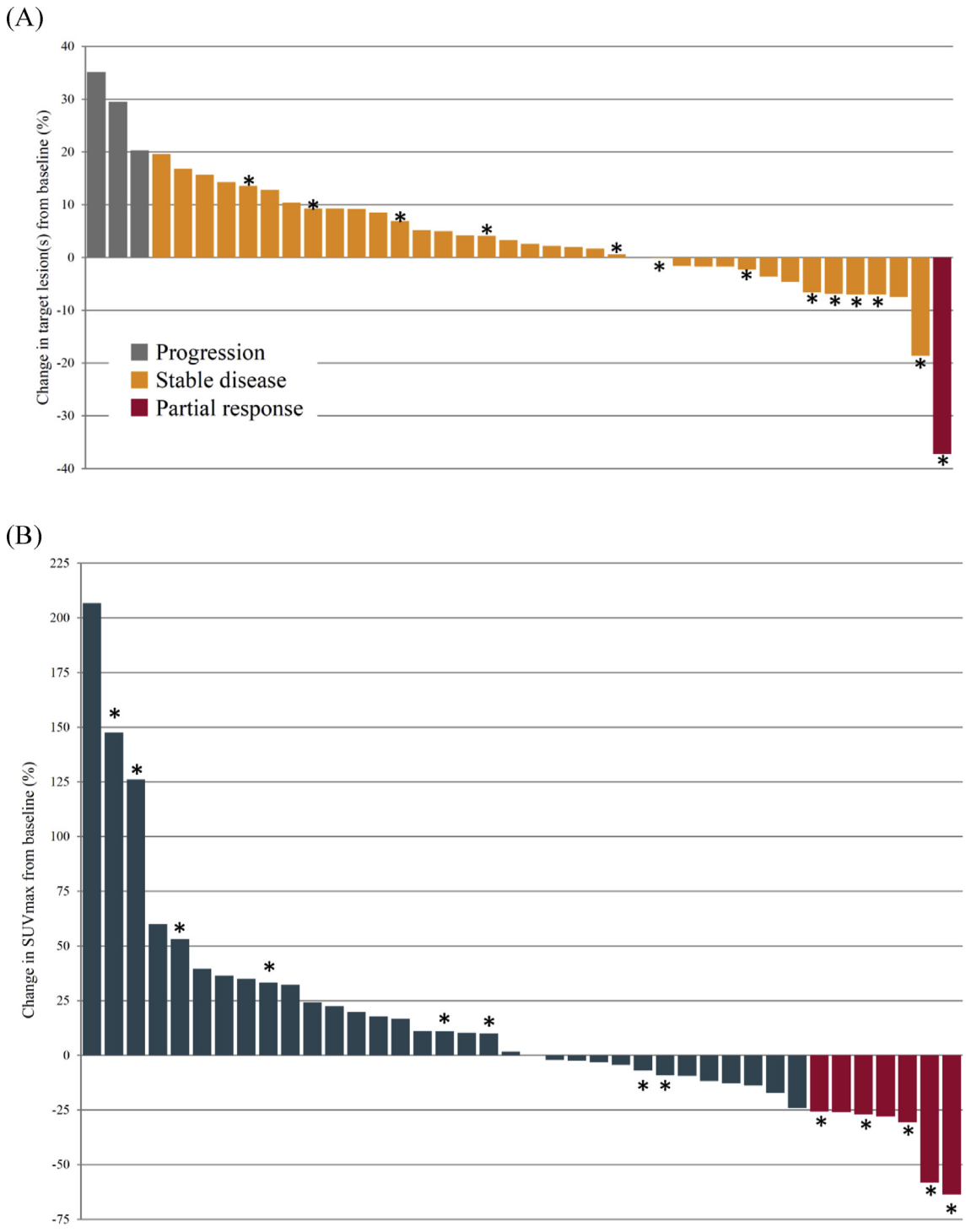
(B)



Number at risk	40	40	35	29	25	16	14	11	8	8	6	3	2	0
(number censored)	(0)	(0)	(3)	(7)	(11)	(19)	(21)	(21)	(23)	(23)	(25)	(28)	(28)	(30)

Analysis Set: FAS. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Fig. 1. Kaplan–Meier plot of progression-free survival (A) and overall survival (B).



*: patients still on administration of TAS-116 as of cut-off date.
Analysis Set: FAS. EORTC, the European Organisation for Research and Treatment of Cancer; RECIST, the Response Evaluation Criteria in Solid Tumours.

Fig. 2. Waterfall plot of response according to RECIST (A) and metabolic response according to EORTC criteria (B) by independent central review.

later-line GIST treatments owing to tumour heterogeneity [27]. Therefore, new treatments are needed to overcome resistance associated with KIT and PDGFRA inhibitors.

HSP90 is a chaperone protein that stabilises approximately 200 client proteins including KIT and PDGFRA. Because compromising the function of HSP90 leads to KIT destabilisation and degradation

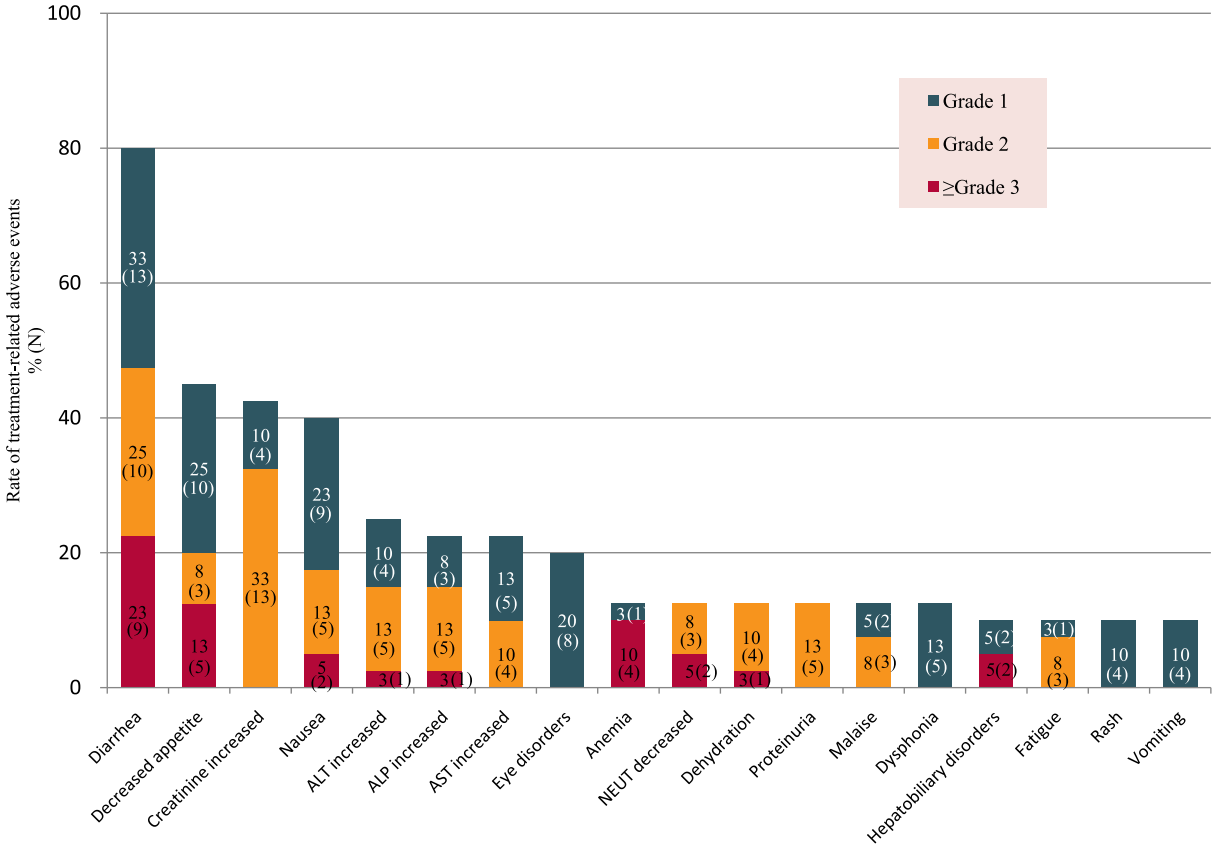


Fig. 3. Treatment-related adverse events occurring in ≥10% of all treated patients. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aminotransferase; NEUT, neutrophil.

with subsequent abolition of downstream signalling regardless of mutational status of *KIT*, several HSP90 inhibitors have been clinically investigated for GIST [12]. A phase III trial of IPI-504 was terminated early owing to increased toxicities, mainly hepatoxicity [28]. AUY922 demonstrated a median PFS of 3.9 months and a response rate of 4.0% in a phase II study in patients with GIST refractory to imatinib and sunitinib. Despite the clinical efficacy, 68% of the patients experienced HSP90-related eye disorders, and 8% of them were of grade 3 [29]. In a phase II study conducted in the third-line setting, ganetespib was administered once weekly for three weeks, followed by one-week rest, and demonstrated a median PFS of 2.7 months and a response rate of 0%. The client protein evaluation in pre- and post-treatment tumour biopsies indicated limited therapeutic efficacy of the once-weekly regimen owing to a lack of continuous KIT inhibition in tumours [30].

In two phase III studies of regorafenib and imatinib in the same third-line setting, the median PFS with best supportive care (BSC) was 0.9 months [5,31]. After all

Table 2
Pharmacokinetic parameters.

Pharmacokinetic parameter, arithmetic mean (SD) (median [minimum, maximum] for t_{max})	All (N = 30)	No prior gastrectomy (n = 19)	Prior partial gastrectomy (n = 9)	Prior total gastrectomy (n = 2)
C_{max} (ng/mL)	3210 (1180)	3455 (916)	2888 (1644)	2330 (NC)
C_{trough} (ng/mL)	689 (330)	670 (359)	782 (273)	452 (NC)
t_{max} (hr)	2.48 (0.95, 8.07)	2.00 (0.95, 8.07)	2.97 (1.97, 7.87)	3.02 (2.03, 4.00)
AUC_{0-t} (ng.hr/mL)	38166 (13337)	39324 (12536)	38219 (16006)	26928 (NC)
$t_{1/2}$ (hr)	11.44 (4.43)[a]	9.96 (3.02)[b]	15.20 (5.46)[c]	9.68 (NC)

C_{max}, maximum plasma concentration; C_{trough}, observed plasma concentration at 24 h after administration; t_{max}, time of maximum plasma concentration; AUC_{0-t}, area under the plasma concentration-time curve up to the last observed concentration; $t_{1/2}$, terminal elimination half-life; NC, not calculated; SD, standard deviation.

[a] n = 28.
[b] n = 18.
[c] n = 8.

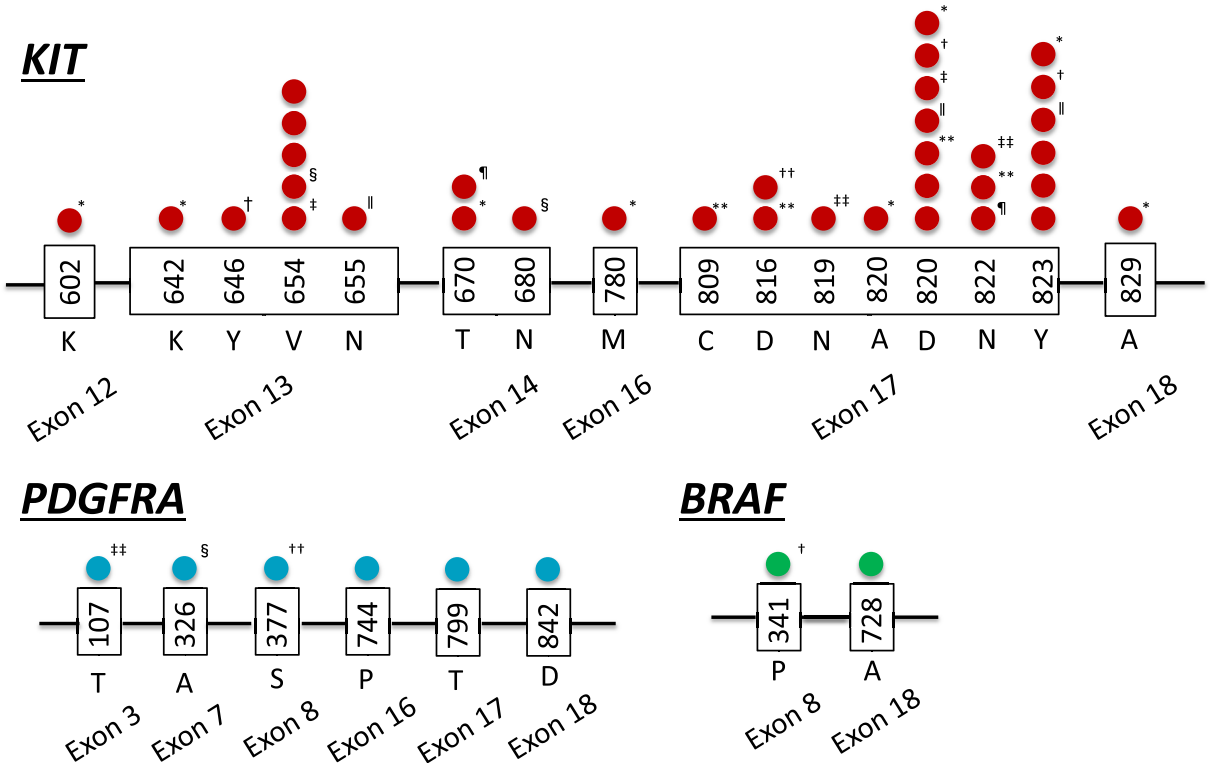


Fig. 4. Distribution and frequency of *KIT* (secondary mutations only)/*PDGFRA*/*BRAF* mutation at enrolment (NGS assays in ctDNA). *, †, ‡, §, ‖, ¶, **, ††, ‡‡: The mutation with same superscript was found in the same patient. ctDNA, circulating tumour DNA; NGS, next-generation sequencing; PDGFRA, platelet-derived growth factor receptor-alpha.

three treatment options approved for advanced GIST had been exhausted, PFS could no longer be expected with BSC. Therefore, the median PFS of 4.4 months in the fourth-line and later treatment settings is clinically meaningful activity of TAS-116 and comparable with the results of a phase III study of regorafenib (the median PFS of 4.8 months) after failure of two or more lines of previous chemotherapy. Although no complete response or partial response was observed with TAS-116, the DCR was 85%. A previous meta-analysis [32] reported that PFS had a strong association with OS in advanced GIST and prolongation of stable disease is more important than tumour shrinkage.

The tumour response according to the criteria used by Choi et al [23], using the same target lesions with RECIST, was not correlated with that according to RECIST. The criteria used by Choi et al were originally used for tumour assessment of GIST with limited number of target lesions during early stage of imatinib treatment. On the contrary, a highly refractory population, such as patients in this study, generally has multiple target lesions where changes in tumour density during treatment vary from a lesion to a lesion. As reported with regorafenib [33], it is suggested that RECIST is well suited to assess the clinical benefit in patients with advanced GIST after failure of TKIs. The usage of the criteria used by Choi et al in this treatment setting needs further investigation.

The PGx results suggest that TAS-116 is also effective in patients with secondary *KIT* and *PDGFRA* mutations. Given the long stable disease period of more than 10 months in the patient with *BRAF* mutation (A728T), TAS-116 may be effective for *BRAF*-mutated GIST. However, there has been no report suggesting that *BRAF* mutation (A728T) is a driver mutation in GIST. The other patient with *BRAF* mutation (F595L) needs further follow-up because the patient had received TAS-116 for only 1.4 months at the data cut-off. In some patients whose disease did not respond to TAS-116, there may be an alternate signalling pathway except client proteins of HSP90 or a compensation mechanism for HSP90 through induction of HSP70 and HSP27 [34].

Ocular toxicities may result in a poor quality of life for patients, even if they are not fatal. In our study, eye disorders were observed in eight (20%) patients; however, all were limited to grade 1 and recovered or resolved upon dose interruption. The most common treatment-related AEs were gastrointestinal disorders and creatinine level increase. Grade 3 diarrhoea tended to occur in the first 14 days of treatment, and all gastrointestinal disorders resolved after dose interruption. The on-target AEs of TAS-116 were considered manageable compared with other HSP90 inhibitors.

We assessed PK parameters to determine whether TAS-116 exposure was influenced by prior gastrectomy

as other weakly basic compounds, such as pazopanib and nilotinib [35–37]. However, further evaluation is needed because the number of patients who underwent total gastrectomy was only two.

To date, no studies have looked at the correlation between the antitumour activity of HSP90 inhibitors and the mutation status of the targeted protein genes using NGS assay. In the light of our results, inhibiting the chaperone functions of HSP90 is expected to be applicable to other cancer therapies because some HSP90 client proteins play important roles in tumour progression.

This is the first study of an HSP90 inhibitor in patients with advanced GIST after failure of standard treatments, and TAS-116 demonstrated clinical benefits including a PFS of 4.4 months, with no treatment discontinuation from TAS-116 toxicities. A phase III study in this population is currently ongoing (JapicCTI-184094).

Author contributions

T.D. had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. T.D., Y.Ko., T.N. and S.O. contributed to concept and design. T.D., Y.Ko., A.S., Y.Ku., M.O., T.T., Y.N. and T.N. contributed to acquisition, analysis or interpretation of data. T.D., T.N. and S.O. contributed to drafting of the manuscript. T.D., T.N., Y.Ko., A.S., Y.Ku., S.O., T.T. and Y.N. contributed to critical revision of the manuscript for important intellectual content. S.O. contributed to statistical analysis. S.O. contributed to administrative, technical, or material support. T.D., T.N. and Y.Ko. contributed to supervision.

Conflict of interest statement

T.D. reports consulting or advisory roles for Lilly Japan, Chugai Pharma, Kyowa Hakko Kirin, MSD, Daiichi Sankyo, Amgen, Sumitomo Dainippon and Taiho Pharmaceutical and research funding from Taiho Pharmaceutical, Novartis, Merck Serono, Astellas Pharma, MSD, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Lilly Japan, Sumitomo group, Chugai Pharma, Kyowa Hakko Kirin, Daiichi Sankyo, Celgene, Bristol-Myers Squibb, AbbVie and Quintiles. Y.Ku. reports honoraria from Taiho Pharmaceutical, Eli Lilly, Yakult Honsha, Ono Pharmaceutical, MSD, Kaken Pharmaceutical, Medtronic, Johnson & Johnson and Stryker Japan. A.S. provided speaker services for Novartis, Pfizer, Bayer, Taiho Pharmaceutical, Lilly, Eisai, Chugai and Yakult and reports research funding from Taiho Pharmaceutical. Y.Ko. reports honoraria from Pfizer, Novartis and Bayer and research funding from Eli Lilly, MSD, Ono Pharmaceutical, Novartis, Bayer, Chugai Pharma, Yakult and Taiho and provided speaker services for Eli Lilly, Chugai Pharma, Merck Serono, Novartis, Pfizer, Bayer and Taiho. M.O. reports honoraria from Pfizer, Novartis, Bayer, Yakult and Taiho Pharmaceutical. T.T. provided speaker services for Novartis Pharma, Pfizer, Bayer and SBI Pharma and reports research funding from SBI Pharma. Y.N. provided speaker services for Taiho Pharmaceutical, Eisai, Chugai Pharma, Novartis, Eli Lilly, Roche Diagnostics, Meiji Seika Pharma, Pfizer, Nippon Kayaku, AstraZeneca, Merck Serono and Bayer and reports research funding from Roche Diagnostics. S.O. reports employment at Taiho Pharmaceutical and has ownership interest in a patent, WO2011004610 A1. T.N. reports honoraria from Pfizer, Novartis, Bayer, Eisai, Sysmex, Taiho, Terumo and Tsumura.

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Role of the funder/sponsor

The funder was involved in design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript and decision to submit the manuscript for publication.

Meeting presentation

The results of this study were partially presented at the ESMO 2017 Congress in Madrid.

Additional contributions

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.009.

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