Published in final edited form as:

Invest New Drugs. 2013 October ; 31(5): 1251–1256. doi:10.1007/s10637-013-9946-7.

Phase I study of tanespimycin in combination with bortezomib in patients with advanced solid malignancies

Erin Schenk, M.D., Ph.D., Andrea E. Wahner Hendrickson, M.D., Donald Northfelt, M.D., David O. Toft, Ph.D., Matthew M. Ames, Ph.D, Michael Menefee, M.D., Daniel Satele, Rui Qin, Ph.D., and Charles Erlichman, M.D.

Division of Medical Oncology. Division of Biostatistics, Department of Biochemistry and Molecular Biology, Mayo Clinic College of Medicine, Rochester, MN

Summary

Purpose—To determine the maximum tolerated dose (MTD) and characterize the dose-limiting toxicities (DLT) of tanespimycin when given in combination with bortezomib.

Experimental design—Phase I dose-escalating trial using a standard cohort “3+3” design performed in patients with advanced solid tumors. Patients were given tanespimycin and bortezomib twice weekly for 2 weeks in a 3 week cycle (days 1, 4, 8, 11 every 21 days).

Results—Seventeen patients were enrolled in this study, fifteen were evaluable for toxicity, and nine patients were evaluable for tumor response. The MTD was 250 mg/m² of tanespimycin and 1.0 mg/m² of bortezomib when used in combination. DLTs of abdominal pain (13%), complete atrioventricular block (7%), fatigue (7%), encephalopathy (7%), anorexia (7%), hyponatremia (7%), hypoxia (7%), and acidosis (7%) were observed. There were no objective responses. One patient had stable disease.

Conclusions—The recommended phase II dose for twice weekly 17-AAG and PS341 are 250 mg/m² and 1.0 mg/m² respectively, on days 1, 4, 8 and 11 of a 21 day cycle.

Keywords

Phase I Trials; tanespimycin; bortezomib; solid tumors

Introduction

Heat-shock protein 90 (HSP90) is an evolutionarily conserved chaperone protein that promotes the folding of a diverse range of nascent proteins, known as “clients.” These client proteins include oncogenes such as EGFR, MEK, p53, AKT, v-Src, BRAF, BCR-ABL and others critical to signal transduction, transcription, and protein trafficking [1]. As a mediator of multiple essential cell pathways, HSP90 is commonly overexpressed in tumor cells and is a rational target for drug development [2, 3].

Geldamycin (GA) is a member of the benzoquinone ansamycin antibiotic family and disrupts the association of HSP90 with client proteins by binding to its N-terminal ATP-binding pocket [4, 5]. Although early data demonstrated antitumor activity of GA, subsequent preclinical animal studies reported significant hepatotoxicity, and GA was determined too toxic for human administration [6, 7]. The GA derivative 17-allylamino-17-

demethoxygeldanamycin (tanespimycin) also disrupts the HSP90 association with client proteins but appears to have a more tolerable toxicity profile [8, 9].

Phase I studies using tanespimycin as a single agent in patients with advanced solid tumors established treatment schedules of 1, 2, or 3 doses weekly that were well tolerated [10–15]. Common dose limiting toxicities were hepatotoxicity, diarrhea, nausea, vomiting, and fatigue [10–16]. No complete or partial responses were seen in these trials but some patients were found to have stable disease for several months [10–16]. Several Phase II trials using tanespimycin as a single agent have been reported in patients with advanced prostate cancer, renal cell carcinoma, and metastatic melanoma [17–20]. Toxicities were similar to those seen in the Phase I trials but no partial or complete responses were observed [17–20]. As a monotherapy, tanespimycin has minimal activity in producing an objective response, but early pre-clinical studies suggest tanespimycin may work best as an adjunct to traditional agents [21–23].

By interfering with the chaperone activity of HSP90, members of the benzoquinone ansamycin class of compounds promote the rapid down-regulation and proteasomal degradation of client proteins such as the HER2/neu and v-src [4, 24, 25]. Experiments with tanespimycin and bortezomib, a proteasome inhibitor, demonstrated that concurrent treatment of a human breast cancer cell line resulted in increased client protein ubiquitination and subsequent accumulation in endoplasmic reticulum-derived perinuclear vacuoles [26, 27]. Importantly, this drug combination was preferentially cytotoxic to transformed cells [26]. Pre-clinical studies in primary multiple myeloma cell lines have also demonstrated that HSP90 inhibition by tanespimycin sensitizes cells to bortezomib [28]. Again, this drug combination resulted in a marked accumulation of ubiquitinated proteins within the myeloma cells through the synergistic suppression of the chymotryptic activity of the 20S proteasome [28]. Taken together, these pre-clinical data suggest that interrupting intracellular protein homeostasis with tanespimycin and bortezomib promotes improved antitumor activity of both compounds.

Based on these pre-clinical data, we undertook a Phase I trial to determine the maximally tolerated dose (MTD) and dose limiting toxicity (DLT) of tanespimycin and bortezomib combination therapy in patients with advanced solid tumors. Patients were given tanespimycin and bortezomib twice weekly for 2 weeks in a 3 week cycle (days 1, 4, 8, 11 with the schedule repeated every 21 days). Once the MTD was determined, patients were given tanespimycin on days 1, 4, 8, and 11 and bortezomib on days 4, 8, and 11 for cycle 1, and then tanespimycin and bortezomib on days 1, 4, 8, and 11 for all subsequent cycles.

Patients and Methods

Patients with histologic proof of malignancy that was refractory to standard treatment for which no other curative or life-extending therapy was available were eligible for the trial. Patients were 18 years old, had a life expectancy 12 weeks, an Eastern Cooperative Oncology Group performance status 2, and were willing to return for follow up care and monitoring. Adequate hematologic, renal, and hepatic function was demonstrated by hemoglobin 9 g/dL, absolute neutrophil count 1500/ μ L, platelets 100,000/ μ L, creatinine 2 $\times$ upper limit of normal (ULN), total bilirubin 2 $\times$ ULN, aspartate aminotransferase (AST) 2.5 $\times$ ULN, and alkaline phosphatase 2 $\times$ ULN or 5 $\times$ ULN if liver involvement.

Exclusion criteria included any chemotherapy, radiation therapy, immunotherapy, or biologic therapy 4 weeks prior to study entry (6 weeks with mitomycin C or nitrosoureas). Patients who received radiation to > 25 % of bone marrow,

radiopharmaceuticals, chest radiation, or those who had failed to fully recover from toxicities of prior therapy were also excluded. Patients with significant cardiac disease including New York Heart Association III or IV heart failure, left ventricular ejection fraction < 40%, history of serious left ventricular tachycardia or fibrillation, history of myocardial infarction or active ischemic heart disease > 1 year prior to study entry, uncontrolled dysrhythmias, antiarrhythmic therapy, current warfarin therapy that could not be switched to low molecular weight heparin, poorly controlled angina, congenital long QT syndrome, QTc > 500 msec, left bundle branch block, or a prior history of cardiac toxicity after receiving anthracyclines were also excluded from the study. Patients with significant pulmonary disease including diseases that require supplemental oxygen, severely limit activity, require medication for dyspnea, pulse oximetry < 88% at rest or with exercise, or a prior history of pulmonary toxicity after receiving anthracyclines were also excluded from the study.

Other exclusion criteria included uncontrolled infections, CNS metastases, seizure disorder, peripheral neuropathy > grade 1, neuropathic pain of any etiology, history of serious allergic reaction to eggs, or use of concomitant medications that are known or suspected to prolong QTc. Patients were excluded if receiving other investigational therapies while on study. Pregnant women, nursing women, and patients of childbearing potential who were unwilling to employ adequate contraception, were excluded.

Dosage and administration

Tanespimycin supplied by the National Cancer Institute as a sterile single-use amber vial containing 50 mg of tanespimycin in 2 mL of dimethylsulfoxide was diluted in an egg phospholipid diluent as previously described and dispensed in a glass bottle [10]. Bortezomib was also supplied by the National Cancer Institute as a sterile single use 10 mL vial, which contained 3.5 mg bortezomib as a lyophilized powder with 35 mg mannitol, USP. The intact vials were stored at room temperature and protected from light, reconstituted with 3.5 mL normal saline, USP, and given without further dilution as an intravenous bolus (over 3–5 seconds). The reconstituted product was discarded within 8 hours after initial entry.

The study was an open-label, multiple dose, phase I clinical trial. Patients first received tanespimycin IV over 1–2 hours followed by an IV push of bortezomib immediately after tanespimycin on days 1, 4, 8, and 11 every 21 days. Only two patients were enrolled at dose level 1 before the dose escalation scheme was modified based on new information that emerged from the NCI regarding the safety and tolerability of this drug combination at higher doses and accrual continued (Table 1). The dose escalation schedule followed the standard cohort “3 + 3” design, with observation for a minimum of 3 weeks before new patients were treated. If a DLT was not seen in any of the 3 patients, 3 new patients were accrued and treated at the next higher dose level. When DLTs were seen in ≥ 2 patients at a given dose level, the next 3 patients were treated at the next lower dose level. In any individual patient, doses could be escalated by 1 dose level 1 time only but only after 3 new patients had completed the next dose level with no DLTs. After enrolling 6 patients at a specific dose level, if a DLT was observed in at least 2 patients, then the MTD was exceeded and defined as the previous dose level. If only 3 patients were treated at the lower dose level, 3 additional patients were treated at MTD so that a total of 6 patients were treated at the MTD to assess the associated toxicities. Once the MTD was determined, an additional 4 solid tumor patients were treated at the MTD. Patients at dose level 3 received tanespimycin on days 1, 4, 8, and 11 immediately followed by an IV push of bortezomib on days 4, 8, and 11. For each subsequent cycle, first tanespimycin then an immediate IV push of tanespimycin was given on days 1, 4, 8, and 11 every 21 days.

DLT was defined as grade 4 neutropenia or grade 3 thrombocytopenia; serum creatinine 2 times baseline or ULN, whichever is higher; QTc prolongation of grade 3 or greater; or day 8 dose omitted during cycle 1. Any other non-hematologic toxicity grade 3 as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was also considered a DLT. Grade 3 nausea, vomiting, or diarrhea with maximal supportive treatments was considered dose limiting. Alopecia was not considered dose-limiting.

Patient evaluation

Each patient underwent a complete history and physical exam, CBC, and chemistry panel including electrolytes, total bilirubin, albumin, total protein, creatinine, AST, and alkaline phosphatase. An EKG, echocardiogram, and pulse oximetry were performed at baseline. Chest x-ray was obtained at baseline and as clinically indicated if chest CT scan was not previously obtained. For patients with measureable disease, a CT scan was obtained at baseline and after every 2 cycles of therapy to assess tumor response. Complete response, partial response, stable disease, and progressive disease were defined according to RECIST criteria.

Statistical Methods

Per NCI CTACE version 3.0 guidelines, adverse event attributions were defined as possibly, probably, or definitely related to study treatment. The number and severity of adverse events were tabulated and summarized within each cohort. Responses were summarized by simple descriptive statistics delineating complete and partial responses as well as stable and progressive disease within each cohort.

Results

Between February 11, 2005 and October 28, 2009, seventeen patients were enrolled into the study and followed for a maximum of 3 months after being off treatment. Patient characteristics are presented in Table 2. The median age of all patients was 61 years with a range of 47 to 85. Sixteen patients were Caucasian, and one patient was American Indian or Alaska Native. Prior to enrollment in the study, all participating patients had previously undergone surgery and chemotherapy. Five patients had received radiation therapy. A variety of solid tumor types were treated in this study including colorectal (n=6), pancreatic (n=2), and soft tissue sarcoma (n=2), neuroendocrine, lung, ovarian, uterine, chondrosarcoma, renal cell, and gastrointestinal (1 each).

The dose escalation scheme is summarized in Table 1. Initial accrual was at 100 mg/m² tanespimycin and 0.7 mg/m² bortezomib. The second dose level was increased significantly because of new information regarding the drug combination from the National Cancer Institute indicating that this drug combination was tolerated at higher doses. Patients received a median of 1 cycle with a range from 1 to 6 cycles received. Nine patients (60%) discontinued treatment because of disease progression while on study, three (20%) due to adverse effects, one (6.7%) due to a complicating disease, one (6.7%) declined further treatment, and one (6.7%) for other reasons.

Adverse Events

Fifteen of the seventeen patients were evaluable for DLT analysis. Table 3 lists the number of DLTs for each cohort. At dose level 1, one patient experienced grade 3 abdominal pain, fatigue, and encephalopathy. No DLTs were observed in the first 6 patients treated at dose level 2. However, one patient of the four additional solid tumor patients entered at that dose level experienced complete atrioventricular block. In contrast, 2 DLTs were observed at dose level 3. One patient experienced grade 4 hyponatremia, abdominal pain, hypoxia, and

colitis in addition to grade 5 acidosis. The other patient experienced grade 3 anorexia. Accordingly, we concluded that the MTD was dose level 2, which corresponds to 250 mg/m² tanespimycin and 1.0 mg/m² bortezomib.

Toxicities at least possibly related to treatment that were grade 2 or higher, in addition to grade 1 toxicities that occurred in >10% of the 15 evaluable patients are listed in Table 3. Grade 3 toxicities observed were encephalopathy, abdominal pain, complete atrioventricular block, hypertension, fatigue, and anorexia. Grade 1 toxicities at least possibly related to treatment occurring in <10% of patients include: decreased platelet count, increased ALT, increased AST, hypoalbuminemia, tremor, blurred vision, eye pain, headache, oral pain, cough, dyspnea, weight gain, weight loss, bruising, nail changes, and acneiform rash.

Antitumor activity

One patient at dose level 2 had stable disease as the best response for 4 cycles. Eight patients progressed in their first or second cycle of treatment. Six patients went off study before tumor responses were assessed. No complete or partial responses were seen.

Discussion

Based on available pre-clinical and phase I data, twice weekly dosing of tanespimycin and bortezomib in combination is a tolerable regimen. Data from an earlier study suggest the inhibition of HSP90 by tanespimycin is effective for 1 to 5 days based on client protein down regulation in tumor samples [11]. Proteasome inhibition by bortezomib was shown to reduce proteasome activity 1 hour post infusion and began returning to base line activity after 24 hours with a complete return to baseline at 72 hours in patients with advanced solid malignancies [29]. Twice weekly treatment of bortezomib resulted in the same level of proteasome inhibition 1 hour post administration, suggesting no change in proteasome sensitivity [29]. Pre-clinical data supports concomitant administration of tanespimycin and bortezomib for improved antitumor activity [26]. Therefore, our phase I study evaluated a twice weekly dosing schedule of tanespimycin and bortezomib in patients with advanced solid malignancies.

When used in combination, the MTD of tanespimycin and bortezomib was 250 and 1.0 mg/m² respectively. This is similar to the MTD for tanespimycin of 200 and 220 mg/m² determined by other single agent phase I trials in patients with advanced solid tumors using twice weekly dosing schedules [13, 14]. A phase I study evaluating twice weekly tanespimycin and weekly paclitaxel demonstrated an MTD for tanespimycin to be 200 mg/m² [30]. Studies of bortezomib as a single agent in patients with advanced solid tumors on a twice weekly dosing schedule have found MTDs of 1.56 and 1.7 mg/m² [29, 31]. In our study, escalation of bortezomib from 1.0 to 1.3 mg/m² in combination with tanespimycin at 250 mg/m² resulted in 2 DLTs. One patient from this cohort experienced grade 3 anorexia and the other patient experienced all the reported grade 4 toxicities including colitis and grade 5 acidosis. A recent phase II trial with a similar dosing scheme treated 22 myeloma patients with 1.3 mg/m² of bortezomib and 50, 175, or 340 mg/m² of tanespimycin [32]. There was no report of acidosis, but grade 3 fatigue and abdominal pain were also observed [32]. These differences in MTD and toxicities seen may be due to the sequence of drug administration or features of the patient populations such as previous therapies. All 22 patients in the phase II trial were previously treated with bortezomib while all patients in our study were bortezomib naïve [32].

In this trial, the most common toxicities were fatigue, nausea, diarrhea, and peripheral sensory neuropathy. Serious liver toxicity that has previously been dose limiting in other trials using tanespimycin was not observed in our study. A tanespimycin dose of 100 mg/m²

was associated with a mild increase in AST and a moderate increase in alkaline phosphatase. At 250 mg/m² of tanespimycin, mild increases in ALT and alkaline phosphatase were reported. Peripheral neuropathy is the most commonly reported DLT after treatment with bortezomib. In our study, only grade 1 sensory and motor neuropathy was found at both dose level 1.0 mg/m² and 1.3 mg/m².

The best tumor response was stable disease for 4 cycles of treatment in a patient enrolled in dose level 2. No partial or complete responses were seen. In other phase I trials using combination therapy with tanespimycin and a second agent, stabilization of disease and partial responses were reported in patients with advanced solid malignancies. Disease stabilization in patients with advanced solid tumors was observed after treatment with tanespimycin and either paclitaxel or irinotecan [30, 33]. Six solid tumor patients experienced partial responses from tanespimycin in combination with gemcitabine, and one patient with advanced breast cancer achieved a partial response after treatment with tanespimycin and trastuzumab [34, 35]. In the myeloma phase II study, 2 patients experienced a partial response, 1 patient had a mixed response, and 10 patients across all cohorts had stable disease [32]. These results suggest that improved tumor responses could be seen if tanespimycin is studied in a specific disease in addition to a more established agent for that patient population.

The lack of response in patients with solid tumors suggests that the underlying hypothesis that inhibiting HSP90 combined with proteasomal inhibition has limited activity in patients solid tumors. This may be in part because bortezomib has demonstrated little activity in solid tumors, however, another possibility is that tanespimycin does not consistently and significantly cause client protein degradation with the doses and schedules used here [36]. The use of other HSP90 inhibitors may overcome this limitation. In conclusion, this phase I clinical trial established a twice weekly administration of tanespimycin and bortezomib that can be safely given at doses of 250 mg/m² and 1.0 mg/m² respectively.

Acknowledgments

Supported by CA69912

References

1. Taipale M, Jarosz DF, Lindquist S. HSP90 at the hub of protein homeostasis: emerging mechanistic insights. *Nat Rev Mol Cell Biol.* 2010; 11(7):515–528. [PubMed: 20531426]
2. Trepel J, et al. Targeting the dynamic HSP90 complex in cancer. *Nat Rev Cancer.* 2010; 10(8):537–549. [PubMed: 20651736]
3. Whitesell L, Lindquist SL. HSP90 and the chaperoning of cancer. *Nat Rev Cancer.* 2005; 5(10): 761–772. [PubMed: 16175177]
4. Whitesell L, et al. Inhibition of heat shock protein HSP90-pp60v-src heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation. *Proc Natl Acad Sci U S A.* 1994; 91(18):8324–8328. [PubMed: 8078881]
5. Grenert JP, et al. The amino-terminal domain of heat shock protein 90 (hsp90) that binds geldanamycin is an ATP/ADP switch domain that regulates hsp90 conformation. *J Biol Chem.* 1997; 272(38):23843–23850. [PubMed: 9295332]
6. Sasaki K, Yasuda H, Onodera K. Growth inhibition of virus transformed cells in vitro and antitumor activity in vivo of geldanamycin and its derivatives. *J Antibiot (Tokyo).* 1979; 32(8):849–851. [PubMed: 500504]
7. Supko JG, et al. Preclinical pharmacologic evaluation of geldanamycin as an antitumor agent. *Cancer Chemother Pharmacol.* 1995; 36(4):305–315. [PubMed: 7628050]

8. Schnur RC, et al. Inhibition of the oncogene product p185erbB-2 in vitro and in vivo by geldanamycin and dihydrogeldanamycin derivatives. *J Med Chem.* 1995; 38(19):3806–3812. [PubMed: 7562911]
9. Schulte TW, Neckers LM. The benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamycin binds to HSP90 and shares important biologic activities with geldanamycin. *Cancer Chemother Pharmacol.* 1998; 42(4):273–279. [PubMed: 9744771]
10. Goetz MP, et al. Phase I trial of 17-allylamino-17-demethoxygeldanamycin in patients with advanced cancer. *J Clin Oncol.* 2005; 23(6):1078–1087. [PubMed: 15718306]
11. Banerji U, et al. Phase I pharmacokinetic and pharmacodynamic study of 17-allylamino, 17-demethoxygeldanamycin in patients with advanced malignancies. *J Clin Oncol.* 2005; 23(18):4152–4161. [PubMed: 15961763]
12. Ramanathan RK, et al. Phase I pharmacokinetic-pharmacodynamic study of 17-(allylamino)-17-demethoxygeldanamycin (17AAG, NSC 330507), a novel inhibitor of heat shock protein 90, in patients with refractory advanced cancers. *Clin Cancer Res.* 2005; 11(9):3385–3391. [PubMed: 15867239]
13. Nowakowski GS, et al. A phase I trial of twice-weekly 17-allylamino-demethoxy-geldanamycin in patients with advanced cancer. *Clin Cancer Res.* 2006; 12(20 Pt 1):6087–6093. [PubMed: 17062684]
14. Ramanathan RK, et al. Phase I and pharmacodynamic study of 17-(allylamino)-17-demethoxygeldanamycin in adult patients with refractory advanced cancers. *Clin Cancer Res.* 2007; 13(6):1769–1774. [PubMed: 17363531]
15. Solit DB, et al. Phase I trial of 17-allylamino-17-demethoxygeldanamycin in patients with advanced cancer. *Clin Cancer Res.* 2007; 13(6):1775–1782. [PubMed: 17363532]
16. Grem JL, et al. Phase I and pharmacologic study of 17-(allylamino)-17-demethoxygeldanamycin in adult patients with solid tumors. *J Clin Oncol.* 2005; 23(9):1885–1893. [PubMed: 15774780]
17. Heath EI, et al. A phase II trial of 17-allylamino-17-demethoxygeldanamycin in patients with hormone-refractory metastatic prostate cancer. *Clin Cancer Res.* 2008; 14(23):7940–7946. [PubMed: 19047126]
18. Solit DB, et al. Phase II trial of 17-allylamino-17-demethoxygeldanamycin in patients with metastatic melanoma. *Clin Cancer Res.* 2008; 14(24):8302–8307. [PubMed: 19088048]
19. Ronnen EA, et al. A phase II trial of 17-(Allylamino)-17-demethoxygeldanamycin in patients with papillary and clear cell renal cell carcinoma. *Invest New Drugs.* 2006; 24(6):543–546. [PubMed: 16832603]
20. Pacey S, et al. A Phase II trial of 17-allylamino, 17-demethoxygeldanamycin (17-AAG, tanespimycin) in patients with metastatic melanoma. *Invest New Drugs.*
21. Nguyen, DfM, et al. Sequence-dependent enhancement of paclitaxel toxicity in non-small cell lung cancer by 17-allylamino 17-demethoxygeldanamycin. *J Thorac Cardiovasc Surg.* 1999; 118(5):908–915. [PubMed: 10534697]
22. Nguyen DM, et al. Enhancement of paclitaxel-mediated cytotoxicity in lung cancer cells by 17-allylamino geldanamycin: in vitro and in vivo analysis. *Ann Thorac Surg.* 2001; 72(2):371–378. discussion 378-9. [PubMed: 11515869]
23. Munster PN, et al. Modulation of Hsp90 function by ansamycins sensitizes breast cancer cells to chemotherapy-induced apoptosis in an RB- and schedule-dependent manner. See: E. A. Sausville, Combining cytotoxics and 17-allylamino, 17-demethoxygeldanamycin: sequence and tumor biology matters, *Clin. Cancer Res.*, 7: 2155–2158, 2001. *Clin Cancer Res.* 2001; 7(8):2228–2236. [PubMed: 11489796]
24. Mimnaugh EG, Chavany C, Neckers L. Polyubiquitination and proteasomal degradation of the p185c-erbB-2 receptor protein-tyrosine kinase induced by geldanamycin. *J Biol Chem.* 1996; 271(37):22796–22801. [PubMed: 8798456]
25. Neckers L, Schulte TW, Mimnaugh E. Geldanamycin as a potential anti-cancer agent: its molecular target and biochemical activity. *Invest New Drugs.* 1999; 17(4):361–373. [PubMed: 10759403]

26. Mimnaugh EG, et al. Simultaneous inhibition of hsp 90 and the proteasome promotes protein ubiquitination, causes endoplasmic reticulum-derived cytosolic vacuolization, and enhances antitumor activity. *Mol Cancer Ther.* 2004; 3(5):551–566. [PubMed: 15141013]
27. Mimnaugh EG, et al. Endoplasmic reticulum vacuolization and valosin-containing protein relocalization result from simultaneous hsp90 inhibition by geldanamycin and proteasome inhibition by velcade. *Mol Cancer Res.* 2006; 4(9):667–681. [PubMed: 16966435]
28. Mitsiades CS, et al. Antimyeloma activity of heat shock protein-90 inhibition. *Blood.* 2006; 107(3):1092–1100. [PubMed: 16234364]
29. Aghajanian C, et al. A phase I trial of the novel proteasome inhibitor PS341 in advanced solid tumor malignancies. *Clin Cancer Res.* 2002; 8(8):2505–2511. [PubMed: 12171876]
30. Ramalingam SS, et al. A phase I study of 17-allylamino-17-demethoxygeldanamycin combined with paclitaxel in patients with advanced solid malignancies. *Clin Cancer Res.* 2008; 14(11):3456–3461. [PubMed: 18519777]
31. Hamilton AL, et al. Proteasome inhibition with bortezomib (PS-341): a phase I study with pharmacodynamic end points using a day 1 and day 4 schedule in a 14-day cycle. *J Clin Oncol.* 2005; 23(25):6107–6116. [PubMed: 16135477]
32. Richardson PG, et al. Tanespimycin with bortezomib: activity in relapsed/refractory patients with multiple myeloma. *Br J Haematol.* 2010; 150(4):428–437. [PubMed: 20618338]
33. Tse AN, et al. A phase I dose-escalation study of irinotecan in combination with 17-allylamino-17-demethoxygeldanamycin in patients with solid tumors. *Clin Cancer Res.* 2008; 14(20):6704–6711. [PubMed: 18927314]
34. Modi S, et al. Combination of trastuzumab and tanespimycin (17-AAG, KOS-953) is safe and active in trastuzumab-refractory HER-2 overexpressing breast cancer: a phase I dose-escalation study. *J Clin Oncol.* 2007; 25(34):5410–5417. [PubMed: 18048823]
35. Hubbard J, et al. Phase I study of 17-allylamino-17 demethoxygeldanamycin, gemcitabine and/or cisplatin in patients with refractory solid tumors. *Invest New Drugs.* 2010
36. Kaufmann SH, Karp JE, Litzow MR, Mesa RA, Hogan W, Steensma DP, Flatten KS, Loegering DA, Schneider PA, Maurer MJ, Smith BD, Chen Y, Reid JM, Ivy SP, Ames MM, Adjei AA, Erlichman C, Karnitz LM. Phase I and pharmacological study of cytarabine and tanespimycin in relapsed and refractory acute leukemia. *Haematologica.* 2011 in press.

Dose escalation scheme.

Table 1

Cohort	Dose Level	Dose (mg/m ²)		Number of Patients	DLTs
		Tanespimycin	Bortezomib		
I	1	100	0.7	2	1
	2	250	1.0	10	1
	3	250	1.3	3	2

Only 2 patients were enrolled and evaluated for DTL at dose level 1 before the dosing scheme was changed based on new information from the NCI regarding the safety and efficacy of the drugs in combination. One patient from dose level 2 was replaced for DLT evaluation.

Table 2

Patient characteristics

	Total (n=17)	Cohort I (n=3)	Cohort IA (n=10)	Cohort II (n=4)
Age				
Median	61	61 (57-76)	66 (50-85)	52 (47-57)
Range	(47-85)			
Gender				
Female	9	2	6	1
Male	8	1	4	3
Performance Score				
0	7	0	6	1
1	9	2	4	3
2	1	1	0	0
Prior Treatments				
Chemotherapy	16	3	9	4
Radiation	5	1	4	0
Surgery	16	3	9	4
Primary Tumor Site				
Colorectal	6	1	2	3
Soft tissue sarcoma	2	0	2	0
Pancreas	2	1	1	0
Other	7	1	5	1

Table 3

Toxicities for all cycles at least possibly related to treatment.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	1	1	0	0	0
Hemolysis	0	1	0	0	0
Thrombocytopenia	1	0	0	0	0
ALT increased	1	0	0	0	0
AST increased	1	0	0	0	0
Alkaline phosphatase increased	1	1	0	0	0
Nasopharyngitis	0	1	0	0	0
Acidosis	0	0	0	0	1
Hypophosphatemia	0	1	0	0	0
Hyponatremia	0	0	0	1	0
Confusion	0	1	0	0	0
Dizziness	2	0	0	0	0
Encephalopathy	0	0	1	0	0
Peripheral motor neuropathy	2	0	0	0	0
Peripheral sensory neuropathy	4	0	0	0	0
Abdominal pain	0	0	1	1	0
Angina pectoris	0	1	0	0	0
Hypoxia	0	0	0	1	0
Atrioventricular block complete	0	0	1	0	0
Hypertension	0	0	1	0	0
Sinus bradycardia	0	1	0	0	0
Fatigue	2	1	1	0	0
Rash	0	1	0	0	0
Cushingoid	0	1	0	0	0
Anorexia	0	1	1	0	0
Colitis	0	0	0	1	0
Constipation	2	0	0	0	0

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dehydration	0	1	0	0	0
Diarrhea	2	2	0	0	0
Nausea	2	2	0	0	0
Vomiting	1	1	0	0	0