ORIGINAL RESEARCH ARTICLE

A Phase 1 Study of Sapanisertib (TAK-228) in East Asian Patients with Advanced Nonhematological Malignancies

Toshio Shimizu[1] · Yasutoshi Kuboki[2] · Chia-Chi Lin[3] · Kan Yonemori[1] · Tomoko Yanai[4] · Douglas V. Faller[5] · Iwona Dobler[5] · Neeraj Gupta[5] · Farhad Sedarati[5] · Kyu-pyo Kim[6]

Abstract

Background Sapanisertib is an oral, highly selective inhibitor of mammalian target of rapamycin complexes 1 and 2.
Objective The aim of this study was to assess the safety, tolerability, pharmacokinetics, preliminary efficacy, and to establish the recommended phase 2 dose (RP2D) of sapanisertib.
Patients and Methods In this dose-escalation and expansion study, East Asian patients with nonhematologic malignancies received increasing sapanisertib doses once-daily (QD; starting at 2 mg) or once-weekly (QW; starting at 20 mg) in 28-day cycles.
Results Among 28 patients (QD dosing, $n = 22$; QW dosing, $n = 6$), three dose-limiting toxicities were reported (stomatitis [$n = 2$], gastrointestinal inflammation, gingivitis, and acute myocardial infarction [all $n = 1$]), all in the 4 mg QD cohort. The RP2D of sapanisertib was 3 mg QD. The most common adverse events were stomatitis (64%), nausea (50%), and decreased appetite (50%) in the QD arm, and nausea (100%), blood alkaline phosphatase increased (67%), and hyperglycemia (67%) in the QW arm. The T_{max} of sapanisertib was ~ 0.5–2.6 h and the $T_{1/2}$ was ~ 5.9–7.6 h. Three patients achieved stable disease for ≥ 6 months (1 each in 3 mg QD, 4 mg QD and 20 mg QW cohorts, respectively); the clinical benefit rate was 45% and 67% in the QD and QW arms, respectively.
Conclusions The RP2D of sapanisertib in East Asian patients (3 mg QD) was lower than in Western patients (4 mg QD), but the pharmacokinetics and safety profiles were similar. Sapanisertib was well tolerated and showed moderate anti-tumor effects in heavily pretreated patients with nonhematologic malignancies.
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✉ Toshio Shimizu
tosshimi@ncc.go.jp

1. Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

2. National Cancer Center Hospital East, Chiba, Japan

3. National Taiwan University Hospital, Taipei, Taiwan

4. Takeda Pharmaceutical Company Limited, Osaka, Japan

5. Millennium Pharmaceuticals, Inc., a Wholly Owned Subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA

6. Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Key Points

In this phase 1 study in East Asian patients with nonhematologic malignancies, the maximum tolerated dose and recommended phase 2 dose of sapanisertib was found to be lower in East Asian patients (3 mg once daily) than in Western patients (4 mg once daily).

There were no apparent differences in sapanisertib pharmacokinetics and safety profiles between patients from East Asian and Western countries.

Moderate anti-tumor effects and a favorable safety profile were observed with sapanisertib in this heavily pretreated patient population.

1 Introduction

Mammalian target of rapamycin (mTOR) is a central regulator of cell growth, metabolism, survival, and angiogenesis that functions in two distinct multiprotein complexes, mTORC1 and mTORC2, in the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mTOR signaling pathway [1, 2]. mTOR kinase plays a key role in several pathways that are frequently dysregulated in human cancers [3] and thus, inhibition of mTOR may inhibit abnormal cell proliferation, tumor angiogenesis, and abnormal cellular metabolism. Inhibitors of mTORC1 (rapamycin analogs, known as rapalogs) such as temsirolimus and everolimus, are approved by the US Food and Drug Administration for the treatment of a variety of cancers [4–7]; however, inhibition of mTORC1, without mTORC2 inhibition, may limit rapalog efficacy by disrupting a negative feedback mechanism and accelerating tumor progression via the activation of AKT, a mechanism which is suspected to play a role in the acquisition of treatment resistance [8]. Dual inhibition of mTORC1/2 may, therefore, offer an advantage over mTORC1 inhibitors by mitigating the feedback activation of AKT.

Sapanisertib (also referred to as TAK-228 or MLN0128) is an investigational, oral, and highly selective adenosine triphosphate-competitive inhibitor of mTOR kinase that exhibits dual specificity against both mTORC1 and mTORC2. In preclinical studies, sapanisertib has demonstrated antitumor activity in acute myeloid leukemia, breast, and renal tumor cell-line xenograft mouse models [9–12]. In subsequent clinical investigations, sapanisertib monotherapy was well tolerated and had a manageable safety profile, which was consistent with other agents that inhibit the PI3K/AKT/mTOR pathway [13–16]. Preliminary antitumor activity of sapanisertib was observed in a phase 1 study of patients with advanced solid tumors, renal or endometrial cancers [14, 15], and in a phase 2 study of patients with stage IV squamous cell lung cancers harboring NFE2L2 or KEAP1 mutations [17]. In a phase 1b/2 study, sapanisertib in combination with exemestane or fulvestrant was well tolerated and exhibited clinical benefit in postmenopausal women with estrogen receptor positive/human epidermal growth factor 2 negative advanced/metastatic breast cancer [16].

To date, clinical studies of sapanisertib have only been conducted in Western patient populations, which established an RP2D of 4 mg once daily (QD) [13–16]. We conducted this phase 1, dose-escalation and expansion study to evaluate the safety, tolerability, and maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of sapanisertib administered QD or once weekly (QW) in East Asian patients with nonhematological malignancies for whom effective standard anticancer treatment was not available or was no longer effective (NCT03370302).

2 Materials and Methods

2.1 Study Design

This was a phase 1, multicenter, open-label, dose-escalation and expansion study of single-agent sapanisertib, conducted at four study centers in Japan, Korea, and Taiwan. Patients were enrolled to two parallel arms receiving single-agent sapanisertib (milled) either QD or QW, administered on an empty stomach in 28-day cycles. Patients received sapanisertib for a maximum of 12 months or until they experienced disease progression, unacceptable toxicity, or withdrew consent. Patients were followed for 30 days after the last dose of sapanisertib. Dose escalation proceeded using standard 3 + 3 rules, with two planned dose levels in each arm; 2 mg and 4 mg QD, or 20 mg and 30 mg QW. The starting doses of 2 mg QD and 20 mg QW were chosen as they were lower than the lowest RP2Ds of 4 mg QD and 30 mg QW that were determined in previous studies of sapanisertib in Western patients [15, 18]. More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing or previously tested dose level were all permissible following discussions and agreement between the investigators and the sponsor, if such measures were needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of sapanisertib. If a dose was deemed safe, a cohort could be expanded up to a total of 12 patients to confirm safety, establish RP2D, and assess pharmacokinetics (PK).

Dose-limiting toxicities (DLTs) included any grade ≥ 3 nonhematologic toxicity (except inadequately treated grade 3 nausea and/or vomiting and grade 3 diarrhea [all patients should have received optimal antiemetic and/or antidiarrheal prophylaxis treatment], grade 3 hyperglycemia lasting ≤ 14 days [all patients should have received optimal antiglycemic treatment, including insulin], and grade 3 rash lasting ≤ 3 days [all patients should have received topical steroid treatment, oral antihistamines, and oral steroids, if necessary]); grade 3 thrombocytopenia with hemorrhage or requiring platelet transfusion, or anemia requiring blood transfusion; grade 4 neutropenia lasting longer than 7 days; grade ≥ 3 neutropenia of any duration accompanied by a fever ≥ 38.5 °C and/or systemic infection; any other ≥ grade 4 hematologic toxicity; the inability to administer at least 75% of planned doses of sapanisertib within cycle 1 due to treatment-related toxicity, or any other clinically significant event that would place patients at an undue safety risk.

The primary objective was to determine the safety, tolerability, MTD/RP2D, and PK of sapanisertib administered

orally on a QD or QW dosing schedule in East Asian patients. The secondary objective was to evaluate the preliminary anti-tumor activity of sapanisertib in patients with advanced nonhematological malignancies.

The study was conducted in accordance with the Declaration of Helsinki, the International Council on Harmonisation Guideline for Good Clinical Practice, and applicable local or regional regulatory requirements. Institutional review boards approved all aspects of the study. All participants provided written informed consent.

2.2 Patients

Eligible patients were of primary East Asian ethnicity, aged ≥ 18 years old with advanced nonhematologic malignancies (except primary brain tumor) who had failed or were not eligible for standard of care therapy, had Eastern Cooperative Oncology Group performance status of 0–1, and had adequate bone marrow, hepatic, renal, and metabolic (fasting serum glucose ≤ 130 mg/dL and fasting triglycerides ≤ 300 mg/dL) function. Patients who had received prior cancer therapy within 2 weeks or systemic corticosteroid therapy within 1 week prior to the first dose of sapanisertib dose were excluded.

2.3 Assessments

Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.03). Disease response was assessed according to Response Evaluation Criteria in Solid Tumors guidelines (Version 1.1). Blood samples were collected serially from patients in both arms in cycle 1 days 1, 2, 8, 15, 16, and 22 to quantify plasma concentration of sapanisertib on an empty stomach. Liquid chromatography tandem mass spectrometry with an assay range of 1.00 to 1000 ng/mL was used for PK analysis. WinNonlin® Professional Version 7.0 or higher (Certara USA, Inc., Princeton, NJ, USA) using the linear log trapezoidal method was used for noncompartmental analysis of PK parameters on cycle 1 days 1 and 15 during the dose escalation and expansion phases.

2.4 Statistical Analysis

The safety population included all patients who received ≥ 1 dose of study drug. The PK population comprised all patients with sufficient dosing and PK data to reliably estimate ≥ 1 PK parameter. Patients were included in the DLT-evaluable population if they received ≥ 75% of the planned doses of sapanisertib in cycle 1 (21 doses for the QD arm and three doses for QW arm) or if their dose was reduced to < 75% of the planned dose in cycle 1 due to treatment-related AEs and they had sufficient follow up data to

determine whether a DLT occurred. For each arm, nine to 12 DLT-evaluable patients were needed for the dose escalation portion. In addition, for each arm, another six patients were needed for safety expansion. Assuming a 20% dropout rate, approximately 23 patients were needed for each arm to have 18 DLT-evaluable patients; the total sample size for this study was 46. All efficacy analyses were performed using the safety analysis set. It was planned to include at least one Japanese patient in each group of three patients enrolled during dose escalation and six were planned to be dosed at the RP2D. Statistical analyses were primarily descriptive in nature, with no formal statistical hypothesis testing.

3 Results

3.1 Patients

From January, 2018 to April 2019, 28 patients were enrolled; 17 (61%) at two study centers in Japan, eight (28%) at one study center in South Korea, and three (11%) at one center in Taiwan. All 28 patients received ≥ 1 dose of sapanisertib and were included in the safety population. A total of 22 patients were enrolled in the QD arm (three patients received 2 mg, six patients received 3 mg, and seven patients received 4 mg in the dose escalation cohort; six patients received 3 mg in the dose expansion cohort) and six patients were enrolled in the QW arm (three patients each received 20 mg and 30 mg in the dose escalation cohort). Enrollment to the QW arm was closed based on observations from other sapanisertib studies: in a phase 2 study in endometrial cancer, treatment with single-agent sapanisertib administered at 30 mg QW did not meet a pre-defined futility threshold, while QD dosing (in combination with paclitaxel) was viable [19], and in a phase 1 study in patients with advanced solid tumors, overall response rate (ORR) and clinical benefit rate were numerically higher with sapanisertib QD dosing compared with QW [14]. All 28 patients had discontinued treatment with sapanisertib at the data cut-off. The most common reason for discontinuation was progressive disease in 14 (64%) and four (67%) patients in the QD arm and in QW arms, respectively. Patient baseline demographics and disease characteristics were similar between arms (Table 1). Median age for patients in the QD and QW arms was 61.0 years and 53.0 years, respectively. The most common cancer type in the QD arm was colon cancer ($n = 4$). All other cancer types occurred in one patient each; one was of unknown primary origin. Diagnoses in the QW arm were breast cancer, colon cancer, pancreatic cancer, rectal cancer, peritoneal cancer, and periampullary carcinoma ($n = 1$ each). The most common disease stage at initial diagnosis in each arm was stage IV ($n = 17$ [77%] in the QD arm; $n = 6$ [100%] in the QW arm). Overall, patients were heavily pretreated; all 28

Table 1 Patient baseline characteristics and demographics

Characteristic	QD dosing Total (n = 22)	QW dosing Total (n = 6)
Median age, years (range)	61 (37–75)	53 (44–68)
Male, n (%)	13 (59)	3 (50)
Asian sub-category, n (%)		
Japanese	13 (59)	4 (67)
Korean	6 (27)	2 (33)
Taiwanese	3 (14)	–
Disease type, n (%)		
Bile duct	1 (5)	–
Bladder	1 (5)	–
Breast	1 (5)	1 (17)
Cervical	1 (5)	–
Cholangiocarcinoma	1 (5)	–
Colon	4 (18)	1 (17)
Endometrial	1 (5)	–
Esophageal	1 (5)	–
Gall bladder	1 (5)	–
Gastrointestinal stromal	1 (5)	–
Head and neck	1 (5)	–
Kidney	1 (5)	–
Pancreatic	1 (5)	1 (17)
Periampullary carcinoma	–	1 (17)
Peritoneum	–	1 (17)
Prostate	1 (5)	–
Rectal	–	1 (17)
Rectal neuroendocrine	1 (5)	–
Renal pelvis	1 (5)	–
Sarcoma	1 (5)	–
Small cell lung cancer	1 (5)	–
Unknown primary nucleus	1 (5)	–
Stage of disease, n (%)		
III	1 (5)	–
IV	17 (77)	6 (100)
IVB	2 (9)	–
Other	1 (5)	–
Not available	1 (5)	–
Number of prior treatment regimens, n (%)		
1	0	0
2	8 (36)	2 (33)
3	7 (32)	0
4	3 (14)	2 (33)
5	1 (5)	1 (17)
≥ 6	3 (14)	1 (17)

QD once daily, *QW* once weekly

patients received previous systemic anticancer therapy; 17 patients in the QD arm and all six patients in the QW arm had previous surgery; seven and one patients had previous radiotherapy in the QD and QW arms, respectively.

3.2 DLTs and MTD Determination

The DLT-evaluable population comprised 15 patients in the QD arm and six patients in the QW arm. The sapanisertib QD MTD/RP2D was determined to be 3 mg based on three patients receiving 4 mg experiencing DLTs of grade 3 stomatitis (n = 2) and grade 3 gastrointestinal inflammation, gingivitis, and acute myocardial infarction (n = 1). The QW MTD was not reached as no patients experienced DLTs at either the 20 mg or 30 mg dose level, so the RP2D was determined to be 30 mg QW.

3.3 Treatment Exposure and Safety

Overall, patients received a median of 2.0 (range, 1–12) and 3.0 (range, 1–7) cycles of treatment with sapanisertib in the QD and QW arms, respectively. A summary of the overall safety profile is shown in Table 2. Across all doses, 100% of patients reported at least one AE. Common AEs were similar between arms and across dose levels (Table 3).

The most common AEs in the QD arm included: stomatitis (64%), decreased appetite and nausea (50% each), hyperglycemia (41%), and fatigue and weight decreased (32% each). The most common AEs in the QW arm included: nausea (100%), blood alkaline phosphatase increased and hyperglycemia (67% each), alanine aminotransferase increased, aspartate aminotransferase increased, decreased appetite, vomiting and weight decreased (50% each). The most common treatment-related AEs were stomatitis (59%), nausea (50%), decreased appetite (45%) and hyperglycemia (41%) in the QD arm and nausea (100%), vomiting (50%), and hyperglycemia (50%) in the QW arm.

Grade ≥ 3 AEs (all cause) were experienced by 14 patients (64%) in the QD arm and four patients (67%) in the QW arm. The most common grade ≥ 3 AEs in the QD arm were: nausea, stomatitis, lymphocyte count decreased, and rash maculo-papular (9% each; Table 4). Gamma-glutamyl-transferase increased was the only grade ≥ 3 AE observed in two or more patients in the QW arm. Six patients (27%) in the QD arm and three patients (50%) in the QW arm experienced a serious AE (SAE); the SAEs were considered to be treatment-related in two patients in the QD arm (grade 3 myocardial infarction and grade 3 genital herpes) and one patient in the QW arm (grade 3 enteritis). The patient who experienced an SAE of acute myocardial infarction was treated with sapanisertib 4 mg QD until cycle 1, day 13, at which point treatment was discontinued. The myocardial

Table 2 Overall safety profile

	QD dosing						QW dosing		
	Dose escalation			Dose expansion	Dose escalation + expansion		Dose escalation		
	2 mg (n=3)	3 mg (n=6)	4 mg (n=7)	3 mg (n=6)	3 mg (n=12)	Total (n=22)	20 mg (n=3)	30 mg (n=3)	Total (n=6)
Any AE, n (%)	3 (100)	6 (100)	7 (100)	6 (100)	12 (100)	22 (100)	3 (100)	3 (100)	6 (100)
Any grade ≥ 3 AE, n (%)	1 (33)	2 (33)	6 (86)	5 (83)	7 (58)	14 (64)	3 (100)	1 (33)	4 (67)
Treatment-related AE, n (%)	3 (100)	6 (100)	7 (100)	6 (100)	12 (100)	22 (100)	3 (100)	3 (100)	6 (100)
Treatment-related grade ≥ 3 AE, n (%)	1 (33)	0	6 (86)	3 (50)	3 (25)	10 (45)	1 (33)	0	1 (17)
SAEs, n (%)	0	2 (33)	3 (43)	1 (17)	3 (25)	6 (27)	2 (67)	1 (33)	3 (50)
Treatment-related SAEs, n (%)	0	0	2 (29)	0	0	2 (9)	1 (33)	0	1 (17)
AEs resulting in discontinuation, n (%)	1 (33)	0	2 (29)	0	0	3 (14)	0	1 (33)	1 (17)
AEs resulting in dose reduction, n (%)	0	0	3 (43)	1 (17)	1 (8)	4 (18)	0	0	0
AEs resulting in dose interruption, n (%)	1 (33)	5 (83)	6 (86)	3 (50)	8 (67)	15 (68)	2 (67)	1 (33)	3 (50)
On-study deaths, n (%)	0	0	0	0	0	0	0	0	0

AE adverse event, *QD* once daily, *QW* once weekly, *SAE* serious adverse event

infarction subsequently completely resolved and the patient discontinued from the study.

Four patients discontinued treatment with sapanisertib due to AEs; three patients in the QD arm (due to myocardial infarction, diarrhea and gastrointestinal inflammation, and rash maculo-papular) and one in the QW arm (due to grade 2 nausea). No clinically meaningful changes were observed in laboratory values, vital signs, electrocardiogram and other safety evaluations, and no on-study deaths occurred during the study.

3.4 PK

PK data were available for all patients in the study. The mean plasma concentration-time profiles of QD and QW sapanisertib on cycle 1 day 1 and cycle 1 day 15 are shown in Fig. 1, and a summary of sapanisertib PK parameters following daily or weekly administration are provided in Supplementary Tables S1 and S2. Following a single dose on cycle 1 day 1, sapanisertib was rapidly absorbed; peak plasma concentrations were achieved at approximately 0.5–2.0 h post-dose in both QD and QW arm, with a median time to first occurrence of maximum concentration (T_{max}) of 0.5–1.0 h across all QD doses, 0.5 h at 20 mg QW, and 2.0 h at 30 mg QW. Sapanisertib plasma concentrations (area under the plasma concentration-time curve [AUC] and maximum plasma concentration [C_{max}]) increased linearly across all doses. The mean C_{max} ranged from 23.9–56.9 ng/mL across all QD doses; 295.7 ng/mL for 20 mg and 293.0 ng/mL for 30 mg QW. Across QD doses, mean AUC from 0–24 h (AUC_{24}) ranged from 138.1–314.6 ng*h/mL. In the QW doses, mean AUC from 0–168 h (AUC_{168}) was 1749.1 ng*h/mL

and 2167.4 ng*h/mL for the 20 mg and 30 mg, respectively. After reaching C_{max}, the plasma concentration of sapanisertib declined in a biphasic manner, with a mean plasma elimination half-life of approximately 6.0–6.8 h across all QD doses, 7.6 h at 20 mg QW, and 6.6 h at 30 mg QW.

On cycle 1 day 15, peak plasma concentrations were achieved at 0.5–3.0 h post-dose in the QD arm, and 0.5–4.1 h post-dose in the QW arm, with a median T_{max} of 1.0–1.5 h across all QD doses, 2.6 h at 20 mg QW, and 2.0 h at 30 mg QW. Mean plasma elimination half-life was 5.24–9.20 h across all QD doses, 8.08 h at 20 mg QW, and 6.96 h at 30 mg QW. The mean C_{max} ranged from 33.4–57.2 ng/mL across all QD doses; 207.5 ng/mL for 20 mg and 379.3 ng/mL for 30 mg QW. The geometric mean accumulation ratio of C_{max} ranged from approximately 0.93–1.30 across all QD dose levels, 0.72 and 1.36 for 20 mg QW and 30 mg QW, respectively. The range of mean AUC_{24} values for QD dosing was 236.8–366.1 ng*h/mL; mean AUC_{168} was 1962.3 ng*h/mL and 3159.7 ng*h/mL for 20 mg and 30 mg dosing, respectively. The geometric mean accumulation ratios of AUC_{168} were 1.14 for 20 mg QW and 1.47 for 30 mg QW dosing, respectively.

3.5 Antitumor Activity

Twenty patients in the QD arm and all six patients in the QW arm were evaluated for disease response. Two patients in the 4 mg QD arm were not evaluable for response. No patients achieved a complete response (CR) or partial response (PR) in either treatment arm. Ten patients (45%) in the QD arm and four patients (67%) in the QW arm achieved a best overall response of stable disease (SD) and 10 patients (45%) in

Table 3 Most common (reported in ≥ 2 patients in either treatment arm) AEs by preferred term

Preferred term, n (%)	QD dosing n=22	QW dosing n=6	Total n=28
Nausea	11 (50)	6 (100)	17 (61)
Stomatitis	14 (64)	2 (33)	16 (57)
Decreased appetite	11 (50)	3 (50)	14 (50)
Hyperglycemia	9 (41)	4 (67)	13 (46)
Weight decreased	7 (32)	3 (50)	10 (36)
Aspartate aminotransferase increased	6 (27)	3 (50)	9 (32)
Fatigue	7 (32)	2 (33)	9 (32)
Vomiting	5 (23)	3 (50)	8 (29)
Alanine aminotransferase increased	4 (18)	3 (50)	7 (25)
Platelet count decreased	6 (27)	1 (17)	7 (25)
Anemia	5 (23)	1 (17)	6 (21)
Rash maculo-papular	5 (23)	–	5 (18)
Lymphocyte count decreased	4 (18)	1 (17)	5 (18)
Pyrexia	4 (18)	1 (17)	5 (18)
Constipation	4 (18)	–	4 (14)
White blood cell count decreased	4 (18)	–	4 (14)
Hypokalemia	3 (14)	1 (17)	4 (14)
Blood alkaline phosphatase increased	–	4 (67)	4 (14)
Gamma-glutamyltransferase increased	2 (9)	2 (33)	4 (14)
Abdominal pain	3 (14)	1 (17)	4 (14)
Urticaria	3 (14)	–	3 (11)
Diarrhea	2 (9)	1 (17)	3 (11)
Erythema	2 (9)	1 (17)	3 (11)
Headache	2 (9)	1 (17)	3 (11)
Erythema multiforme	2 (9)	–	2 (7)
Gastrointestinal inflammation	2 (9)	–	2 (7)
Neutrophil count decreased	2 (9)	–	2 (7)
Pruritus	2 (9)	–	2 (7)
Rash erythematous	2 (9)	–	2 (7)
Rash pustular	2 (9)	–	2 (7)
Blood bilirubin increased	–	2 (33)	2 (7)
Hiccups	–	2 (33)	2 (7)

AE adverse event, *QD* once daily, *QW* once weekly

the QD arm and two patients (33%) in the QW arm had a best overall response of progressive disease. Three patients maintained SD for ≥ 6 months (one patient with sarcoma in the 3 mg QD cohort, one patient with rectal neuroendocrine tumor in the 4 mg QD cohort, and one patient with periampullary carcinoma in the 20 mg QW cohort). The clinical benefit rate (the proportion of patients with a best overall response of CR, PR, or SD of any duration) was 45% and 67% in the QD arm and QW arm, respectively.

4 Discussion

This was an open-label dose-escalation and expansion study designed to characterize the safety, tolerability, and PK of sapanisertib and to determine the MTD and RP2D in East Asian patients with non-hematological malignancies. This study aimed to compare the RP2D, safety, preliminary efficacy, and PK of sapanisertib in East Asian patients with that reported previously in Western patients.

The MTD and RP2D of sapanisertib QD was determined to be 3 mg QD, which is lower than that reported in the majority of previous phase 1 studies conducted in Western countries. RP2D was determined to be 3 mg QD in one study in patients with advanced solid tumors in the United States [14], but was higher in three other studies: 4 mg QD in patients with hematological malignancies from the United States [13], 4 mg QD (in combination with exemestane or fulvestrant) in patients with advanced/ metastatic breast cancer in the United States, Belgium, and France [16], and 5 mg QD in patients with advanced solid tumors in the United States and Spain [15]. It should be noted that the 3 mg QD MTD/RP2D in Asian patients reported here is attributable mainly to an increased rate of stomatitis. The rate of stomatitis is likely influenced by limited patient numbers and individual patient-related factors including genetic, environmental, hormonal and emotional factors, oral hygiene, and bacterial flora of the oral cavity [20, 21]. The MTD and RP2D for the QW regimen in this study was determined to be 30 mg, which is consistent with two studies of patients with advanced solid tumors in the United States and Spain [14, 15]. However, it is difficult to make meaningful comparisons with other data, due to the low patient numbers (n = 3 receiving each QW dosing schedule).

Treatment with sapanisertib was generally well-tolerated in East Asian patients; the safety profile was consistent with previous studies in Western patients [14, 15, 22]. No meaningful differences in the incidence or pattern in commonly reported AEs or treatment-related AEs across the dosing schedules or dose levels were detected. The incidence of any-grade stomatitis in this study was higher than that previously reported in studies of patients from the United States [14]. Sixty-four percent of East Asian patients treated with QD sapanisertib experienced stomatitis compared with 35% for patients treated with sapanisertib 2–7 mg QD [15] and 18% for patients treated with sapanisertib 3 or 4 mg QD [14] in previous studies. Similarly, 33% of patients in the present study treated QW with sapanisertib experienced stomatitis compared with 30% for patients treated with sapanisertib 7–40 mg QW [15] and 10% for patients dosed at 20 or 30 mg QW [14] previously. However, the incidence of grade ≥ 3 stomatitis

Table 4 Grade ≥ 3 AEs

AE (preferred term), n (%)	QD dosing (n = 22)	QW dosing (n = 6)	Total (n = 28)
Patients with ≥ 1 grade 3 or higher AE	14 (64)	4 (67)	18 (64)
Lymphocyte count decreased	2 (9)	1 (17)	3 (11)
Gamma-glutamyltransferase increased	1 (5)	2 (33)	3 (11)
Jaundice cholestatic	1 (5)	–	1 (4)
Nausea	2 (9)	–	2 (7)
Stomatitis	2 (9)	–	2 (7)
Aspartate aminotransferase increased	1 (5)	1 (17)	2 (7)
Rash maculo-papular	2 (9)	–	2 (7)
Renal impairment	1 (5)	–	1 (4)
Post herpetic neuralgia	1 (5)	–	1 (4)
Decreased appetite	1 (5)	–	1 (4)
Acute myocardial infarction	1 (5)	–	1 (4)
Diarrhea	1 (5)	–	1 (4)
Gastrointestinal inflammation	1 (5)	–	1 (4)
Alanine aminotransferase increased	–	1 (17)	1 (4)
Enteritis	–	1 (17)	1 (4)
Cholangitis acute	–	1 (17)	1 (4)
Hyperglycemia	–	1 (17)	1 (4)
Malignant neoplasm progression	–	1 (17)	1 (4)
Blood creatine phosphokinase increased	1 (5)	–	1 (4)
Neutrophil count decreased	1 (5)	–	1 (4)
Platelet count decreased	1 (5)	–	1 (4)
White blood cell count decreased	1 (5)	–	1 (4)
Genital herpes	1 (5)	–	1 (4)
Gingivitis	1 (5)	–	1 (4)
Rash pustular	1 (5)	–	1 (4)
Sepsis	1 (5)	–	1 (4)
Pruritus	1 (5)	–	1 (4)
Urticaria	1 (5)	–	1 (4)

AE adverse event, *QD* once daily, *QW* once weekly

was similar to previous studies [13, 22, 23]. SAEs were mostly grade 2 or 3 and included one incident of a grade 3 acute myocardial infarction, which has not been reported in previous studies of sapanisertib. No new safety signals were detected and there were no on-study deaths.

Antitumor activity of sapanisertib has been reported previously in phase 1 studies in Western patients [14, 15, 22]. Similarly, in East Asian patients, moderate anti-tumor effects of sapanisertib were detected across different dosing schedules. A best response of SD was observed in 45% of patients in the QD arm and 67% of patients in the QW arm; three patients maintained SD for ≥ 6 months. No patients achieved a CR or PR, leading to a much lower ORR (0%) than those (12% and 22%) reported in previous phase 1 studies of sapanisertib in Western patients with nonhematologic malignancies/solid tumors [14, 15]. A lower ORR in the present study could be explained by the enrollment of a heavily pretreated population. The moderate anti-tumor activity

and clinical benefit (45% and 67% of patients treated QD and QW, respectively) observed with sapanisertib monotherapy in this study could be potentiated if sapanisertib is administered in combination with novel or existing treatments. It should be noted that sapanisertib is currently being investigated in combination with TAK-117 (an oral phosphoinositide-3-kinase alpha inhibitor; NCT02724020), paclitaxel (NCT01351350), docetaxel (NCT04267913), and osimertinib (NCT02503722) for the treatment of various malignancies.

In East Asian patients, oral sapanisertib was rapidly absorbed with a T_{max} ranging from 0.5 to 2.6 h across all doses in both arms. Median T_{max} appeared delayed in the 30 mg cohort compared with the 20 mg cohort likely due to a high level of variability caused by small patient numbers (n = 3 each). Sapanisertib plasma exposures were generally linear, dose-dependent, and did not accumulate in plasma to any appreciable extent when administered QD or QW across

Fig. 1. Mean plasma concentration–time profiles (semi-log plot) of sapanisertib in patients at cycle 1 day 1 after a single dose of **a** 2–4 mg QD or **b** 20–30 mg QW, and at cycle 1 day 15 after a single dose of **c** 2–4 mg QD or **d** 20–30 mg QW. Concentrations represented at 0 h are collected right before the dosing. The LLOQ for sapanisertib is 1 ng/mL. For the estimation of summary statistics BLQ values were replaced by zero. For the calculation of the mean concentrations at predose, plasma concentrations less than the BLQ are set to half of the lower limit of quantification. *BLQ* below the limit of quantification, *LLOQ* lower limit of quantification, *QD* once daily, *QW* once weekly
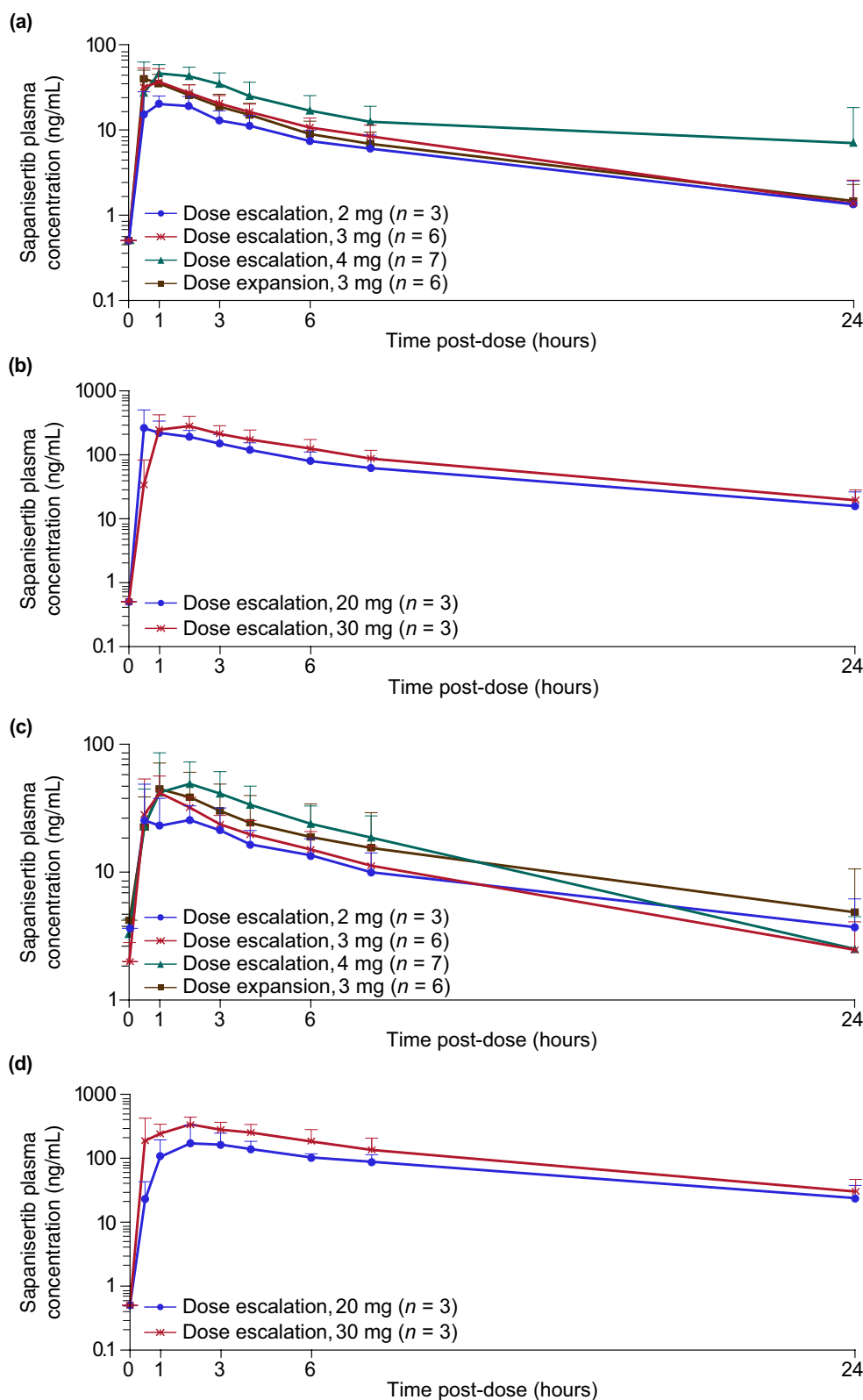
any of the dose levels. The observed PK of sapanisertib was consistent during both PK assessment periods (cycle 1 day 1 and cycle 1 day 15) and at all dose levels. Sapanisertib

PK profiles in East Asian patients were similar to those of a previous study, which was administered under similar conditions (milled capsules, fasted status) in Western patients

[22]. Sapanisertib plasma PK parameters (AUC and C_{max}) were similar between Asian and Western patients across all doses after cycle 1 day 1 and cycle 1 day 15. A similar PK profile supporting both daily and intermittent schedules of sapanisertib have been reported elsewhere in Western patients over a dose range of 2–40 mg [13, 15].

In conclusion, the MTD and RP2D of sapanisertib in East Asian patients was determined as 3 mg QD, which is slightly lower than the 4 mg determined for patients from Western countries. However, there was no apparent difference in PK or safety profiles between East Asians and patients from Western countries. The moderate anti-tumor effects and favorable safety profile in this heavily pretreated population warrants further investigation, as a single-agent in less heavily pretreated patients, and in combination with other anticancer therapies.

Declarations

Conflict of interest Toshio Shimizu has received grants/grants pending from Takeda Pharmaceutical Company Limited, Novartis, Eli Lilly, Daiichi-Sankyo, Bristol-Myers Squibb, Eisai, AbbVie, AstraZeneca, Incyte, Pfizer, Chordia Therapeutics, 3D-Medicine, Symbio Pharmaceuticals, PharmaMar, and Five Prime outside the submitted work, and consulting fees or honorarium from Takeda Pharmaceutical Company Limited and Daiichi Sankyo. Yasutoshi Kuboki has received grants/grants pending from Amgen, Takeda Pharmaceutical Company Limited, AstraZeneca, Ono Pharmaceutical Company Limited, Taiho Pharmaceutical Company Limited, Boehringer Ingelheim GmbH, AbbVie, GSK, Chugai Company Limited, Daiichi-Sankyo, and Genmab K.K., consulting fees or honorarium from Takeda Pharmaceutical Company Limited, and payment for lectures including services on speakers bureau from Taiho, Sanofi, Bayer Yakuhin, and Ono Pharmaceutical Company Limited. Chia-Chi Lin has received consulting fees from Blueprint Medicines, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, and Novartis, honorarium from Eli Lilly, Novartis, and Roche, and travel support from BeiGene and Eli Lilly. Kan Yonemori has received consulting fees or honorarium from Takeda Pharmaceutical Company Limited, Eisai, Chugai, AstraZeneca, Elli Lilly, Pfizer, Novartis, and Ono Pharmaceutical Company Limited. Tomoko Yanai is employed by Takeda Pharmaceutical Company Limited. Douglas V. Faller is employed by Millennium Pharmaceuticals, Inc, Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. lwona Dobler is employed by Millennium Pharmaceuticals, Inc. and has stock/stock options with Takeda Pharmaceutical Company Limited. Neeraj Gupta is employed by Millennium Pharmaceuticals, Inc. Farhad Sedarati is employed by Millennium Pharmaceuticals, Inc. Kyu-pyo Kim has no conflict of interests to declare.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki, the International Council on Harmonisation Guideline for Good Clinical Practice, and applicable local or regional regulatory requirements. Institutional review boards approved all aspects of the study.

Consent to participate All patients who participated in the study provided written informed consent.

Consent for publication Not applicable.

Availability of data and material The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Code availability Not applicable.

Author contributions Toshio Shimizu, Yasutoshi Kuboki, Chia-Chi Lin, lwona Dobler, and Neeraj Gupta contributed to the acquisition, analysis, or interpretation of data for the work; reviewed the work critically for important intellectual content; approved the final version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Kan Yonemori contributed to the conception or design of the work; contributed to the acquisition, analysis, or interpretation of data for the work; revised the work critically for important intellectual content; approved the final version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Tomoko Yanai contributed to the acquisition, analysis, or interpretation of data for the work; reviewed the work critically for important intellectual content; approved the final version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Douglas V. Faller contributed to the conception or design of the work; reviewed the work critically for important intellectual content; approved the final version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Farhad Sedarati contributed to the conception or design of the work; reviewed the work critically for important intellectual content; approved the final version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Kyu-pyo Kim contributed to the acquisition, analysis, or interpretation of data for the work; revised the work critically for important intellectual content; approved the final version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR signaling in cancer. Front Oncol. 2014;4:64. https://doi.org/10.3389/fonc.2014.00064.

2. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;169(2):361–71. https://doi.org/10.1016/j.cell.2017.03.035.

3. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol. 2011;12:21–35. https://doi.org/10.1038/nrm3025.

4. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372:449–56. https://doi.org/10.1016/s0140-6736(08)61039-9.

5. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520–9. https://doi.org/10.1056/NEJMoa1109653.

6. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968–77. https://doi.org/10.1016/s0140-6736(15)00817-x.

7. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356:2771–81.

8. O'Reilly KE, Rojo F, She QB, Solit D, Mills GB, Smith D, et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. Cancer Res. 2006;66:1500–8. https://doi.org/10.1158/0008-5472.CAN-05-2925.

9. Ingels A, Zhao H, Thong AE, Saar M, Valta MP, Nolley R, et al. Preclinical trial of a new dual mTOR inhibitor, MLN0128, using renal cell carcinoma tumorgrafts. Int J Cancer. 2014;134:2322–9. https://doi.org/10.1002/ijc.28579.

10. Gokmen-Polar Y, Liu Y, Toroni RA, Sanders KL, Mehta R, Badve S, et al. Investigational drug MLN0128, a novel TORC1/2 inhibitor, demonstrates potent oral antitumor activity in human breast cancer xenograft models. Breast Cancer Res Treat. 2012;136:673–82. https://doi.org/10.1007/s10549-012-2298-8.

11. Zeng Z, Wang R, Qiu YH, Mak DH, Coombes K. MLN0128, a novel mTOR kinase inhibitor, disrupts survival signaling and triggers apoptosis in AML and AML stem/progenitor cells. Oncotarget. 2016;7:55083–97.

12. García-García C, Ibrahim YH, Serra V, Calvo MT, Guzman M, Grueso J, et al. Dual mTORC1/2 and HER2 blockade results in antitumor activity in preclinical models of breast cancer resistant to anti-HER2 therapy. Clin Cancer Res. 2012;18:2603–12. https://doi.org/10.1158/1078-0432.CCR-11-2750.

13. Ghobrial IM, Siegel DS, Vij R, Berdeja JG, Richardson PG, Neuwirth R, et al. TAK-228 (formerly MLN0128), an investigational oral dual TORC1/2 inhibitor: a phase I dose escalation study in patients with relapsed or refractory multiple myeloma, non-Hodgkin lymphoma, or Waldenstrom's macroglobulinemia. Am J Hematol. 2016;91:400–5. https://doi.org/10.1002/ajh.24300.

14. Moore KN, Bauer TM, Falchook GS, Chowdhury S, Patel C, Neuwirth R, et al. Phase I study of the investigational oral mTORC1/2 inhibitor sapanisertib (TAK-228): tolerability and food effects of a milled formulation in patients with advanced solid tumours. ESMO Open. 2018;3: e000291. https://doi.org/10.1136/esmoopen-2017-000291.

15. Voss M, Gordon M, Mita M, Rini B. Phase 1 study of mTORC1/2 inhibitor sapanisertib (TAK-228) in advanced solid tumours, with an expansion phase in renal, endometrial, or bladder cancer. Br J Cancer. 2020. https://doi.org/10.1038/s41416-020-01041-x.

16. Diamond J, David P, Salkeni M, Silverman P, Haddad T, Forget F, et al. Phase 2 safety and efficacy results of TAK-228 in combination with exemestane or fulvestrant in postmenopausal women with ER-positive/HER2-negative metastatic breast cancer previously treated with everolimus. Cancer Res. 2019;79(4_suppl):PD1-09. https://doi.org/10.1158/1538-7445.SABCS18-PD1-09.

17. Paik PK, Ahn LSH, Plodkowski AJ, Fan PD, Rudin CM. Phase II study of TAK228 in patients with advanced non-small cell lung cancer (NSCLC) harboring NFE2L2 and KEAP1 mutations. J Clin Oncol. 2020;38(15_suppl):9607. https://doi.org/10.1200/JCO.2020.38.15_suppl.9607.

18. Lim B, Potter DA, Salkeni MA, Silverman P, Haddad TC, Forget F, et al. Sapanisertib plus exemestane or fulvestrant in women with hormone receptor-positive/HER2-negative advanced or metastatic breast cancer. Clin Cancer Res. 2021;27(12):3329–38. https://doi.org/10.1158/1078-0432.CCR-20-4131.

19. Scambia G, Han SN, Oza AM, Colombo N, Oaknin A, Raspagliesi F, et al. Randomized phase II study of sapanisertib (SAP) + paclitaxel (PAC) versus PAC alone in patients (pts) with advanced, recurrent, or persistent endometrial cancer. J Clin Oncol. 2020;38(15 suppl):6087.

20. Peterson DE, O'Shaughnessy JA, Rugo HS, Elad S, Schubert MM, Viet CT, et al. Oral mucosal injury caused by mammalian target of rapamycin inhibitors: emerging perspectives on pathobiology and impact on clinical practice. Cancer Med. 2016;5:1897–907. https://doi.org/10.1002/cam4.761.

21. Boers-Doets CB, Raber-Durlacher JE, Treister NS, Epstein JB, Arends AB, Wiersma DR, et al. Mammalian target of rapamycin inhibitor-associated stomatitis. Future Oncol. 2013;9:1883–92. https://doi.org/10.2217/fon.13.141.

22. Burris HA 3rd, Kurkjian C, Hart L, Pant S, Murphy P. TAK-228 (formerly MLN0128), an investigational dual TORC1/2 inhibitor plus paclitaxel, with/without trastuzumab, in patients with advanced solid malignancies. Cancer Chemother Pharmacol. 2017;80:261–73.

23. Patel C, Goel S, Patel MR, Rangachari L, Wilbur JD, Shou Y, et al. Phase 1 study to evaluate the effect of the investigational anticancer agent sapanisertib on the QTc interval in patients with advanced solid tumors. Clin Pharmacol Drug Dev. 2020;9:876–88. https://doi.org/10.1002/cpdd.808.

24. Battisti WP, Wager E, Baltzer L, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med. 2015;163:461–4.