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ORIGINAL ARTICLE

Phase I trial of pimasertib monotherapy in Japanese patients with solid tumors and those with hepatocellular carcinoma

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Abstract

Purpose This study aimed to confirm the recommended phase II dose (RP2D) of pimasertib in Japanese patients.

Methods This two-part, phase I dose-escalation and expansion study was conducted in Japanese patients (≥ 18 years old) with advanced solid tumors (ST) including hepatocellular carcinoma (HCC). In Part 1, patients with ST (Arm A) and HCC (Arm B) received escalating doses (3 + 3 design) of oral pimasertib [starting at 45 mg twice daily (BID)] in 21-day cycles, until disease progression or unacceptable toxicity. Dose levels could be escalated/de-escalated depending on tolerance. The primary outcome was the number of patients who experienced ≥ 1 dose-limiting toxicity (DLT). Safety and efficacy were also studied. Part 2 aimed to confirm observations in Part 1.

Results In total, 26 patients (ST, $n = 19$; HCC, $n = 7$) were treated with pimasertib in Part 1: 30 mg (ST, $n = 4$; HCC, $n = 5$), 45 mg (ST, $n = 9$; HCC, $n = 2$), and 60 mg (ST, $n = 6$). Four patients reported DLTs [ST: hypokalemia (60 mg), and both stomatitis and muscle weakness (60 mg); HCC: retinal detachment (30 mg) and diarrhea (45 mg)]. All patients had ≥ 1 treatment-related adverse event. Partial response ($n = 3$) and stable disease ($n = 1$) were seen in patients with ST (pimasertib 45 mg).

Conclusion A maximum tolerated dose of pimasertib 45 mg BID was established in Japanese patients with ST, but not established in patients with HCC. The global RP2D of 60 mg BID was not confirmed in Japanese patients. Pimasertib monotherapy in unselected patients with ST may not warrant further investigation; Part 2 was not conducted.

Keywords Pimasertib · Solid tumors · Hepatocellular carcinoma (HCC) · Japan

Introduction

The mitogen-activated protein kinase (MAPK) signaling pathway comprises kinases involved in regulating cell growth and function. This pathway includes the kinases MEK1 and MEK2, which are responsible for activating ERK1 and ERK2 leading to cell growth and cell cycle function [1, 2]. The MAPK pathway has been shown to be dysregulated in various human cancers, making members of this pathway intuitive therapeutic targets [3].

Pimasertib (AS703026) is a selective MEK1 and MEK2 inhibitor that binds to an allosteric site near the adenosine triphosphate (ATP) binding site of MEK. In preclinical studies, inhibition of MEK1/2 with pimasertib in vitro resulted in reduced growth and survival of multiple myeloma cells through cell cycle arrest, and in vivo MEK inhibition led to a reduction in tumor growth by induction of apoptosis [4]. Similarly, pimasertib has been shown to downregulate ERK in *KRAS*-mutated colorectal tumor cell lines, which led to decreased tumor growth both in vitro and in vivo [5].

Pimasertib has been investigated as monotherapy and as a combination therapy in phase I and phase I/II clinical studies in patients with solid tumors or hematological malignancies. In a phase I study, pimasertib monotherapy demonstrated an acceptable safety profile; the main dose-limiting toxicities (DLTs) were skin rash and ocular adverse events (AEs) [6].

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Ocular AEs were also reported in a phase I/II study of pimasertib in combination with leucovorin, 5-fluorouracil and irinotecan in which all ocular AEs were Grade 1 or 2 with the majority resolving within a few months of the day of onset [7]. Pharmacokinetic (PK) analysis in a phase II study of pimasertib monotherapy supported twice daily (BID) administration and the maximum tolerated dose (MTD) was found to be pimasertib 60 mg BID in patients with hematological malignancies [8]. In studies conducted outside of Japan, the recommended phase II dose (RP2D) in patients with solid tumors was pimasertib 60 mg BID given continuously [6].

The primary objective of this study was to confirm whether the RP2D and dosing schedule identified in global studies for pimasertib monotherapy could be applied safely to Japanese patients with solid tumors including hepatocellular carcinoma (HCC). The secondary objectives of the study were to investigate the efficacy and safety of pimasertib in these patients.

Materials and methods

Study design and treatment

This was a Japanese phase I, multicenter, open label, dose-escalation and expansion two-part study of pimasertib monotherapy given orally to patients with solid tumors including HCC (NCT01668017; EMR200066-010). The overall study design is shown in Online Resource 1. Prior to study start, patients underwent a screening period of up to 28 days.

In Part 1 (dose-escalation phase), successive cohorts of three to six patients received pimasertib in continuous 21-day cycles. The study was a standard 3 + 3 design, with an initial starting dose of pimasertib 45 mg BID in the first cohort after which the dose was escalated to pimasertib 60 mg BID (if ≤ 1 DLT occurred as reviewed by a safety monitoring committee) or de-escalated to pimasertib 30 mg BID (if ≥ 2 DLTs occurred). Treatment continued until disease progression, unacceptable toxicity, patient decision to withdraw from the study, or discontinuation due to investigator's decision. The MTD was defined as the dose level below the one at which a DLT occurred in > 1 patient per cohort. If ≤ 1 patient per cohort experienced a DLT at the target MTD of pimasertib 60 mg BID, it was regarded as confirmation of the target MTD. The MTD was determined independently in patients with solid tumors and HCC.

In Part 2 (dose-expansion phase), expansion of both arms was planned to confirm the MTDs as defined in Part 1 and to investigate safety and preliminary efficacy in patients with solid tumors and HCC.

The protocol was approved by Independent Ethics Committee(s) or Institutional Review Board(s) of the participating centers, and an independent Efficacy and Safety Evaluation Committee assessed AEs and serious adverse events (SAEs). The study was conducted in accordance with the ethical principles of the International Conference on Harmonization guidelines for Good Clinical Practice and the Declaration of Helsinki, and all applicable local regulations. Written informed consent was obtained from each patient.

Eligibility criteria

Japanese men or women aged ≥ 18 years old were eligible if they had a histologically or cytologically confirmed the diagnosis of advanced solid tumors (Arm A) or HCC (Arm B), which was either refractory after standard therapy or for which no effective standard therapy was available. In Arm B, patients were required to have a Child–Pugh score of A.

Patients were excluded if they had hematological or liver function abnormalities, renal impairment, a history of central nervous system metastases, or previous treatment with MEK inhibitors. A full list of the inclusion and exclusion criteria for this study are provided in Online Resource 2.

Endpoints

Primary endpoint

The primary endpoint was the number of DLTs at the RP2D or confirmation of the MTD. A DLT was defined using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0, as any Grade 3 or more non-hematological toxicity; judged to be possibly or probably related to the study drug by the investigator and/or the sponsor. DLTs were assessed in the first 21 days after the initiation of the trial treatment for each patient enrolled in Part 1. This observation period could be extended by two weeks if treatment was delayed due to a treatment-related AE.

Secondary endpoints

Secondary endpoints included tumor response, PK and pharmacodynamic evaluation, and safety analysis. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 after every two cycles by computerized tomography or magnetic resonance imaging. Analysis of anti-tumor activity was measured using different variables including best overall response (BOR). BOR was the best response recorded from the start of treatment until disease progression, based on overall responses provided by the investigator and established by applying the confirmation criteria from RECIST 1.1 across all time points. The BOR was reported as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or not evaluable (NE; no scans or baseline assessments were available). Other variables used to

measure anti-tumor activity were: the objective response rate (ORR), which included patients with a BOR of CR or PR; and the disease control rate (DCR), which included patients with a BOR of CR, PR or SD.

Mutational status, cancer classification and staging were assessed at study entry. Tumor biopsy tissue (taken during the screening period or at Day 1 pre-morning dose of Cycle 1) was used to assess genetic alterations associated with aberrant activation of the MAPK (e.g., *KRAS*, *BRAF*, and *NRAS* mutations) or phosphatidylinositol-3 kinase (PI3K) pathways. Blood samples and DNA from peripheral blood mononuclear cells (PBMCs) were also taken and nucleotide variations analyzed to assess genes involved in response to pimasertib treatment.

PK parameters were derived using noncompartmental methods with Phoenix® WinNonlin® Version 6.3 (Pharsight Corporation, a Certara Company, Princeton, New Jersey), and all PK computations were performed using Phoenix WinNonlin 6.3 or SAS® Version 9.2 (SAS Institute). Graphics were prepared with SAS Version 9.2 and SigmaPlot® 12.5.

Values and changes over time in pharmacodynamic biomarker phosphorylated ERK (pERK) were assessed during the study, with pERK inhibition used as a marker of MEK activity.

Safety was assessed through AEs graded by severity (Grades 1–5: mild, moderate, severe, life-threatening/disabling and death related to an AE, respectively). Events leading to death were reported as SAEs and the causal relationship was determined by the investigator. Adverse events of special interest (AESI) included: retinal vein occlusion (RVO), serous retinal detachment (SRD)/serous macular detachment/similar retinal abnormality characterized by accumulation of serous fluid in the retina, increased creatine phosphokinase (CPK) Grade > 1 (i.e., > 2.5 × upper limit of normal), and acute renal failure Grade > 1 (i.e., creatinine ≥ 2 × above baseline, considering overall symptoms). Safety laboratory parameters, vital signs, electrocardiogram, and physical examinations were also assessed at screening, on Days 1–3, 8 and 15 of Cycle 1, Days 1, 8 and 15 of Cycle 2, Day 1 of Cycles ≥ 3, end of treatment and post treatment. Dose-escalation decisions were made by the safety monitoring committee, based on a review of any AE/DLT and safety evaluations.

Statistics

Statistical analyses were predominately based on descriptive statistics summarizing baseline, safety, and efficacy data. The PK concentrations and parameters were summarized by dose, cycle, and day, as appropriate, using descriptive statistics. Secondary analyses included assessment of anti-tumor activity, relative change in tumor size, BOR, biomarker endpoint analysis, PK and safety analysis.

The total sample size was planned for up to 60 patients considering both Part 1 and Part 2. The final sample size was dependent on the number of DLTs observed at the different dose levels, and any patients who were NE for dose escalation were replaced to ensure that the required number of patients were evaluable for DLT at each dose level.

The safety analysis set included all patients who received at least one dose of pimasertib. The DLT analysis set included all patients who experienced a DLT during Cycle 1 regardless of the number of doses of pimasertib administered or patients who received more than 85% of all planned pimasertib doses during Cycle 1 (those that did not meet these criteria were replaced). The efficacy analysis set was used for anti-tumor activity and included patients who received at least one dose of pimasertib and had at least one efficacy assessment after the first dose. The PK analysis set included patients who received at least one dose of pimasertib and had at least one measurable post-dose PK concentration.

Results

Patients

In total, 26 patients were enrolled into the study and received treatment (Table 1, Online Resource 3): 19 patients into Arm A (solid tumors) in the pimasertib 30 mg (n = 4), 45 mg (n = 9), and 60 mg (n = 6) BID cohorts, and seven patients into Arm B (HCC), in the pimasertib 30 mg (n = 5) and 45 mg (n = 2) BID cohorts. All 26 enrolled patients were included in the safety analysis, with 16 and 20 patients included in the DLT and efficacy analysis sets, respectively.

In Arm A, the main reason for treatment discontinuation (n = 9/19) and study discontinuation (n = 8/19) was PD. In Arm B, the main reason for treatment discontinuation was AEs (n = 3/7), while the reasons for study discontinuation were AEs, PD, and withdrawal by the patient (all n = 2/7). One patient was required to delay a treatment cycle by more than 14 days due to radiotherapy.

In Arm A, six patients (31.6%) had adenocarcinoma [primary tumor sites: bile duct carcinoma (n = 1), colon cancer (n = 1), gallbladder cancer (n = 1), and non-small cell lung carcinoma (n = 3)]; all patients had previously received chemotherapy, all cancers at study entry were stage IV, and one patient had hepatitis B virus infection (Table 1). There were similar numbers of male and female patients with solid tumors, most of whom were ≥ 65 years old (n = 10/19; 52.6%) and the median age was comparable across the dose cohorts (65.5, 65.0, and 62.5 years in the pimasertib 30, 45 and 60 mg BID cohorts, respectively).

Table 1 Patient demographics (safety analysis set)

	Solid tumor (Arm A) ($n=19$)	HCC (Arm B) ($n=7$)
Sex, *n* (%)		
Female	10 (52.6)	3 (42.9)
Male	9 (47.4)	4 (57.1)
Age (years)		
Median (range)	65.0 (39–73)	63.0 (38–72)
Race, *n* (%)		
Asian	19 (100)	7 (100)
Ethnicity, *n* (%)		
Japanese	19 (100)	7 (100)
ECOG PS		
0	11 (57.9)	3 (42.9)
1	8 (42.1)	4 (57.1)
Tumor type, *n* (%)		
HCC	0 (0)	7 (100)
Adenocarcinoma	6 (31.6)	0 (0)
Malignant melanoma	3 (15.8)	0 (0)
Squamous cell carcinoma	2 (10.5)	0 (0)
Other[a]	8 (42.1)	0 (0)
Stage, *n* (%)		
III[b]	0 (0)	2 (28.6)
IV[b]	19 (100)	5 (71.4)
Type of prior anti-tumor drug therapy		
Chemotherapy	19 (100)	4 (57.1)
Infections and infestations		
Hepatitis B	1 (5.3)	2 (28.6)
Hepatitis C	0	1 (14.3)

The 'safety analysis set' included all patients who received at least one dose of pimasertib. Patients who were replaced for evaluation of DLT due to noncompliance were also included if this criterion applied

DLT dose-limiting toxicity, *ECOG PS* Eastern Cooperative Oncology Group performance status, *HCC* hepatocellular carcinoma

[a]Includes one patient each with adenocarcinoma of the bile duct, cholangiocarcinoma, gallbladder carcinoma, intermediate differentiated adenocarcinoma, intrahepatic cholangiocarcinoma (poorly differentiated adenocarcinoma), pheochromocytoma, poorly differentiated carcinoma (derived from widely invasive follicular carcinoma), urothelial carcinoma

[b]Includes stage III and IIIB tumors, and IV and IVB tumors

No patient had an Eastern Cooperative Oncology Group performance status (ECOG PS) > 1.

In Arm B, most patients with HCC had stage IV disease ($n=5/7$; 71.4%), four had received previous chemotherapy ($n=4/7$, 57.1%), two had hepatitis B and one had hepatitis C viral infections (Table 1). There were similar numbers of male and female patients, and most patients were < 65 years old ($n=4$; 57.1%) with the median age comparable across the dose cohorts (63.0 and 56.5 years in the pimasertib 30 and 45 mg BID cohorts, respectively). No patient had an ECOG PS > 1.

Outcomes

DLTs

The DLT analysis set comprised 12 patients in Arm A and four patients in Arm B (Table 2). In Arm A, 2/12 patients (16.7%) had at least one DLT. Three patients were enrolled in an initial cohort at pimasertib 45 mg BID, and no DLTs were experienced; however, a review of the initial data from these first three patients by the sponsor's safety monitoring committee board led to a de-escalation

Table 2 DLTs by system organ class and preferred term (DLT analysis set)

n (%)	Solid tumor (Arm A)				HCC (Arm B)		
	30 mg (*n* = 3)	45 mg (*n* = 6)	60 mg (*n* = 3)	Overall (*n* = 12)	30 mg (*n* = 3)	45 mg (*n* = 1)	Overall (*n* = 4)
Patients with at least one DLT	0	0	2 (66.7)	2 (16.7)	1 (33.3)	1 (100)	2 (50.0)
Eye disorders	0	0	0	0	1 (33.3)	0	1 (25.0)
Retinal detachment	0	0	0	0	1 (33.3)	0	1 (25.0)
Gastrointestinal disorders	0	0	1 (33.3)	1 (8.3)	0	1 (100)	1 (25.0)
Stomatitis	0	0	1 (33.3)	1 (8.3)	0	0	0
Diarrhea	0	0	0	0	0	1 (100)	1 (25.0)
Metabolism and nutrition disorders	0	0	1 (33.3)	1 (8.3)	0	0	0
Hypokalemia	0	0	1 (33.3)	1 (8.3)	0	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (33.3)	1 (8.3)	0	0	0
Muscular weakness	0	0	1 (33.3)	1 (8.3)	0	0	0

The 'DLT analysis set' included all patients who met at least one of the following criteria: patients who experienced any DLT during Cycle 1 regardless of the number of doses of pimasertib administered; patients who received > 85% of all planned doses of pimasertib during Cycle 1. Patients who did not receive the 85% of planned dose in the first 21 days for reasons other than a DLT were not used for assessment of dose escalation and additional patients were to be recruited to replace them. The observation period could be expanded by 2 weeks in case of treatment delay due to a study drug-related TEAE. The replacement patients were to be included in the DLT analysis set if they met at least one of the above two criteria

DLT dose-limiting toxicity, *HCC* hepatocellular carcinoma; *TEAE,* treatment-emergent adverse event

of the dose to 30 mg BID for the next three patients. No DLTs were experienced in the 30 mg BID cohort and the dose was re-escalated to 45 mg BID in a total of six patients eligible for DLT analysis in this cohort. No DLTs were experienced in the 45 mg BID cohort and the dose was escalated to an additional cohort at the RP2D (60 mg BID). In the pimasertib 60 mg BID cohort 2 patients had DLTs; one had hypokalemia (Grade 3), which led to treatment interruption, and the other patient had stomatitis and muscular weakness (both Grade 3), which led to treatment interruption and treatment withdrawal, respectively (Table 2).

In Arm B, 2/4 patients (50.0%) had at least one DLT. One patient was enrolled in an initial cohort at pimasertib 45 mg BID, who experienced a DLT of diarrhea (Grade 2), resulting in treatment interruption before subsequently being withdrawn. Given this, it was judged appropriate by the sponsor to investigate a lower dose. Three patients were subsequently enrolled at pimasertib 30 mg BID; one patient (33.3%) had retinal detachment (Grade 1) and treatment was withdrawn (Table 2).

All DLTs resolved by the end of the study. As DLTs occurred in the pimasertib 60 mg BID cohort, the MTD was established as pimasertib 45 mg BID in Japanese patients with solid tumors. The MTD could not be established in Japanese patients with HCC, as DLTs occurred in both the pimasertib 45 mg and 30 mg BID cohorts.

Treatment-emergent adverse events (TEAEs)

All patients had at least one treatment-related AE (Table 3). In patients with solid tumors (Arm A) the most frequently reported treatment-related TEAEs included increased blood CPK (*n* = 15/19, 78.9%), retinal detachment (*n* = 14/19, 73.7%), dermatitis acneiform (*n* = 10/19; 52.6%) and peripheral edema (*n* = 9/19; 47.4%; Table 3). Overall, treatment-related Grade ≥ 3 TEAEs occurred in 10/19 patients (52.6%; Table 3), including four patients (21.1%) with increased blood CPK levels. TEAEs leading to treatment discontinuation occurred in four patients (21.1%; Table 3), three of which were treatment related: one patient had Grade 3 infection; another had Grade 3 muscular weakness (both in the pimasertib 60 mg BID cohort); and the third patient (in the pimasertib 45 mg BID cohort) had Grade 2 visual impairment.

Four deaths occurred in Arm A: two in the pimasertib 30 mg BID cohort; one in the pimasertib 45 mg BID cohort; and one the pimasertib 60 mg BID cohort. Three out of four patients had TEAEs leading to death, one of which was regarded as treatment related. This patient was a 60-year old female (in the pimasertib 60 mg BID cohort) with general physical health deterioration (Table 3). Prior to receiving the first dose of pimasertib, however, she was reported to have had tumor-associated fever and abnormal hepatic function. The TEAEs leading to death in the other two patients were

Table 3 Overview of TEAEs and treatment-related TEAEs (incidence > 20% in either arm) (safety analysis set)

n (%)	Solid tumor (Arm A) (*n* = 19)	HCC (Arm B) (*n* = 7)
Any TEAEs	19 (100)	7 (100)
Any related TEAEs	19 (100)	7 (100)
Serious TEAEs	6 (31.6)	2 (28.6)
Related serious TEAEs	2 (10.5)	0 (0)
TEAEs Grade ≥ 3	16 (84.2)	4 (57.1)
Related TEAEs Grade ≥ 3	10 (52.6)	4 (57.1)
TEAEs leading to permanent treatment discontinuation	4 (21.1)	3 (42.9)
Related TEAEs leading to treatment discontinuation	3 (15.8)	3 (42.9)
TEAEs leading to permanent treatment modification	19 (100)	7 (100)
Related TEAEs leading to treatment modification	18 (94.7)	6 (85.7)
TEAEs leading to death	3 (15.8)	0 (0)
Related TEAEs leading to death	1 (5.3)	0 (0)
Patients with ≥ 1 TEAE	19 (100)	7 (100)
Eye disorders	17 (89.5)	5 (71.4)
Retinal detachment	14 (73.7)	4 (57.1)
Gastrointestinal disorders	12 (63.2)	6 (85.7)
Diarrhea	8 (42.1)	4 (57.1)
Stomatitis	6 (31.6)	2 (28.6)
Nausea	5 (26.3)	3 (42.9)
Vomiting	3 (15.8)	3 (42.9)
General disorders and administration site conditions	14 (73.7)	4 (57.1)
Edema peripheral	9 (47.4)	0 (0)
Pyrexia	6 (31.6)	1 (14.3)
Fatigue	2 (10.5)	2 (28.6)
Investigations	16 (84.2)	5 (71.4)
Blood CPK increased	15 (78.9)	2 (28.6)
AST increased	7 (36.8)	2 (28.6)
ALT increased	5 (26.3)	1 (14.3)
Metabolism and nutrition disorders	9 (47.4)	1 (14.3)
Decreased appetite	6 (31.6)	0 (0)
Skin and subcutaneous tissue disorders	16 (84.2)	4 (57.1)
Dermatitis acneiform	10 (52.6)	4 (57.1)
Dry skin	5 (26.3)	1 (14.3)
Rash	5 (26.3)	0 (0)

The 'safety analysis set' included all patients who received at least one dose of pimasertib. Patients who were replaced for evaluation of DLT due to noncompliance were also included if this criterion applied

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CPK* creatine phosphokinase, *DLT* dose-limiting toxicity, *HCC* hepatocellular carcinoma, *TEAE* treatment-emergent adverse event

regarded as unrelated to treatment (PD in the pimasertib 30 mg BID cohort and pulmonary hemorrhage in the pimasertib 45 mg BID cohort). The fourth death occurred in a patient who discontinued treatment due to PD and died during the study follow up.

Seventeen of the 19 patients (89.5%) with solid tumors (Arm A) had ocular TEAEs. Of the pre-defined AESI, 14 patients (73.7%) had SRD TEAEs, five of which were recurrent (Table 4). No patients reported RVO TEAEs. Increases in blood CPK levels were reported in 15/19 patients (78.9%), 11 of which were recurrent (Table 4). Increases in blood CPK Grade ≥ 3 were reported in 4/19 patients (21.1%), one of whom experienced concurrent neck pain. All Grade 4 increases in blood CPK levels resolved. No new safety concerns with pimasertib were identified in patients with solid tumors.

In patients with HCC (Arm B) the most frequently reported treatment-related TEAEs were diarrhea (*n* = 4/7; 57.1%), retinal detachment (*n* = 4/7; 57.1%) and dermatitis acneiform (*n* = 4/7; 57.1%; Table 3). Overall, treatment-related Grade ≥ 3 TEAEs occurred in 4/7 patients (57.1%; Table 3) including diarrhea (*n* = 1/7; 14.3%), increased

Table 4 Overview of patients with ocular TEAEs and TEAEs of special interest (safety analysis set)

n (%)	Solid tumor (Arm A) (*n* = 19)	HCC (Arm B) (*n* = 7)
Ocular TEAEs[a]	17 (89.5)	5 (71.4)
Patients with Grade ≥ 3	0 (0)	0 (0)
Patients with recurrent ocular event	8 (42.1)	3 (42.9)
Leading to treatment discontinuation	1 (5.3)	2 (28.6)
Leading to treatment modification	11 (57.9)	5 (71.4)
SRD TEAEs	14 (73.7)	4 (57.1)
Patients with Grade ≥ 3	0 (0)	0 (0)
Patients with recurrent SRD TEAEs	5 (26.3)	2 (28.6)
Leading to treatment discontinuation	0	2 (28.6)
Leading to treatment modification	10 (52.6)	4 (57.1)
CPK (all) TEAEs	15 (78.9)	2 (28.6)
Patients with Grade ≥ 3	4 (21.1)	1 (14.3)
Patients with recurrent CPK TEAEs	11 (57.9)	1 (14.3)
Leading to treatment discontinuation	0 (0)	0 (0)
Leading to treatment modification	6 (31.6)	1 (14.3)

The 'safety analysis set' included all patients who received at least one dose of pimasertib. Patients who were replaced for evaluation of DLT due to noncompliance were also included if this criterion applied

CPK creatine phosphokinase, *DLT* dose-limiting toxicity, *HCC* hepatocellular carcinoma, *RVO*, retinal vein occlusion, *SRD* serous retinal detachment, *TEAE* treatment-emergent adverse event

[a]No RVO reported

aspartate aminotransferase (*n* = 2/7; 28.6%) and increased blood CPK (*n* = 1/7; 14.3%). Treatment-related TEAEs leading to treatment discontinuation occurred in three patients: two patients had Grade 1 retinal detachment (one in the pimasertib 30 mg BID cohort and one in the pimasertib 45 mg BID cohort); and one patient had Grade 2 diarrhea (in the pimasertib 45 mg BID cohort). No deaths were reported in Arm B.

Out of the seven patients in Arm B, five (71.45%) had ocular TEAEs. Of the pre-defined AESI, SRD and increased blood CPK levels (Grade > 1) were reported (Table 4). Four patients had SRD, two of which were recurrent. No patients reported RVO. Two patients (28.6%) had asymptomatic increases in blood CPK levels, one Grade ≥ 3 and one being recurrent. Arm B was discontinued prematurely after DLTs/TEAEs were reported in patients with HCC. There was no apparent relationship between TEAEs and the study drug dose.

In patients with solid tumors and HCC, no trend was observed in change from baseline vital signs in (data not shown). No shift from baseline-corrected QT interval using Fridericia's formula (QTcF) values < 450 ms to worst on-treatment values > 450 ms were reported across all dose cohorts in both arms. There was no shift observed from baseline left ventricular ejection fraction values to worst on-treatment values ≥ 20% across all dose cohorts.

Efficacy

Twelve patients were assessed for mutational status: two had *KRAS* mutations (30 mg BID and 60 mg BID cohorts) and two had *BRAF* mutations (both in the pimasertib 45 mg BID cohorts). All four of these patients had solid tumors. No patients had *NRAS* or *PIK3CA* mutations.

Out of the 14 patients with solid tumors (Arm A) in the efficacy analysis set, three patients had PR as their BOR; all had stage IV metastatic melanoma (primary tumor classification *T*× with lymph node [N] and metastasis [M] classifications of Nx M1, Nx M1c and N3 M1), one had a *BRAF* mutation and all were in the pimasertib 45 mg BID cohort. One patient with non-small cell lung carcinoma with adenocarcinoma histology (pimasertib 45 mg BID) had SD, eight patients had PD and two were NE. An ORR of 21.4% [90% confidence interval (CI): 6.1–46.6] and a DCR of 28.6% (90% CI: 10.4–54.0) was reported (Table 5), suggesting some anti-tumor activity with pimasertib 45 mg BID in patients with solid tumors, particularly for patients with melanoma.

Out of the six patients with HCC (Arm B) in the efficacy analysis set, four had a BOR of PD and two were NE. An ORR and a DCR of 0% was reported (Table 5).

Pharmacokinetics

There was a general dose-dependent increase in pimasertib geometric mean exposure [area under the concentration–time curve during a dosing interval (AUC_{tau}) and maximum observed concentration (C_{max})] between Day 1 and 15 in patients with solid tumors, but this increase was highly variable (Fig. 1). The mean terminal half-life ($t_{½}$) of pimasertib in Arm A ranged from 3.6 to 3.9 h across all doses and was 5.3 h in Arm B (data not shown). PK parameters could not be determined in Arm B due to a small sample size ($n < 3$).

Pharmacodynamics

MEK1/2 inhibition with pimasertib treatment was demonstrated using pERK inhibition as a surrogate marker. Within two hours after initial dosing on Day 1 of Cycle 1, the range of fluorescent intensity levels of pERK decreased (0.84–5.80) compared with pre-dose (4.34–9.57) in all patients and dose cohorts. This decrease was maintained at Day 8 (0.86–4.21 pre-dose) and Day 15 (0.33–5.39 pre-dose). After dosing on Day 15, the levels of pERK decreased to 0.88–1.52 post-dose (data not shown).

Table 5 Best overall response (efficacy analysis set)

	Solid tumor				HCC		
	30 mg (*n*=3)	45 mg (*n*=7)	60 mg (*n*=4)	Overall (*n*=14)	30 mg (*n*=4)	45 mg (*n*=2)	Overall (*n*=6)
BOR, *n* (%)							
CR	0	0	0	0	0	0	0
PR	0	3 (42.9)	0	3 (21.4)	0	0	0
SD	0	1 (14.3)	0	1 (7.1)	0	0	0
PD	2 (66.7)	3 (42.9)	3 (75.0)	8 (57.1)	3 (75.0)	1 (50.0)	4 (66.7)
NE	1 (33.3)	0	1 (25.0)	2 (14.3)	1 (25.0)	1 (50.0)	2 (33.3)
BOR rate							
ORR (CR + PR), *n* (%)	0	3 (42.9)	0	3 (21.4)	0	0	0
90% CI (exact)[a]	–	12.9–77.5	–	6.1–46.6	–	–	–
Disease control							
DCR (CR + PR + SD[b]), *n* (%)	0	4 (57.1)	0	4 (28.6)	0	0	0
90% CI (exact)[a]	–	22.5–87.1	–	10.4–54.0	–	–	–

The 'efficacy analysis set' included all patients who received at least one dose of pimasertib and had at least one efficacy assessment after the first dose

BOR best overall response, *CI* confidence interval, *CR* complete response, *DCR* disease control rate, *HCC* hepatocellular carcinoma, *NE* not evaluable, *ORR* objective response rate, *PD* progressive disease, *PR* partial response, *SD* stable disease

[a]Clopper–Pearson method

[b]At least 12 weeks after treatment

Expansion phase (part 2)

Due to the changing landscape of current therapeutic options, the sponsor decided not to pursue pimasertib as a monotherapy; therefore, the expansion phase (Part 2) of the study was not conducted.

Discussion

In this phase I, dose-escalation and expansion study, an MTD of pimasertib 45 mg BID was established in Japanese patients with solid tumors. This was lower than the MTD of pimasertib reported in patients with advanced solid tumors in a global study [6]. In this same study, the global RP2D for pimasertib was established as 60 mg BID, which was not confirmed in the current study in Japanese patients.

In patients with HCC, DLTs occurred at the lowest dose (pimasertib 30 mg BID) and, therefore, an MTD could not be established. Patients with HCC are more susceptible to toxicities related to anti-tumor therapies due to their poor general condition including decreased liver function [9].

Despite this, the safety profile of pimasertib was consistent with previous pimasertib global studies, with no new safety signals observed. Furthermore, there was no link between pimasertib dose and incidence of AEs. In the current study, 17/19 patients with solid tumors reported ocular TEAEs. Ocular events are commonly reported in patients treated with MEK inhibitors but tend to resolve in all patients after discontinuation of treatment [10]. These data confirm previous studies that showed pimasertib has an acceptable safety profile [6, 7]. Pimasertib showed some preliminary clinical anti-tumor activity in Japanese patients with solid tumors. Although the number of patients in this study was small and, therefore, no firm conclusions can be drawn, the PRs observed in three patients with melanoma treated with pimasertib 45 mg BID suggests that pimasertib has some anti-tumor activity in this setting, which is consistent with previous reports of pimasertib efficacy in Caucasian patients with melanoma in global studies [11, 12]. In a phase I, dose-escalation trial of pimasertib in 89 Caucasian patients with melanoma, 11 patients had a CR or PR to pimasertib, nearly half of which were at pimasertib doses of 45–75 mg BID [11]. Recently, a phase II study of patients with melanoma treated with pimasertib showed that although overall survival was not improved, significant improvement in progression-free survival and consistent trends in favor of pimasertib for ORR and DCR were observed compared with dacarbazine [12].

In the current study, of those patients assessed for mutational status, two had *BRAF*-mutated solid tumors, one of whom experienced a PR. This patient had *BRAF*-mutated melanoma, which is consistent with the efficacy of pimasertib in Caucasian patients with *BRAF*- and/or *NRAS*-mutated melanoma where 5/23 patients with *BRAF* mutations had a PR [11]. BRAF inhibitors such as dabrafenib and vemurafenib are standard of care for *BRAF*-mutated metastatic melanoma and combining BRAF and MEK

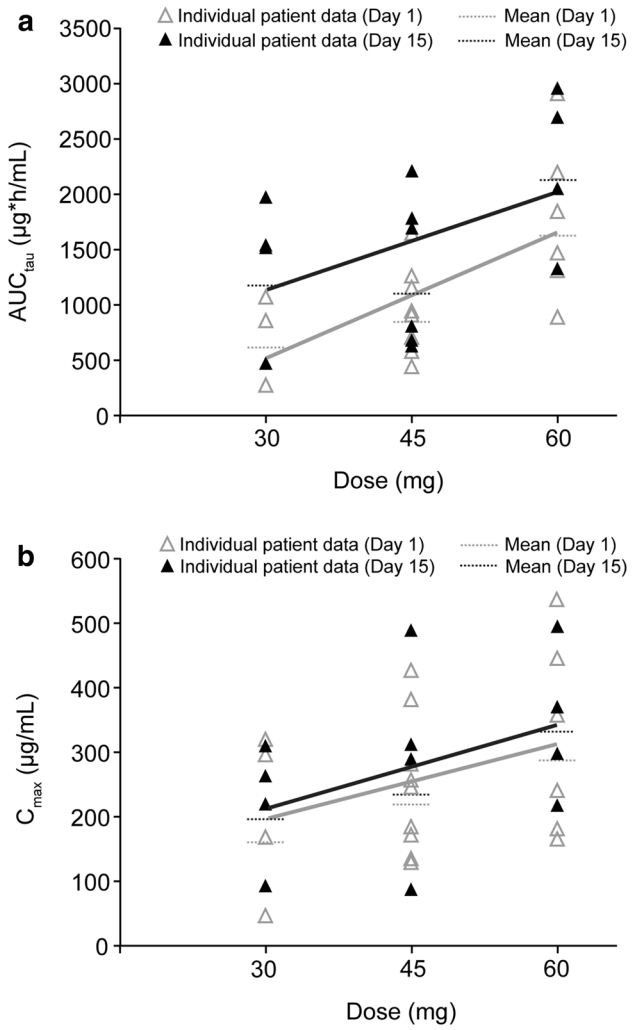

Fig. 1 Pimasertib exposure in patients with solid tumors (PK analysis set) **a** AUC_{tau} **b** C_{max}. The 'PK analysis set' included all patients who received at least one dose of pimasertib and had at least one measurable post-dose PK concentration. Patients with important protocol deviations or events, which may have impacted the quality of the PK data, were excluded from the PK analysis set and from descriptive statistics. *AUC_{tau}* area under the concentration–time curve during a dosing interval, *C_{max}* maximum observed concentration, *PK* pharmacokinetic

inhibitors may overcome the growing resistance seen with these current therapies [13]. Pimasertib targets the MAPK pathway. However, incomplete inhibition of the MAPK pathway may result from compensatory activation of other pathways. In vivo studies have demonstrated that while single-agent therapies have modest efficacy, combination therapy with PI3K and MEK inhibitors have shown greater efficacy compared with monotherapies [14]. The PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways are two of the most frequently dysregulated pathways in human cancers and can interact [15]. Therefore, MEK1/2 inhibition may lead to reciprocal activation of the PI3K pathway. Similarly, antibodies targeting T cell check-point molecules (i.e., check-point blockers), such as CTLA-4 and PD-1/L1, have been investigated in combination with MEK inhibitors to treat T-cell-driven tumors. MEK inhibition was found to complement anti-CTLA-4-mediated immunity in vivo and enhanced anti-tumor activity compared with anti-CTLA-4 therapy alone [16]. It is reported that MEK inhibition upregulates major histocompatibility complex class 1 expression, which can increase antigen presentation on the surface of tumor cells for recognition by CD8 + T-cells. Targeting these T-cells with the combination of a MEK inhibitor and anti-PD-L1 treatment resulted in tumor growth inhibition and durable responses, including some complete regressions [17]. Combining targeted therapies may help prevent drug resistance and ensure efficacy through dual pathway inhibition.

Pimasertib exposure (AUC_{tau} and C_{max}) was variable and increased with ascending doses. These data support previous studies with pimasertib monotherapy that showed dose-dependent rapid absorption following single dosing of pimasertib [8]. The mean $t_{½}$ of 3.6–3.9 h across all pimasertib doses in patients with solid tumors, and 5.3 h in patients with HCC, are consistent with previous studies that showed a mean $t_{½}$ of ~ 3 h with pimasertib [8]. These data also support pimasertib BID dosing. To date, most of the clinical data with pimasertib has been in Caucasian patients. However, drug exposure and response can differ between ethnic groups [18]. For example, Caucasian and Asian populations have different percentage body fat to bond-mass index relationships; Asian populations tend to have more percentage body fat than Caucasians for the same body-mass index [19], which may have an effect on drug pharmacodynamics and PK. Overall, in the present study in Japanese patients, exposure [20] and dose-normalized exposure [data not shown] appeared, in general, to be higher than those observed in non-Japanese patients; however, it is difficult to draw any firm conclusions as to the reason for this due to the small study size. In addition, rapid and consistent MEK inhibition (demonstrated by inhibition of pERK) with pimasertib in Japanese patients was consistent with global pimasertib studies [6, 8].

Conclusions

An MTD of pimasertib 45 mg BID was established in Japanese patients with solid tumors but could not be determined in patients with HCC. The global RP2D of pimasertib 60 mg BID could not be confirmed in Japanese patients. No new safety concerns were found with pimasertib monotherapy and some clinical activity in solid tumors was observed; however, further investigation of pimasertib as monotherapy in unselected with solid tumors was not warranted, partly

due to the general move towards anti-tumor therapies being given in combination rather than as monotherapies. The possibility of combining pimasertib with other therapies should be further investigated.

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Compliance with ethical standards

Conflict of interest KY has received lecture fees from Merck Serono. TD has received research funding from Taiho, Novartis, Merck Serono, Merck Sharpe and Dohme, Boehringer Ingelheim, Pfizer, Lilly, Sumitomo Dainippon, Kyowa Hakko Kirin, Daiichi Sankyo, Bristol-Myers Sqiibb, Abbvie and Eisai, and has consulted/advised Kyowa Hakko Kirin, Merck Sharpe and Dohme, Amgen, Sumitomo Dainippon, Taiho, Takeda, Abbvie, Novartis and Bayer. MI has received research grants from Bayer Yakuhin, Kyowa Hakko Kirin, Eli Lilly Japan, Eisai, Chugai Pharmaceutical, and Bristol-Myers Sqiibb, and a speaker honorarium from Bayer Yakuhin and Eisai. MI is a member of advisory boards of Bayer Yakuhin and Eisai. AS is an employee of Merck Healthcare KGaA, Darmstadt, Germany. MW is an employee of Merck Serono Co Ltd, Tokyo, Japan. TO and AO declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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