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Phase I trial of 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG), a heat shock protein inhibitor, administered twice weekly in patients with advanced malignancies ☆

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ABSTRACT

Purpose: Phase I dose-escalation study to determine the toxicity and maximum tolerated dose (MTD) of 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG), a heat shock protein 90 (Hsp90) inhibitor, administered on a twice weekly schedule in patients with advanced cancer.

Experimental design: 17-DMAG was administered as a 1- to 2-h infusion twice weekly in 4-week cycles. An accelerated titration design was followed until toxicity was observed, at which point standard dose-escalation proceeded. MTD was defined as the dose at which no more than one of the six patients experienced a dose-limiting toxicity (DLT). Pharmacokinetics were assessed, and Hsp70 mRNA, whose gene product is a chaperone previously shown to be upregulated following the inhibition of Hsp90, was measured in peripheral blood mononuclear cells (PBMCs).

Results: A total of 31 patients received 92 courses of treatment. The MTD was 21 mg/m^2/d; 20 patients were enrolled at this dose level. Nine patients had stable disease for a median of 4 (range 2–22) months. Both C_{max} and AUC increased proportionally with dose. The most

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common toxicities were grade 1 or 2 fatigue, anorexia, nausea, blurred vision and musculoskeletal pain. DLTs were peripheral neuropathy and renal dysfunction. Expression of Hsp70 mRNA in PBMCs was highly variable.

Conclusion: Twice-weekly i.v. infusion of 17-DMAG is well tolerated, and combination phase I studies are warranted.

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1. Introduction

Heat shock proteins (Hsps) are intracellular molecular chaperones that maintain correct protein folding and prevent non-specific aggregation of misfolded or unfolded proteins. Hsp90 has emerged as an important chaperone in cancer cells, where it helps maintain the stability, and consequently function, of proteins necessary for a wide range of signalling pathways, including tumour proliferation, metastasis, angiogenesis and resistance to apoptosis.[1,2] Hsp90 is therefore a target of considerable interest for oncologic drug development. Hsp90 activity is dependent on an ATP binding site in the N-terminus of Hsp90. Molecules that bind to this site are able to disrupt the interaction of Hsp90 with various client proteins, such as HER-2, RAF, mutant p53, cyclin-dependent kinase 4, Src, AKT and nuclear factor-kB,[3–9] many of which are involved in maintaining the malignant phenotype,[3,5,10] resulting in increased ubiquitin-mediated proteasomal degradation of these proteins.

The benzoquinone ansamycin geldanamycin was the first inhibitor of Hsp90 to be identified, but it caused significant hepatotoxicity and was not developed further. A 17-carbon derivative of geldanamycin, 17-allylamino-17-demethoxygeldanamycin (17-AAG), was investigated in clinical trials; however, the drug was also associated with hepatotoxicity and is poorly soluble, necessitating the use of dimethyl sulfoxide and egg phospholipids for solubilisation.[11] 17-Dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG), also a benzoquinone ansamycin, is a water-soluble analogue of 17-AAG. 17-DMAG was more potent and had a lower IC_{70} than 17-AAG in *in vitro* clonogenic assays evaluating 64 different patient-derived tumour explants.[12] 17-DMAG also demonstrated anti-tumour effects in a wide range of xenograft models, including MDA-MB-231 (breast), NCI-H522 (adenocarcinoma), melanomas MEXF 989 and MEXF 276, and an orthotopic liver metastasis model using the AsPC-1 human pancreatic tumour.[13,14]

We designed a phase I dose-escalation study to evaluate the toxicity and determine the MTD of 17-DMAG administered on a twice-weekly schedule in 28-d cycles. To assess drug effect on its target we used peripheral blood mononuclear cells (PBMCs) and measured levels of Hsp70 mRNA, whose gene product is a chaperone previously shown to be upregulated following the inhibition of Hsp90.[15,16]

2. Patients and methods

2.1. Eligibility criteria

Patients (age $\geqslant$18 years) were eligible for this study if they had pathologically confirmed metastatic or unresectable malignancy for which there were no acceptable standard therapies; an Eastern Cooperative Oncology Group performance status $\leqslant$2 (Karnofsky $\geqslant$50%); and adequate organ and marrow function defined as leucocytes $\geqslant 3.0\times10^9$/L, absolute neutrophil count $\geqslant 1.5\times10^9$/L, platelets $\geqslant 100\times10^9$/L, total bilirubin $\leqslant$ 1.5 × the upper limit of normal (ULN), aspartate aminotransferase and/or alanine aminotransferase <2.5 × ULN and creatinine within normal institutional limits.

Prior anticancer therapy must have been completed at least 4 weeks before starting the study drug; toxicities were required to have recovered to eligibility levels. Patients were excluded if they had an uncontrolled intercurrent illness, were pregnant or lactating, or had brain metastases within the past 6 months. Other exclusion criteria included patients with a history of symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within 1 year of study entry, or cardiac arrhythmias.

This trial was conducted under a National Cancer Institute (NCI)-sponsored IND with institutional review board approval. The protocol design and conduct followed all applicable regulations, guidances and local policies. ClinicalTrials.gov identifier: NCT00088868.

2.2. Trial design

This was an open-label, single-arm phase I study of 17-DMAG in patients with advanced malignancies. 17-DMAG was supplied by the Division of Cancer Treatment and Diagnosis, NCI under a Collaborative Research and Development Agreement with Kosan Pharmaceuticals, Inc. 17-DMAG was administered intravenously as a 1- to 2-h infusion twice weekly in 4-week cycles. The doses were separated by at least 72 h but not more than 96 h each week.

We used a Simon accelerated titration design with intrapatient dose-escalation.[17] One patient per cohort was entered, and doses were increased in 100% increments during the first three dose levels and then in 50% increments until dose level 5 and subsequently continued in 30% increments. The accelerated phase ended when one patient experienced DLT during the first course or two patients experienced moderate toxicity (any grade 2 haematologic or non-haematologic toxicity). Once the accelerated phase ended, standard dose-escalation proceeded using a modified Fibonacci escalation, whereby groups of three to six patients were treated at each dose level.[17] Higher dose levels were not opened to accrual until the patients in the previous cohort had completed at least one cycle. Intrapatient dose-escalation was allowed as long as the patient tolerated the previous cycle (grade $\leqslant$2 drug-related toxicity) and a new patient had safely completed a cycle on the higher dose. Patients were considered evaluable for toxicity for the purpose of cohort dose-escalation if they

experienced a DLT or received six of the eight planned doses in a 4-week period and had been followed for one full cycle without DLT.

Adverse events were graded according to NCI Common Toxicity Criteria version 3.0. DLT was defined as an adverse event that occurred in cycle 1, was felt to be related to the study drug, and fulfilled one of the following criteria: grade 3 or greater non-haematologic toxicity (except for nausea/vomiting and diarrhoea without maximal symptomatic/prophylactic treatment) or grade 4 haematologic toxicity. When the accelerated phase ended, the dose level was expanded to three patients. If none of the three patients experienced a DLT, subsequent patients were enrolled at the next higher dose level. If one of three patients experienced a DLT, three additional patients were added at that dose level, for a total of six patients. If two of three or two of six patients experienced a DLT, no further patients were started at that dose level, and the dose level was determined to have exceeded the MTD. Three additional patients were then entered on the next lower dose level. The MTD was defined as the dose at which no more than one of six patients or $\leqslant$33% experience a DLT (one dose level below the dose at which at least two of three to six patients experience DLT).

2.3. Safety and efficacy evaluations

A complete patient history, physical examination and EKG were performed at baseline and once a week on treatment. Complete blood counts with differential and serum chemistries were performed at baseline and twice weekly during the study. Radiographic evaluation was performed at baseline and every two cycles to assess for tumour response based on the Response Evaluation Criteria in Solid Tumours.[18]

2.4. Pharmacokinetics

For the assessment of first-dose pharmacokinetics during the first cycle only, blood samples (7 mL) were collected in heparin-containing tubes prior to the start of infusion, approximately 5 min before the end of infusion, and at 5, 10, 30 and 60 min and 2, 4, 8, 16, 24 and 48 h after the end of the infusion. Blood was collected from a site remote from the 17-DMAG infusion line, and sample tubes were immediately placed on ice. Plasma was separated by centrifugation at 1200*g* for 5 min at 4 °C, and was transferred into cryovials for storage at –70 °C until the time of analysis. 17-DMAG was quantitated using a validated method based on high-performance liquid chromatography coupled with mass spectrometric detection.[19] The assay is robust and sensitive, with a lower limit of quantitation of 1 ng/mL.

Noncompartmental pharmacokinetic data analysis was performed using WinNonlin, v.5 (Pharsight). The maximum plasma concentration (C_{max}) and the time of maximal plasma concentration (T_{max}) were the observed values. The area under the concentration–time curve (AUC) from time zero to the time of the final quantifiable sample (AUC_{last}) was calculated using the linear trapezoidal method. AUC_{inf} (the AUC from time zero to infinity) was calculated by extrapolation by dividing C_{last} (the last measurable drug concentration) by the rate constant of the terminal phase λ^z. This constant was determined from the slope of the terminal phase of the concentration–time curve using weighted least-squares. Estimated pharmacokinetic parameters included the volume of distribution during the terminal phase (V_z), the half-life ($T_{1/2}$), and the systemic clearance (Cl), which was calculated as dose divided by AUC_{inf}. Clearance and volume of distribution are expressed per m^2 due to the body surface area dosing employed.

2.5. Pharmacodynamics

Blood samples were collected before and 24 and 48 h after drug administration on day 1 of cycle 1 for the assessment of Hsp70 mRNA in PBMCs by real-time reverse transcription-PCR (RT-PCR). BD Vacutainer Cell Preparation tubes containing sodium citrate were centrifuged for 20 min (1720*g*) at 20 °C. The PBMC layer was transferred to a conical tube. Repeated washing and centrifugation (170*g*, 5 min) was performed. The resulting pellet was transferred to a microcentrifuge tube, flash frozen and then stored at –80 °C until analysis.

RNA was isolated from patient PBMC samples using a RiboPure Kit (Cat# AM1924, Ambion) as described by the manufacturer. Real-time RT-PCR was performed to quantify the expression of human Hsp70 using primers (Hs00359147_s1) from Applied Biosystems (ABI). cDNA was prepared with 0.2 μg of RNA from each sample using Reverse Transcriptase and Master Mix containing Taq polymerase for the PCR as described by the manufacturer (ABI). The PCR products were detected using the iCycler Real-Time PCR System (Bio-Rad). The level of human beta-actin (Hu-ACTB; ABI primers #4352935) in each sample was measured, and the Hsp70 mRNA level was presented relative to the internal actin control. Hsp70 mRNA levels were presented as a ratio (Hsp70 (ng)/Hu-ACTB (ng) $\times$ 100).

2.6. Statistical methods for pharmacokinetic and pharmacodynamic evaluations

For additional exploratory analyses of pharmacodynamic parameters, data were assessed from 30 patients, of whom 20 were treated at the MTD (21 mg/m^2). A Wilcoxon signed rank test was used to test whether the Hsp70/actin ratios observed at baseline as compared to 24 and 48 h post-dose were equal to 1, which would indicate that there was no change between the pre-treatment and corresponding 24- or 48-h values. In addition, Spearman correlation analyses were performed to determine the association of ln (C_{max}) and ln (AUC) with 24- and 48-h Hsp70/actin values and ratios compared with baseline. Correlations such as $|r| > 0.70$ would be interpreted as strong, $0.5 < |r| < 0.70$ as moderate, $0.3 < |r| < 0.5$ as weak to moderate, and $|r| < 0.30$ as weak. All *P* values are two-tailed and presented without adjustment for multiple comparisons.

3. Results

3.1. Patients

Patient characteristics are detailed in Table 1. Thirty-one patients enrolled between December 2004 and July 2007 are

Table 1 – Patient characteristics

No. of patients (evaluable)		31
	Male	17
	Female	14
Age (years)	Median	56
	Range	24–74
ECOG performance status	0	1
	1	29
	2	1
Tumour types	Colorectal	6
	Lung	4
	Pancreas	3
	Pheochromocytoma	1
	Peritoneal mesothelioma	1
	Other[a]	16
No. of lines of prior therapy (range 0–7)		
	0–2	9
	⩾3	22

ECOG, Eastern Cooperative Oncology Group.
a Ocular melanoma (1), melanoma (1), renal cell carcinoma (1), adrenocortical carcinoma (1), thyroid carcinoma (1), thymoma (1), sarcoma (2), follicular lymphoma (2), hepatocellular carcinoma (1), biliary carcinoma (1), adenocarcinoma of the oesophagus (1), adenocarcinoma of the external ear (1), carcinoid (1), head and neck cancer (1).

included in the analysis. One male patient went off study before receiving 17-DMAG and is therefore not included in the analysis. Twenty-three patients had at least three prior chemotherapy regimens (range, zero to seven regimens).

3.2. *Toxicity*

Patients received 92 courses of treatment at nine different dose levels (Table 2). The median number of courses was two (range, 1–23 courses). No cumulative toxicities were observed. Grade 3 DLT occurred in two patients at the 27 mg/m^2 dose level; one patient had grade 3 renal failure reversible in 5 d with conservative management, and the other patient, who had previously received paclitaxel and cisplatin for squamous carcinoma of the neck, developed grade 3 reversible neurologic-motor deficit in his left lower extremity. The neurologic deficit was reversible in 7 d, and the patient was retreated at the 21 mg/m^2 dose level without recurrence of the neurologic event. Given the two observed DLTs, the next lower dose level of 21 mg/m^2 was explored and established as the MTD. The MTD was expanded, and a total of 20 patients were treated to obtain additional safety data and to perform correlative studies. The most common drug-related toxicities were grade 1 or 2 fatigue, anorexia, nausea, blurred vision and musculoskeletal pain. No objective signs of eye inflammation were observed during the episodes of blurry vision, which spontaneously improved in all the patients. Almost all patients complained of grade 1 musculoskeletal pain starting from dose level 6 (12 mg/m^2). No objective signs of muscle weakness were noted, and there was no associated elevation in creatine kinase. All patients were treated symptomatically with NSAIDs. During the conduct of this study, additional information became available regarding prolongation in QTc, bradycardia and hypotension observed in trials of 17-AAG, a related compound. Thus, to ensure patient safety, eligibility criteria for this trial were amended to exclude patients with prolonged QTc at baseline (defined as >450 ms in males, >470 ms in females), and the use of concomitant drugs that are known to cause QTc prolongation was restricted. Patients were also monitored with repeat EKGs while on study. However, no significant increases in QTc, cardiac arrhythmias or hypotension were observed in this trial.

3.3. *Anti-tumour activity*

Response assessments were available for all patients. None of the 31 patients had a response as defined by RECIST criteria. Nine patients (29%) had stable disease at restaging (median time to progression of 4 months [range 2-22 months]). One patient with peritoneal mesothelioma, who had previously undergone surgical debulking and intraperitoneal chemotherapy with cisplatin with disease progression, received 22 cycles of 17-DMAG with appreciable symptomatic improvement. A patient with advanced head and neck squamous cell

Table 2 – Dose levels and observed adverse events at least grade 2 and possibly related to study drug

Dose level	Dose (mg/m^2/d)	No. of patients treated	Adverse event(s)
1	1	1	
2	2	1	
3	4	1	
4	6	1	
5	9	1	Vomiting (grade 2)
6	12	2	
7	16	1	
8	21 (MTD)	20	Anorexia, nausea, arthritis, elevated creatinine, blurred vision, pneumonitis/pulmonary infiltrates (grade 2, 1 patient each); rash, fatigue, transaminitis (grade 2, 2 patients each); platelets (grade 2, 3 patients); diarrhoea (grade 3, 1 patient)
9	27	3	Thrombocytopaenia (grade 2, 1 patient); motor neuropathy[a] (grade 3, 1 patient); renal failure[a] (grade 3, 1 patient)

MTD, maximum tolerated dose.
a Dose–limiting toxicity.

Table 3 – Plasma pharmacokinetics of 17-DMAG

Dose (mg/m^2)	n	$T_{1/2}$ (h)		T_{max} (h)		C_{max} (ng/mL)		C_{max}/dose (ng/mL per mg/m^2)		AUC_{inf} (h * ng/mL)		AUC_{inf}/dose (h * ng/mL per mg/m^2)		Cl (L/h/m^2)		V_z (L/m^2)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	1	27.9	–	0.9	–	42.2	–	42.2	–	549	–	549	–	1.8	–	73.3	–
2	1	21.4	–	0.9	–	24.3	–	12.2	–	191	–	95.4	–	10.5	–	324	–
4	1	26.1	–	1.0	–	72.6	–	18.2	–	774	–	194	–	5.2	–	194	–
6	1	14.4	–	0.9	–	39.7	–	6.6	–	312	–	52.0	–	19.2	–	398	–
9	1	24.2	–	0.9	–	141	–	15.6	–	2134	–	237	–	4.2	–	147	–
12	2	14.1	5.0	1.0	0.04	196	87.5	16.3	7.3	1222	58.0	102	4.8	9.8	0.5	201	80.6
16	1	54.1	–	2.1	–	172	–	10.8	–	1915	–	120	–	8.4	–	652	–
21	20	21.9	9.7	1.0	0.2	499	274	23.8	13.0	2671	1507	127	71.8	10.2	5.0	290	131
27	3	22.5	9.9	0.9	0	443	320	16.4	11.8	4144	2914	154	108	9.2	6.2	254	116
All Dose Levels	31	22.3	10.4	1.0	0.2	–	–	21.2	7.5	–	–	143	101	9.7	5.0	278	140

$T_{1/2}$, half-life; T_{max}, time of maximal plasma concentration; C_{max}, maximum plasma concentration; AUC_{inf}, the area under the concentration–time curve from time zero to infinity; Cl, systemic clearance; V_z, terminal phase; SD, standard deviation.

carcinoma, status post-cisplatin and radiation therapy, followed by paclitaxel and re-irradiation at progression, was enrolled on dose level 8 (21 mg/m^2). His disease remained stable for 8 cycles of therapy prior to progression.

3.4. *Pharmacokinetics*

Pharmacokinetic parameter estimates are listed in Table 3. Drug clearance was variable and did not change significantly with dose. At the MTD (21 mg/m^2), mean clearance was 10.2 ± 5.0 L/h/m^2 (range 3.3–18.9 L/h/m^2). Both C_{max} and AUC increased with dose, and no evidence of non-linearity was apparent. The half-life across all dose levels ranged from 9.9 to 54.1 h (median, 18.2 h). At the MTD (21 mg/m^2), C_{max} was determined to be 499 ± 274 ng/mL. High inter-individual variability (CV = 56.4%) was found for drug exposure in the MTD cohort, with a mean AUC_{inf} of 2671 ± 1507 h ng/mL. Plasma concentration–time profiles for all patients in the MTD cohort are shown in Fig. 1.

3.5. *Pharmacodynamics*

Hsp70 mRNA expression was evaluated in PBMCs from the samples obtained 24 and 48 h after the first dose of 17-DMAG in 30 patients. Expression of Hsp70 mRNA in PBMCs was highly variable (Table 4). Thus, there was no statistically significant change in the expression of Hsp70 following the administration of the first dose of 17-DMAG. However, in the MTD cohort, a moderate correlation was observed between ln (C_{max}) and the ratio of 48 h post-dose/baseline Hsp70 mRNA expression observed ($r = 0.52$; $P = 0.019$), as shown in Fig. 2.

4. Discussion

The development of small molecule benzoquinone ansamycin inhibitors of Hsp90 has been hindered by toxicities and poor solubility. 17-DMAG was developed as a water-soluble analogue of 17-AAG that was more potent than 17-AAG in preclinical testing. 17-DMAG has undergone clinical evaluation with varying schedules of daily and weekly administration.[16,20–22] Intermittent dosing was shown to improve the safety profile of this drug. Additionally, xenograft models showed that drug effect on Hsp90 client proteins lasted for at least 24 h after 17-DMAG administration.[14] Therefore, we decided to evaluate a twice-weekly schedule of 17-DMAG, with drug administration separated by 72 h. The intent of evaluating such a schedule where 17-DMAG is given uninterrupted throughout the 4-week period twice weekly was to eventually combine it with radiation as a radiation sensitiser. Other 17-DMAG schedules evaluated in single-agent studies include daily × 3 or 5 d, every 3 weeks (1.5–46 mg/m^2; phase I study);[16] weekly (2.5–80 mg/m^2; phase I study);[20] twice weekly × 2 weeks, every 3 weeks (8–32 mg/m^2; phase I study);[21] and weekly × 3 weeks, every 4 weeks (80 mg/m^2; phase II study).[23] 17-DMAG has also been investigated in combination with trastuzumab alone (phase I study)[22] and trastuzumab with or without paclitaxel, at weekly doses of 60–100 mg/m^2 (phase I/II study).[24]

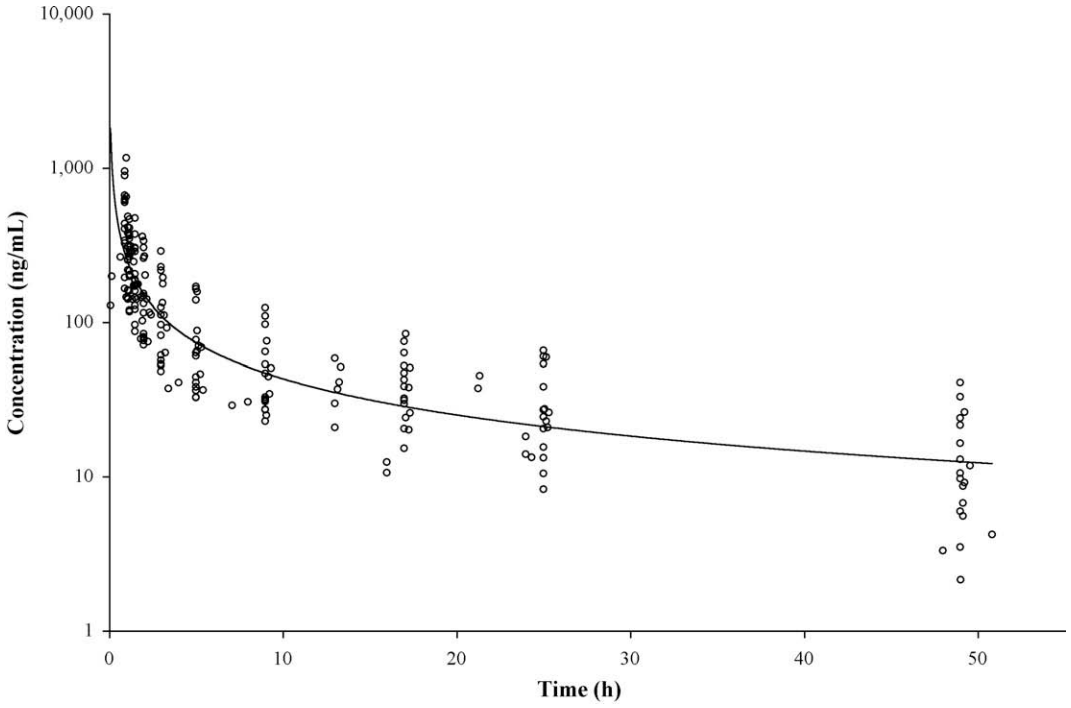

Fig. 1 – Mean plasma concentration–time profile for all patients in the MTD cohort (21 mg/m^2, *n* = 20). Each circle represents a single sample from a single patient.

Table 4 – Statistical analysis of Hsp70 mRNA expression levels in peripheral blood mononuclear cells

Cohort	Ratio of post-dose/baseline Hsp70 mRNA expression			
	Mean	SD	Median	Range
All patients				
24 h post-dose (*n* = 29)	1.82	2.02	1.12	0.09–7.18
48 h post-dose (*n* = 30)	1.70	1.81	1.13	0.08–9.46
MTD cohort				
24 h post-dose (*n* = 19)	1.67	2.07	0.8	0.09–7.18
48 h post-dose (*n* = 20)	1.59	1.25	1.26	0.08–4.74

MTD, maximum tolerated dose; SD, standard deviation.

Based on our trial, the recommended phase II dose of 17-DMAG administered twice weekly is 21 mg/m^2/dose. The DLTs of peripheral neuropathy and renal dysfunction have not been reported in the other trials of 17-DMAG with different schedules.[16,20–22] The underlying pathogenesis of these DLTs remains unclear. However, both toxicities were reversible upon discontinuation of study drug. Musculoskeletal pain was frequently observed and was related to study drug administration. No objective signs of muscle weakness or elevation in enzyme levels indicating muscle damage were documented. The symptoms responded to NSAIDs.

The induction of Hsp70, a co-chaperone protein known to be anti-apoptotic, has been demonstrated in preclinical models following the inhibition of Hsp90, raising concerns that this may limit the clinical efficacy of Hsp90 inhibitors. This phenomenon was also observed in PBMCs and tumour biopsies collected 24 h post-treatment from eight of the nine patients with advanced malignancies in a phase I trial of 17-AAG.[2] However, in another phase I trial of 17-AAG no consistent changes in the levels of Hsp90 or Hsp70 in PBMCs were observed following drug administration.[15] We did not observe consistent changes in the levels of Hsp70 mRNA following 17-DMAG administration. In the MTD cohort, a moderate correlation between maximal drug concentration and Hsp70 induction was observed. As observed in our trial, the inconsistency of effect on Hsp70 and the significance of this effect, as it pertains to the anti-tumour effect of Hsp inhibitors, raises the question of assessing additional correlative studies such as functional imaging. Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG-PET) has been used to assess anti-tumour response for agents such as imatinib in gastrointestinal stromal tumour.[25] As HER-2/neu is a client protein for Hsp90, a similar approach has been utilised to assess early response to 17-DMAG using FDG and ^{64}Cu-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-trastuzumab as PET probes in ovarian cancer xenograft models.[26] Smith-Jones and colleagues utilised an *F(ab′)* fragment of trastuzumab linked to ^{68}Ga-DOTA as a probe for PET scanning

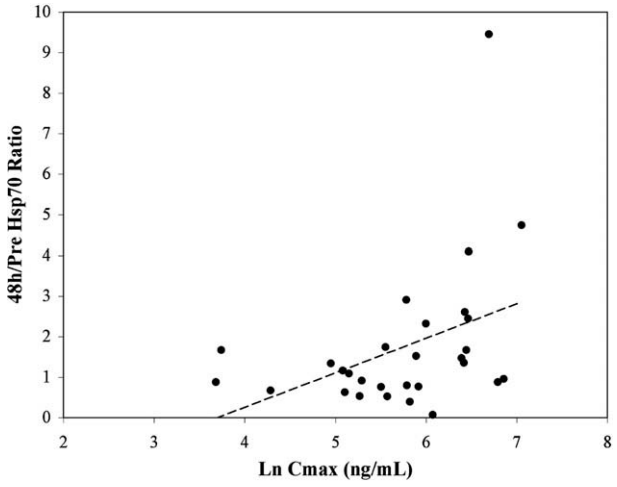

Fig. 2 – Association between ln C_{max} and ratio of 48 h post-dose/baseline Hsp70 mRNA expression in the MTD cohort (21 mg/m^2, n = 20).

in xenograft models treated with Hsp90 inhibitors.[27] Plasma levels of the extracellular domain of HER-2/neu and insulin-like growth factor binding protein 2 have been used in some trials as pharmacodynamic markers of Hsp90 inhibitor effects.[28,29] However, the data to support the use of these biomarkers are not conclusive; similar to Hsp70, different studies have shown inconsistent results for the use of these markers to monitor drug effect.

No evidence of non-linearity in the pharmacokinetics of 17-DMAG was found; increases in dose resulted in increases in drug exposure. However, drug exposure was highly variable across all dose levels.

17-DMAG has also been formulated to be administered orally, and two different schedules of drug administration, QOD or QD for 4 of 6 weeks, have been evaluated.[30] DLTs at 50 mg QOD and 30 mg QD were thrombocytopaenia, haemorrhagic colitis, nephrotic syndrome and dehydration. Bioavailability equalled 52%, with modest drug accumulation upon repeated dosing.

The potential of Hsp90 to modulate numerous critical signalling pathways justifies the recent focus on developing Hsp90 inhibitors for solid tumours and haematologic malignancies. There is significant interest in evaluating this class of drugs in combination with other targeted or conventional chemotherapeutic agents, or radiotherapy. *In vitro* and *in vivo* preclinical studies have shown an additive or synergistic effect of Hsp90 inhibitors in combination with several traditional and targeted antitumour agents. Evidence of activity has been reported in a clinical trial of 17-DMAG in combination with trastuzumab in patients with refractory, HER-2 positive metastatic breast cancer and ovarian cancer.[22]

In summary, a twice-weekly intravenous infusion of 17-DMAG is well tolerated, and is a regimen that should be evaluated further in combination phase I studies of 17-DMAG with targeted agents or radiation therapy.

Conflict of interest statement

None declared.

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