First-in-Human Phase I Dose Escalation Study of a Second-Generation Non-Ansamycin HSP90 Inhibitor, AT13387, in Patients with Advanced Solid Tumors

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Abstract

Purpose: AT13387 is a potent second-generation, fragment-derived HSP90 inhibitor. This phase I study investigated the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) and safety, pharmacokinetic, and pharmacodynamic profiles of two AT13387 regimens in a refractory solid tumor population.

Experimental Design: Standard 3+3 dose escalation was used. MTD and RP2D determinations were based on the occurrence of dose-limiting toxicities (DLT) and overall toxicity, respectively. Pharmacokinetic parameters were measured after single and multiple doses. AT13387-mediated induction of HSP70 was evaluated in plasma, peripheral blood mononuclear cells, and paired tumor biopsies.

Results: Sixty-two patients were treated with doses ranging from 10 to 120 mg/m² twice weekly and 150 to 310 mg/m² once weekly (both for 3 weeks every 28 days). One DLT of visual disturbance occurred at 120 mg/m², which was considered the MTD and RP2D for the twice-weekly regimen. No formal DLTs occurred in the once-weekly regimen, but multiple moderately severe toxicities, including diarrhea, nausea, vomiting, fatigue, and systemic infusion reactions, led to selection of 260 mg/m² as the RP2D. Exposures of AT13387 increased proportionally with dose. Target engagement as measured by HSP70 induction occurred in plasma and tumor biopsy samples. One patient with gastrointestinal stromal tumor (GIST) who had progressive disease on imatinib had a partial response and remained on treatment for 10 months. Twenty-one patients (34%) had stable disease, which lasted >120 days in 7 patients.

Conclusion: AT13387 administered once or twice weekly has an acceptable safety profile and demonstrated evidence of target engagement and preliminary antitumor activity. Clin Cancer Res; 21(1); 87–97. ©2014 AACR.

Introduction

HSP90 is an abundant and ubiquitously expressed molecular chaperone that is crucial for the stability and function of many oncogenic drivers, including receptor tyrosine kinases and hormone receptors, such as KIT protein tyrosine kinase (c-KIT), EGFR, HER2, and anaplastic lymphoma kinase (ALK), androgen receptors, as well as proteins in key signaling pathways, including AKT/protein kinase B (PKB; refs. 1–3). HSP90-dependent clients are therefore involved in multiple neoplastic processes, including growth factor independence, invasion, and metastasis, sustained angiogenesis, cell survival, and resistance to antigrowth signals. In the absence of HSP90, these clients are ubiquitinated and targeted for degradation via the proteasome (4), so that inhibition of HSP90 is an attractive anticancer therapeutic strategy (5). First-generation geldanamycin-based HSP90 inhibitors such as 17-AAG and IPI-504 have shown evidence of clinical activity, but have been limited by formulation and toxicity issues (6). Hence, there is a need for improved HSP90 inhibitors, which has led to the development of second-generation compounds that are currently in clinical development (7–10).

Using a combination of NMR and high-throughput X-ray crystallography, we discovered a number of low-affinity fragment hits against the N-terminal ATPase domain of the HSP90 protein. Structure-aided drug design allowed for the rapid optimization of a key fragment hit into a lead compound with inhibitory activity in the low nanomolar range. Subsequent improvement of the physicochemical properties of the hit series allowed for the identification of a clinical candidate, AT13387, which was formulated for intravenous dosing as a potential cancer therapeutic (11).
As a novel HSP90 inhibitor, AT13387 has the potential for broad utility in the treatment of advanced solid and hematologic malignancies that are resistant or refractory to standard therapies. Prolonged drug accumulation in tumors despite rapid systemic clearance is well recognized for several HSP90 inhibitors (12, 13). AT13387 has a half-life of up to 65 hours in tumor xenografts leading to prolonged knockdown of HSP90 client proteins in these tumors, suggesting the potential for an extended pharmacodynamic effect following a single dose of the compound (11). In vivo studies have shown potent antitumor activity at doses that are well tolerated in several different human tumor xenograft models in mice, including those derived from non–small cell lung cancers (NSCLC), melanomas, and gastrointestinal stromal tumors (GIST; refs. 14, 15). In NSCLC, NCI-H1975 xenografts harboring EGFR L858R/T790M, suppression of mutant EGFR expression occurred up to 72 hours after a single dose, with tumor growth inhibition achieved with twice-weekly dosing (14). Higher doses of AT13387, administered once weekly, also produced significant tumor growth inhibition (14). In addition, once-weekly dosing of AT13387 was effective against imatinib-sensitive and resistant GIST xenografts (15).

Toxicology studies of 1-cycle duration (28 days), with 1-hour intravenous infusion twice weekly for 3 weeks, showed a clear dose–effect relationship in dogs; histopathology revealed changes in the bone marrow, thymus, and testes, with doses tolerated up to 3 mg/kg (60 mg/m² human equivalent). Overall effects were transient and reversible, except for testicular lesions, which did not reverse in 14 days of recovery. In the 1-cycle study in rats using the same regimen, doses up to 50 mg/kg (300 mg/m²) were tolerated with minimal changes in hematology parameters and infusion-site findings of inflammation. AT13387 is metabolized mainly by conjugation. In vitro studies in human hepatocytes showed formation of glucuronide- and sulphate conjugates as the main metabolites formed.

On the basis of preclinical efficacy and pharmacodynamic client suppression in xenografts, as well as dosing regimens of first-generation HSP90 inhibitors, this phase 1, open-label, dose-escalation study was designed to determine the maximum tolerated doses (MTD) and recommended phase II dose (RP2D) of AT13387 given as a 1-hour intravenous infusion every twice weekly or once weekly for 3 of every 4 weeks in patients with metastatic solid tumors that were refractory to standard therapy (16, 17). Secondary objectives included characterization of safety and tolerability, as well as assessment of the pharmacokinetic and pharmacodynamic profiles of the drug.

Patients and Methods
Patient selection
Patients included in the study were ≥18 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and histologic or cytologic evidence of a metastatic solid tumor, including lymphoma that was refractory to standard therapy. Patients had to have adequate bone marrow function (hemoglobin > 9 g/dL, neutrophils > 1.4 x 10⁹/L and platelets ≥ 100 x 10⁹/L), hepatic function [serum bilirubin < 2.5 times the upper limit of reference range (ULLR); alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase < 2.5 times ULLR, unless due to the presence of liver metastases, when ALT and AST could have been up to 5 times the ULLR or bone metastases, when an isolated alkaline phosphatase < 5 times ULLR was acceptable], renal function [serum creatinine ≤ 1.5 times ULLR, without evidence of more than 1+ proteinuria on 2 occasions], and cardiac function (left ventricular ejection fraction > 50% on echocardiogram or multigated acquisition (MUGA) scan and QTc ≤ 460 msec according to Fridericia correction). Main exclusion criteria were pregnant or lactating females, ongoing central nervous system metastases, treatment with any anticancer therapies, or with known cytochrome P450 inducers, within 4 weeks of the start of AT13387, history of ischemic cardiac event, myocardial infarction or unstable cardiac disease within 3 months of study entry, prior history of infection with HIV or known active HBV or HCV infection, and any evidence of severe or uncontrolled systemic conditions.

Study design and treatment administration
This was an open-label, dose-escalation (3+3 design) cohort expansion study of single-agent AT13387. The primary objective of the study was to identify the MTD and RP2D for twice-weekly and once-weekly administration regimens. The protocol defined the MTD to be the dose one level below which a DLT occurred in more than one patient (during the study, however, the MTD was determined more conservatively, as described in the Results). Secondary objectives were to characterize the safety and tolerability of AT13387 and to identify DLTs; to define the pharmacokinetics of AT13387 in plasma and urine, and to demonstrate the pharmacodynamic activity of AT13387 in plasma, in peripheral blood mononuclear cells (PBMC), and in paired tumor biopsies obtained in consenting patients treated at one of the RP2Ds. The initial study design assessed a twice-weekly regimen (dosing days 1, 4, 8, 11, 15, and 18 of a 28-day cycle) and was subsequently amended to evaluate a once-weekly regimen (dosing days 1, 8, and 15 of a 28-day cycle). Doses for the twice-weekly regimen were 10, 20, 40, 80, and 120 mg/m²; cohorts of 3 to 6 patients each were enrolled, with escalation determined by a modified Fibonacci sequence until the MTD was achieved. A Safety Monitoring Committee determined the dose escalations according to the toxicity observed in the previous cohorts. On the
basis of the safety and tolerability data of the 120 mg/m² twice-weekly cohort, a starting dose of 150 mg/m² was chosen for the once-weekly regimen with a maximal escalation of 25% until the MTD was reached. The doses administered on this regimen were 150, 180, 220, 260, and 310 mg/m². On both regimens, up to 12 additional patients could be enrolled at the MTD/RP2D in an expansion phase of the study to further evaluate safety, tolerability, and pharmacodynamics.

AT13387 was administered as a 1-hour intravenous infusion, based on body surface area in both regimens, via peripheral or central venous access using an appropriate calibrated infusion pump.

The study (ClinicalTrials.gov ID: NCT00878423) was conducted according to good clinical practice guidelines and the Declaration of Helsinki. The Institutional Review Boards of the 4 participating U.S. centers approved the study, and patients gave written informed consent before enrollment.

**DLT definitions and safety assessments**

Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0. A DLT was defined as neutropenia (neutrophil count <0.5 x 10⁹/L) for >5 days; neutropenia (neutrophil counts <1 x 10⁹/L) with fever; thrombocytopenia (platelet count <25 x 10⁹/L) accompanied by bleeding, or thrombocytopenia (platelet counts <10 x 10⁹/L); any grade 3 or 4 nonhematologic toxicity that was not a consequence of tumor progression (other than nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis); and more than 1 individual toxicity that was not a consequence of tumor progression, other than nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis; and more than 1 individual toxicity that was not a consequence of tumor progression, other than nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis; and more than 1 individual toxicity that was not a consequence of tumor progression, other than nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis; and more than 1 individual toxicity that was not a consequence of tumor progression, other than nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis.

Each patient underwent a full medical history and physical examination at study screening. Safety parameters were assessed at baseline and at regular intervals during the study. Safety assessments included the reporting of all adverse events (AE), changes in clinical laboratory parameters (hematology, serum chemistries, coagulation, urinalysis), vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings. In addition, serial measurements of left ventricular ejection fraction were performed, as cardiotoxicity was observed in first generation HSP90 inhibitors (18). Ophthalmologic evaluation, including external examination, fundoscopy, visual acuity, intraocular pressure, assessment of visual fields, and measurement of color vision, was tested at baseline and at alternate cycles starting on day 1 of cycle 3. Ophthalmologic assessments were introduced after the study was initiated, so that not all patients underwent the procedures.

**Response assessments**

Tumor response was assessed by CT or MRI at screening and every 2 months during the first 6 months, every 3 months for the next 6 months, and every 6 months thereafter if patients continued to receive treatment with AT13387. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (19).

**Pharmacokinetics**

Blood samples for pharmacokinetic analyses were collected on cycle 1, day 1 and cycle 1, day 18 in the twice-weekly regimen or cycle 1, day 1 and cycle 2, day 15 in the once-weekly regimen. Collection times in both regimens were immediately before infusion start and at 0.5, 1 (before infusion end), 1.5, 1.75, 2, 2.5, 3, 4, 7, 12, and 24 hours. Urine samples for pharmacokinetic analyses were collected at the first void on day 1 predose and at 0 to 7 hours, 7 to 24 hours and 24 to 48 hours during and after the start of the first cycle of treatment. AT13387 concentrations were measured using AT13387-specific liquid chromatography with mass spectrometric detection. The lower limit of quantitation for AT13387 in plasma was 1.0 ng/mL and in urine was 1.0 ng/mL. The linear range for the validated method was 1.00 to 1,000 ng/mL, with acceptance criteria for precision and accuracy of ±15.0%.

Pharmacokinetic parameters of AT13387 were estimated in plasma and urine using standard noncompartmental analyses using WinNonlin version 5.3 (Pharsight Corp.). Calculated pharmacokinetic parameters included area under the concentration-time curve from 0 to 24 hours (AUC₀₋₂₄), maximum observed concentration (Cₘₐₓ), elimination half-life (t₁/₂), total body clearance (Cl), and volume of distribution (Vz). Urine concentration values of AT13387 were used to calculate the following parameters: cumulative urinary excretion from time zero to time t (AUC₀₋ₚ)}, maximum rate of urinary excretion (Rₘₐₓ), time of Rₘₐₓ (Tₘₐₓ), and percent recovered. Rₘₐₓ was calculated by dividing the amount of drug excreted in each collection interval by the time over which it was collected.

**Pharmacodynamics**

Pharmacodynamic assessments of biologic activity of AT13387 in plasma, PBMCs, and tumor tissue were performed. Blood samples (15 mL) for pharmacodynamic analyses were collected before infusion and at 3, 7, and 24 hours after the start of infusion during cycle 1 and immediately before the first infusion on cycle 2, day 1. Both plasma and PBMCs were isolated.

Measurement of HSP70 levels in plasma was evaluated by ELISA and run as recommended by the manufacturer (ELISA; R&D Systems; Human/Mouse/Rat Total HSP70/HSPA1A Surveyor or IC; Cat# SUV1663; ref. 20). In addition, several HSP90 client proteins were measured in PBMC lysates by Western blot analysis. Optional pretreatment tumor biopsy samples were taken at screening or before the start of infusion on cycle 1, day 1. Posttreatment tumor biopsy samples were taken on cycle 1, day 19 for patients on the twice-weekly regimen and on cycle 1, day 16 for patients on the once-weekly regimen. HSP70 levels were measured by immunohistochemistry. If feasible, the HSP90 client proteins CDK4, RAF-1, AKT, and S6, as well as p AKT, pS6, and caspase-3 were also assessed. pS6 is a downstream target of mTOR phosphorylation, which controls for mTOR inhibition; mTOR is a downstream target of PI3K/AKT.

**Results**

**Patient disposition and characteristics**

Sixty-three patients were enrolled (62 patients received AT13387; 1 patient withdrew after enrollment but before treatment) in the study between May 2008 and August 2013. Table 1 shows patient characteristics. Most patients (58; 94%) received prior chemotherapy and 45 patients (73%) received 3 or more prior chemotherapy regimens. The median number of prior regimens was 4 (range 0–14). Thirty-four patients (55%) received prior radiotherapy.

The median number of cycles administered was 2, with a range of 1 to 12 cycles. Eight patients (13%) completed at least 6 cycles of study treatment. The remaining 55 patients (87%)
discontinued earlier: 41 patients (65%) due to disease progression, 3 (5%) due to death, and 2 (3%) for other reasons (stated as clinical progression and investigator decision). All patients who received study treatment were evaluable for safety. Forty-four patients (71%) were evaluable for best response to therapy (RECIST based on the investigator assessment [16 patients (26%) of patients treated per dose level was 4 at 10 mg/m², 3 at 20 mg/m², 3 at 40 mg/m², 5 at 80 mg/m², 13 at 120 mg/m² (all twice-weekly regimen), 4 at 150 mg/m², 3 at 180 mg/m², 9 at 220 mg/m², 13 at 260 mg/m², and 5 at 310 mg/m² (all once-weekly regimen). The dose escalation is summarized in Supplementary Table S1.

For the twice-weekly regimen, doses were escalated from 10 to 120 mg/m². One patient of the first 3 enrolled in the 120 mg/m² treatment group had a protocol-defined DLT involving grade 3 visual disturbances with associated electroretinogram changes that were later reversible. This cohort was expanded to a total of 6 patients, and no further DLTs occurred in the dose-escalation phase of the 120 mg/m² treatment group. However, grade 1 and 2 infusion reactions in 2 of 6 patients (including dizziness, hyperhidrosis, facial flushing, tachycardia, hypotension, bradycardia, and abdominal pain, both during and after infusion) and grade 1 prolonged fatigue in 2 of 6 patients (starting 16 and 43 days, respectively, after treatment with AT13387) prompted a decision not to escalate further. Thus, the 120 mg/m² dose level was considered to be both the MTD and the RP2D for the twice-weekly regimen. The tolerability of this dose level was confirmed with the treatment of an additional 7 patients.

For the once-weekly regimen, dosing started at 150 mg/m² and was escalated to 310 mg/m². While no protocol-defined DLTs were observed, 260 mg/m² was considered the RP2D based on the occurrence of several moderately severe toxicities, including grade 2 diarrhea, nausea, vomiting, fatigue, and systemic infusion reactions in patients enrolled in the 310 mg/m² treatment group. Additional patients were enrolled in the 260 mg/m² treatment group for a total of 13.

Safety

Tables 2 and 3 show the most common AEs considered related to AT13387 occurring in ≥10% of patients. Across the study, the majority of patients (73%) experienced diarrhea, 45% experienced visual disturbances, 29% experienced injection site events, and 27% experienced systemic infusion reactions. In addition to diarrhea, other gastrointestinal toxicities included nausea, dry
Table 2. Summary of study treatment-related adverse events occurring in ≥10% of patients (twice-weekly schedule)

<table>
<thead>
<tr>
<th>AEa preferred term</th>
<th>Group term</th>
<th>Overall total</th>
<th>AT13387 twice-weekly</th>
<th>10 mg/m² twice-weekly</th>
<th>20 mg/m² twice-weekly</th>
<th>40 mg/m² twice-weekly</th>
<th>80 mg/m² twice-weekly</th>
<th>120 mg/m² twice-weekly</th>
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<tr>
<td></td>
<td></td>
<td>(N = 62)</td>
<td>Gr 1-2</td>
<td>Gr 3-4</td>
<td>Gr 1-2</td>
<td>Gr 3-4</td>
<td>Gr 1-2</td>
<td>Gr 3-4</td>
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<td>Diarrhea</td>
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<tr>
<td>Vision disturbancesb</td>
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<td>28 (45)</td>
<td>10 (36)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
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<td>11 (39)</td>
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<td>0 (0)</td>
<td>1 (33)</td>
<td>0 (0)</td>
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<tr>
<td>Nausea</td>
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<td>23 (37)</td>
<td>6 (21)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Injection site eventsb</td>
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<td>Systemic infusion reactionsb</td>
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<td>Dizziness</td>
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<td>7 (25)</td>
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<td>10 (16)</td>
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<td>0 (0)</td>
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<td>Muscle spasms</td>
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<td>3 (11)</td>
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<tr>
<td>Decreased appetite</td>
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<tr>
<td>Dysphonia</td>
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<td>Hemoglobin decreased</td>
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<tr>
<td>Pruritus</td>
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<td>0 (0)</td>
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</tr>
</tbody>
</table>

aAEs considered possibly, probably, or definitely related to the study treatment.

bFor both study treatment-related and unrelated AEs in this study, the group term visual disturbances included the AE preferred terms chloropsia, diplopia, halo vision, night blindness, photopsia, tunnel vision, vision blurred, visual impairment, and vitreous floaters. The group term injection site events included the adverse event preferred terms extravasation, infusion site inflammation, infusion site pain, injection site reaction, and injection site pain. The group term systemic infusion reactions included the adverse event preferred terms chills, flushing, hyperhidrosis, hypersensitivity, infusion-related reaction, pruritus, and pyrexia, but only if these events were definitely or possibly related to study treatment and occurred within 24 hours of a dose.

cPatients who received the maximum tolerated dose during the dose-escalation phase and the cohort expansion phase.
### Table 3. Summary of study treatment-related AEs occurring in ≥10% of patients (once-weekly schedule)

<table>
<thead>
<tr>
<th>AE(^a) preferred term/ group term(^b)</th>
<th>Overall total ((N = 62))</th>
<th>AT13387 once-weekly ((n = 34))</th>
<th>150 mg/m(^2) once-weekly ((n = 4))</th>
<th>180 mg/m(^2) once-weekly ((n = 3))</th>
<th>220 mg/m(^2) once-weekly ((n = 9))</th>
<th>260 mg/m(^2) once-weekly ((n = 13))</th>
<th>310 mg/m(^2) once-weekly ((n = 5))</th>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>45 (75)</td>
<td>27 (79)</td>
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<td>7 (78)</td>
<td>1 (8)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Visual disturbances(^b)</td>
<td>28 (45)</td>
<td>18 (53)</td>
<td>1 (25)</td>
<td>0 (0)</td>
<td>5 (96)</td>
<td>0 (0)</td>
<td>4 (80)</td>
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<td>Fatigue</td>
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<td>15 (44)</td>
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<td>0 (0)</td>
<td>5 (33)</td>
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<tr>
<td>Nausea</td>
<td>25 (37)</td>
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<td>1 (33)</td>
<td>0 (0)</td>
<td>8 (62)</td>
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<tr>
<td>Injection site events(^b)</td>
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<td>17 (50)</td>
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<td>1 (33)</td>
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<td>Systemic infusion reactions(^b)</td>
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<td>0 (0)</td>
<td>4 (44)</td>
<td>0 (0)</td>
<td>6 (46)</td>
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<td>2 (22)</td>
<td>8 (62)</td>
<td>3 (60)</td>
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<tr>
<td>Dry mouth</td>
<td>14 (23)</td>
<td>9 (26)</td>
<td>3 (75)</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td>1 (11)</td>
<td>2 (22)</td>
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<tr>
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<td>6 (18)</td>
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<td>3 (22)</td>
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<td>0 (0)</td>
<td>5 (96)</td>
<td>0 (0)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>10 (16)</td>
<td>10 (29)</td>
<td>1 (25)</td>
<td>0 (0)</td>
<td>3 (55)</td>
<td>4 (44)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (15)</td>
<td>6 (18)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td>0 (0)</td>
<td>3 (22)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (15)</td>
<td>8 (24)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (55)</td>
<td>0 (0)</td>
<td>3 (22)</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (13)</td>
<td>5 (15)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (55)</td>
<td>0 (0)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>8 (13)</td>
<td>8 (24)</td>
<td>1 (25)</td>
<td>0 (0)</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (11)</td>
<td>7 (21)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (11)</td>
<td>4 (31)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>6 (10)</td>
<td>6 (18)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (11)</td>
<td>4 (31)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>6 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6 (10)</td>
<td>5 (15)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (10)</td>
<td>5 (15)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (11)</td>
<td>2 (22)</td>
<td>3 (60)</td>
</tr>
</tbody>
</table>

\(^a\) AEs considered possibly, probably, or definitely related to the study treatment.

\(^b\) For both study treatment-related and unrelated AEs in this study, the group term visual disturbances included the AE preferred terms chlorosis, diplopia, halo vision, night blindness, photopsia, tunnel vision, vision blurred, visual impairment, and vitreous floaters. The group term injection site events included the adverse event preferred terms extravasation, infusion site inflammation, infusion site pain, injection site reaction, and injection site pain. The group term systemic infusion reactions included the adverse event preferred terms chills, flushing, hyperhidrosis, hypersensitivity, infusion-related reaction, pruritus, and pyrexia, but only if these events were definitely or possibly related to study treatment and occurred within 24 hours of a dose.

\(^c\) Patients who received the maximum tolerated dose during the dose-escalation phase and the cohort expansion phase.
mood, and abdominal pain. Most of the gastrointestinal-related AEs were of grade 1 or 2 severity, responsive to supportive medications and reversible. Minimal effects on liver function were observed, with only mild elevations of transaminases [maximal increase of ≤2 times upper limit of normal (ULN)], which were transient, without clinical symptoms and not dose limiting.

Forty-seven percent of patients had at least one episode of visual disturbance. These events occurred only in patients receiving doses of 80 mg/m² or above and included transient visual flashes and changes in light/dark accommodation. Patient descriptions also included “squiggles,” “moving objects,” and “blobs of light.” Except in the one case that resulted in a DLT, these events were all of grade 1 or 2 severity and did not affect patients’ daily lives. The duration varied from 1 day (last ing generally a few seconds to a few minutes) to ongoing at study discontinuation. Aside from one patient with grade 1 visual impairment still ongoing at the last follow up (3 months from the start of the event), these events were fully reversible. All of the treatment-related systemic infusion reactions or injection site events were mild to moderate (grade 1 or 2) and resolved within treatment-related systemic infusion reactions or injection site events were mild to moderate (grade 1 or 2) and resolved within 48 hours of infusion.

Central ECG recordings (n = 60) revealed no change in heart rate, atrioventricular conduction (PR interval), or depolarization (QRS duration). There were no clear signals of any change in repolarization (QTcF duration) up to the 120 mg/m² twice-weekly regimen. On the once-weekly regimen, doses of 220 to 310 mg/m² showed a slight trend of QTcF increase in the 10 ms to 15 ms range at the time of Cmax.

Eleven patients had 1 or more drug-related grade 3 or 4 AEs, including diarrhea and syncope (in 2 patients each), and dyspnea, urticaria, prolonged QTc on ECG, hypotension, hypertension, visual disturbance, and asthenia (in 1 patient each). Except for visual disturbance, none were DLTs (diarrhea was excluded if not maximally treated, and the other events were either not considered to be related to treatment by the safety monitoring committee or occurred in cycle 2 or later). Four of the 11 patients discontinued treatment due to drug-related grade 3 or 4 AEs, and the remaining 6 (excluding the DLT, described above) received medication. All drug-related grade 3 or 4 AEs resolved before study completion, except for hypotension and asthenia. Seven patients (11%) died within 30 days of last study treatment. Six of these were due to disease progression and one was from pneumonia/sepsis (not considered related to treatment).

Across the study, AT13387 dose was reduced due to AEs in 9 patients (in the 80, 120, 260, and 310 mg/m² dose levels). The dose reductions were all for grade 1 or 2 AEs, except for 1 patient with grade 3 hyponatremia, an event that occurred during cycle 2, and so was not considered dose limiting.

Pharmacokinetic analyses

The pharmacokinetics of AT13387 showed a dose-proportional increase in AUC0–24, and Cmax from 10 to 120 mg/m² (twice weekly) from 10 to 150 to 310 mg/m² (once weekly) with relatively low interindividual variability (Table 4, Fig. 1). The t1/2 was dose-independent and ranged from 6.6 to 11.5 hours. There was no notable accumulation or reduction in exposures between cycle 1, days 1 and day 18 in the twice-weekly regimen or cycle 1, day 1 and cycle 2, day 15 in the once-weekly regimen. Plasma clearance of AT13387 was relatively high, independent of dose, and ranged between 40.9 and 69.1 L/h/m², likely related to the known conversion to circulating metabolites, including two isomeric O-glucuronide conjugates. The volume of distribution was high (427–872 L/m²).

Urinary excretion of AT13387 was low. The maximum rate of excretion was observed within 3.50 to 11.9 hours (mean Tmax) following intravenous infusion for the 10 to 120 mg/m² dose levels. The percent of the dose recovered in urine ranged from 0.92% to 2.98%. The two isomeric O-glucuronide conjugates representing the major metabolites were detectable in urine. The low recovery of the drug dose in urine suggests the existence of alternative pathway(s) of excretion. ADME studies in humans have not yet been conducted; however, results of studies in nonclinical toxicology models suggest that excretion of AT13387 and its conjugated metabolites is mainly through the biliary pathway.

Pharmacodynamic analyses

In addition to client protein degradation, induction of HSP70 typically follows pharmacologic HSP90 inhibition; therefore, HSP70 upregulation is commonly used as biomarker evidence of HSP90 inhibition and target engagement in clinical trials (6). HSP70 expression was assessed in plasma and tumor biopsy samples when possible. Increased levels of HSP70 in plasma were detected across all dose levels and were dose-dependent up to the fifth dose level (120 mg/m²; ~2- to 6-fold increase) in the twice-weekly regimen. In the once-weekly regimen, HSP70 induction appeared to be dose-dependent until the eighth dose level (220 mg/m²; Fig. 2A). Pre- and posttreatment tumor biopsy samples were taken and successfully analyzed from 4 patients treated at the MTD (120 mg/m²) for the twice-weekly regimen. A consistent increase in HSP70 staining was detected in 3 of the 4 samples (Fig. 2B). No relationship was observed between

Table 4. Summary of pharmacokinetic parameters mean (±SD) for AT13387 (cycle 1, day 1)

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dose (mg/m²)</th>
<th>Dose regimen</th>
<th>AUC0–24 (h ng/mL) Mean (SD)</th>
<th>t1/2 (h) Mean (SD)</th>
<th>Cmax (ng/mL) Mean (SD)</th>
<th>CI (L/h/m²) Mean (SD)</th>
<th>Vz (L/m²) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (N = 4)</td>
<td>10</td>
<td>TW</td>
<td>165.1 (53.9)</td>
<td>11.2 (2.0)</td>
<td>69.4 (40.7)</td>
<td>52.0 (14.7)</td>
<td>872 (386)</td>
</tr>
<tr>
<td>2 (N = 3)</td>
<td>20</td>
<td>TW</td>
<td>309.6 (8.4)</td>
<td>9.1 (2.1)</td>
<td>105.5 (35.3)</td>
<td>56.5 (2.28)</td>
<td>733 (140)</td>
</tr>
<tr>
<td>3 (N = 5)</td>
<td>40</td>
<td>TW</td>
<td>754.5 (606)</td>
<td>10.7 (2.1)</td>
<td>453.5 (509)</td>
<td>45.1 (7.4)</td>
<td>708 (322)</td>
</tr>
<tr>
<td>4 (N = 5)</td>
<td>80</td>
<td>TW</td>
<td>1.499 (307)</td>
<td>9.4 (2.6)</td>
<td>526.1 (755)</td>
<td>48.1 (10.4)</td>
<td>639 (174)</td>
</tr>
<tr>
<td>5 (N = 13)</td>
<td>120</td>
<td>TW</td>
<td>1.530 (558)</td>
<td>11.5 (2.7)</td>
<td>714.0 (405)</td>
<td>57.0 (21.1)</td>
<td>807 (180)</td>
</tr>
<tr>
<td>6 (N = 4)</td>
<td>150</td>
<td>OW</td>
<td>2.836 (660)</td>
<td>8.4 (1.1)</td>
<td>1.570 (744)</td>
<td>51.4 (16.5)</td>
<td>671 (165)</td>
</tr>
<tr>
<td>7 (N = 3)</td>
<td>180</td>
<td>OW</td>
<td>2.414 (216)</td>
<td>8.1 (0.8)</td>
<td>0.970 (182)</td>
<td>69.1 (7.88)</td>
<td>802 (16.8)</td>
</tr>
<tr>
<td>8 (N = 5)</td>
<td>220</td>
<td>OW</td>
<td>3.192 (302)</td>
<td>7.7 (1.5)</td>
<td>2.540 (865)</td>
<td>40.9 (8.45)</td>
<td>448 (93.3)</td>
</tr>
<tr>
<td>9 (N = 12)</td>
<td>260</td>
<td>OW</td>
<td>4.905 (719)</td>
<td>6.6 (1.6)</td>
<td>1.790 (422)</td>
<td>50.6 (10.7)</td>
<td>491 (79.4)</td>
</tr>
<tr>
<td>10 (N = 5)</td>
<td>310</td>
<td>OW</td>
<td>7.293 (1966)</td>
<td>7.0 (0.6)</td>
<td>3.790 (2820)</td>
<td>42.0 (8.69)</td>
<td>427 (118)</td>
</tr>
</tbody>
</table>

Abbreviations: TW, twice weekly; OW, once weekly.
clinical outcome and HSP70 induction. Best response was either PD (2 patients) or not evaluable (1 patient).

Depletion of HSP90 client proteins in PBMCs showed large variability and differences in effect. Depletion of HSP90 client proteins (Raf-1, CDK4, phospho-S6, and levels of cleaved caspase-3) in pre- and posttreatment tumor biopsies taken from the 4 patients treated at the MTD for the twice-weekly regimen (120 mg/m²) showed large variability across the samples studied. Increased plasma HSP70 was observed in all cohorts; therefore, HSP70 induction in plasma was not sufficient to predict response of HSP90 inhibitors by evidence of target engagement.

Antitumor activity
Disease response was also assessed during the study. One patient (2%) had a partial response, 21 patients (34%) had stable disease (SD), and 22 patients (35%) had progressive disease as best response to therapy based on the investigator’s assessment of response to treatment.

Across the study, 7 patients had SD for at least 120 days (median 184 days, range 155–335 days; Table 5), including 2 patients on the twice-weekly regimen (20 and 80 mg/m², respectively), and 5 patients on the once-weekly regimen (220–310 mg/m²).

The partial response occurred in a 60-year-old male with gastrointestinal stromal tumors (GIST), who had previously been treated with imatinib (doses escalated from 300 to 800 mg/day). He received AT13387 at 220 mg/m² on the once-weekly regimen, with successive decreases in tumor size resulting in a partial response by RECIST after 6 months. He remained progression-free for an additional 113 days (~3.8 months), so that he was on AT13387 for approximately 10 months. Direct DNA sequencing results for this patient’s tumor at diagnosis (imatinib sensitive) and recurrence (imatinib resistant) showed that this patient had a primary 
\[cKIT\] mutation (exon 11 deletion 558–572) at diagnosis, and secondary mutations (exon 17 mutations D816H, D820H) associated with resistance to imatinib and other tyrosine kinase inhibitors (TKI; ref. 21) after recurrence and before treatment with
AT13387, so that the response to AT13387 occurred despite the presence of mutations conferring TKI resistance. Among 6 additional patients with GIST, 3 had a best response of stable disease. These patients remained progression-free for 43 days (~1.4 months), 231 days (~7.7 months), and 335 days (~11.2 months), respectively. A 59-year-old male was progression-free for 231 days. He had a tumor in the liver and had received prior imatinib. He was treated with AT13387 at 220 mg/m² once weekly and had interval decrease in the size and metabolism of the hepatic lesion [standardized uptake volume (SUV) decrease of 48% on ¹⁸F-fluorodeoxyglucose positron emission tomography]. A 64-year-old female was progression-free for 335 days. She had widespread abdominal tumor seeding following surgery for GIST involving the terminal ileum and colon. Although she was not able to tolerate more than 30 days of treatment with imatinib due to neutropenia, AT13387 (260 mg/m² once weekly) afforded nearly 1 year of disease control by study end, with multiple implants observed during surgery but not measurable according to RECIST (by CT scan). The most recent CT scan (3 years later) showed no progressive disease.

Ten heavily pretreated patients with NSCLC were enrolled representing a variety of genomic subsets, although none with known ALK rearrangement. Four patients achieved a best response of stable disease, including 3 patients with EGFR wild-type disease and 1 patient with tumor harboring a HER2 exon 12 insertion mutation. However, stabilizations were brief, lasting 47 to 85 days. Two patients with tumor harboring an EGFR exon 20 insertion and a KRAS G12D mutation, respectively, had progressive disease as the best response and 1 patient with tumor harboring an EGFR exon 19 deletion was not evaluable.

Discussion

This first-in-human, phase 1 study of AT13387 identified the MTD and RP2D for 2 regimens in 62 patients with previously treated solid tumors. Single-agent AT13387 has an acceptable safety profile and exhibited linear pharmacokinetic properties. Exposure increased proportionally with increasing dose and demonstrated no accumulation or reduction on day 15 or day 18 versus day 1. Systemic pharmacokinetic exposures in the clinic at MTD dose(s) achieved levels associated with efficacy in preclinical xenograft studies when adjusted for differences in protein binding between nude mice and humans (11, 14).

AEs commonly observed with other HSP90 inhibitors are gastrointestinal disorders (nausea/vomiting/diarrhea), visual disturbances, and hepatic toxicity (7–9, 22–24). The gastrointestinal toxicity of AT13387 includes grade 1–2 diarrhea that was mostly self-limited or managed with antidiarrheals. Visual disturbances also occurred; these events were typically transient and low grade. Ophthalmologic toxicity may be an inherent property of potent water-soluble HSP90 inhibitors, as these findings have been reported with other agents, including 17-DMAG and AUY922.
(8, 25, 26). Other commonly occurring AT13387 treatment-related AEs (~30%) included nausea and injection site events and systemic infusion reactions, all of which were grade 1 or 2 and managed prophylactically or treated symptomatically.

The unfavorable hepatotoxicity of first-generation ansamycin class of HSP90 inhibitors (17-AAG, DMAG, and IPI-504) that hampered clinical development was not observed in this study (22, 27, 28). In the few patients with any changes in hepatic transaminases considered possibly-related to AT13387, the changes were mild (≤2X ULN) and generally transient, which is consistent with findings with other second-generation HSP90 inhibitors (9). In addition, cardiotoxicity was not detected in this study. Independent central cardiac review did not show a significant effect on QTc interval.

HSP90 inhibitors have been evaluated on multiple regimens. First-generation geldanamycins and second-generation non-geldanamycin agents, including AT13387, as well as AIY922 and ganetespib, demonstrate preferential accumulation in tumors, with long intratumoral t1/2 (often detectable for 7–10 days in tumor), justifying once-weekly regimens (11–14). Here, AT13387 has demonstrated preliminary activity against KIT-driven GIST, including a partial response in a patient with tumor harboring mutations conferring resistance to TKIs. This partial response was in a patient receiving AT13387 on the once-weekly regimen, implying that regimen is sufficient to produce antitumor activity in sensitive tumors.

AT13387 has been shown to be active in GIST xenograft models (15) and imatinib-resistant GIST remains largely c-KIT–dependent hence targeting c-KIT via inhibition of the HSP90 chaperone, essential for stability of all mutant KIT proteins, has been an attractive clinical setting for HSP90 inhibitors (15). Enrollment of patients with GIST who failed previous TKI treatment was enriched in the once-weekly regimen to explore the hypothesis that patients with acquired resistance to imatinib due to secondary resistance mutations within c-KIT might respond to AT13387, with 2 additional patients achieving prolonged stable disease. On the basis of these findings, a trial in which AT13387 is combined with imatinib in patients with GIST is currently underway (NCT01294202).

Defining the optimal regimen for AT13387 and other HSP90 inhibitors has proved complex. Despite the long intratumoral t1/2 noted with these agents, the suppression of client protein expression has been noted to be more transient. For example, in mutant EGFR (L858R/T790M) NCI-H1975 NSCLC xenografts, depletion of mutant EGFR has been demonstrated to last a duration of 72 hours or shorter in response to a single dose of AT13387 or ganetespib (13, 14). In a clinical evaluation of once-weekly ganetespib in GIST (29), tumor biopsies demonstrated only transient depletion of KIT and inhibition of downstream signaling pathways, suggesting that the once-weekly regimen was suboptimal for producing prolonged client protein depletion. Similarly, in one of the first phase 1 studies of the geldanamycin 17-AAG, depletion of c-RAF and CDK4 in tumor biopsies could be demonstrated at 24 hours, but not at 5 days after treatment (22). These results have prompted the evaluation of more frequent dosing regimens, including the twice-weekly regimen evaluated here, as well as consecutive day dosing (NCT01246102), the latter producing the most prolonged client depletion in various preclinical studies (13). This study demonstrates that twice-weekly dosing of AT13387 is tolerable with clear evidence of target engagement in tumor, documented by induction of HSP70 in posttreatment biopsy samples (30). Future studies incorporating biopsies at additional time points, focusing on longevity of client protein depletion in conjunction with clinical activity in sensitive populations, will be instructive to justify continued development of the more frequent dosing regimens. In the consecutive day dosing trial of AT13387, indium-labeled trastuzumab scanning will be used to evaluate the drug effect on HER2 levels in patients with HER2-expressing tumors. Whether twice-weekly or consecutive-day dosing of an HSP90 inhibitor will improve efficacy may be dependent on the specific clinical setting (disease type, specific client protein targeted for depletion, whether single agent or in combination) and ultimately will require randomization to the once-weekly regimen for direct comparison of toxicity and efficacy in homogeneous patient populations.

There has been substantial interest in the activity of HSP90 inhibitors in oncogene-driven subsets of NSCLC. In particular, twice-weekly retaspimycin and once-weekly AIY922 and ganetespib have been evaluated in phase II trials. These studies have routinely demonstrated activity in ALK-dependent tumors (7, 31, 32), which along with HER2, may be one of the most sensitive HSP90 clients. More variable activity has been demonstrated in EGFR-mutant tumors. In this study, only 2 patients with EGFR-mutant NSCLC were enrolled, and the 1 evaluable patient had progressive disease as the best response. Currently, AT13387 is being evaluated in combination with crizotinib in a phase I/II trial for patients with NSCLC harboring ALK rearrangement. Once doses of the combination are defined, this study will evaluate both AT13387 alone and the combination in patients who have progressed on crizotinib (NCT01712217).

In summary, we have demonstrated that AT13387 is tolerable in patients with advanced solid tumors, with linear pharmacokinetics, evidence of target engagement, and preliminary antitumor activity. In addition to the current clinical evaluation in GIST and ALK-rearranged NSCLC, AT13387 is also being investigated both alone and in combination with abiraterone in castration-resistant prostate cancer (NCT01685268; the trial has completed enrollment). In addition, we have demonstrated the activity of AT13387 in preclinical models of BRAF and MEK inhibitor-resistant BRAF mutant melanoma, so that further work is also planned in this disease. These trials should provide further insight into the activity of AT13387 as monotherapy and in combination with TKIs or hormonal therapy in cancers driven by HSP90 clients.

Disclosure of Potential Conflicts of Interest

G.I. Shapiro and M. Yule are consultant/advisory board members for Astex. J. Lyons is an employee of Astex. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: G.I. Shapiro, B.J. Dezube, M. Yule Development of methodology: G.I. Shapiro, B.J. Dezube Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G.I. Shapiro, E. Kwal, B.J. Dezube, J. Lyons Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G.I. Shapiro, E. Kwal, B.J. Dezube, J. Ayrton, J. Lyons Writing, review, and/or revision of the manuscript: G.I. Shapiro, E. Kwal, B.J. Dezube, M. Yule, J. Lyons, D. Mahadevan Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G.I. Shapiro, J. Ayrton Study supervision: G.I. Shapiro, M. Yule Other (conducted the trial as the principal investigator at the Arizona site and wrote part of the manuscript): D. Mahadevan
Phase I Dose Escalation Trial of AT13387 in Metastatic Solid Tumors

Grant Support
This study was sponsored, monitored, and funded by Astex Pharmaceuticals, Inc. (formerly SuperGen, Inc.).

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Received April 20, 2014; revised August 12, 2014; accepted September 9, 2014; published OnlineFirst October 21, 2014.

References
First-in-Human Phase I Dose Escalation Study of a Second-Generation Non-Ansamycin HSP90 Inhibitor, AT13387, in Patients with Advanced Solid Tumors

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