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A phase I trial of docetaxel and pulse-dose 17-allylamino-17-demethoxygeldanamycin in adult patients with solid tumors

Gopa Iyer,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Michael J. Morris,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Dana Rathkopf,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Susan F. Slovin,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Macaulay Steers,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Steven M. Larson,

Department of Nuclear Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Lawrence H. Schwartz,

Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Tracy Curley,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Anthony DeLaCruz,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Qing Ye,

Department of Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Glenn Heller,

Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Merrill J. Egorin,

Molecular Therapeutics/Drug Discovery Program, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

S. Percy Ivy,

Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Centers, National Cancer Institute, Bethesda, MD, USA

Neal Rosen,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Department of Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Howard I. Scher, and

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

David B. Solit

Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

The Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Abstract

Purpose—To define maximum tolerated dose (MTD), clinical toxicities, and pharmacokinetics of 17-allylamino-17-demethoxygeldanamycin (17-AAG) when administered in combination with docetaxel once every 21 days in patients with advanced solid tumor malignancies.

Experimental design—Docetaxel was administered over 1 h at doses of 55, 70, and 75 mg/m². 17-AAG was administered over 1–2 h, following the completion of the docetaxel infusion, at escalating doses ranging from 80 to 650 mg/m² in 12 patient cohorts. Serum was collected for pharmacokinetic and pharmacodynamic studies during cycle 1. Docetaxel, 17-AAG, and 17-AG levels were determined by high-performance liquid chromatography. Biologic effects of 17-AAG were monitored in peripheral blood mononuclear cells by immunoblot.

Results—Forty-nine patients received docetaxel and 17-AAG. The most common all-cause grade 3 and 4 toxicities were leukopenia, lymphopenia, and neutropenia. An MTD was not defined; however, three dose-limiting toxicities were observed, including 2 incidences of neutropenic fever and 1 of junctional bradycardia. Dose escalation was halted at docetaxel 75 mg/m²-17-AAG 650 mg/m² due to delayed toxicities attributed to patient intolerance of the DMSO-based 17-AAG formulation. Of 46 evaluable patients, 1 patient with lung cancer experienced a partial response. Minor responses were observed in patients with lung, prostate, melanoma, and bladder cancers. A correlation between reduced docetaxel clearance and 17-AAG dose level was observed.

Conclusions—The combination of docetaxel and 17-AAG was well tolerated in adult patients with solid tumors, although patient intolerance to the DMSO formulation precluded further dose escalation. The recommended phase II dose is docetaxel 70 mg/m² and 17-AAG 500 mg/m².

Keywords

17-AAG; Geldanamycin; Hsp90; Docetaxel; Phase I

Introduction

Heat shock protein 90 (Hsp90) is an abundant cellular chaperone that is required for refolding of unfolded proteins, cellular survival under stress conditions, and the

conformational maturation of a variety of proteins that play key roles in transducing proliferative and anti-apoptotic signals [1, 2]. 17-allylamino-17-demethoxygeldanamycin (17-AAG), a derivative of the natural product geldanamycin, was the first Hsp90 inhibitor to enter clinical testing [3–7]. Geldanamycin and its derivatives bind to a regulatory ATP/ADP pocket in the aminoterminal portion of Hsp90 that is conserved across species [8]. Occupancy of the pocket by drug leads to the degradation of Hsp90 client proteins, many of which play central roles in tumor initiation, maintenance of the transformed phenotype, and tumor progression [9, 10]. These Hsp90 clients include steroid receptors such as the androgen and estrogen receptors and a subset of serine/threonine and tyrosine kinases, including Raf-1, Akt, HER2, and insulin-like growth factor-1 receptor [11–15].

In cell culture models, 17-AAG synergistically enhances the activity of chemotherapeutics including paclitaxel and doxorubicin [16–18]. 17-AAG induces a potent G1 arrest in tumors with intact retinoblastoma protein 1 (RB1) function, and thus, sensitization to cell cycle-specific cytotoxics is schedule dependent in most systems [16]. For example, in tumors with intact RB1 function, 17-AAG enhances the antiproliferative and pro-apoptotic effects of paclitaxel when the 2 agents are administered either simultaneously or when the taxane precedes 17-AAG [16, 19]. In contrast, pretreatment with 17-AAG in such systems induces G1 cell cycle arrest and antagonizes the pro-apoptotic effects of the taxane. In human xenograft models, maximal enhancement occurs when the taxane and 17-AAG are administered on the same day, suggesting that a mechanistic interaction between these agents is responsible for the observed synergy [13]. Further exploration of the mechanisms responsible for synergy in HER2-driven breast cell lines suggested that inactivation of PI3 kinase/Akt signaling following Hsp90 inhibition was required for synergy [13]. Notably, a pulsatile 17-AAG dosing regimen with no single-agent activity that inhibits Akt activity for 24–48 h was sufficient to sensitize tumors to paclitaxel [13].

On the basis of these preclinical data, we initiated a phase I clinical trial of docetaxel in combination with pulse-dosed 17-AAG in patients with advanced solid tumor malignancies. The primary objectives of the study were to define the maximum tolerated dose (MTD) of 17-AAG as well as clinical toxicities of the combination. Secondary endpoints included pharmacokinetic studies and the effects of treatment on the expression of Hsp90 clients in peripheral blood mononuclear cells (PBMCs).

Materials and methods

Patient eligibility

The trial was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center on January 23, 2003 (clinicaltrials.gov identifier: NCT00058253). All patients signed written informed consent. Patients were required to have a histologically confirmed malignancy that was metastatic or unresectable and for which curative or palliative measures did not exist or were no longer effective. Progressive disease could be documented either by new lesions or an increase in preexisting lesions on bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), or by physical examination. For patients with prostate cancer, a rising prostate-specific antigen (PSA) alone was sufficient to document progression.

Patients were required to be over 18 years of age, have a Karnofsky Performance Status 70%, and a life expectancy >6 months. Intact hepatic, renal, and bone marrow function as defined by specific laboratory ranges was a prerequisite for enrollment.

Exclusion criteria included prior chemotherapy, radiotherapy, or other investigational therapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C); active brain metastases

or epidural disease; symptomatic peripheral neuropathy Grade 2; a history of severe hypersensitivity reaction to paclitaxel, docetaxel, or polysorbate 80; and allergy to egg or egg products (because of its inclusion in the EPL diluent vehicle).

Cardiac-specific exclusion criteria were altered during the course of the trial. The initial 43 patients enrolled required screening radionuclide angiography or echocardiogram for suspected or documented congestive heart failure with a depressed ejection fraction, coronary artery disease, or arrhythmia other than atrial fibrillation. Following reports of prolonged QTc intervals on other 17-AAG trials, we also excluded from this study patients with significant cardiac disease including heart failure that met New York Heart Association (NYHA) class III or IV definitions, a history of myocardial infarction or active ischemic heart disease within 12 months of study entry, uncontrolled dysrhythmias, and individuals requiring antiarrhythmic drugs. Patients with the following were also excluded: history of serious ventricular arrhythmia (VT or VF lasting ≥ 3 consecutive beats); QTc > 450 ms for men and >470 ms for women; congenital long QT syndrome; left bundle branch block; history of prior radiation that potentially included the heart in the field (e.g., mantle); or LVEF < 40% by multi-gated acquisition scan or echocardiography. Medications previously shown to prolong the QTc interval were restricted.

Treatment

On a 21-day cycle, patients were treated intravenously with docetaxel over 1 h followed immediately by 17-AAG. The infusion duration of 17-AAG at doses of 450 mg/m² or higher was 2 h, while doses of 375 mg/m² or less were infused over 1 h. All patients received dexamethasone premedication to reduce the incidence and severity of fluid retention or hypersensitivity reactions.

Patient assessment

Pharmacokinetic samples were drawn at specific time points on day 1 (pretreatment, 30 and 55 min after initiation of docetaxel infusion, and 30 min, 1, 2, 3, 4, and 6–8 h after initiation of 17-AAG infusion), and also on days 2 and 3 of cycle 1.

PBMCs were assessed for changes in Hsp70, Raf-1, and Akt by immunoblot. Blood samples were drawn into heparin-containing tubes and PBMCs were isolated by centrifugation. Up to 6 samples were drawn during cycle 1 only. Cells were lysed in NP40 lysis buffer (50 mM Tris [pH 7.4], 1% NP40, 150 mM NaCl, 40 mM NaF, 1 mM Na₃VO₄, 1 mM phenylmethylsulphonylfluoride, and 10 mg/ml each of leupeptin, aprotinin, and soybean trypsin inhibitor) for 30 min on ice. Lysates were centrifuged at approximately 13,000×g for 10 min, and the protein concentration of the supernatant was determined by bicinchoninic acid (BCA) assay (Pierce, Rockford, IL). Equal amounts of total protein were resolved by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS–PAGE) and transferred onto nitrocellulose membranes. Blots were probed overnight at 4°C with the primary antibody. After incubation with horseradish peroxidase-conjugated secondary antibodies, proteins were detected using chemiluminescence. The following primary antibodies were used: Akt (Cell Signaling, Beverly, MA), Hsp70 (StressGen, Victoria, BC, Canada), p85 subunit of PI3 kinase (Upstate Biotechnology, Lake Placid, NY), and Raf-1 (Santa Cruz Biotechnology, Santa Cruz, CA). The p85 subunit of PI3 kinase was used as a loading control since its expression is unaffected by 17-AAG.

Although response was not the primary endpoint of this trial, patients with measurable disease were assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Toxicity and MTD

Toxicities and adverse events were assessed using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0. Dose-limiting toxicity (DLT) was defined as the occurrence of any of the following events during cycle 1 of treatment:

1. Grade 4 neutropenia lasting greater than 7 days (defined as 2 or more consecutive CBC with differentials documenting grade 4 neutropenia drawn 8 days apart)
2. Febrile neutropenia ($\text{ANC} < 1,000/\text{mm}^3$ and temperature $\geq 38.5^\circ\text{C}$)
3. Grade 3 or greater thrombocytopenia, or other grade 3 or higher neurologic, gastrointestinal, or cardiovascular toxicities attributable to the study treatment
4. Grade 3 or greater QTc interval prolongation ($\text{QTc} > 0.50 \text{ s}$)

The MTD was defined as the highest dose level with an observed incidence of DLT in no more than 1 out of 6 patients treated at a particular dose level. The dose escalation scheme was as follows: if none of an initial 3 patients at a given dose level experienced a DLT, the next dose level was studied in another cohort of 3 patients. Escalation then continued if none or one of the additional patients experienced a DLT. If 1 of the initial 3 patients at a given dose level experienced a DLT, up to 3 additional patients were treated at that same dose level. Escalation then continued if none of the additional patients experienced a DLT. If 2 or 3 of the first 3 patients experienced a DLT, or 2 or more patients out of a cohort of 6 experienced a DLT at a given dose level, the MTD was defined as the preceding dose level. If 3 or fewer patients were treated at a dose under consideration as the MTD, additional patients to total 6 were to be treated at that level to confirm the MTD.

Analytical chemical methods and pharmacokinetic data analysis

Concentrations of 17-AAG and its metabolite 17-AG were measured using a high-performance liquid chromatography (HPLC) assay with absorbance detection [20], while docetaxel plasma concentrations were quantitated with a liquid chromatography-mass spectrometry assay, both of which were developed and validated in the Egorin laboratory [21]. Plasma concentration was correlated with time data for 17-AAG and 17-AG non-compartmentally using the LaGrange function [22] as implemented by the Lagran computer program [23].

Results

Patients

A total of 49 patients were treated, with 46 evaluable for response. Baseline demographics are shown in Table 1. Three patients were not evaluable for response due to removal from the study for toxicity during cycle 1. Nine patients were removed before the first scheduled restaging at 9 weeks due to rapid progression of disease. The dose escalation scheme as well as the number of patients treated at each dose level is shown in Table 2. The mean number of cycles was 4 (range 1–13).

Safety and tolerability

Toxicities observed during cycle 1 that were probably or definitely attributable to the study drugs are listed in Table 3. The most common grade 3 and 4 drug-related toxicities in cycle 1 included leukopenia (22 and 8%, respectively) and neutropenia (20 and 16%, respectively). Three patients developed dose-limiting toxicities in cycle 1, including 2 episodes of neutropenic fever (1 patient each on dose levels 6 and 9) and 1 episode of junctional bradycardia (dose level 11). These dose levels were thus expanded to 6 patients each. One patient enrolled in dose level 11 (docetaxel 75 mg/m^2 and 17-AAG 650 mg/m^2)

developed third-degree AV block associated with asymptomatic bradycardia (HR of 43 bpm) immediately posttreatment on day 1 of cycle 1. The heart block and bradycardia resolved spontaneously. This event was classified as a DLT and the patient was not rechallenged with 17-AAG; however, subsequent treatment with single-agent docetaxel occurred without incident. One patient enrolled in cohort 8 was not evaluable for liver toxicity. This patient had a normal AST and grade 1 ALT elevation at the time of screening evaluation 10 days prior to first treatment, but on day 1 had asymptomatic Grade 4 AST and ALT elevations pretreatment. As these abnormalities were present pretreatment, they were not drug related. This patient tolerated treatment well and the liver function abnormalities resolved by day 40. The patient was later rechallenged with the study drugs and in total received 9 cycles of 17-AAG and docetaxel without further Grade 2 or greater transaminitis. During cycle 1, 6 patients experienced grade 3 hyperglycemia, 3 patients experienced grade 3 hyponatremia, and 1 patient grade 4 hypophosphatemia. These events were not associated with clinical symptoms and were not thought to be related to 17-AAG therapy.

Table 4 lists the grade-specific frequency of any toxicities that occurred with grade 3 or 4 severity as well as any grade 1 and 2 toxicities which occurred at a frequency of 25% or greater, regardless of causality. As expected with a docetaxel-based combination regimen, cytopenias were frequently observed, including grade 3 leukopenia and lymphopenia (41% each), as well as grade 4 neutropenia (47%). Two patients developed delayed grade 3 or greater transaminitis. In one instance, grade 4 elevation of bilirubin, AST, and ALT occurred following cycle 4 in a patient with colon cancer treated at the highest dose level (dose level 11: 17-AAG 650 mg/m²). These liver abnormalities were associated with biliary duct obstruction secondary to disease progression and thus were unlikely to be drug related. The second patient (dose level 9: 17-AAG 450 mg/m²) developed grade 3 nausea, dehydration, and AST elevation following cycle 4. This patient also developed grade 3 neutropenic fever. As a result of these adverse events, the patient was dose-reduced and rechallenged with the combination and went on to receive 2 additional cycles of treatment which were tolerated well.

As preclinical studies suggested a role for Hsp90 in the maturation of the hERG cardiac potassium channel [24], QTc was assessed pre and posttreatment. The mean QTc interval for all patients was 425 ms; mean posttreatment QTc interval was 428 ms. No patient had a QTc interval posttreatment of greater than 500 ms. PR interval prolongation was observed in several patients. The mean pretreatment PR interval was 158 ms; mean posttreatment PR interval was 174 ms. Six patients on the study developed first-degree AV block posttreatment. Two additional patients had preexisting first-degree AV block. Further, as described previously, 1 patient enrolled on dose level 11 (docetaxel 75 mg/m² and 17-AAG 650 mg/m²) developed asymptomatic junctional bradycardia immediately posttreatment on day 1 of cycle 1 which resolved spontaneously.

An intolerance of the odor related to the DMSO-based formulation of 17-AAG, with associated nausea and vomiting at higher dose levels, ultimately led to discontinuation of this trial in favor of alternative formulations of 17-AAG currently in development.

Antitumor activity

Of 46 evaluable patients, 1 patient with non-small cell lung cancer had a partial response to therapy. Nineteen patients (41%) experienced stable disease lasting 3 cycles: 11 (24%) experienced stable disease for at least 6 cycles, and 4 (9%, all melanoma and prostate cancer) having stable disease lasting 9 cycles or greater.

In patients with prostate cancer ($n = 16$), 4 patients exhibited a PSA decline of 20% or greater, and 2 of these patients had received prior docetaxel treatment. The patient who

experienced the greatest PSA response had received 1 dose of the study drugs, with subsequent removal from the study due to febrile neutropenia. At 3 weeks postdrug administration, the patient had a 69.5% decline in PSA (baseline 13.73, nadir 3.19). This patient was taxane-naïve.

Pharmacokinetics

The pharmacokinetics of 17-AAG, its active metabolite 17-AG, and docetaxel were examined during cycle 1. Estimates of pharmacologic parameters grouped by dose level are listed in Table 5. Peak plasma concentrations of both 17-AAG and 17-AG were greater than those required for antitumor effects in preclinical models. At the 450 mg/m² dose level ($n = 9$), the mean C_{max} was 15.9 ± 0.5 μmol/L, and the $t_{1/2}$ and clearance values for 17-AAG were 2.9 ± 0.1 h and 13.3 ± 0.4 L/h/m², respectively. A linear increase in 17-AAG C_{max} was observed with increasing dose (Table 5), while clearance of docetaxel was inversely proportional with the 17-AAG dose (Fig. 1). 17-AG was detected at all dose levels. At the 220 mg/m² 17-AAG dose level, a mean peak 17-AG level of 1.4 ± 0.3 μmol/L was observed 1.7 h after initiation of the 17-AAG infusion, and the mean $t_{1/2}$ was 5.9 ± 0.6 h (Table 5).

Lymphocyte studies

To assess for inhibition of Hsp90, PBMCs were collected pretreatment and following drug administration. As has been reported with single-agent administration of 17-AAG [3], increased expression of Hsp70 was observed in the majority of patients treated at or above the 110 mg/m² dose level. Representative immunoblots from 4 patients treated at the docetaxel 75 mg/m² and 17-AAG 450 mg/m² dose level are shown in Fig. 2. A consistent pattern of changes in Raf1 or Akt expression was not observed.

Discussion

This phase I trial was initiated to determine the maximal tolerated dose of the Hsp90 inhibitor 17-AAG that could be coadministered with docetaxel when each agent was pulse dosed on an every 3 week schedule. Hsp90 is overexpressed in cancer cells, and Hsp90 inhibitors have been shown to be selectively toxic to tumor cells [25, 26]. These observations and the antitumor activity of 17-AAG in preclinical models prompted several groups, including our own, to initiate phase I clinical trials of 17-AAG in patients with advanced cancer [3–7]. Demonstrable single-agent clinical activity with Hsp90 inhibitors has been limited, however. In patients with solid tumors, the most compelling clinical data to date with Hsp90 inhibitor monotherapy have been observed in patients with HER2-amplified breast cancer and non-small cell lung cancer [27–30]. Due to evidence of synergy between 17-AAG and a broad range of cytotoxic agents, a logical iterative approach in the clinical development of this compound was to combine it with standard cytotoxics.

A 3-week interval dosing schedule was chosen because every 3 week docetaxel administration has been shown to be optimal for many solid tumors, and our preclinical data suggested that concurrent administration of 17-AAG only on those days on which the taxane was administered would maximize synergy between the two agents [13]. Using this schedule, we were able to safely and with minimal toxicity deliver doses of 17-AAG as high as 650 mg/m² in combination with the full standard dose of docetaxel to a population of heavily pretreated cancer patients. The antitumor responses noted with 17-AAG in breast cancer when administered weekly at a dose of 450 mg/m² [31] suggest that the dose levels achieved in this trial were likely sufficient to induce the degradation of at least some Hsp90 clients, such as HER2. As pre and posttreatment tumor biopsies were not incorporated into this study, however, the complement of Hsp90 clients degraded at the dose levels achieved remains unknown.

PBMCs were collected to assess the effects of docetaxel/17-AAG treatment on the expression of Hsp70, Akt, and Raf-1. While the posttreatment rise in Hsp70 levels in most patients suggests Hsp90 target modulation, a dose-dependent pattern of Akt and Raf-1 degradation was not observed. As recent studies have indicated that the affinity of 17-AAG for Hsp90 may vary between normal and tumor tissues [26], the utility of normal tissues for pharmacodynamic studies of Hsp90 inhibitors may be limited. Therefore, such studies do not prove that these clients were not degraded in the corresponding tumors and they should not be considered a substitute for the assessment of changes in the expression and activation of Hsp90 clients in tumor tissue.

An MTD was not defined for this study. Dose escalation was halted at the 650 mg/m² dose level because of cumulative toxicities that were attributable in part to the DMSO-based 17-AAG formulation. Specifically, for the majority of patients treated at this dose level, the odor associated with the DMSO formulation was the primary treatment-associated complaint. For this reason, and with the subsequent development of non-DMSO-based 17-AAG formulations, further dose escalation was not felt to be warranted.

Our results do suggest that docetaxel can be combined safely with an inhibitor of Hsp90 at doses above those sufficient to induce responses in patients with breast and lung cancers. On the basis of these results, a phase I trial of docetaxel and IPI-504 [32], an Hsp90 inhibitor that does not use a DMSO-based formulation, was proposed and is now ongoing.

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Fig. 1. Effect of 17-AAG dose on docetaxel clearance ($n = 33$). Docetaxel pharmacokinetic data were not collected from patients receiving 80 mg/m² 17-AAG

Fig. 2.
Immunoblot studies of peripheral blood mononuclear cells collected pretreatment and days 2, 3, 8, and 15 of cycle 1. The four representative patients shown were all treated at the docetaxel 75 mg/m² and 17-AAG 450 mg/m² dose level

Table 1

Baseline demographics and characteristics

Characteristics	
Patients treated	49
Age, years	
Median	61
Range	32–78
Sex	
Male	42
Female	7
Race	
White non-Hispanic	44
White Hispanic	1
Black non-Hispanic	3
Black Hispanic	1
KPS [*]	
Median	90
Range	70–90
No. prior chemotherapy regimens	
Median	2
Range	0–8
Primary tumor site	
Prostate	16
Melanoma	12
Head/Neck	7
Renal	4
Bladder	3
Lung	3
Breast	2
Other	2

* Karnofsky Performance Status; available on 48 patients

Table 2

Dose escalation scheme

Dose level	Docetaxel (mg/m ²)	17-AAG (mg/m ²)	No. of patients	No. of cycles	
				Median	Range
1	55	80	3	3	3
2	70	80	3	6	2-6
3	70	110	3	5	2-5
4	70	160	3	3	3
5	70	220	3	2	2-3
6	70	300	6	3	1-9
7	70	375	3	6	2-11
8*	70	450	4	9	3-9
9	75	450	6	2.5	1-6
10	75	540	3	3	3-6
11	75	650	6	2	1-4
12	70	500	6	3.5	3-13

* One patient enrolled on dose level 8 was replaced as the patient was non-evaluable for toxicity, as described in the text

Table 3

Drug-related toxicities during cycle 1 of therapy, in 49 evaluable patients

Toxicity, n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Lymphopenia	0	0	7 (14)	0
Leukocytes	11 (22)	16 (33)	11 (22)	4 (8)
Neutrophils/granulocytes	5 (10)	10 (20)	10 (20)	8 (16)
Platelets	2 (4)	0	0	0
Gastrointestinal				
Nausea	2 (4)	0	0	0
Vomiting	1 (2)	0	0	0
Constipation	1 (2)	0	0	0
Anorexia	1 (2)	0	0	0
Hepatic				
SGOT (AST)	12 (24)	3 (6)	0	0
SGPT (ALT)	9 (18)	0	0	0
Alkaline phosphatase	1 (2)	0	0	0
Cardiovascular				
Nodal/junctional arrhythmia *	0	1 (2)	0	0
Infection				
Febrile neutropenia *	0	0	2 (4)	0
Neurologic				
Insomnia	1 (2)	0	0	0
Constitutional symptoms				
Fatigue	2 (4)	0	0	0
Fever	1 (2)	0	0	0
Other	2 (4)	0	0	0

* Dose-limiting toxicity

Table 4

All grade 3/4 toxicities, and any grade 1/2 toxicity present in >25% patients, regardless of causality, during all cycles

Toxicity, n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Hemoglobin (Hgb)	23 (47)	13 (27)	9 (18)	0
Transfusion pRBCs	0	0	2 (4)	0
Leukocytes	6 (12)	11 (22)	20 (41)	8 (16)
Lymphopenia	0	0	20 (41)	0
Neutrophils/granulocytes	5 (10)	9 (18)	9 (18)	23 (47)
Coagulation				
PT	24 (49)	0	1 (2)	0
PTT	19 (39)	2 (4)	0	0
Endocrine				
Hyperglycemia	13 (27)	22 (45)	11 (22)	2 (4)
Hypoglycemia	3 (6)	0	0	1 (2)
Infection				
Febrile neutropenia	0	0	2 (4)	0
Infection without neutropenia	2 (4)	2 (4)	2 (4)	0
Infection with Grade 3/4 neutropenia	0	0	4 (8)	1 (2)
Gastrointestinal				
Anorexia	22 (45)	0	0	0
Dehydration	0	0	1 (2)	0
Dysphagia	5 (10)	1 (2)	1 (2)	0
Nausea	19 (39)	2 (4)	1 (2)	0
Vomiting	13 (27)	0	1 (2)	0
Diarrhea	21 (43)	3 (6)	0	0
Constipation	17 (35)	6 (12)	0	0
Abdominal pain	11 (22)	1 (2)	1 (2)	0
Other	4 (8)	0	2 (4)	0
Cardiovascular				
Chest pain	1 (2)	0	1 (2)	0
Supraventricular tachycardia	0	1 (2)	1 (2)	0
Thrombosis	0	0	1 (2)	0
Metabolic/Laboratory				
Hyperkalemia	8 (16)	4 (8)	4 (8)	0
Hypokalemia	4 (8)	0	1 (2)	0
Hyponatremia	24 (49)	0	3 (6)	0
Hypocalcemia	17 (35)	4 (8)	1 (2)	0
Hypophosphatemia	1 (2)	9 (18)	7 (14)	2 (4)
Hyperuricemia	0	0	0	1 (2)
Alkaline phosphatase	23 (47)	4 (8)	2 (4)	0

Toxicity, n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Bilirubin	10 (20)	4 (8)	1 (2)	1 (2)
AST	15 (31)	4 (8)	2 (4)	1 (2)
ALT	19 (39)	3 (6)	1 (2)	1 (2)
Hypoalbuminemia	27 (55)	4 (8)	0	0
Renal/Genitourinary				
Creatinine	16 (33)	0	0	1 (2)
Urinary frequency	24 (49)	0	0	0
Pulmonary				
Dyspnea	0	18 (37)	1 (2)	1 (2)
Pneumonitis	0	0	0	1 (2)
Musculoskeletal				
Myalgias	18 (37)	0	0	0
Arthralgia	9 (18)	1 (2)	1 (2)	0
Bone pain	6 (12)	0	1 (2)	0
Neurologic				
Neuropathy—sensory	16 (33)	5 (10)	1 (2)	0
Other	0	0	1 (2)	0
Constitutional symptoms				
Fatigue	33 (67)	13 (26)	0	0
Weight loss	23 (47)	4 (8)	0	0
Other	5 (10)	1 (2)	0	1 (2)
Pain				
Headache	9 (18)	1 (2)	1 (2)	0
Tumor pain	11 (22)	3 (6)	2 (4)	0
Other	6 (12)	2 (4)	1 (2)	0

Table 5

Pharmacokinetic parameters

Dose level	n	17-AAG Dose (mg/m ²)	Docetaxel Dose (mg/m ²)	17-AAG C _{max} (μmol/L)	17-AAG C _{max} (μmol/L)	17-AG C _{max} (μmol/L)	17-AAG AUC (μmol/L h)	17-AG AUC (μmol/L h)	17-AG t _{1/2} (h)	17-AAG t _{1/2} (h)	17-AG CL (L/h/m ²)
A. 17-AAG and 17-AG pharmacokinetic parameters as a function of 17-AAG dose (n = 41)											
1, 2	5	80	55–70	3.1 ± 0.5	0.4 ± 0.0	7.5 ± 0.8	2.1 ± 0.3	2.3 ± 0.1	5.0 ± 0.6		22.5 ± 2.1
3	3	110	70	5.6 ± 1.6	1.5 ± 0.4	9.4 ± 1.0	3.5 ± 0.4	3.6 ± 0.5	3.8 ± 0.4		21.5 ± 2.6
4	2	160	70	2.9 ± 0.3	0.7 ± 0.1	9.6 ± 1.6	3.3 ± 0.6	2.2 ± 0.4	3.4 ± 1.0		30.1 ± 4.9
5	3	220	70	7.2 ± 0.7	1.4 ± 0.3	19.3 ± 0.9	10.1 ± 2.6	3.7 ± 0.4	5.9 ± 0.6		19.7 ± 1.0
6	6	300	70	12.9 ± 0.6	2.9 ± 0.2	36.3 ± 1.4	24.1 ± 1.4	7.7 ± 1.9	4.4 ± 0.2		14.9 ± 0.6
7	3	375	70	19.1 ± 0.7	7.0 ± 0.6	47.9 ± 2.7	69.8 ± 6.5	4.2 ± 0.3	6.9 ± 1.4		13.6 ± 0.7
8, 9	9	450	70–75	15.9 ± 0.5	5.3 ± 0.4	60.9 ± 2.4	53.9 ± 4.7	2.9 ± 0.1	5.6 ± 0.3		13.3 ± 0.4
10	2	540	75	20.6 ± 3.5	7.1 ± 1.1	68.3 ± 19.5	53.2 ± 15.4	2.1 ± 0.2	5.5 ± 1.9		16.2 ± 4.6
11	6	650	75	29.8 ± 1.2	12.3 ± 0.9	139.9 ± 11.2	172.5 ± 17.9	4.6 ± 0.9	5.6 ± 0.3		9.6 ± 0.7
12	2	500	70	15.1 ± 1.6	7.6 ± 3.1	62.3 ± 3.0	48.6 ± 15.8	3.1 ± 0.9	3.9 ± 0.4		13.8 ± 0.7

Dosage (mg/m ²)	Patients (n)	C _{max} (μmol/L)	T _{1/2} (h)	AUC (μmol/L h)	CL _{tb} (L/h/m ²)	CL _{tb} (L/h)
B. Docetaxel pharmacokinetic parameters as a function of docetaxel dose (n = 37)						
70	23	2.5	24.2	3.3	28.1	55.2
75	14	3.3	22.5	4.4	24.1	51.1

Pharmacokinetic parameters are shown as value ± SD
CL_{tb} Total Body Clearance