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Phase I trial of MEK 1/2 inhibitor pimasertib combined with mTOR inhibitor temsirolimus in patients with advanced solid tumors

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Abstract

Background—Dual inhibition of activated MAPK and mTOR signaling pathways may enhance the antitumor efficacy of the MEK 1/2 inhibitor pimasertib and the mTOR inhibitor temsirolimus given in combination.

Methods—In this phase I study, patients with refractory advanced solid tumors (NCT01378377) received once-weekly temsirolimus plus once-daily oral pimasertib in 21-day cycles in a modified 3+3 dose-escalation design. The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of pimasertib in combination with temsirolimus, safety and pharmacokinetics (PK) were investigated.

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Compliance with Ethical Standards: **Ethical Approval**: Written informed consent was obtained from all patients prior to study initiation. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution of the participating centers and with the 1964 Helsinki declaration and its later amendments.

Results—Of 33 patients evaluated, all experienced ≥1 treatment-emergent adverse event (TEAE) and 31 had treatment-related TEAEs, most frequently stomatitis and thrombocytopenia. TEAEs were reversible. No deaths were attributed to treatment. Nine patients had dose-limiting toxicities (stomatitis, thrombocytopenia, serum creatinine phosphokinase increase, visual impairment) and the MTD was determined as 45 mg/day pimasertib plus 25 mg/week temsirolimus. However, due to overlapping toxicities no further investigations were performed and the RP2D was not defined. PK profiles of both agents were not adversely affected. Seventeen patients (17/26 patients) had a best response of stable disease; five had stable disease lasting >12 weeks.

Conclusions—The RP2D was not defined and the pimasertib plus temsirolimus combination investigated did not warrant further study.

Keywords

MAPK; MEK; pimasertib; safety; solid tumors; temsirolimus

Introduction

The PTEN/PI3K/AKT/mTOR (mTOR) and RAS/RAF/MEK/ERK (MAPK) signaling pathways are among the most frequently deregulated in cancer, and play a key role in carcinogenesis [1]. Mutations in any of the elements of these pathways can lead to pathway activation, aberrant signaling and loss of regulation, ultimately resulting in abnormal cell growth and tumor formation [2]. Aberrant activation of the mTOR and MAPK pathways is seen in a broad spectrum of human cancers [3,4].

The mTOR and MAPK pathways have extensive cross-talk [2,1,5] and co-activation of these pathways has been shown in a number of tumor types, including prostate, colorectal and thyroid cancer and melanoma [6-10]. As a consequence of the marked cross-talk between these pathways, one pathway may provide compensatory signaling when the other is inhibited [11,1] and the activation of one pathway can influence resistance to targeted inhibition of the other pathway [4,5]. However, simultaneous inhibition of the MAPK and mTOR signaling cascades may lead to greater antitumor activity than targeting either pathway alone [2,1,12].

In preclinical studies, the simultaneous inhibition of MEK and mTOR substantially enhanced antitumor activity in a variety of xenograft cancer models including breast, prostate, colorectal, thyroid, pancreatic, liver and non-small cell lung cancer (NSCLC) and melanoma [13-17,6,18,19]. Similarly, targeting PI3K/AKT and the MAPK pathway had favorable effects on antitumor efficacy (with tumor regression ranging from 2 to 64%) in patients with advanced cancer [12]. In addition to enhanced antitumor efficacy, dual inhibition of the MAPK and mTOR signaling pathways is a strategy that can also be used to overcome resistance to mTOR inhibition, and has been proposed as a means of enhancing mTOR targeted anticancer therapies [20].

Pimasertib (MSC1936369B) is an orally bioavailable and selective small-molecule inhibitor of MEK1 and MEK2 that prevents the activation of MEK1/2-dependent effector proteins and transcription factors [21,22]. It has demonstrated robust antitumor activity in preclinical

studies, including tumor growth reduction in murine myeloma xenografts [21] and tumor regression in a mouse model of D-MUT colorectal cancer [22], and it has also been shown to circumvent resistance to BRAF inhibition in human melanoma cells [23].

Pimasertib given as a single agent showed acceptable toxicity with a maximum tolerated dose (MTD) that depended on the treatment schedule in patients with advanced solid tumors [24]; with continuous twice daily administration, the MTD was 75 mg. When pimasertib was given in combination with FOLFIRI (5-fluorouracil/folinic acid/irinotecan), the MTD was reached at 45 mg/day in a 5 days on/2 days off schedule in patients with *KRAS*-mutated metastatic colorectal cancer [25].

Pimasertib has been evaluated in combination with a variety of mTOR pathway inhibitors (MSC2208382 [a selective PI3K inhibitor], everolimus, sorafenib or regorafenib) in preclinical studies [26]. These have shown synergistic effects on the inhibition of cell growth and induction of apoptosis, with sustained blockade of MAPK- and AKT-dependent signaling pathways in pimasertib-resistant human colon carcinoma and lung adenocarcinoma cell lines and delayed tumor growth and increased survival in mice with colon carcinoma and lung adenocarcinoma xenografts [26].

The mTOR inhibitor temsirolimus (CCI-779) is approved for the treatment of advanced renal cell carcinoma (RCC) [27] and has shown efficacy in phase II trials including patients with neuroendocrine tumors, breast cancer and endometrial cancer [28-30]. Following on from the promising preclinical outcomes of pimasertib in combination with mTOR inhibitors, the primary aim of the present phase I study (NCT01378377) was to determine the MTD of pimasertib and a dosage suitable for phase II study in combination with temsirolimus in patients with advanced solid tumors.

Materials and Methods

Patients

Patients were eligible for enrolment if they were ≥ 18 years old with histologically or cytologically confirmed solid tumors, which were refractory to standard therapy or for which no effective standard therapy was available. Tumor samples were required at baseline for histological or cytological confirmation and characterization of molecular aberrations activating the PI3K/mTOR or MEK pathways.

All patients provided written, informed consent prior to study initiation. The study adhered to Good Clinical Practice and the Declaration of Helsinki, and had institutional ethics review board approval from the participating centers.

Study design

In this phase I study (www.ClinicalTrials.gov, NCT01378377), the primary objective was to determine the MTD and the recommended phase II dose (RP2D) of the combination of pimasertib and temsirolimus, and to evaluate tolerability and dose-limiting toxicities (DLTs). Secondary objectives included safety, pharmacokinetics (PK) of pimasertib and

temsirolimus alone and in combination, and the antitumor activity of the two drugs in combination.

Patients received intravenous (i.v.) temsirolimus once a week plus oral pimasertib once a day (15 days on then 6 days off) in a 21-day cycle at three dose levels (Fig 1). These were (1) pimasertib 45 mg/day, temsirolimus 12.5 mg/week; (2) pimasertib 45 mg/day, temsirolimus 25 mg/week; and (3) pimasertib 75 mg/day, temsirolimus 25 mg/week. A modified 3 + 3 dose-escalation design for pimasertib was used, with three to six patients at each level.

Patients were assigned to sequential cohorts, starting with the first cohort at the first dose level (pimasertib 45 mg/day, temsirolimus 12.5 mg/week). Temsirolimus was escalated to the maximum dose of 25 mg/week from the second cohort onwards. Dose escalation of pimasertib began in the third cohort, and proceeded until the MTD of pimasertib as monotherapy (75 mg twice daily continuously, determined previously from the first in human pimasertib single-agent trial [24]) was reached or the RP2D was determined. The dose escalation scheme is summarized in Fig 1

Treatment continued until disease progression or intolerable toxicity, or at the discretion of the investigator or patient. Safety follow-up assessment was 30 days after final study drug administration.

Safety evaluation, DLTs and MTD

Treatment-emergent adverse events (TEAEs) and DLTs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

DLTs were defined as any of the following toxicities observed in the first treatment cycle and judged not to be related to underlying disease or concomitant medications: any grade ≥ 3 non-hematologic toxicity (with certain exceptions); grade 4 neutropenia lasting > 5 days or febrile neutropenia lasting > 1 day; grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia; any treatment interruption of > 2 weeks that was due to adverse events (AEs) not related to the underlying disease or concomitant medication; and any severe or life-threatening condition not defined by NCI-CTCAE that was attributable to study treatment.

The MTD of the combined treatment was defined as the dose level below the one at which > 1 out of 3 or 6 patients experienced drug-related DLTs during the 21-day DLT observation period.

AEs of special interest (AESIs) in this study were serous retinal detachment (SRD), retinal vein occlusion (RVO) and serum creatine phosphokinase (CPK) elevation. Skin disorders and cardiac events received particular attention, but were not classed as AESIs.

PK parameters

Concentration-time profiles for pimasertib were obtained in plasma, and in whole blood for temsirolimus. PK parameters were calculated using standard non-compartmental analyses

and key plasma PK parameters were assessed: peak plasma concentration (C_{max}) and time to C_{max} (t_{max}); area under the curve of plasma concentration versus time extrapolated to infinity ($AUC_{0-\infty}$) and for the dosing interval (AUC_{τ}); plasma elimination half-life ($t_{½}$); apparent clearance (CL/F); and apparent volume of distribution (V_Z/F). PK parameters for temsirolimus were C_{max}, t_{max}, $AUC_{0-1/2}$, $t_{½}$, CL (clearance) and V_Z (volume of distribution).

A drug-drug interaction (DDI) study investigated the potential effects of coadministration of pimasertib and temsirolimus on exposure to either compound. Patients included in the DDI study were those enrolled in the first cohort and (if deemed necessary by the safety monitoring committee) up to 12 patients in the expansion part of the MTD cohort. All assessments and procedures related to DDIs were carried out during cycle 1.

Temsirolimus administration was delayed by 1 day for DDI study patients to allow evaluation of the effect of temsirolimus on the PK of pimasertib.

Efficacy

Tumor response was assessed using computed tomography or magnetic resonance imaging every two cycles for the first six cycles, then at least once every four cycles (12 weeks). Tumors were also assessed at the end of treatment, at safety follow-up or at disease progression. Tumor responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.0). Objective response and disease control rates were calculated.

Statistical considerations

The study followed a classical 3 + 3 design. Descriptive statistics were used to summarize the trial data for each dose level cohort. Geometric least-squares mean ratios (pimasertib + temsirolimus/temsirolimus alone) for C_{max} on Day 9/Day 1, and for AUC_{τ}, on Day 9/ $AUC_{0-\infty}$ on Day 1, and for C_{max} and $AUC_{0-\infty}$ for Day 9/Day 16 were calculated with 90% confidence intervals (CIs), and compared with a predefined equivalence interval for the CI of 0.80-1.25.

Results

Patient baseline characteristics

In total, 46 patients were screened, of whom 33 received treatment with pimasertib and temsirolimus: pimasertib 45 mg + temsirolimus 12.5 mg (45 PIM/12.5 TEM; $n = 4$), pimasertib 45 mg + temsirolimus 25 mg (45 PIM/25 TEM; $n = 23$) and pimasertib 75 mg + temsirolimus 25 mg (75 PIM/25 TEM; $n = 6$). Table 1 shows the baseline characteristics and demographics. All patients had been heavily pretreated with a median of five prior lines of anticancer therapies (range: 1, 13).

All patients were off-treatment at the time of analysis. The most common reason for withdrawal was disease progression (63.6%), followed by withdrawal of consent (18.2%) and AEs (12.1%).

Safety

In total, nine patients had a DLT (Table 2). No DLTs were reported at the lowest dose. One DLT occurred in the six patients originally treated with 45 mg PIM/25 mg TEM group (grade ≥3 visual impairment) and the dose was escalated (Table 2). However, two DLTs occurred in the 75 mg PIM/25 mg TEM group (stomatitis and thrombocytopenia). The MTD was therefore established as 45 mg PIM/25 mg TEM as predefined in the protocol, and an expansion cohort of 11 patients was treated with this dose regimen. Six of these 11 patients had DLTs (stomatitis, serum CPK increase and thrombocytopenia) (Table 2). As the toxicity profile and PK data did not justify further reduction in the dosing of agents, the RP2D was not defined.

All patients experienced at least one TEAE and > 75% had a grade ≥ 3 TEAE (Table 3). The most common TEAEs reported (> 20% of patients overall) were stomatitis (69.7%), thrombocytopenia (57.6%), fatigue (51.5%), anemia (42.4%), diarrhea (36.4%), pyrexia (33.3%), rash (33.3%), decreased appetite (30.3%), dyspnea (30.3%), edema peripheral (27.3%), aspartate aminotransferase (AST) increased (27.3%), dehydration (27.3%), hypokalemia (27.3%), oral candidiasis (21.2%), pneumonia (21.2%) and urinary tract infection (21.2%). Most of the grade ≥ 3 TEAEs reported were gastrointestinal disorders (17/33, 51.5%), notably stomatitis (8/33, 24.2%; Supplementary Table 1).

Treatment-related TEAEs (any study drug) were observed in 75.0% (3/4 patients), 95.7% (22/23 patients) and 100% (6/6 patients) of patients in the 45 mg PIM/12.5 mg TEM, 45 mg PIM/25 mg TEM and 75 mg PIM/25 mg TEM groups, respectively (Table 3). The most frequent events related specifically to pimasertib (any grade, ≥ 30% of patients) were stomatitis (22/33; 66.7%), thrombocytopenia (15/33; 45.5%), fatigue (11/33; 33.3%), and rash (10/33; 30.3%) (Table 3). Grade ≥ 3 TEAE related to any trial drug were most commonly thrombocytopenia and stomatitis; only one grade 4 TEAE (thrombocytopenia) was reported (Table 4). No deaths due to toxicity were reported, but four patients discontinued treatment because of a TEAE (abdominal wall abscess, visual impairment, pneumonia and vaginal fistula).

In terms of AEs known to be associated with MEK inhibition, three patients had SRD events, none of which was severe or necessitated discontinuation of study medication. There were no RVO events. One case of grade 4 CPK elevation was classed as pimasertib-related and as a DLT. Of the skin disorders, rash was reported most frequently (11/33; 33.3%), but only one event was grade 3 (45 mg PIM/25 mg TEM group).

Pharmacokinetics

The median t_{max} of pimasertib was 1.0 to 2.3 hours post-dose on day 1 and day 9 for the two treatment groups in the DDI cohorts (45 mg PIM/12.5 mg TEM and 45 mg PIM/25 mg TEM). Median $t_{½}$ values were ~ 6 hours on both days for pimasertib (Supplementary Table 2). There was no apparent accumulation of pimasertib and temsirolimus had no relevant effect on pimasertib PK. The 90% CIs for the geometric least-squares mean ratios (pimasertib + temsirolimus *vs* pimasertib alone) for C_{max} (ratio 1.012; 95% CI 0.841–1.219)

and AUC_{τ} on day 9 *vs* $AUC_{0-\infty}$ on day 1 of pimasertib (0.970; 0.810– 1.175) were contained within the equivalence interval of 0.80–1.25.

In contrast, pimasertib had a small effect on temsirolimus C_{max}. Although median C_{max} and $AUC_{0-\infty}$ values for temsirolimus were generally similar on day 9 (temsirolimus + pimasertib) and day 16 (temsirolimus alone) for the two DDI treatment groups (Supplementary Table 3), one patient in the 45 mg PIM/12.5 mg TEM group had a low C_{max} (13.2 ng/mL) on day 16 relative to the median value of 281.1 ng/mL. The 90% CI for the $AUC_{0-\infty}$ of temsirolimus (1.043; 0.920–1.182), but not that for C_{max} (1.008; 0.564–1.801), was entirely contained within the equivalence interval,.

Plasma and blood concentration *vs* time profiles for pimasertib and temsirolimus are shown in Fig 2.

Efficacy

No patients experienced partial remission, but 17 of 26 had a best response of stable disease, including five patients who had stable disease lasting > 12 weeks. These were three patients with colorectal cancer, one with NSCLC, and one with breast cancer. Because of the premature termination of the study, no formal statistical analyses were carried out. Fig 3 shows tumor response to treatment over time.

Discussion

Targeting either of the MAPK or mTOR pathways individually can attenuate aberrant signaling [31]. However, cancer cell proliferation and survival are driven by multiple effector pathways in solid tumors (i.e., those with concurrent activation of RAS and PI3KCA genes) [32-34]. Therefore, targeting of both the MAPK and mTOR pathways simultaneously could be significantly more effective than targeting either pathway alone.

The primary objective of this phase I study was to determine the MTD and RP2D of pimasertib, a selective inhibitor of MEK 1/2 [21], combined with the mTOR inhibitor temsirolimus. Because of the potential for overlapping toxicities with this drug combination, lower starting doses were selected for both drugs relative to previously tested highest tolerated doses of pimasertib in a monotherapy trial [24] and the labelled dose of temsirolimus [27]. This was done to facilitate the early detection, evaluation and active management of any synergistic or additive toxicity. Of the 33 patients who received pimasertib plus temsirolimus within a 21-day cycle, nine had a DLT, predominantly in the 45 mg PIM/25 mg TEM group (seven of a total of 17 patients, with one event occurring in the first six patients enrolled), with two DLTs reported in the 75 mg PIM/25 mg TEM group. Based on these observations the MTD was reached at dose level 1 (45 mg PIM/25 mg TEM).

During the study, all patients had a TEAE, the most common of which were thrombocytopenia, anemia, stomatitis and fatigue; approximately 75% of patients had a TEAE of grade ≥ 3 (thrombocytopenia and stomatitis) or a serious AE (SAE). The TEAEs observed in this study were similar to those reported elsewhere with these therapies. The

increased risk of diarrhea and stomatitis with mTOR inhibitors is well documented [35,36]. In one review of 11 randomized controlled trials in 4752 patients who received everolimus or temsirolimus, the incidence of stomatitis (all grades) was 33.5%, with a 4.1% incidence of high-grade lesions [36]. A recent meta-analysis of 18 trials in over 8000 patients who received everolimus, temsirolimus or ridaforolimus showed relative risks of all-grade diarrhea and stomatitis of 1.94 and 3.54, respectively; the relative risks of high-grade diarrhea and stomatitis were 3.49 and 6.98 [35]. Thrombocytopenia and rash are also established as common AEs with temsirolimus [27]. Thrombocytopenia is listed among events seen in at least 30% of patients, and grade 3/4 maculopapular rash has been documented as a DLT in two out of three patients receiving temsirolimus 15 mg weekly in combination with sunitinib 25 mg/day.

Previous clinical experience also points to increased risk of stomatitis/mucositis with temsirolimus-based combination therapies *vs* single-agent temsirolimus treatment [37]. Three phase I studies in 87 patients who were treated with temsirolimus combined with metformin, cixutumumab or pimasertib showed a significantly greater risk of mucositis (41.3%; $P = 0.0003$) when temsirolimus was used in combination with another agent rather than alone [37].

The most frequent TEAEs associated with pimasertib treatment include diarrhea, nausea, vomiting, rash and asthenia, as shown by phase I data obtained in patients with metastatic colorectal cancer who received pimasertib 45 mg or 60 mg daily with FOLFIRI chemotherapy [25]. Other pimasertib-related TEAEs were mucositis, stomatitis and neutropenia, which are consistent with the findings of the present study.

Marked ocular toxicity (a class effect of MEK inhibitors [38]) was not noted in this study. Eleven patients had one or more ocular events, only one of which was grade 3 (visual impairment reported as a DLT). No cases of SRD were classed as severe, and there were no instances of RVO. Similarly, in a trial of pimasertib in combination with FOLFIRI, ocular events (43.8%) were all grade 1 except for a single case of grade 2 SRD; no RVO was reported [25]. The assessment of other AESIs showed that there were no treatment-related cardiac events of special note, rash was the most common skin disorder (one grade 3 case), and there was a single grade 4 CPK elevation event that was classed as a DLT.

Analysis of the PK profiles of the two study drugs alone and in combination showed that neither drug adversely affected the absorption, distribution or elimination of the other, suggesting a low potential for direct DDIs. The evidence from this study and from other studies reported in the literature suggest that the safety signals raised for pimasertib plus temsirolimus at relatively low doses were likely due to overlapping toxicities, possibly due to an interaction at the level of the pharmacological target and not due to a pharmacokinetic interaction.

At the conclusion of our study RP2D for concomitant administration of an mTOR and a MEK inhibitor was not defined despite efforts to consider alternative dosing options to further investigate this combination, including a reduction in the temsirolimus dose. Doses lower than 45 mg PIM/25 mg TEM were not explored due to strong signals towards

overlapping toxicities, even at the low doses of pimasertib investigated, and because the potential dose of temsirolimus needed would have been lower than the approved dose. This potential for overlapping toxicities between mTOR and MEK inhibitors has been previously reported in a phase IB trial of similar design to the present study [39]. Tolcher *et al.* explored combinations of trametinib and everolimus in 67 patients with advanced solid tumors and reported high frequencies of mucosal inflammation (40%), stomatitis (25%), fatigue (54%) and diarrhea (42%). As with the combinations of pimasertib and temsirolimus studied here, these authors were unable to recommend an RP2D for trametinib plus everolimus as a result of difficulty in combining them such that the combination would provide acceptable tolerability with adequate drug exposure. In addition, and similarly to the present study, PK characterization of the two drugs investigated showed no evidence of clinically relevant DDIs. Based on the toxicity profile and PK data, the combination of pimasertib and temsirolimus did not justify further investigation, and the study was therefore terminated. Consequently, the frequency of DLTs and limited scope for the dose escalation of pimasertib and temsirolimus meant that a meaningful RP2D could not be defined in this trial.

In summary, the rationale for combining MEK inhibitors with drugs targeting the mTOR pathway remains sound as 19% of evaluable patients derived clinical benefit and 65% of evaluable patients had stable disease as their best overall response. However, the interaction at the target level of this combination of pimasertib and temsirolimus resulted in a level of toxicity that prevented the identification of a RP2D. Future studies targeting the MEK and mTOR pathways simultaneously should consider investigating different agents or different schedules of agents, depending on the target in these pathways, which may reduce the potential for overlapping toxicities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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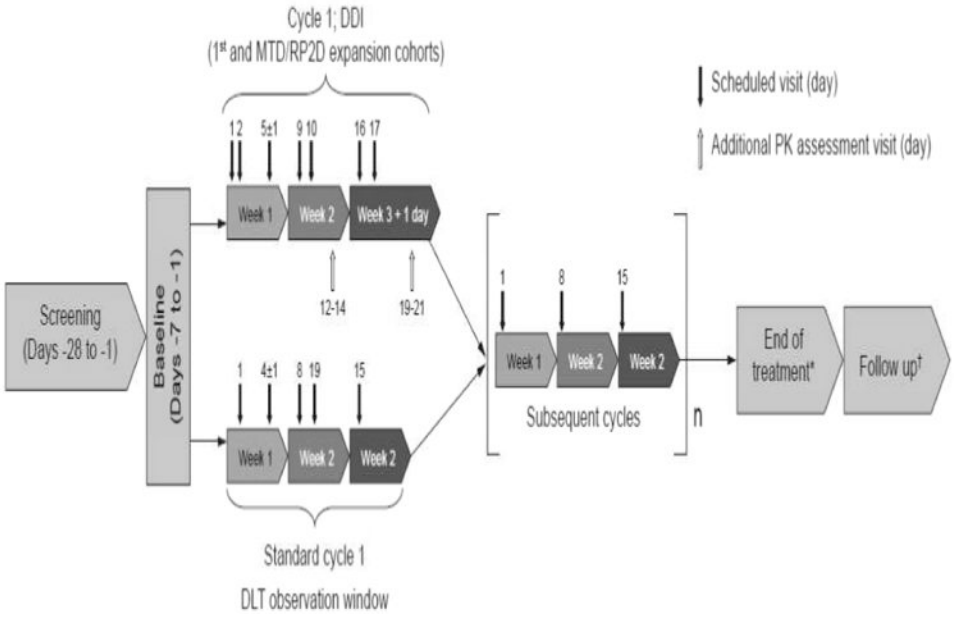

Fig 1. Trial design

*End of treatment visit: For subject not eligible for treatment. Visit scheduled for within 7 days of last treatment

†Follow up visit performed within 30±7 days of last treatment

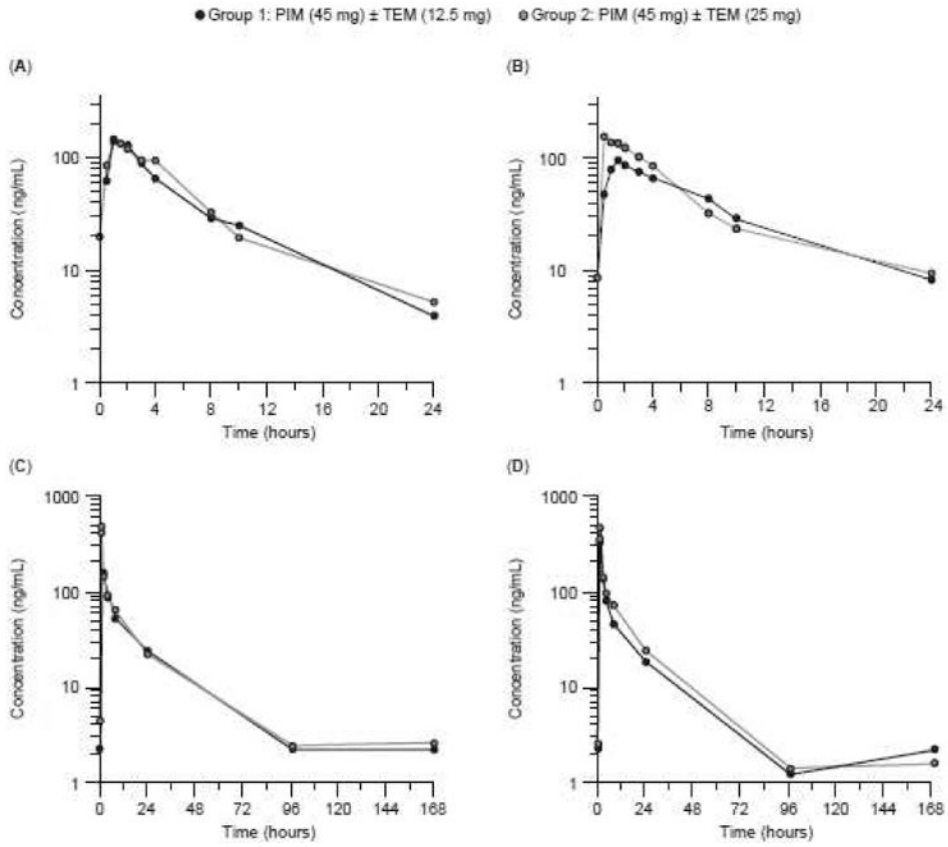

Fig 2. Plasma or blood concentration *vs* time plots for pimasertib

(**A**) alone (Day 1) and (**B**) in the presence of temsirolimus (Day 9), and for temsirolimus (**C**) in the presence of pimasertib (Day 9) and (**D**) alone (Day 16), in the DDI (Drug-Drug Interaction) cohorts who received pimasertib (45 mg) and either temsirolimus 12.5 mg (Group 1) or 25 mg (Group 2)

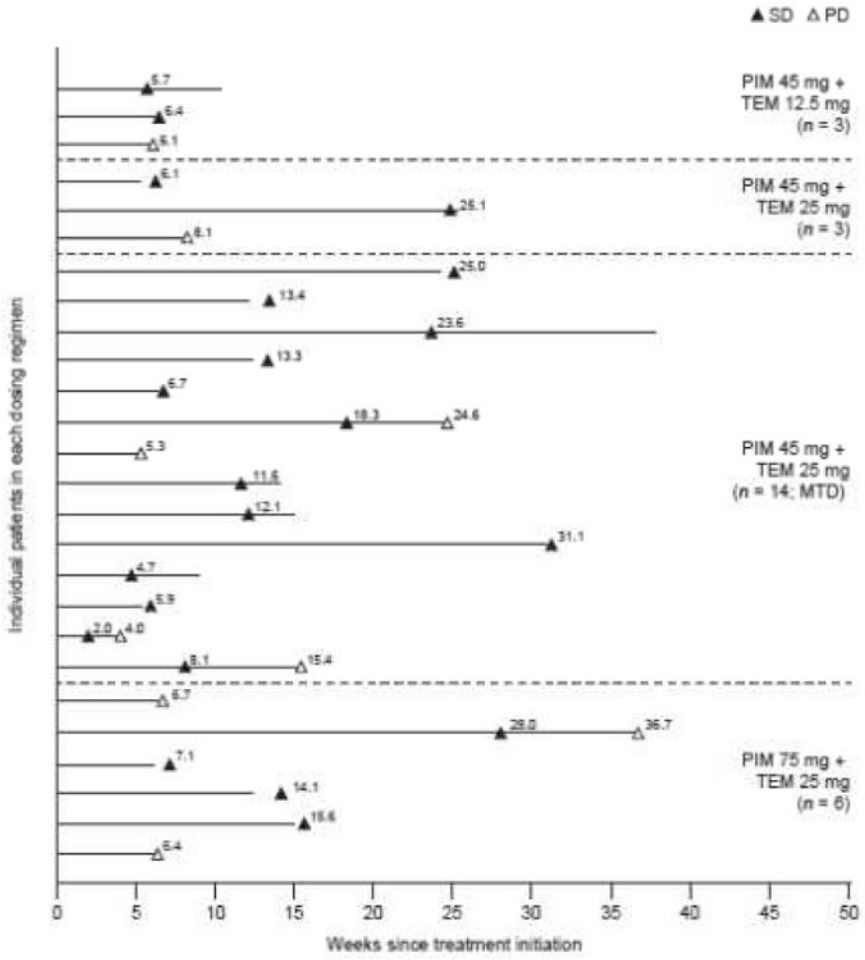

Fig 3. Tumor response over time and best response in patients receiving PIM plus TEM from treatment initiation

Table 1

Patient demographics and baseline characteristics in the safety analysis set.

Characteristic	Cohort			
	45 mg PIM/ 12.5 mg TEM *N* = 4	45 mg PIM/ 25 mg TEM *N* = 23	75 mg PIM/ 25 mg TEM *N* = 6	All *N* = 33
Gender, *n* (%)				
Male	2 (50.0)	7 (30.4)	2 (33.3)	11 (33.3)
Female	2 (50.0)	16 (69.6)	4 (66.7)	22 (66.7)
Age (years)				
Median (range)	63.0 (50–77)	57.0 (22–84)	54.5 (50–66)	57.0 (22–84)
Race, *n* (%)				
White	3 (75.0)	18 (78.3)	16 (100.0)	27 (81.8)
Black/African American	1 (25.0)	1 (4.3)	0	2 (6.1)
Asian	0	3 (13.0)	0	3 (9.1)
Other	0	1 (4.3)	0	1 (3.0)
ECOG PS, *n* (%)				
0	0	5 (21.7)	3 (50.0)	8 (24.2)
≥ 1	4 (100.0)	18 (78.3)	3 (50.0)	25 (75.8)
Type of tumor at diagnosis				
Breast	0	3 (13.0)	1 (16.7)	4 (12.1)
Colorectal	1 (25.0)	8 (34.8)	1 (16.7)	10 (30.3)
Renal cell	0	1 (4.3)	0	1 (3.0)
Gastric	0	1 (4.3)	0	1 (3.0)
Melanoma	0	1 (4.3)	0	1 (3.0)
Thyroid	0	0	1 (16.7)	1 (3.0)
Non-small cell lung	1 (25.0)	3 (25.0)	1 (13.0)	5 (15.2)
Ovarian	2 (50.0)	5 (21.7)	0	7 (21.2)
Endometrial	0	0	1 (16.7)	1 (3.0)
Other	0	1 (4.3)	1 (16.7)	2 (6.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PIM, pimasertib; TEM, temsirolimus.

Table 2

Overall summary and description of dose limiting toxicities occurring in patients in the dose escalation set.

	PIM 45 mg QD + TEM 12.5 mg (*N* = 3)	PIM 45 mg QD + TEM 25 mg (*N* = 6)	PIM 75 mg QD + TEM 25 mg (*N* = 6)	PIM 45 mg QD + TEM 25 mg (expansion on MTD) (*N* = 11)	Overall (*N* = 26)
Patients with ≥1 DLT,[a] *n* (%)	0 (0.0)	1 (16.7)	2 (33.3)	6 (54.5)	9 (34.6)
1	0 (0.0)	1 (16.7)	2 (33.3)	5 (45.5)	8 (30.8)
≥ 2	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	1 (3.8)
Patients with DLTs[a], *n* (%)					
A TEAE that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose patients to unacceptable risk	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any grade ≥ 3 non-hematological toxicity (for exclusion factors please refer to Protocol)	0 (0.0)	1 (16.7)	1 (16.7)	6 (54.5)	8 (30.8)
Grade 4 neutropenia of > 5 days duration or febrile neutropenia of > 1 day duration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia	0 (0.0)	0 (0.0)	1 (16.7)	1 (9.1)	2 (7.7)
Any treatment interruption > 2 weeks due to AEs not related to the underlying disease or concomitant medication at any dose level	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any severe, impairing daily functions or life-threatening, complication or abnormality not defined in the NCI-CTCAE that is attributable to the therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with ≥ 1 DLT documented on the AE CRF page, *n* (%)	0 (0.0)	1 (16.7)	2 (33.3)	6 (54.5)	9 (34.6)
Patients with specific PT of DLTs[b], *n* (%)					
Blood CPK increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	1 (3.8)
Stomatitis	0 (0.0)	0 (0.0)	1 (16.7)	5 (45.5)	6 (23.1)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (16.7)	1 (9.1)	2 (7.7)
Visual impairment	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.8)

[a] Reported in DLT eCRF.

[b] Reported in TEAE eCRF.

Abbreviations: AEs, adverse events; CPK, creatine phosphokinase; CRF, case report form; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PIM, pimasertib; PT, preferred term; QD, daily; SMC, Safety Monitoring Committee; TEAE, treatment emergent adverse event.

Table 3

Overall safety profile for pimasertib plus temsirolimus in the safety analysis set.

Event	Cohort			
	45 mg PIM/ 12.5 mg TEM *N* = 4	45 mg PIM/ 25 mg TEM *N* = 23	75 mg PIM/ 25 mg TEM *N* = 6	All *N* = 33
Any DLT, n (%)	0	7 (30.4)	2 (33.3)	9 (27.3)
TEAEs, n (%)				
≥ 1 TEAE	4 (100.0)	23 (100.0)	6 (100.0)	33 (100.0)
≥ 1 TEAE grade ≥ 3	3 (75.0)	20 (87.0)	6 (100.0)	29 (87.9)
≥ 1 ocular TEAE	1 (25.0)	10 (43.5)	0 (0.0)	11 (33.3)
≥ 1 SRD TEAE	1 (25.0)	2 (8.7)	0 (0.0)	3 (9.1)
≥ 1 RVO TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related TEAEs, n (%)				
≥ 1 TEAE related to pimasertib	3 (75.0)	22 (75.0)	6 (100.0)	31 (93.9)
≥ 1 TEAE related to any trial drug	3 (75.0)	22 (95.7)	6 (100.0)D	31 (93.9)
≥ 1 TEAE related to pimasertib grade ≥ 3	1 (25.0)	14 (60.9)	3 (50.0)	18 (54.5)
≥ 1 TEAE related to any trial drug grade ≥ 3	1 (25.0)	15 (65.2)	4 (66.7)	20 (60.6)
≥ 1 SAE related to pimasertib	0 (0.0)	3 (13.0)	1 (16.7)	4 (12.1)
≥ 1 SAE related to any trial drug	0 (0.0)	4 (17.4)	2 (33.3)	6 (18.2)
SAEs, n (%)				
≥ 1 SAE	3 (75.0)	17 (73.9)	5 (83.3)	25 (75.8)
≥ 1 SAE with fatal outcome	0 (0.0)	1 (4.3)	0 (0.0)	1 (3.0)
Treatment discontinuation, n (%)				
≥ 1 TEAE leading to permanent discontinuation of pimasertib	1 (25.0)	2 (8.7)	1 (16.7)	4 (12.1)
≥ 1 TEAE leading to permanent discontinuation of any trial drug	1 (25.0)	2 (8.7)	1 (16.7)	4 (12.1)
Treatment modification[a], n (%)				
≥ 1 TEAE leading to treatment modification of pimasertib	2 (50.0)	17 (73.9)	6 (100.0)	25 (75.8)
≥ 1 related TEAE leading to treatment modification of any trial drug	2 (50.0)	19 (82.6)	6 (100.0)	27 (81.8)

[a]Includes temporary interruptions, treatment delays and dose interruptions.

Abbreviations: DLT, dose-limiting toxicity; PIM, pimasertib; TEAE, treatment-emergent adverse event; TEM, temsirolimus; RVO, retinal vein occlusion; SAE, serious adverse event; SRD, serious retinal detachment.

Table 4

Overall incidence of grade ≥ 3 TEAEs related to any trial drug (≥ 5% of patients overall) in all treatment cycles in the safety analysis set.

Event	Cohort			
	45 mg PIM/ 12.5 mg TEM *N* = 4	45 mg PIM/ 25 mg TEM *N* = 23	75 mg PIM/ 25 mg TEM *N* = 6	All *N* = 33
SOC[a] and PT				
Patients with ≥ 1 event, n (%)	0	15 (65.2)	4 (66.7)	20 (60.6)
Blood and lymphatic system disorders	**0**	**9 (39.1)**	**2 (33.3)**	**11 (33.3)**
Anemia, n (%)				
Grade 3	0	2 (8.7)	0	2 (6.1)
Neutropenia, n (%)				
Grade 3	0	1 (4.3)	1 (16.7)	2 (6.1)
Thrombocytopenia, n(%)				
Grade 3	0	6 (26.1)	0	6 (18.2)
Grade 4	0	2 (8.7)	1 (16.7)	3 (9.1)
Gastrointestinal disorders	**0**	**7 (30.4)**	**2 (33.3)**	**9 (27.3)**
Diarrhea, n (%)				
Grade 3	0	2 (8.7)	0	2 (6.1)
Stomatitis, n (%)				
Grade 3	0	6 (26.1)	2 (33.3)	8 (24.2)
Metabolism and nutrition disorders	**1 (25.0)**	**3 (13.0)**	**0**	**4 (12.1)**
Dehydration, n (%)				
Grade 3	0	2 (8.7)	0	2 (6.1)

[a]Total for SOC includes all events from listing (including infrequent events with overall incidence < 5% not shown here).

Abbreviations: PIM, pimasertib; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; TEM, temsirolimus.