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A phase 1 study of the heat shock protein 90 inhibitor retaspimycin hydrochloride (IPI-504) in patients with gastrointestinal stromal tumors or soft tissue sarcomas

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Abstract

Purpose—Heat shock protein 90 (Hsp90) is required for the proper folding, function, and stability of various client proteins, two of which (KIT and PDGFRα) are critical in the pathogenesis and progression of gastrointestinal stromal tumors (GIST). This phase 1 study investigated the safety and maximum tolerated dose (MTD) of retaspimycin hydrochloride (IPI-504), a novel potent and selective Hsp90 inhibitor, in patients with metastatic and/or unresectable GIST or other soft-tissue sarcomas (STS).

Experimental Design—IPI-504 was administered intravenously at doses ranging from 90 to 500 mg/m² twice weekly for 2 weeks on/1 week off. Safety, pharmacokinetic, and pharmacodynamic profiles were determined. Response was assessed by Response Evaluation Criteria for Solid Tumors (RECIST) 1.0 and optionally via 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) imaging.

Results—Fifty-four patients received IPI-504; 37 with GIST and 17 with other STS. The MTD was 400 mg/m² twice weekly for 2 weeks on/1 week off. Common related adverse events were fatigue (59%), headache (44%), and nausea (43%). Exposure to IPI-504, 17-AAG, and 17-AG increased with IPI-504 dose. Stable disease (SD) was observed in 70% (26/37) of patients with GIST and 59% (10/17) of patients with STS. There was one confirmed partial response (PR) in a

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patient with GIST and one PR in a patient with liposarcoma. Metabolic partial responses occurred in 11/29 (38%) of GIST patients.

Conclusions—In this study of advanced GIST or other STS, IPI-504 was generally well-tolerated with some evidence of anti-tumor activity, serving as a clinical proof-of-concept that HSP90 inhibition remains a promising strategy.

Keywords

IPI-504; Hsp90; GIST; STS; phase 1; retaspimycin hydrochloride

Introduction

Sarcomas are a heterogeneous group of malignant tumors linked by a common mesenchymal origin.¹ Gastrointestinal stromal tumors (GISTs), the most common subset of soft-tissue sarcomas, harbor driver gene mutations in approximately 80% of cases involving *KIT* or, in a separate 15%, *PDGFRA*; these mutations result in ligand-independent signaling through the activated *KIT* or platelet-derived growth factor receptor α (PDGFR α) receptor tyrosine kinases.^{2,3} The remaining GISTs do not have identified tyrosine kinase mutations, but often have genomic aberrancies in succinate dehydrogenase subunits.⁴ Small molecule tyrosine kinase inhibitors (TKIs), such as imatinib and sunitinib, block *KIT* and PDGFR α signaling, resulting in significantly improved outcomes for patients with advanced GIST as well as in patients who receive adjuvant therapy following resection of primary localized GIST at high risk of recurrence.⁵⁻¹⁰ Despite the dramatic improvements in the treatment of advanced GIST, the majority of patients who initially benefit from TKIs will eventually develop polyclonal GIST that is resistant to TKI therapy, most often due to emergence of secondary *KIT* mutations.^{6, 11-16} Novel strategies that bypass specific mutations which result in structural resistance to TKIs in order to target fundamental pathways that support aberrant oncoprotein activation might be effective in TKI-resistant GIST.

Heat shock protein 90 (Hsp90) is a molecular chaperone that uses the energy of ATP hydrolysis to increase the stability and activity of its client proteins, many of which are involved in key pathways important in malignancy.¹⁷⁻¹⁹ The repertoire of client proteins of Hsp90 includes a host of proteins important to tumor growth and proliferation. These proteins influence the hallmark traits of cancer such as growth factor independence, resistance to antigrowth signals, unlimited replicative potential, tissue invasion and metastasis, evasion of apoptosis, and sustained angiogenesis.²⁰ The Hsp90 chaperone complex facilitates the conformational maturation, stability, and activation of numerous wild type and mutated oncoproteins, including *KIT* and PDGFR α , while preventing proteasome-mediated degradation.²¹ Because activating mutations in *KIT* and *PDGFRA* play a critical role in the pathogenesis and progression of GIST, and because the cellular proteins from these genes rely on Hsp90 for optimal processing and function, we hypothesized that Hsp90 inhibition could have beneficial effects in patients with GIST. Preclinical models supported this hypothesis,¹¹ and this clinical trial was the translation of that concept to patients.

IPI-504 is an Hsp90 inhibitor uniquely designed to overcome the therapeutic limitations of earlier Hsp90 inhibitors with potential advantages over those currently in development.^{22, 23}

IPI-504 is the hydrochloride (HCl) salt of the hydroquinone of 17-AAG (a quinone) and in vivo, the hydroquinone and quinone exist in a dynamic equilibrium.²³ Inside cells, 17-AAG is enzymatically reduced to the hydroquinone (free base of IPI-504) which is a 40- to 60-fold more potent inhibitor of Hsp90 than 17-AAG.^{24, 25} IPI-504 is also subject to oxidative metabolism via CYP3A4 to produce the active metabolite 17-amino-17-demethoxygeldanamycin (17-AG). Previous clinical studies of 17-AAG demonstrated some evidence of activity but were limited by formulation concerns and toxicities due to these formulations (e.g., Cremophor, DMSO) that were required because of aqueous insolubility.^{23, 26-28} In human GIST cell lines characterized either by sensitivity or resistance to imatinib, Hsp90 inhibitors, including IPI-504, suppress cell growth and inhibit activation of oncogenic KIT and PDGFR α as well as the relevant downstream signaling molecules (e.g., AKT and MAPK).^{11, 29, 30} In addition, single-agent IPI-504 treatment significantly reduces tumor volume in GIST xenografts.³¹ Other soft-tissue sarcomas, driven by fusion proteins that are the result of chromosomal translocations, such as Ewing sarcoma and synovial sarcoma, may also be sensitive to Hsp90 inhibition.^{32, 33} Based on these promising preclinical data, a phase 1 trial was conducted to determine the safety and the recommended phase 2 dose and schedule of IPI-504 in patients with advanced (metastatic and/or unresectable) imatinib-resistant GIST or other soft-tissue sarcomas (STS).

Materials and Methods

Patients

Patients were eligible if they had histologic confirmation of either (1) metastatic and/or unresectable GIST that was imatinib-resistant or (2) another form of soft-tissue sarcoma (STS) not amenable to curative therapy by conventional multimodality options. Main inclusion criteria were as follows: 18 years old; primary or secondary resistance to, or unacceptably severe medical intolerance of, imatinib for patients with GIST; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients were excluded for any of the following: prior exposure to any known Hsp90 inhibitor; treatment with an investigational drug or kinase inhibitor within two weeks of study start; NYHA class 3 or 4 congestive heart failure or left ventricular ejection fraction <40%; prior radiation therapy that potentially included the heart in the field; myocardial infarction or active ischemic heart disease within 6 months; history of arrhythmia; baseline QTc $\geq$ 450 msec; congenital long QT syndrome or first degree relative with unexplained sudden death under 40 years of age; left bundle branch block on electrocardiogram (ECG); grade $\geq$ 3 peripheral neuropathy; serum creatinine >1.5 x upper limit of normal (ULN); alkaline phosphatase >2.5 x ULN; amylase and lipase >1.5 x ULN; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 x ULN; hemoglobin <9.0 g/dL; platelets $<100,000$ mm³; absolute neutrophil count $<1,500$ cells/mm³; active infection or systemic use of antibiotics within 72 hours of treatment; or breast feeding. Concurrent treatment with radiation therapy, agents that alter CYP3A or agents that may prolong the QTc interval were not permitted. All patients provided written informed consent, and the study was approved by the local institutional review boards (Trial Registration ID: NCT00276302).

Study design and dosing

This was a multicenter, Phase 1, open-label, sequential inter-cohort dose-escalation study designed primarily to evaluate safety, identify the MTD, and determine the recommended phase 2 dose and schedule of IPI-504 for patients with metastatic and/or unresectable GIST or other STS. Secondary objectives were to determine pharmacokinetic parameters, assess anti-tumor activity, and explore biological markers of IPI-504 activity. The study sponsor was Infinity Pharmaceuticals, Inc. (Cambridge, MA), which also provided IPI-504 (sterile lyophilized powder).

IPI-504 was administered as a 30-minute intravenous infusion via one of two different schedules: Schedule 1 comprised twice weekly dosing (Days 1, 4, 8, and 11) for 14 consecutive days followed by a 10-day rest period, while Schedule 2 administered twice-weekly dosing (Days 1, 4, 8, 11, 15, and 18) for 21 consecutive days. Safety and efficacy data are reported here only from Schedule 1, due to early termination of Schedule 2 (data from Schedule 2 has been presented elsewhere).³⁴ However, pharmacokinetic parameters were determined and reported here from patients on both schedules. Although study drug administration was generally stopped if disease progression occurred, the study allowed continued study drug administration if patients were deriving clinical benefit in the judgement of the local investigator.

Based on preclinical toxicology data, the starting dose of IPI-504 was 90 mg/m². Dose escalation in subsequent cohorts followed the modified Fibonacci 3+3 design, increasing in increments of approximately 66%, 50%, 33%, 33%, 25%, and 25% of the preceding dose level in the absence of dose-limiting toxicities (DLTs). If one of the three initial patients experienced a DLT, the cohort was expanded to 6 patients. The MTD was defined as the highest dose at which fewer than 33% of at least 6 patients experienced a DLT during the first cycle of treatment during the dose escalation phase. Twenty-six additional patients were enrolled at the MTD to evaluate safety with greater confidence.

DLTs included any of the following events that occurred during the first cycle and were attributed as at least possibly related to study drug: death, grade 4 neutropenia lasting ≥ 5 days, grade 3 febrile neutropenia with elevated temperature (>101.5°F) confirmed on two occasions, grade 4 thrombocytopenia with platelets <10,000/mm³, any other hematologic toxicity of grade ≥ 4, grade 3 nausea, vomiting, or diarrhea despite maximal medical management, QTc prolongation [Grade 3 if it occurred on Day 1 at 5 minutes or 1 hour post initial infusion; Grade 2 if it occurred on Day 1 at 6 hours post initial infusion, or at any subsequent baseline ECG, or if it occurred for the first time during a subsequent infusion (Days 4, 8, and 11) at baseline or 5 minutes], and any other non-hematologic toxicity of grade ≥ 3 with the exception of asymptomatic lipase elevation in the absence of any clinical signs or symptoms of pancreatitis.

Safety

Patients underwent clinical safety assessments including physical examination, history, concomitant medications, ECGs, clinical laboratory tests and adverse events (AEs). AEs were graded according to the National Cancer Institute Common Terminology Criteria for

Adverse Events (NCI CTCAE) version 3.0. ECGs were obtained in triplicate within a 5-minute period. During cycle 1, ECGs were performed on day 1 at baseline and 5, 60, and 360 minutes post dose-administration, on days 4, 8, and 11 pre-dose and 5 minutes post-dose administration, and on day 21 pre-dose only.

Pharmacokinetics

Blood samples for pharmacokinetic analyses were obtained at baseline on cycle 1, day 1 prior to IPI-504 infusion and serially at 5 minutes, 30 minutes, and 1, 2, 6, and 24 hours after the end of the infusion. Additional samples were collected on cycle 1, day 11 (dose 4) prior to infusion and 5 minutes, 30 minutes, and 1 hour after the end of the infusion. Pharmacokinetic parameters were determined from 60 patients following administration of the dose on cycle 1, day 1.

Plasma concentrations of IPI-504, 17-AAG, and 17-AG were determined using a validated liquid chromatographic method with mass spectrometry detection. The following parameters were determined for IPI-504, 17-AAG, and 17-AG on cycle 1 day 1 using noncompartmental pharmacokinetic analysis methods: maximum concentration (C_{max}), the time of maximum concentration (T_{max}), area-under the concentration-time curve extrapolated to infinity [$AUC_{(0-\infty)}$], and terminal elimination half-life($t_{1/2}$). In addition, systemic clearance (CL) and volume of distribution at steady state (V_{ss}) were determined for IPI-504. Pharmacokinetic parameters were calculated for each patient using the actual time of sample collection relative to the beginning of infusion.

Pharmacodynamics

Peripheral-blood leukocytes (PBL) were isolated from blood collected prior to and 24 hours following the first IPI-504 dose of cycle 1. PBL protein lysates were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis, transferred to nitrocellulose membranes, and incubated first with primary anti-Hsp70 antibodies (Cell Signaling Technology, Inc., Danvers, MA) and then with secondary antibodies (goat anti-mouse HRP antibodies; Amersham Biosciences, UK). Proteins were visualized by chemiluminescence (ECL, Amersham Biosciences, UK) on BioMax film.

Antitumor response criteria and statistical analysis

Tumor response was assessed per RECIST v1.0.³⁵ Computed tomography (CT) scans were obtained at baseline and at the end of cycle 1. After cycle 1, CT scans were obtained approximately every 2 cycles or according to institutional standard.

Functional imaging with 18-FDG-PET using maximal Standardized Uptake Values (SUV_{max}) was performed optionally to gain additional insight to potential anti-tumor activity of IPI-504 in patients with FDG-avid disease at baseline. PET scans were obtained at baseline, after the second or third dose of IPI-504 in cycle 1, and again at the end of the “drug holiday” in the first cycle. PET responses were evaluated according to European Organization for Research and Treatment of Cancer (EORTC) criteria, using SUV_{max} values as quantification metric.³⁶

Progression-free survival (PFS) was measured from the date of first dose to the date of documented progression or death, whichever came first. Time to tumor progression (TTP) was the duration in weeks from the date of the first dose until the date of confirmed progressive disease (PD) using conventional RECIST definitions. Survival analyses were carried out using Kaplan-Meier life test methods.

Results

Patients

Between December 19, 2005 and June 7, 2010, a total of 54 patients (37 GIST, 17 STS) were enrolled on study and received IPI-504 twice weekly for 2 weeks on/1 week off in 6 dosing cohorts, ranging from 90 to 500 mg/m². Baseline characteristics and disease history are summarized in Table 1. All patients with GIST had received prior therapy with imatinib, and the majority (78%) received an imatinib dose greater than 400 mg after initial progression. In addition, more than one third (38%) of patients with GIST also received prior sunitinib, and the majority (81%) of patients had received 3 or more prior therapies. Patients with STS had received a median of 6 prior anti-cancer therapies.

Identification of Dose Limiting Toxicities and Maximum Tolerated Dose

One patient in the first dose level (IPI-504 90 mg/m²) experienced asymptomatic elevation in circulating lipase, which was initially considered a DLT prior to a protocol amendment that excluded asymptomatic lipase elevation from the DLT definition in the absence of any clinical signs or symptoms of pancreatitis. No other DLTs were observed in the first four dose levels (90 to 300 mg/m²). A single DLT of grade 5 intra-cerebral hemorrhage occurred in the 400 mg/m² dose level. This cohort was expanded to 6 patients, with no further DLTs observed at this dose level. Of the 6 patients in the 500 mg/m² cohort, a DLT of grade 3 headache occurred in 1 patient, and a second DLT of grade 3 myalgia occurred in another patient. Because the rate of DLTs in the 500 mg/m² cohort exceeded the limit defined in the protocol, the MTD was established as 400 mg/m² administered twice weekly for 2 weeks on/1 week off, and an additional 26 patients were enrolled at this dose and schedule for further evaluation.

Dose modifications and Reasons for Withdrawal

Patients were on study for a median of 53 days (range, 4-824) and received a median of 11 doses of IPI-504 on study; one patient with GIST who continues to receive IPI-504 at the time of this publication through a single-patient access program has been on study for approximately 5 years. Dose reductions were required in 7 of 32 patients in the 400 mg/m² cohort, and 3 of 7 patients in the 500 mg/m² cohort, most commonly for fatigue. Interruptions of study drug dosing occurred in 24 (44%) patients and were not dose-dependent. Reasons for discontinuation from the study included progressive disease in 26 (48%) patients, other reasons in 20 (37%) patients (typically attributed to disease progression), adverse events in 3 (5.6%) patients (two cases of liver function test elevation and one of pain), withdrawal by subject in 3 (5.6%) patients, and death in 2 (3.7%) patients.

Safety

All patients reported at least one treatment-emergent adverse event (AE) during the study. The most common AEs regardless of causality were fatigue, nausea, headache, diarrhea, and vomiting (Table 2), with the majority being Grade 1 or 2. Grade 1 sinus bradycardia and tachycardia occurred in 11 (20%) and 5 (9%) patients, respectively. Grade 1 and Grade 2 QTc prolongation occurred in 9 (17%) and 1 (2%) of patients, respectively, and no patients had a QTc increase >60 msec or a QTc >475 on study. A more detailed account of the cardiac monitoring of patients receiving IPI-504 has been presented previously.³⁷

The most common grade 3 and 4 related AEs with a frequency >5% were fatigue (9.3%), increased aspartate aminotransferase (7.5%), and increased alanine aminotransferase (5.6%).

Two patients died on study of causes considered at least possibly related to therapy. A 68-year-old male patient with GIST and numerous metastases to the lung, liver, peritoneum, thoracic vertebrae, and left acetabulum developed hepatic and renal failure leading to death after receiving two doses of 400 mg/m² IPI-504. A 60-year-old female patient with GIST and one metastasis to the liver had intra-cerebral hemorrhage leading to death after receiving two doses of 400 mg/m² IPI-504. Autopsy did not reveal structural causes for this hemorrhage.

Serious adverse events were reported for 20 (37%) patients. Seven patients experienced serious AEs that were considered at least possibly related to therapy, including dehydration, diarrhea, nausea, vomiting, increased aspartate aminotransferase, fatigue, headache, increased lipase, myalgia, and the two Grade 5 events described above.

Pharmacokinetics

Following administration of the first dose of IPI-504, the mean concentration profiles of IPI-504 and 17-AAG displayed similar shapes, with peak plasma concentrations observed at the end of the infusion, followed by bi-exponential decline (Supplemental Fig 1). Peak plasma concentrations of 17-AAG were observed slightly later, followed by mono-exponential decline. Pharmacokinetic parameters for IPI-504, 17-AAG and 17-AG following IPI-504 administration on cycle 1 day 1 are summarized in Supplemental Table 1. At the MTD of 400 mg/m², C_{max} values for IPI-504 and 17-AAG were 6740 and 7823 ng/mL, respectively, while the C_{max} for 17-AG was slightly lower (3381 ng/mL). On average, exposure to 17-AAG approximated that of IPI-504, whereas 17-AG exposure was typically twice that of the parent drug. Overall, exposure to 17-AG accounted for ~50% of the total exposure, determined as the sum of the AUCs for IPI-504, 17-AAG and 17-AG.

Mean clearance (CL) values for IPI-504 across the evaluated doses ranged from 70.9 to 121 L/h, with the exception of the 300 mg/m² dose group, where CL was estimated to be 141 L/h. Volume of distribution (V_{ss}) values averaged 119 to 275 L across the dose levels, with the exception of the 300 mg/m² dose level (V_{ss} = 291). Mean elimination half-life values for IPI-504 and 17-AAG ranged from 1.4 to 3.3 hours after single-dose administration; 17-AG elimination was slightly slower, with a mean elimination half-life of 4.3 to 7.5 hours. There was no accumulation of IPI-504 or its metabolites observed after repeated dosing on a twice

weekly administration schedule based on a comparison of the AUCs observed through 1.5 hours at the end of cycle 1 to the first dose in cycle 1 (data not shown).

Pharmacodynamic assay for Hsp90 inhibition

Induction of Hsp70, which was used as a marker for Hsp90 inhibition, was observed in 8 of 10 patients from whom evaluable PBL samples were obtained. All 7 patients treated at the 225 mg/m² dose level or higher showed a pharmacodynamic response, and one of the two patients treated with 150 mg/m² also demonstrated an increase in Hsp70 protein expression. The patient treated at 90 mg/m² did not show an induction of Hsp70 expression (Supplemental Fig 2).

Antitumor activity

Antitumor clinical activity was assessed in all patients (n=54). In the 37 patients with GIST, the overall objective response rate was 3% (1 patient with a PR), with 73% of patients achieving SD or PR for at least 6 weeks, and 16% at 12 weeks. RECIST outcome for patients with GIST is shown in Figure 1A. Prior to study participation, the patient with a PR had had progression of disease on imatinib (400 mg and 800 mg) and sunitinib (37.5 mg and 50 mg), and has been receiving IPI-504 for approximately 5 years at the time of this publication (Fig 1B).

KIT genotyping was available for 15 GIST patients. Of these, 8 had primary mutations in exon 11, 4 in exon 9, 1 in exon 13, and 2 were without identified mutations in *KIT*, including the tumor that exhibited a PR. Six tumors had secondary mutations in Exon 13 or 17. There was no correlation between outcome and primary mutation; however, 3 of 5 sequenced tumors with minor or partial responses had secondary mutations, compared with 3 of 10 sequenced tumors with disease progression as best response. While it is difficult to make any conclusions based on this small sample size, these data are consistent with preclinical data suggesting that more heavily mutated KIT is more sensitive to HSP90 inhibition than singly mutated KIT¹¹.

Of the 17 patients with STS, the overall response rate was 6% (1 patient with metastatic dedifferentiated liposarcoma exhibited a durable PR for 2.25 years after initiation of IPI-504), with 59% of patients having SD for at least 6 weeks, and 18% at 12 weeks (Table 3 and data not shown). RECIST outcome for patients with STS is shown in Figure 1C.

18-FDG-PET analysis was performed on 29 of 37 patients with GIST. Responses were evaluated according to the EORTC criteria.³⁷ Of the 29 patients in whom PET imaging was performed, the overall response rate was 38% (all metabolic PRs). Nineteen (66%) patients had some overall reduction in FDG avidity, while two (7%) patients exhibited metabolic progression of disease as best response (Fig 2). PET imaging performed during the drug holiday week of cycle 1 showed variable changes in SUVmax compared to on-drug imaging. All 4 patients with FDG-PET partial responses on C1D11 had a rebound of SUVmax on C1D21 but it remained less than baseline imaging, with 1 patient continuing with a metabolic PR. Of the 8 patients with minor reductions in SUVmax on C1D11, 2 had further reduction on C1D21 (1 resulting in a metabolic PR), 2 showed no change between

C1D11 and C1D21, 1 showed less of a decrease, and 2 showed an increase in SUV_{max} (1 resulting in metabolic PD). Although a “flare phenomenon” was observed in some patients, there was no clear pattern in regards to changes in FDG-PET imaging during the washout week.

Median PFS was 9.1 weeks (95% CI: 6.7, 12.0) for all patients and 10.6 weeks (95% CI: 6.4, 12.1) for patients with GIST (Fig 3). Median time to tumor progression was 10.6 weeks (95% CI: 8.9, 12.1) for all patients and 12 weeks (95% CI: 9.0, 12.6) for patients with GIST. There were no obvious correlations between changes in FDG-PET and either CT response or duration of disease control.

Discussion

In this phase 1 open-label, dose-escalation study, IPI-504 was generally well tolerated by patients. Moreover, evidence of anti-tumor activity was observed, most frequently as metabolic responses by functional ¹⁸F-FDG-PET imaging in patients with GIST. In this heavily pretreated population, all GIST patients had previously progressed on imatinib therapy, and many had also received prior sunitinib treatment. Nearly 40% of GIST patients had received 3 or more therapies prior to study entry. Despite this degree of pretreatment, 38% of patients with GIST had a metabolic partial response to IPI-504. The disease control rate (defined as a RECIST PR, CR or SD for at least 6 weeks) was 73% for the patients with GIST, despite the low overall objective response rate (3%, representing a single patient with GIST).

Based on these data, an international randomized phase 3 trial of IPI-504 at this dose and schedule (400 mg/m² twice weekly for two weeks on/1 week off) was initiated in patients with advanced GIST following failure of prior imatinib and sunitinib. This trial was terminated early, however, due to safety concerns of hepatic toxicity in the IPI-504 arm, which was both more common and more severe in the phase 3 trial, highlighting the challenges of moving from a small Phase 1 experience to broader studies, even in the same patient population.³⁸ Further clinical studies have demonstrated that a once-weekly schedule of administration is associated with greater hepatic safety than is a twice-weekly schedule of administration, and clinical studies of IPI-504 moving forward are incorporating once-weekly dose administration.

No clinically meaningful effects on cardiac function or repolarization were observed in this study. While episodes of first-degree AV block, sinus bradycardia, and sinus tachycardia were observed occasionally, none of these adverse events ever exceeded Grade 1, and all were rapidly reversible without requiring a dose modification or any other intervention. Importantly, the QTc interval was not significantly affected with IPI-504 treatment, consistent with previous findings indicating that there is no relationship between 17-AAG and the QT interval among patients with advanced cancers.³⁹

In conclusion, in this phase 1 study administered to patients with advanced GIST or other STS intravenous IPI-504 was generally well tolerated with evidence of anti-tumor activity. Importantly, however, further clinical work has demonstrated that IPI-504 at 400 mg/m²

twice weekly for 2 weeks on/1 week off is not an appropriate dose and schedule in this patient population. IPI-504 is currently being evaluated in a phase 2, randomized, double-blind, placebo-controlled study with a once weekly schedule of administration in combination with docetaxel in patients with stage IIIb/IV NSCLC with a history of heavy smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Translational Relevance

Gastrointestinal stromal tumors (GIST) are a subset of soft-tissue sarcomas, approximately 85% of which harbor gain of function mutations in the gene encoding the KIT receptor tyrosine kinase. Despite the dramatic improvements in the treatment of advanced GIST, the majority of patients who initially benefit from tyrosine kinase inhibitors (TKIs) develop polyclonal GIST that is resistant to TKI therapy, most often due to emergence of secondary KIT mutations. Heat shock protein 90 (Hsp90) inhibition may be effective in TKI-resistant GIST since it bypasses kinase mutational status, and targets a fundamental pathway that supports oncoprotein activation. This phase 1 study investigated the safety and maximum tolerated dose (MTD) of retaspimycin hydrochloride (IPI-504), a water-soluble Hsp90 inhibitor, in 54 patients with metastatic and/or unresectable GIST or other soft-tissue sarcomas (STS). IPI-504 was generally well tolerated with sufficient evidence of anti-tumor activity to justify further clinical investigation.

B

Fig. 1. Outcomes of Patients with Metastatic GIST or Other STS Treated with IPI-504. (A). Changes in GIST size according to RECIST. (B). CT scans from patient treated at 400 mg/m² Twice Weekly for 2 Weeks on/1 Week off Following Failure of Imatinib and Sunitinib. (C). Changes in STS size according to RECIST.

Fig. 2.
SUVmax Best Percent Change from Baseline for Subset of Patients with GIST Using
EORTC PET Criteria

Fig. 3.
Kaplan-Meier Estimate of Progression-Free Survival for Subset of Patients with GIST

Table 1

Baseline patient and disease characteristics for patients who received IPI-504 on the twice weekly for 2weeks on/1 week off schedule (n=54)

Characteristic	GIST (n=37)	STS (n=17)	All patients (n=54)
Median age (range), years	58 (30-80)	52 (22-69)	53 (22-80)
Sex, n (%)			
Male	26 (70)	8 (47)	34 (63)
Female	11 (30)	9 (53)	20 (37)
Racial, n (%)			
White	33 (89)	15 (88)	48 (89)
Black/African-American	2 (5)	1 (6)	3 (6)
Asian	2 (5)	0 (0)	2 (4)
Other	0 (0)	1 (6)	1 (2)
ECOG performance status, n (%)			
0	18 (49)	9 (53)	27 (50)
1	19 (51)	8 (47)	27 (50)
Primary tumor type, n (%)			
GIST	37 (100)	0 (0)	37 (69)
Other STS	0 (0)	17 (100)	17 (32)
Leiomyosarcoma	0 (0)	5 (29)	5 (9)
Synovial sarcoma	0 (0)	4 (24)	4 (7)
Liposarcoma	0 (0)	3 (18)	3 (6)
Other *	0 (0)	5 (29)	5 (9)
Median months since diagnosis (range)	53 (15-109)	34 (4-202)	49 (4-202)
Median prior treatments (range)	5 (2-17)	6 (3-15)	6 (2-17)
Failure of prior imatinib, n (%)	37 (100)	3 (18)	40 (74)
Reason for imatinib failure, n (%)			
Primary resistance	8 (22)	0 (0)	8 (15)
Progression after initial response	27 (73)	2 (12)	29 (54)
Intolerance	2 (5)	1 (6)	3 (6)

* Other STS subtypes included 1 each of leiomyosarcoma, fibromyxoid sarcoma, chordoma, unclassified spindle and round cell tumor, and unclassified sarcoma

Table 2

Incidence of all treatment-emergent adverse events by dose group in 20% of patients, and all AE Grade 3 or 4 laboratory changes in 5% of patients (n=54)

Adverse Event	IPI-504 Dose (mg/m ²)						All Doses (n=54) n (%)
	90 (n=6) n (%)	150 (n=3) n (%)	225 (n=3) n (%)	300 (n=3) n (%)	400 (n=32) n (%)	500 (n=7) n (%)	
Fatigue	5 (83)	3 (100)	2 (67)	2 (67)	23 (72)	5 (71)	40 (74)
Nausea	2 (33)	2 (67)	1 (33)	0 (0)	17 (53)	6 (86)	28 (52)
Headache	0 (0)	0 (0)	0 (0)	1 (33)	20 (63)	6 (86)	27 (50)
Diarrhea	2 (33)	0 (0)	1 (33)	0 (0)	18 (56)	4 (57)	25 (46)
Vomiting	4 (67)	0 (0)	1 (33)	1 (33)	11 (34)	3 (43)	20 (37)
Arthralgia	1 (17)	0 (0)	1 (33)	1 (33)	13 (41)	0 (0)	16 (30)
Myalgia	1 (17)	1 (33)	0 (0)	1 (33)	11 (34)	1 (14)	15 (28)
Infusion site pain	2 (33)	1 (33)	1 (33)	1 (33)	6 (19)	3 (43)	14 (26)
Constipation	1 (17)	1 (33)	1 (33)	0 (0)	7 (22)	3 (43)	13 (24)
First degree AV block	1 (17)	0 (0)	1 (33)	1 (33)	5 (16)	4 (57)	12 (22)
Back pain	2 (33)	2 (67)	1 (33)	0 (0)	7 (22)	0 (0)	12 (22)
Sinus bradycardia	0 (0)	0 (0)	1 (33)	1 (33)	6 (19)	3 (43)	11 (20)
Grade 3 or 4 Laboratory Changes							
AST increased	0 (0)	0 (0)	1 (33)	0 (0)	5 (16)	0 (0)	6 (11)
ALT increased	0 (0)	0 (0)	1 (33)	0 (0)	3 (9)	0 (0)	4 (7)
Alkaline phosphatase increased	1 (17)	1 (33)	0 (0)	1 (33)	1 (3)	0 (0)	4 (7)
Lipase increased	1 (17)	0 (0)	0 (0)	1 (33)	2 (6)	0 (0)	4 (7)

Table 3

Best RECIST response among patients with GIST and other STS who received IPI-504 on the twice weekly for 2weeks on/1 week off schedule^a

	Patients with GIST n=37	Patients with STS n=17
Confirmed PR, n (%)	1 (3%)	1 (6%)
SD, n (%)	26 (70%)	10 (59%)
PD, n (%)	5 (14%)	4 (24%)

Note: Both PRs were confirmed.

^aFirst RECIST assessment was performed on Day 21.