A Phase I Study of the Heat Shock Protein 90 Inhibitor Alvespimycin (17-DMAG) Given Intravenously to Patients with Advanced Solid Tumors

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Abstract

**Purpose:** A phase I study to define toxicity and recommend a phase II dose of the HSP90 inhibitor alvespimycin (17-DMAG; 17-dimethylaminoethylamino-17-demethoxygeldanamycin). Secondary end-points included evaluation of pharmacokinetic profile, tumor response, and definition of a biologically effective dose (BED).

**Patients and Methods:** Patients with advanced solid cancers were treated with weekly, intravenous (i.v.) 17-DMAG. An accelerated titration dose escalation design was used. The maximum tolerated dose (MTD) was the highest dose at which ≤1/6 patients experienced dose limiting toxicity (DLT). Dose de-escalation from the MTD was planned with mandatory, sequential tumor biopsies to determine a BED. Pharmacokinetic and pharmacodynamic assays were validated prior to patient accrual.

**Results:** Twenty-five patients received 17-DMAG (range 2.5–106 mg/m²). At 106 mg/m² of 17-DMAG 2/4 patients experienced DLT, including one treatment-related death. No DLT occurred at 80 mg/m². Common adverse events were gastrointestinal, liver function changes, and ocular. Area under the curve and mean peak concentration increased proportionally with 17-DMAG doses 80 mg/m² or less. In peripheral blood mononuclear cells significant (P < 0.05) HSP72 induction was detected (≥40 mg/m²) and sustained for 96 hours (≥40 mg/m²). Plasma HSP72 levels were greatest in the two patients who experienced DLT. At 80 mg/m² client protein (CDK4, LCK) depletion was detected and tumor samples from 3 of 5 patients confirmed HSP90 inhibition. Clinical activity included complete response (castration refractory prostate cancer, CRPC 124 weeks), partial response (melanoma, 159 weeks), and stable disease (chondrosarcoma, CRPC, and renal cancer for 28, 59, and 76 weeks, respectively).

**Conclusions:** The recommended phase II dose of 17-DMAG is 80 mg/m² weekly i.v. 

Introduction

The molecular chaperone HSP90 ensures correct folding and function of numerous client proteins (1–4) including the androgen receptor and oncogenic kinases such as BRAF (for an up-to-date list visit website of Dr. Didier Picard; http://www.picard.ch/downloads/Hsp90interactors.pdf). HSP90 inhibition targets client proteins for proteasomal destruction (3). The resulting combined effect on multiple oncogenic client proteins, their associated biochemical pathways, and hallmark cancer traits (5) forms the basis for the observed anticancer activity (6–10).

HSP90 inhibition results in a well-characterized, mechanism-based change in expression of specific proteins (11, 12). Depletion of client proteins (e.g., CDK4, ERBB2, and LCK) together with induction of certain heat shock proteins (e.g., HSP72, the inducible isoform of HSP70) constitute a molecular signature of HSP90 inhibition that can be measured as a pharmacodynamic endpoint (13–15).

The HSP90 inhibitor alvespimycin (17-dimethylaminooethylamino-17-demethoxygeldanamycin; 17-DMAG) exhibits reduced metabolic liability, lower plasma protein binding, increased water solubility, higher oral bioavailability, and superior antitumor activity compared with...
Multiple critical oncopgenic signaling pathways are disrupted by inhibition of the molecular chaperone HSP90. Interesting hints of clinical activity have been reported in early phase studies with agents such as 17-AAG. The 17-AAG analogue 17-DMAG was chosen for its superior pharmaceutical and therapeutic properties. In this phase I study we utilized a novel study design which aimed to define a biologically effective dose (BED) by incorporating a dose de-escalation phase after defining the maximum tolerated dose (MTD). BED was assessed by measurement of HSP90 inhibition in tumor tissue. Previously determined as fit for purpose, that is, robust and validated commensurate with the stage of clinical drug development, Western blot or ELISA assays were used to measure HSP72 and client proteins. We showed evidence of clinical activity (including complete and partial responses) and target inhibition in tumor at MTD. Although the strict criteria did not allow us to define a BED lower than MTD, the study design proved to be robust and provided a valid template for defining BED in future studies of molecularly targeted novel anticancer therapy.

The starting dose was 2.5 mg/m², approximately one tenth the dose lethal (LD₅₀) to dogs (7). The study design incorporated an accelerated dose escalation scheme (26). Toxicities were assessed by the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0. Dose limiting toxicities (DLT) were defined as any of the following causally related to 17-DMAG within the first 28 days of treatment: absolute neutrophil count less than 0.5 × 10⁹/L for more than 5 days or with associated fever; platelet count less than 25 × 10⁹/L; any other nonhematologic toxicity (≥ Grade 3) except nausea, vomiting, diarrhea, rash, arthralgia, or myalgia without appropriate prophylactic measures or alopecia (grade 1 or 2); or toxicity that prevented completion of 4 weeks 17-DMAG treatment. Patients who did not complete 4 weeks 17-DMAG for reasons other than toxicity were replaced.

Cohorts of 3 patients were entered and dose doubling performed until Grade 2 or more toxicity occurred. Further dose escalations were limited to 50%, in event of Grade 2 toxicity or 33% following Grade 3 or more toxicity.

After observing DLT, the cohort increased to maximum 6 patients. The maximum administered dose (MAD) was that at which ≥ 2/6 patients experienced DLT. The MTD was the previous dose level tested at which ≤ 1/6 patients experienced DLT.

The first patient at each dose level completed 2 weeks of 17-DMAG prior to other patients being treated. No delay was mandated between treating the second and subsequent patients.

Pre- and post-17-DMAG tumor biopsies were planned. Once MTD was determined, additional patients with bioplastic disease were entered, initially at MTD level, to yield 5, paired, predose and postdose biopsies per dose cohort. Detection of HSP90 inhibition (HSP72 induction with either CDK4 and/or ERBB2 depletion) in tumor from ≥ 4/5 patients allowed dose de-escalation to the prior dose level. A BED was defined as the lowest dose at which the HSP90 inhibition was detected in tumor samples from ≥ 4/5 patients.

The study was conducted under a Clinical Trial Authorisation (no. 21106/0224/001) sponsored by Cancer Research UK, and monitored by the Cancer Research UK Drug Development Office (DDO). The study was managed and conducted in accordance with the principles of Good Clinical Practice and according to Cancer Research UK DDO’s Standard Operating Procedures. Two centers participated, the Royal Marsden NHS Foundation Trust, Sutton, United Kingdom and the Belfast City Hospital, Belfast, Northern Ireland, United Kingdom. The protocol was reviewed by the Cancer Research UK Central Internal Review Board, the NCI, the Metropolitan Multi-centre Research Ethics Committee (Southampton) and clinical research committees of both institutions. The trial was registered on the NCI Clinical Trials Registry (NCT 00248521). Patients gave informed, written consent prior to study entry with additional consent for tumor biopsies.

Translational Relevance

The study design proved to be robust and provided a valid template for defining BED in future studies of molecularly targeted novel anticancer therapy.

Patients and Methods

Study design

A phase I trial of weekly i.v. 17-DMAG was performed with dose escalation (to determine MTD) and planned subsequent dose de-escalation (to define a BED).
Inclusion and exclusion criteria

Patients, aged 18 years or more, with histologically/
cytologically confirmed solid tumors refractory to available
therapy were entered. Prior treatment, radiotherapy (except
for palliative reasons), endocrine therapy, immunotherapy,
or chemotherapy was completed at least 4 weeks
(6 weeks for nitrosoureas and mitomycin-C) prior to 17-
DMAG. All toxic manifestations of previous treatments had
resolved (except alopecia or peripheral neuropathy CTCAE
Grade 1 allowed). Concomitant use of bisphosphonates,
erthropoietin, or LHRH analogues in patients with castra-

tion-resistant prostate cancer (CRPC) and a rising PSA were
allowed. Eastern Collaborative Oncology Group (ECOG)
performance status was 0/1 and patients’ life expectancy
estimated to exceed 12 weeks. Adequate organ function was
defined as ANC > 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L,
hemoglobin ≥ 9.0 g/dL, serum creatinine within normal
limits (WNL) or calculated creatinine clearance WNL,
hemoglobin

5 minutes at 4°C to obtain plasma which was stored at
−80°C until analyzed.

The analytical method was validated prior to trial recruit-
ment (27). Pharmacokinetics were analyzed by a noncom-
partmental model (model 202), with constant infusion
input for plasma by WinNonLin software version 5.2. Dose

Pharmacokinetic sampling and analysis

Western blotting. Blood samples were collected into BD
Vacutainer tubes for analysis predose, end of infusion, and
1, 8, 24, 48, and 96 hours after 17-DMAG. A further sample
was taken 24 hours after the fifth weekly infusion. Periph-
eral blood mononuclear cells (PBMC) were separated by
using the Ficoll-Hypaque method and stored at −80°C.

Potential for DLT or toxicity risking patient
safety. Patients were allowed re-treatment at full dose on
response to Grade 1 or less (allowing alopecia, nausea,
vomiting, or diarrhea if appropriate prophylactic or ther-
apeutic measures were not undertaken).

Exclusion criteria were pregnancy, lactation, prior ther-
apy with 17-AAG (there was no restriction on prior treat-
ment with any tyrosine kinase inhibitor or monoclonal
antibody), active treatment with another anticancer inves-
tigational agent, known central nervous system metas-
tases, uncontrolled intercurrent illness, active second
malignancy, patients known to be hepatitis B/C or HIV
positive, left bundle branch block, serious ventricular
dysrhythmia, symptomatic pulmonary disease requiring
medication, moderate/severe dry eye syndrome, or cor-
neal disease.

Drug administration

17-DMAG was supplied by the NCI and Kusan Biosci-
cences. The final concentration for intravenous adminis-
tration was 0.1 to 1.0 mg/mL in 0.9% saline or 5% dextrose.

Drug was administered over 1 hour, every week, continu-
ously and 1 cycle was defined as 4 weeks of treatment.

Dose adjustments

Dose reductions to the previous dose tested were made
for patients who experienced DLT or toxicity risking patient
safety. Patients were allowed re-treatment at full dose on
days 8, 15, or 22 of a cycle where ANC > 1.0 × 10^9/L,
platelets ≥ 75 × 10^9/L and other drug-related toxicity had
resolved to Grade 1 or less (allowing alopecia, nausea,
vomiting, or diarrhea if appropriate prophylactic or ther-
apeutic measures were not undertaken).

Pharmacokinetic sampling and analysis

Plasma concentrations of 17-DMAG were analyzed by
high performance liquid chromatography–mass spectro-
scopy. During the first course of 17-DMAG, blood samples
were taken before; during (30 and 60 minutes after infu-
sion commenced); and 5, 15, 30, 60, and 90 minutes, 2, 4,
6, 8, 16, 24, 48, 72, and 96 hours after the end of infusion.

Blood samples (5 mL) were collected into heparinized
tubes and stored on ice until centrifuged at 252 × g for

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Characterization of response

Tumors were assessed before 17-DMAG and 8 weekly by RECIST criteria version 1.0 (30), CA125 (31), or PSA (32) criteria. All responses [complete response (CR) or partial response (PR)] were confirmed with repeat measurements not less than 4 weeks apart and were reviewed by an independent clinician and radiologist.

Results

Demographics

Between February 2006 and April 2008, 25 patients were recruited to the study and all received at least one 17-DMAG dose (Table 1). The male/female ratio was 14:11, with median age of 58 (range 38–78) years. Malignant melanoma (7 of 25) was the commonest histologic subtype. All patients had an ECOG performance status of 0 or 1.

Dose escalation and de-escalation

The starting dose was 2.5 mg/m², which doubled incrementally to 80 mg/m² except for one single larger escalation from 5 to 20 mg/m² (based on safety data from parallel 17-DMAG studies).

In the first cohort, 1 patient experienced grade 3 lymphopenia and at 5 mg/m² grade 3 hyponatremia was detected in 1 patient. Both events occurred after completion of cycle 1, not influencing dose escalation. One additional patient was added in the 5 and 80 mg/m² cohorts to replace patients who progressed early. Further Grade 2 toxicity related to 17-DMAG was not reported until 80 mg/m² (fatigue, vomiting, blurred vision, and dry eye in 2 patients).

The next dose level was 106 mg/m² (chosen in light of toxicity data from parallel 17-DMAG studies). DLT occurred in 2 of 4 patients, which was Grade 3 fatigue and hypoalbuminemia in 1 patient. The fourth patient in this cohort, with malignant melanoma, experienced rapid (within 24 hours of treatment) onset Grade 4 AST rise, Grade 3 diarrhea with Grade 2 nausea, vomiting, fever, and anorexia. Subsequent Grade 4 hypotension and Grade 3 dehydration, hyponatremia, acidosis with creatinine elevation preceded anuric renal failure by day 4 posttreatment. Dialysis was commenced; however, the patient died 5 days following the last dose of 17-DMAG. An autopsy request was declined, cause of death was assessed as related to 17-DMAG. Two other patients were treated at 106 mg/m²; 1 died 16 days after receiving 17-DMAG following a gastrointestinal hemorrhage, subsequent pulmonary edema and myocardial infarction. Endoscopy (gastroscopy and colonoscopy) confirmed that colonic infiltration by tumor caused the hemorrhage and subsequent events were not attributed to 17-DMAG. Rapid disease progression necessitated removal and replacement of the third patient in this cohort.

Four additional patients were entered at 80 mg/m² to generate 5 evaluable pre- and post-17-DMAG tumor biopsies. The criteria for further dose de-escalation were not met; therefore, the study was declared complete and closed. No DLT occurred in 8 patients who received 80 mg/m² 17-DMAG.

Toxicity

17-DMAG was well tolerated at doses of 80 mg/m² or less. Common adverse events (AE) of nausea, vomiting, fatigue, and liver enzyme disturbances were low grade and reversible (Table 2). Four patients experienced 10 ocular AEs related to 17-DMAG, comprising blurred vision (3), dry eye (3), keratitis (2), conjunctivitis, or ocular surface disease (2). Most (9 of 10) events occurred at doses 80 mg/m² or more and all were Grade 2 or less; 2 patients required a dose reduction. At 106 mg/m², severe toxicities were encountered including one treatment-related death.

Pharmacokinetics of 17-DMAG

Table 3 summarizes the pharmacokinetic data for each cohort. At the MTD, 80 mg/m², plasma 17-DMAG concentration exceeded 63 nmol/L (mean IC₅₀ for 17-DMAG in the NCI 60 human tumor cell line panel) for more than 24 hours in all patients (Fig. 1A). At this dose the mean volume of distribution was 385 L, mean clearance 18.9 L/h, and mean peak concentration (Cₘₕₐₓ) 2,680 nmol/L. Both the area under the curve (AUC) and Cₘₕₐₓ of 17-DMAG increased proportional to drug doses of 80 mg/m² or less (r² values 0.88 and 0.75, respectively). Including the 106 mg/m²...
m² AUC data decreased the r² values suggesting a nonlinear relationship between 17-DMAG dose and AUC (Fig. 1B).

Pharmacodynamics of 17-DMAG

Using Western blotting, transient HSP72 induction (<24 hours) was detected in PBMCs at doses of 17-DMAG ≥ 5 mg/m². Doses of 20mg/m² or more were required to achieve sustained HSP72 induction up to 96 hours post-17-DMAG (Fig. 2A). Measured by ELISA/DELFIA (see Fig. 2B and C), baseline HSP72 expression varied in both PBMC (mean 1.5, range <LLD to 3.3 fmol/mg protein extract) and plasma (mean 76, range <LLD to 702 fmol/mL). HSP72 induction was detected in PBMC from patients treated at doses 20 mg/m² or more (Fig. 2B). Mean HSP72 expression 24 hours after 17-DMAG was significantly different compared with 2.5 mg/m² at 20, 80, and 106 mg/m² dose levels (P = 0.01, 0.02, and 0.03, respectively). Mean plasma HSP72 did not differ significantly between dose levels (Fig. 2C). However, the highest HSP72 plasma levels post–17-DMAG of 1,250 and 5,610 fmol/mL were observed in 2 patients with DLT, compared with a mean 86/±140 fmol/mL in all other patients.

In PBMC, early LCK induction, as seen with 17-AAG (22), followed by later depletion was observed in individual patients exposed to 17-DMAG dose of 40mg/m² or more (Supplementary Figure 2). CDK4 depletion was shown in PBMC in some patients treated at doses 80 mg/m² or more (Supplementary Figure 2).

The complete HSP90 inhibition pharmacodynamic signature (HSP72 induction with depletion of CDK4) was detected in PBMC from 2 of 8 patients at 80 mg/m² and in 2 of 3 patients at 106 mg/m², respectively (Supplementary Table 2).

HSP72 was induced in 4 of 5 tumors 24 hours after an 80 mg/m² dose and client protein depletion (CDK4 or ERBB2)
was detected in 3 of 5 tumors. Overall, HSP90 inhibition was detected in 3 of 5 patients. In the single set of samples available, HSP90 inhibition was confirmed in tumor following 106 mg/m² 17-DMAG (Fig. 3).

**Efficacy**

Twenty patients were evaluable for tumor response. Nine patients had progressive disease (PD), 4 within the first treatment cycle. Prolonged stable disease more than
6 months occurred in 3 patients, with chondrosarcoma (5 mg/m²) escalated to 20 mg/m²), CRPC (20 mg/m²), and clear cell renal cancer (80 mg/m²) on study for 28, 59, and 76 weeks, respectively. Another patient with CRPC had a CR confirmed by CT and PSA measurements. Previous treatment included bicalutamide and radical radiotherapy to the prostate, LHRH antagonist, and bicalutamide withdrawal. At this time he had lymph node metastasis and was treated with 17-DMAG at 5 mg/m², then escalated to 20 mg/m² and remained on treatment for 124 weeks before PD (Fig. 4A).

A patient with metastatic melanoma, treated at 40 mg/m², had a PR and was on treatment for 159 weeks before PD (Fig. 4B). Prior treatment was adjuvant interferon, followed by combination chemotherapy (dacarbazine and sorafenib) on diagnosis of metastases. Progression of known intrapulmonary and lymph node metastasis preceded trial entry.

Discussion

The MTD of weekly 17-DMAG was 80 mg/m² i.v. Nausea, vomiting, fatigue, and liver enzyme disturbances were the commonest toxicities, all low grade and reversible at doses 80 mg/m² or less. A significant number of patients experienced ocular AEs and prophylactic lubricating eye drops were recommended with doses ≥ 80 mg/m².

DLT (at 106 mg/m²) occurred in 2 patients and included a drug-related death (Grade 5 renal failure), Grade 4 AST rise and hypotension, Grade 3 dehydration, hyponatremia, acidosis, creatinine elevation, fatigue, diarrhea, and hypoalbuminemia.

Pharmacokinetic studies showed that both $C_{\text{max}}$ and $AUC_{0-\infty}$ increased proportionately with dose 80 mg/m² or less (Fig. 1). The 2 patients with DLTs had the highest drug exposures (Fig. 1C). Increased drug exposure due to nonlinear pharmacokinetics at 106 mg/m² may explain the adverse toxicity and the narrow therapeutic window observed.

In PBMC, sustained induction (at least 96 hours) of HSP72 was detected following 17-DMAG (≥20 mg/m²) dose. Mean HSP72 levels 24 hours after 17-DMAG (≥20 mg/m²) dose were significantly increased ($P < 0.05$) as measured by ELISA. Preliminary data suggest high plasma HSP72 levels might be a pharmacodynamic toxicity marker. CDK4 depletion was detected after 80 mg/m² or more 17-DMAG dose and modulation of LCK was detected.
at doses 40 mg/m\textsuperscript{2} or more. As defined by the molecular signature of client protein depletion and HSP72 induction, HSP90 was inhibited in tumor samples from 3 of 5 patients taken 24 hours after 80 mg/m\textsuperscript{2} 17-DMAG.

Clinical activity was observed across a range of dose levels including CRPC (CR), melanoma (PR), renal cancer, CRPC, and chondrosarcoma (>6 months stable disease). The CR occurred following antiandrogen withdrawal; however, marked, durable (>1-year) responses are rarely reported in this context (33–35). A hypothesis to explain this activity is that androgen receptor stability and function are known to be dependent on HSP90 (36), similar to other oncogenic client proteins such as ERBB2 (37), EGFR (38), and BRAF (39, 40). Other investigators have reported CR in patients with refractory acute myeloid leukemia (AML; ref. 41) and prolonged (>6 months) stable disease (42–44).

Studies employing alternative 17-DMAG schedules have been reported (41, 43–45) although pharmacodynamic studies were only informative in a study of AML patients (41). In our study, although HSP90 inhibition was confirmed in 3 of 5 patients at MTD, predefined criteria to select

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**Figure 3.** Pharmacodynamic changes following 17-DMAG administration in tumor samples. A, expression of ERBB2, inducible HSP70 (HSP72) and CDK4 detected by Western blots from patients treated with 80 or 106 mg/m\textsuperscript{2} of 17-DMAG. GAPDH is included as a loading control. Samples are predose (0), 24 hours after 17-DMAG (24) or HT29 human colon adenocarcinoma positive control (+). B, table summarizing pharmacodynamic changes in tumor. For each patient samples are marked positive (●) or negative (○) for induction of HSP70 and/or depletion of a client protein (CDK4 or ERBB2). If both changes were detected then the sample was positive for detecting the molecular signature of HSP90 inhibition. *, One sample set did not pass quality control.

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**Figure 4.** Selected patient case histories. A, PSA changes in a patient with prostate adenocarcinoma treated with 17-DMAG. Time-points marked: initial diagnosis and commencement of bicalutamide (1), radical radiotherapy (2), LHRH antagonist (3), bicalutamide withdrawal (4) and starting 17-DMAG (5), PSA and CT confirmed CR (6), and progression of disease (7). B, CT scans (above - lung and below - soft tissue windows) from a patient with metastatic melanoma at commencement of study and 30 months after starting 17-DMAG. Prior therapy had been adjuvant interferon and combination chemotherapy with dacarbazine and sorafenib. Patient received 159 weeks of 17-DMAG prior to PD.
a BED might have been suboptimal. Validating Western blotting as fit for purpose (23, 46) limited the protein panel analyzed and practical limitations restricted sampling to one time-point. It remains challenging to balance acceptable scientific rigor (i.e., validation) with the currently limited knowledge of the molecular biology of HSP90 client proteins in human cancers, especially which client protein(s) is/are critical for tumorigenesis in an individual tumor, given the range of HSP90 client proteins and their differential sensitivity to HSP90 inhibition.

Clinical benefit was observed over a range of dose levels and robust definition of BED would aid dose and schedule selection for future studies. The challenges to defining a BED should not deter investigators from future efforts (47). Combination studies of HSP90 inhibitors have enjoyed early success in clinical trials, for example, HSP90 inhibition with trastuzumab in breast cancer (48, 49) or bortezomib in myeloma (50). Use of BED in combination studies potentially minimizes toxicity and requires thorough pharmacokinetic and pharmacodynamic measurements (25, 47, 51–53).

Our data support further evaluation of HSP90 inhibitors. However, at this time there are no phase II or III studies using the weekly schedule of 17-DMAG that we are aware of. Future studies of 17-DMAG should consider using alternative schedules or administration routes to minimize side effects in light of the severe toxicity observed at the highest dose level tested.

Disclosure of Potential Conflicts of Interest

P. Workman and his team received research funding on the development of HSP90 inhibitors from Vernalis Ltd., and intellectual property from this program was licensed to Vernalis Ltd. and Novartis. S. Pacey, I. Judson, I.S. de Bono, U. Banerji, F. Raynard, J. Moreno-Farre, W. Ahern, A. Harcastle, and P. Workman are/or were employees of The Institute of Cancer Research, which has a commercial interest in HSP90 inhibitors under development by Novartis Ltd. P. Workman has been a consultant to Novartis. F. Raynard has undertaken consultancy work for Elara Pharma. 17-DMAG was supplied by the NCI and Kosan Biosciences Ltd.

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