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ORIGINAL ARTICLE

A phase 1 trial of 4-(N-(S-penicillaminylacetyl)amino)-phenylarsonous acid (PENAO) in patients with advanced solid tumours

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Abstract

Purpose This phase I study was conducted to evaluate the safety and Maximum Tolerated Dose of PENAO (4-(N-(S-penicillaminylacetyl)amino)-phenylarsonous acid), a second-generation organic arsenical with anti-mitochondrial activity, when given as a continuous intravenous infusion (CIVI), in patients with advanced solid tumours.

Methods Eligibility criteria for this trial included age ≥ 18 years, advanced solid tumour, ECOG Performance Status ≤ 1 and adequate organ function. PENAO was administered by CIVI, with dose levels initially increased by infusion duration in a 21-day cycle at a fixed daily dose and then increased daily dose. Standard dose-limiting toxicity (DLT) definitions were used in a "3 + 3" design. Patients had regular monitoring of toxicity and efficacy. Pharmacokinetic assays of serum and urine As were performed.

Results Twenty-six patients were treated across 8 dose levels. The only dose-limiting toxicity (DLT) observed was fatigue, that occurred in one patient treated at the highest dose level of 9 mg/m^2/day. No significant organ toxicity or objective responses were observed, although there were two patients with stable disease lasting up to 7 months. Pharmacokinetic analysis unexpectedly indicated a half-life of 9–19 days, invalidating the CIVI dosing resulting in discontinuation of the study before the RP2D was defined.

Conclusions PENAO was administered by CIVI at dose levels up to 9 mg/m^2/day with only one DLT noted. Pharmacokinetic studies invalidated the rationale for continuous dosing and led to discontinuation of the trial without defining a RP2D. Future clinical development of PENAO will use intermittent dosing schedule, alone and in combination with rapamycin.

Keywords Phase I · PENAO · Novel arsenical compound · Clinical trial · Mitochondrial inhibitor

Introduction

Cancers manipulate normal glucose utilisation methods to produce a metabolic phenotype that drives growth and invasion. In particular, they are more dependent on glycolysis rather than oxidative phosphorylation [1]. Cancers harness the enzyme hexokinase II (HKII) to entrap and channel glucose toward glycolysis, while normal tissues depend on hexokinase IV [2] that favours oxidative phosphorylation. HKII is bound to mitochondria, allowing it access to

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mitochondrial ATP through the inner-membrane transport protein adenine nucleotide translocase (ANT). ANT plays a critical role in mitochondrial permeability, and deactivation leads to uncoupling of oxidative phosphorylation, resulting in ATP depletion, mitochondrial depolarization and cellular apoptosis [3].

GSAO (4-(N-(S-glutathionylacetyl)amino)-phenylarsonous acid) is an organic arsenical and a covalent inhibitor of ANT. In pre-clinical studies, its anti-tumour effects are mediated predominantly by inhibition of proliferating endothelial cells. In a phase I study, it was administered as daily IV infusions on days 1–5 and days 8–12 in a 21-day cycle. Thirty-five patients were treated at 9 dose levels, using a standard '3 + 3' design. Overall GSAO was well tolerated with most toxicity being grade 1 or 2. The most common adverse effects were fatigue, lymphopenia and nausea, but cardiac toxicity was noted (QTc prolongation in 8 patients, and arrhythmias in 4). Hepatic DLTs were observed, but the dose-limiting toxicity was neurological, including one patient with seizure and another with grade 3 encephalopathy. The maximum tolerated dose was 22 mg/m^2/day. Pharmacokinetic studies revealed rapid clearance with a half-life of 10.1 min. Of 20 patients assessable for efficacy, no patient had an objective response although 8 had stable disease [4].

PENAO is a novel organic arsenical, resulting from replacement of a cysteine residue in a key metabolite of GSAO with D-penicillamine. Its mechanism of action is also mediated by covalent inhibition of ANT, but pre-clinical models suggest a more favourable therapeutic index than GSAO, as it causes apoptotic tumour cell death, in addition to anti-angiogenic activity seen with GSAO. Murine studies demonstrated intracellular accumulation of PENAO occurring at 85-fold the rate of GSAO, a 44-fold increase in anti-proliferative activity compared to GSAO, and anti-tumour efficacy was approximately 20-fold greater [5]. Drug efficacy of PENAO was optimised by continuous exposure, but drug clearance was rapid, with a rat half-life of 0.4–1.7 h, necessitating a continuous drug delivery method to achieve continuous exposure. Here, we report the results of the first in-human, dose-escalation study of PENAO in adult patients with advanced solid tumours. Our primary objectives included defining the safety and toxicity profile of PENAO when given as a continuous intravenous infusion (CIVI), and to define a recommended phase II dose (RP2D). Secondary objectives included investigating the pharmacokinetic profile of PENAO as a CIVI, and determining objective response rate.

Materials and methods

Patient eligibility criteria

Eligible patients were adults with histologically or cytologically confirmed advanced solid tumours that were refractory to conventional treatment, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a life expectancy of greater than 3 months. Adequate organ function was defined as: haemoglobin $\geq$ 10 g/dL, neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, bilirubin $\leq$ 1.5 times the upper limit normal (ULN), ALT and AST $\leq$ 2.5 times ULN, glomerular filtration rate > 65 ml/min as calculated by Cockcroft–Gault formula or assessed by nuclear scan, normal left ventricular ejection fraction and QTc interval. Serum potassium and magnesium were required to be normal. Patients were excluded if they had baseline proteinuria or history of glomerular renal disease, cardiac arrhythmia or history of recent heart disease, known brain metastases or pre-existing peripheral neuropathy > grade I, known HIV or active hepatitis B infection, an uncontrolled inter-current illness, or were on therapeutic anti-coagulant therapy. Wash-out periods from previous anti-cancer therapies were defined.

Study design and toxicity assessment

This was an investigator-initiated, open-label, multi-centre, first-in-man phase I clinical study. The trial was sponsored by the University of New South Wales, and the protocol (PENAO-01, ANZCTR No: 362898) was approved by the Human Research Ethics Committees at participating institutions. PENAO was manufactured and packaged by Dr Reddy's Laboratories Limited (DRL) in India. Patients were enrolled at Peter MacCallum Cancer Centre and Royal Melbourne Hospital in Melbourne, and Royal Prince Alfred Hospital in Sydney. All patients signed consent forms detailing the investigational nature of the trial, and the study was conducted according to GCP standards.

In designing this first-in-man trial, renal, hepatic, cardiac and neurological events were identified as toxicities of interest from animal model toxicity of PENAO, the results of the phase I trial of GSAO, and the clinical toxicity profile of arsenic trioxide, an inorganic arsenical registered for use in acute promyelocytic leukaemia [4, 6–9]. Animal models of PENAO had demonstrated both predominant renal excretion and possible renal tubular toxicity, indicating potential for self-perpetuating escalation of drug accumulation and renal toxicity. The hepatic, cardiac and neurological toxicities seen with GSAO are all recognised as potential toxicities of arsenic trioxide, and were regarded as potential class effects. Given the risk of non-reversible toxicity in these organs, the

trial design included tight renal, cardiac and neurological eligibility criteria, and a conservative dose-escalation plan.

Due to the drug's short half-life in murine studies, and the short half-life of GSAO in its phase I trial, it was expected that PENAO would also have a short half-life in humans. As pre-clinical studies had shown that the drug was most effective with continuous exposure, PENAO was given by continuous intravenous infusion (CIVI), using a central venous catheter connected to a continuous ambulatory delivery device (CADD) pump. The starting dose of PENAO was 2 mg/m^2/day over 4 days, amounting to a total dose of 8 mg/m^2 per each 21-day cycle. Dose escalation in dose levels 1–4 used the same daily dose, but increased the number of days the CIVI was administered each cycle from 4 days initially to 21 days (i.e. no break between cycles) at dose level 4. The maximum administration duration of the pump was 7 days, so the pump was refilled with a new cartridge each week at dose levels with a longer administration time. Once the safety of the CIVI over 21 days was established, further dose escalations increased the daily dose, as described in Table 1. To minimise the risk of drug accumulation, no intra-patient dose escalation was allowed. Patients were assigned consecutively to the next treatment spot and dose level depending on availability.

Adverse events were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4. Treatment was continued until disease progression, unacceptable adverse event, withdrawal by the patient, or treatment delay > 3 weeks.

Dose escalations and definitions of DLT, and RPTD

Assessment for dose-limiting toxicities was limited to the first treatment cycle (21 days) for the purpose of dose level escalation, but extended to two cycles (42 days) for defining the recommended phase II dose. To be regarded as dose limiting, adverse events had to be possibly, probably or definitely related to study drug, and regarded as dose dependent. Toxicities regarded as dose-limiting included any grade 3 or 4 non-haematological event (excluding blood test results of no clinical significance), any grade 4 haematological event, any complicated grade 3 haematological event (thrombocytopenia with bleeding, neutropenia with fever), any grade 2 adverse event that adversely impacted on activities of daily living for more than 7 days, and any toxicity that led to dose interruption of more than 7 days or dose reduction. Complications related to venous access devices and allergic events were regarded as dose independent. The recommended phase II dose (RP2D) was defined as the highest dose level at which less than three of ten evaluable patients experienced a DLT in the first two cycles of treatment, in those patients that have received infusion for at least 14 days.

Pharmacokinetics

Analysis of both PENAO and total arsenic pharmacokinetics were studied in both blood and urine. PENAO measurements were found to be unreliable because many of the samples were below or near the lower limit of detection. Measurements of As atom levels was more sensitive and more reliable and were used as the basis of pharmacokinetics analysis. The use of total arsenic in blood has been validated as a surrogate for drug levels in studies of other organoarsenicals [10]. Total arsenic concentrations were measure in blood using an inductively couple plasma atomic emission spectroscopy method according to Standard Operating Procedures at an external laboratory. The pharmacokinetic analysis was conducted using standard non-compartmental analytical procedures. Blood and urine samples for pharmacokinetic analysis were taken on Day 1 of Cycle 1 (pre-dose, and at 0.5, 1, 2, 4 and 6 h after commencing infusion). Additional samples were taken prior to CADD cassette change on the last day of the infusion (Day 5, 8 or 15 according to dose level) in Cycle 1, on Day 1 and the last day of the infusion in Cycle 2, and on Day 1 of Cycles 3 and 4. Further samples were taken at the end of treatment visit, and then weekly to D28 after discontinuation of drug.

Table 1 Dose levels and patient accrual

Dose level	Total dose per cycle (mg/m^2)	Dose per 24 h (mg/m^2)	Infusion duration (days)	Number of patients	Number of evaluable treatment cycles
1	8	2	4	4 (3 treated)	13
2	14	2	7	3	7
3	28	2	14	3	6
4	42	2	21	4	8
5	56.7	2.7	21	5	10
6	84	4	21	3	6
7	126	6	21	3	14
8	189	9	21	2	3

Response assessments

The pharmacodynamic effects of PENAO were assessed by tumour responses as assessed according to RECIST 1.1. CT scans were performed at baseline and after every 2 treatment cycles (6 weeks). FDG-PET scans were performed in patients with measurable disease treated at Dose Level 3 or greater, at baseline, Cycle 1 Day 8, and Cycle 3 Day 8. When relevant to histology, serum tumour markers were measured at screening and prior to each cycle.

Results

Patient demographics

Between July 2012 and August 2015, 27 patients were enrolled at the 3 participating centres. The trial was closed to accrual in December 2015, and the last patient discontinued treatment in January 2016. One patient failed screening criteria, and 26 patients received treatment. The mean age of treated patients was 55 years with 58% being male. 81% of patients were ECOG 1. Eight patients had gastrointestinal primaries (colorectal carcinoma (5), cholangiocarcinoma, small cell anal cancer, mucinous gall bladder carcinoma), six patients had nervous system primaries (olfactory neuroblastoma (2), astrocytoma (2), meningioma, schwannoma), three patients had gynaecological primaries (cervical carcinoma (2), ovarian carcinoma), two patients had genitourinary primaries (bladder transitional cell carcinoma, renal cell carcinoma), and seven patients had other primaries (melanoma, thyroid carcinoma, nasopharyngeal carcinoma, clear cell myoepithelial cancer, adenoid cystic carcinoma, myxoid liposarcoma, and an undifferentiated carcinoma of unknown primary).

Safety and toxicity

Twenty-three of the 26 treated patients were evaluable for DLT. One of four patients treated at dose level 4, and two of five patients at dose level 5, were considered not evaluable for Cycle 1 toxicity, as they came off trial without DLT prior to completion of cycle 1, due to complications of rapid disease progression, leaving three patients evaluable for DLT at dose levels 1–7, and two patients at dose level 8. PENAO was generally well tolerated; treatment emergent adverse events (TEAE) are detailed in Table 2. The most common TEAEs were fatigue that occurred in seven patients, and nausea that occurred in five. Five patients had line complications (thrombosis in four, and infection in one). Four patients had rash, including one patient with bullous pemphigoid in Cycle 2 at dose level 5, but rash was generally manageable with anti-histamine, with or without steroid. The only DLT was grade 3 fatigue, observed in a patient treated at dose level 8. Four patients required treatment interruptions due to fatigue, nausea (1 patients), fever (3 patients), rash (1 patient), and neutropenia (1 patient). The only cardiac event was an asymptomatic grade 1 QTc interval prolongation, observed in a patient treated at dose level 7. Of note, no renal, hepatic, or neurological toxicities were observed, and no sub-clinical toxicity concerns were identified on functional imaging.

Anti-tumour activity

Twenty-four patients received at least 2 cycles of treatment, and were evaluable for response assessment. Two patients had inadequate baseline imaging. No objective responses were observed. One patient with cervical carcinoma, treated on dose level 5, had a 19% reduction in the sum of longest diameters with stable disease for 3 months, and one patient with an anaplastic astrocytoma, treated on dose level 7, had stable disease over 10 cycles (7 months).

Pharmacokinetics

Complete pharmacokinetics were available from 25 patients. The results of PENAO pharmacokinetics were unreliable, as many of the samples were below or near the lower limit of detection, and total arsenic levels were used as a surrogate. An observed increase in AUC and C_{max} was not proportional (Table 3). The half-life of arsenic ranged from 9.39 ($\pm$6.516) days in Cohort 4 to 19.94 days ($n=1$) in Cohort 6 and did not appear to change with dose (Table 3). Mean steady state clearance values of 40 L/day/m^2 and volume of distribution between 548 and 1.022 L/day/m^2 were determined following the 21-day infusion. Blood samples taken weekly after cessation of treatment indicated that arsenic was still detectable in blood 28 days after cessation of the drug infusion (Fig. 1). These results indicated that the half-life of the drug in human was far longer than that predicted from mouse models, and sufficiently long to invalidate the need to deliver the drug by continuous infusion. The trial was, therefore, terminated before a maximal tolerated dose or RP2D was reached.

Discussion

This report describes the first-in-human phase I trial of PENAO, a novel small-molecule covalent inhibitor of adenine nucleotide translocase, with pre-clinical anti-angiogenic and anti-tumour activity [5]. No recommended phase II dose was defined as the trial was stopped when pharmacokinetic data invalidated the rationale for treating patients

Table 2 Treatment emergent adverse events (TEAEs)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Dose-dependent TEAEs, Cycle 1 (DLT evaluation period)					
Constitutional					
Fatigue		1 (DL 5)	2 (DL 3 and 5)	**1 (DL 8)**[a]	
Fever/chills			1 (DL 8)		
Gastrointestinal					
Nausea		1 (DL7)	2 (DL 3 and 5)		
Anorexia			1 (DL3)		
Constipation		1 (DL8)			
Vomiting		1 (DL5)			
Diarrhoea		1 (DL5)			
Dysgeusia		1 (DL5)			
Other					
Heightened sense of smell		1 (DL7)			
Eye pain		1 (DL8)			
Proteinuria		1 (DL8)			
QTc prolongation		1 (DL7)			
Arthralgia		2 (DL 2 and 8)			
Dose-dependent TEAEs, worst grade per patient, all cycles					
Fatigue	19	4	2	1	
Nausea	21	3	2		
Other	18	4	2	2[b]	
Non-dose-dependent TEAEs, worst grade per patient, all cycles					
Central line complication					
Line thrombosis/PE		1 (DL7)	2 (DL8)		1 (DL4)
Line infection				1 (DL 1)	
Skin					
Bullous pemphigoid				1 (DL5)	
Generalised rash		3 (DL1, 7 and 8)			
PICC dressing allergy			1 (DL1)		
All TEAEs worst grade per patient, all cycles					
Dose dependent	14	7	2	3	0
Non-dose dependent	19	4	3	2	1
Any	12	6	2	5	1

[a]Dose-limiting toxicity

[b]Gamma GT (dose level 7, cycle 2), neutrophils (dose level 8, cycle 2)

Table 3 Selected mean (SD) blood total arsenic

Cohort	Dose mg/m^2/day	Cmax (ng/mL)	Tmax (days)	Css (ng/mL)	AUC0-tlast (day ng/mL)	AUC0-inf (day ng/mL)	t1/2 (days)	CLss (L/day/m^2)
1 ($n=3$)	2	38.7 (4.93)	12.00 (12.124)	8.33 (2.887)	855.5 (352.49)	1073.5 (364.69)	16.15 (N/A)*	200.00 (0.000)
2 ($n=3$)	2	66.0 (26.51)	15.33 (12.702)	8.67 (7.371)	797.8 (643.72)	1269.0 (N/A)*	16.33 (N/A)*	372.55 (276.603)
3 ($n=3$)	2	72.0 (30.79)	27.00 (10.817)	35.70 (9.037)	1288.5 (684.00)	ND	ND	58.93 (17.246)
4 ($n=3$)	2	106.0 (55.56)	24.06 (34.814)	49.00 (9.539)	4093.1 (4329.10)	4238.0 (4488.78)	9.39 (6.516)	42.01 (9.204)
5 ($n=5$)	2.7	148.0 (108.24)	27.60 (17.352)	70.60 (70.352)	3299.5 (3015.06)	6695.4 (268.58)	11.83 (3.068)	40.00 (10.802)
6 ($n=3$)	4	168.7 (121.07)	31.33 (10.693)	95.90 (45.854)	5394.1 (5020.79)	12456.5 (NA)*	19.94 (N/A)*	47.97 (20.073)
7 ($n=3$)	6	193.7 (32.96)	82.67 (74.849)	153.00 (11.358)	17240.8 (16909.99)	17724.8 (17100.39)	14.29 (6.499)	39.37 (3.044)
8 ($n=2$)	9	195.5 (51.62)	25.50 (14.849)	195.50 (51.619)	6360.2 (3930.17)	7266.9 (4077.99)	15.35 (3.706)	47.70 (12.594)

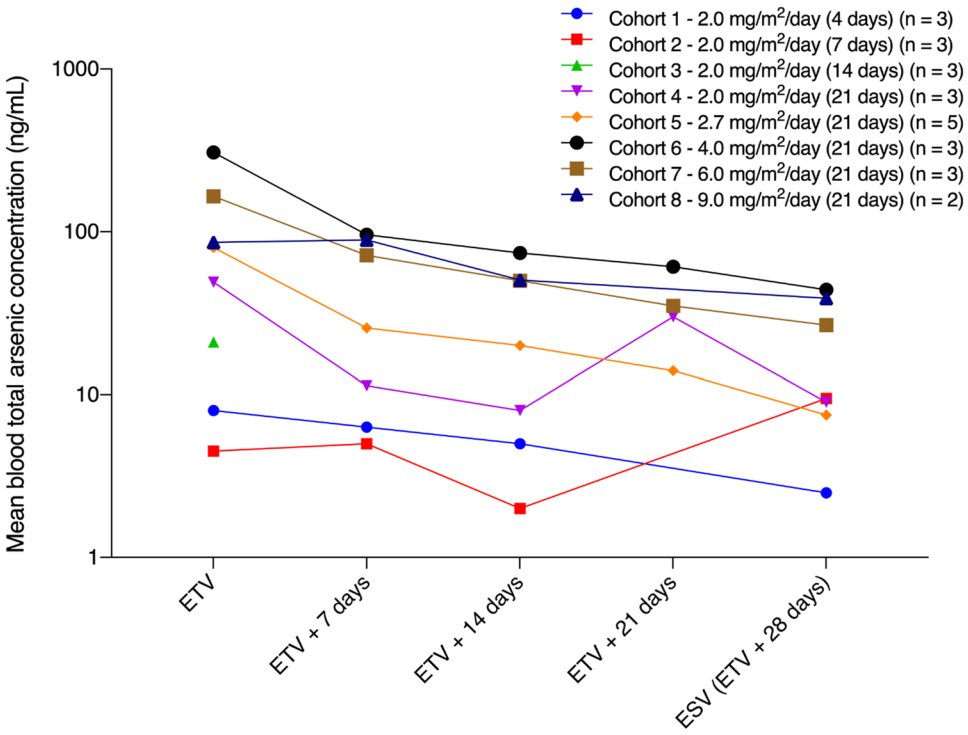

Fig. 1 Pharmacokinetics: mean end of treatment visit as concentration vs time for each cohort

by continuous infusion. A simultaneous interruption to drug supply, related to the requirement for routine stability re-certification of the existing drug supply, contributed to the decision to close the trial, rather than amend the protocol to explore an intermittent dosing schedule. The dosing plan in this trial was necessarily conservative, given the potential for life-threatening or irreversible renal, cardiac and neurological toxicity, and the risk of drug-induced renal impairment compounding drug retention. In addition, pre-clinical models for pharmacokinetic and toxicology assessments could not enable an accurate assessment of a continuous dosing regimen, thus needing to rely more substantively on human data to determine optimal dosing and scheduling. Patients were treated to 9 mg/m^2/day by continuous infusion, with one of two patients treated at that dose level experiencing dose-limiting fatigue. The drug was otherwise well tolerated, with nausea and rash the only other toxicities of note, occurring in a minority of patients.

The results of this trial cannot be interpreted without reference to the pharmacokinetic results. As PENAO measurements in human plasma were unreliable, total arsenic levels were used as a validated surrogate of PENAO exposure. The most important finding was that the drug half-life was 9–19 days, as opposed to the predicted value of 2.88 h, invalidating the rationale for continuous drug dosing, and the inconvenience to patients of carrying a CADD pump [11, 12]. This finding, which only became available after initial dose levels were completed, critically impacted the trial's progress, and the drug's ongoing development. This unexpected pharmacokinetic difference between animal models and human underlines the immense value of real time pharmacokinetic studies in early phase clinical trials, to detect early any possible discrepancy. The pharmacokinetic findings also reinforce the limitations of predicting half-life from animal models. Pre-clinical studies in mice suggested a bi-exponential function could represent the plasma concentrations of PENAO and the parameters of this function were used to predict pharmacokinetic parameters in man by an empirical allometric scaling approach. Difficulties arise in using a single species as a model as opposed to those that use a number of animal models and extrapolate from that data the possible pharmacokinetics in humans in an attempt to minimise interspecies differences in metabolism that are not taken into account in an allometric method [13, 14]. The second finding of note was that only 5 patients, treated at dose levels 7 and 8, achieved pharmacokinetic levels considered therapeutic in pre-clinical models, and this may affect the interpretation of the toxicity and efficacy findings, particularly when the trial was terminated before full exploration of therapeutic dose levels, and definition of an RP2D.

The primary cytotoxic effects of arsenic are mediated through its effect on mitochondria and build-up of free oxygen radicals leading to increased oxidative stress [15]. These effects underlie the clinical toxicity profile of arsenic and arsenic-containing agents that include cardiac toxicity, renal toxicity, encephalopathy, hepatotoxicity, nausea, fatigue and rash [4, 16–20]. Mild nausea, fatigue and rash were documented in this trial, but no significant cardiac,

neurological, hepatic or renal toxicity was observed. Of note, however, is that the drug levels measured in most patients in this trial were below the threshold that would be expected to cause organ toxicity. In pre-clinical studies, it was noted that PENAO affected the endothelial cells with evidence of a potential anti-angiogenic effect. Hypertension and proteinuria are among the most common toxicities of anti-angiogenic drugs that block the VEGF signalling pathway [21–23]. Given that an anti-angiogenic mechanism of action was predicted, hypertension and proteinuria were also potential toxicities, but neither of these was observed. This may be due to the low level of drug exposure in most of our patients, but may also reflect an anti-angiogenic effect mediated by mechanisms other than VEGF.

Patients had a variety of heavily pre-treated histologies, and the conservative dosing plan resulted in sub-therapeutic drug exposure in most patients. Of the five patients treated at potentially therapeutic dose levels, only four completed two cycles of treatment, and were regarded as evaluable for objective response. No objective responses were observed at any dose level, but one patient with an anaplastic astrocytoma, treated at dose level 7, had stable disease over 10 cycles (7 months). The only other signal of activity was a patient with cervical carcinoma, who had a minor radiological response. This patient was treated on dose level 5 that was regarded as sub-therapeutic.

Since this study was conducted, ongoing pre-clinical studies have indicated that PENAO and temsirolimus, an mTOR inhibitor, are strongly synergistic in in vitro models of endometrial cancer [24] and diffuse intrinsic pontine glioma [25]. Resistance to PENAO in an endometrioid cell line was mediated by an adaptive switch to glycolytic metabolism to minimise the agent's interference in oxidative phosphorylation. The use of an mTOR inhibitor that decreases glycolytic metabolism reversed this resistance. Ongoing clinical development of PENAO will investigate an intermittent IV dosing schedule, without or with rapamycin in patients with tumours with an activated mTOR pathway.

Compliance with ethical standards

Conflict of interest Ben Tran has received financial support from Amgen and Astellas Pharma. Ben Tran has received honoraria from Astellas Pharma, Janssen-Cilag, Sanofi, Tolmar and Amgen. Ben Tran has received institutional research funding from Astellas Pharma, Janssen-Cilag, Amgen, Pfizer, Genentech, AstraZeneca, Bayer, Bristol-Myers Squibb, Merck Sharp and Dohme and Ispen. Danny Rischin received grants from Merck, Bristol-Myers Squibb, Roche and Regeneron. Danny Rischin has also received grants and personal fees from GlaxoSmithKline and Merck Sharp and Dohme. Ben Tran has acted in an advisory or consultant role for Amgen, Astellas Pharma, Bayer, Sanofi, Tolmar, Janssen-Cilag, Bristol-Myers Squibb, Ipsen, Merck Sharp and Dohme and AstraZeneca. Peter Savvas has acted as an uncompensated Consultant for Roche-Genentech. Danny Rischin has had uncompensated role on Trial Steering Committees and/or advisory boards for Merck Sharp and Dohme, Bristol-Myers Squibb, GlaxoSmithKline, Regeneron and Sanofi.

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