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Multicenter Phase 2 Trial of the Hsp-90 Inhibitor, IPI-504 (retaspimycin hydrochloride), in Patients with Castration-Resistant Prostate Cancer

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Abstract

Objectives—Evaluation of clinical activity and safety of IPI-504 (retaspimycin hydrochloride) in patients with castration-resistant prostate cancer (CRPC).

Methods—A single arm trial was conducted in two cohorts: Group A (chemotherapy-naïve), Group B (docetaxel-treated). IPI-504 was administered intravenously at 400 mg/m² on Days 1, 4, 8, and 11 of a 21-day cycle. Trial expansion was planned if at least one prostate specific antigen (PSA) or radiographic response was noted per cohort. Pharmacokinetic samples were collected following the first dose; safety was assessed throughout.

Results—Nineteen patients were enrolled (4 in Group A; 15 in Group B), with a median age of 66 years (range 49-78). Group B had received a median of 2 prior chemotherapy regimens. All Group B patients had bone metastases; 66% had measurable soft tissue or visceral metastases. One Group A patient remained on trial for 9 cycles; PSA declined 48% from baseline. No PSA responses were observed in other patients. Adverse events reported in >25% of the study population included nausea (47%), diarrhea (42%), fatigue (32%), anorexia (26%), and arthralgia (26%). Two patients in Group B died on study, involving study drug-related events of hepatic failure and ketoacidosis, respectively.

Conclusions—In this study, Hsp90 inhibition with IPI-504 administered as a single agent had a minimal effect on PSA or tumor burden and was associated with unacceptable toxicity in several

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patients; therefore, further evaluation in CRPC patients is not warranted. IPI-504 is being investigated at less intensive doses and schedules in other tumor types.

Keywords

Castration-resistant prostate cancer; CRPC; Hsp90 inhibition; chemotherapy

Introduction

Many of the proteins implicated in the pathogenesis of castration-resistant prostate cancer (CRPC) are clients for the chaperone protein heat shock protein 90 (Hsp90).¹ Inhibition of Hsp90 may disrupt multiple mitogenic pathways simultaneously.² Solit et al demonstrated dose-dependent growth inhibition of both androgen-dependent and androgen-independent prostate cancer xenografts after treatment with the Hsp90 inhibitor 17-allylamine-17-demethoxygeldanamycin (17-AAG).^{1,3} Clinical trials of 17-AAG in patients with CRPC have demonstrated negligible antitumor activity;⁴ however, the drug is highly insoluble⁵ and has complex pharmacokinetics, raising questions of the adequacy of drug delivery.

IPI-504 (retaspimycin hydrochloride) is a novel, water-soluble hydroquinone hydrochloride salt derivative of 17-AAG and a potent Hsp90 inhibitor.⁶ Once delivered to the systemic circulation, IPI-504 is deprotonated under physiologic conditions, and the free base hydroquinone is oxidized to the quinone moiety (17-AAG) under physiologic conditions.^{7,8} 17-AAG is subsequently reduced back to the hydroquinone via cellular reductase enzymes, such that the two moieties exist in a dynamic equilibrium in vivo.⁷ Based on the scientific rationale for Hsp90 inhibition in advanced prostate cancer, favorable pharmacologic properties of IPI-504,⁹ and significant preclinical activity,¹⁰ an open label, multi-center, phase II trial of IPI-504 was initiated in patients with CRPC.

Material and Methods

Patient Population

Adults (> 18 years of age) with progressive CRPC, defined as either two serial rises in prostate specific antigen (PSA) or progressive radiographic metastases in the setting of castrate levels of serum testosterone (testosterone < 50 ng/mL), were eligible for enrollment. Patients were enrolled into either Group A (chemotherapy-naïve), or Group B (evidence of radiographic metastases, progression on or intolerance to docetaxel-based chemotherapy, and no more than three prior chemotherapeutic regimens). All patients were required to have an Eastern Cooperative Oncology Group performance status of 0-1 and adequate hematologic, hepatic, and renal function. The Institutional Review Board at each participating institution approved the protocol. Informed consent was obtained from all patients prior to enrollment.

Treatment Plan

IPI-504 (400 mg/m²) was administered as a 30-minute intravenous infusion on days 1, 4, 8, and 11 of a 21-day cycle. This starting dose was chosen based on several phase 1 studies¹¹ in which 400 mg/m² twice-weekly was found to be at or below the maximum tolerated dose of IPI-504 as a single agent. No premedications were required. In the absence of treatment-limiting toxicities, patients could continue on treatment until the time of disease progression. Toxicity assessments were performed on the day of each treatment using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 3.0.

Safety was evaluated during the study through monitoring of adverse events (AEs) and clinical laboratory data. PSA response as a study endpoint was defined according to the NCI PSA Working Group as a decline in serum PSA of $\geq 50\%$, compared to pre-treatment values, on two serial measurements performed at least 28 days apart.¹² Rising PSA levels ($\geq 25\%$ compared with nadir or $\geq 50\%$ from baseline if no PSA response occurred) were used to signal disease progression.

Pharmacokinetics/Pharmacodynamics

Heparinized blood samples (~5 mL) were collected on Cycle 1, Day 1 prior to dose administration, immediately before the infusion ended, and after dose completion at 15 minutes, 30 minutes, and 1.5-, 3.5-, and 24 hours to examine plasma for concentrations of IPI-504, 17-AAG, and 17-AG using a validated liquid chromatography assay with tandem mass spectrometric detection. The lower limit of quantitation for the assay was 50 ng/mL for all analytes, and the assay was linear between 50- and 2000 ng/mL. Concentration data were analyzed by noncompartmental methods using Phoenix WinNonLin version 6.1 (Pharsight Corporation, Mountainview, CA). Area under the plasma concentration time curve extrapolated to infinity (AUC_{∞}), maximum plasma drug concentration (C_{max}), half-life ($T_{1/2}$), clearance (CL), and steady-state volume of distribution (V_{ss}) are reported.

Statistical Design

A Simon two-stage phase 2 design was employed and applied separately to both groups.¹³ The sample size determination was based upon the primary endpoint response rate. Assuming that $\leq 5\%$ was an unacceptably low response rate, and $\geq 25\%$ was the desirable response rate, the trial was designed to have 90% power to reject the null hypothesis of a response rate of $\leq 5\%$ when the true response rate was $\geq 25\%$. The design required accrual of 15 patients to each group in the first stage. If 0/15 patients in Group A or B achieved the primary endpoint response, further accrual to that group would be terminated due to lack of activity. The probability of early termination if the null hypothesis was truly correct was 46%. If 1 or more patients in either group achieved the primary endpoint, accrual to that group would proceed with 10 additional patients enrolled in the second stage. The treatment would be declared promising for either group if 4 or more patients within the group achieved the primary endpoint. Using this design, there was a 10% probability of rejecting a promising treatment (β) and a 3.4% probability of accepting an uninteresting treatment (α).

Results

Patient enrollment, characteristics, disposition, and exposure

A total of 34 patients were screened for enrollment (6 in Group A and 28 in Group B). Nineteen patients met all inclusion criteria and were enrolled and treated with IPI-504. Baseline characteristics of Group A (n=4) and Group B (n=15) are presented in Table 1. The majority of patients in both groups had bone metastases and measurable disease. The majority of patients in both groups had previously been treated with multiple lines of hormonal therapy, and patients in Group B had received a median of two prior chemotherapeutic regimens.

Overall (N=19), the median number of study drug cycles started was 2 (range: 1 to 34) with a median number of 5 study drug doses received (range: 1 to 129). The median cumulative amount of study drug received across all administrations was 4000 mg (range: 728 to 83111 mg).

An unplanned interim analysis was performed after 2 deaths were assessed by the investigator as being related to IPI-504 (discussed below). The analysis revealed no

clinically meaningful antitumor activity; therefore, in consideration of the overall risk-benefit ratio not justifying the continuation of the trial, new accrual to the trial was halted and all patients were permitted to continue on-study at a reduced dose of 300 mg/m² after consulting with their physicians. At that point, 3 patients in Group A and 4 patients in Group B were withdrawn from the study. One patient in Group A remained on study until discontinuation approximately 2 years later due to disease progression. In Group B, reasons for the remaining patients' discontinuations included progressive disease (n=3) and AE (n=8).

Adverse Events

Of the 19 patients enrolled and treated, 18 patients (95%) were reported with treatment-emergent AEs (TEAEs) and 11 (58%) with CTCAE Grade 3 or higher TEAEs. The TEAEs of 2 patients (11%) resulted in death and are discussed below. TEAEs reported in at least 2 patients during the study are summarized in Table 2.

TEAEs occurring in > 25% of the study population included nausea (47%), diarrhea (42%), fatigue (32%), anorexia (26%), and arthralgia (26%). The majority of patients entered the study with liver enzymes (AST and ALT) at normal levels that remained normal or worsened to Grade 1 in severity during the study. Shifts in these liver enzymes from normal at baseline to Grade 3 or 4 were observed as TEAEs in 2 patients. The AST elevation to 397 U/L (Grade 3) in one patient at Cycle 2, Dose 3 prompted study drug discontinuation, and the patient's AST level returned to normal 4 days later. In the second patient, ALT elevation to 659 U/L (Grade 3) from a normal baseline level was reported at Cycle 1, Dose 2 with concurrent AST elevation to 863 U/L (Grade 4) from 32 U/L (Grade 1) at baseline. After study drug discontinuation, the events of ALT and AST elevation resolved. In addition, two patients in Group B, a 57-year old male and a 60-year old male, both with metastatic disease, died during Cycle 2 and Cycle 1, respectively, due to TEAEs involving hepatic failure in one patient and insulin-resistant hyperglycemia with ketoacidosis and multi-organ failure in the other patient. The event of hepatic failure in the first patient occurred 1 day after study drug was administered inappropriately in the setting of a Grade 3 AST elevation (339 U/L). The latter patient had a medical history of steroid-related hyperglycemia and was receiving corticosteroids at the time of the event. Both patients had concurrent Grade 3 or Grade 4 elevations in liver enzymes. Based on the hepatic findings and the temporal relationship of the events to study drug administration, the study investigators assessed the patients' deaths to be related to study drug.

Pharmacokinetics

Pharmacokinetic data were evaluated in 14/19 patients enrolled in the study (Table 3). Peak plasma concentrations for IPI-504 and 17-AAG were observed at the end of the infusion in all but 1 patient, where the peak 17-AAG concentration was observed 20 minutes after infusion completion. The time of peak 17-AG concentrations varied, ranging from the end of the infusion to 1.5 hours post-infusion. Mean AUC_{0-∞} for IPI-504 and 17-AAG were similar (11,712- and 9,847 ng*hr/mL, respectively). Exposure to 17-AG exceeded that for parent drug and accounted for approximately 68% of the total measured exposure (determined as the sum of IPI-504, 17-AAG, and 17-AG without adjustment for small differences in molecular weight). Plasma concentrations of 17-AG declined more slowly (mean T_{1/2}, 5.2 hours) compared to IPI-504 and 17-AAG (mean T_{1/2}, 2.3 hours and 1.4 hours, respectively).

There was significant interpatient variability in C_{max} and AUC_{0-∞} across all the analytes, with coefficients of variation ranging 36% - 65%. The limited number of samples collected and shape of the plasma concentration profile prevented determination of AUC_{0-∞} and T_{1/2}

in 2 patients for 17-AAG and in 4 patients for 17-AG. In the remaining patients, the median percentage of AUC extrapolated beyond the last measurable concentration was 8.6% (range, 3.1 to 30.7) for 17-AAG and 7.6% (range, 1.8 to 53.0%) for 17-AG. Exposure (reported as $AUC_{0-\infty}$ or AUC_{0-last}) to IPI-504, 17-AAG, and 17-AG tended to be higher in the 2 patients who died compared to the mean values reported in Figure 1. One patient who died (hepatic failure) was reported with maximum exposure values for IPI-504 and 17-AAG (26,363 ng*h/mL and 23,606 ng*h/mL, respectively) and also was with reported elevated exposure to 17-AG.

Antitumor Outcomes

No patients on study achieved $\geq 50\%$ post-treatment decline in PSA (Figure 2). One patient in Group A remained on treatment for 9 cycles with a PSA decline of 48% from baseline.

Comment

In this study of IPI-504 in patients with both chemotherapy-naïve and docetaxel-treated CRPC, negligible activity and two treatment-related deaths were observed, one attributed to hepatic failure and the other to ketoacidosis. Hepatotoxicity has been observed with several Hsp90 inhibitors, which has limited the clinical development of geldanamycin,¹⁴ and was a dose limiting toxicity in several phase I trials exploring 17-AAG.¹⁵⁻¹⁷ The causality and mechanism of hyperglycemia in the patient who died of ketoacidosis was less clearly defined. This patient had a history of steroid-induced hyperglycemia and was receiving corticosteroids. One patient in the study achieved a 48% decline in PSA and continued on study for > 40 weeks, suggesting that Hsp90 inhibition may be an effective strategy in a small subset of patients with CRPC. Overall, however, the results of the study and other studies exploring Hsp90 inhibitors in CRPC have been disappointing. The precise mechanism of action of Hsp90 inhibitors in sensitive tumors remains unclear, and may be related to an overall increased dependence on chaperone function rather than reliance on any specific client(s).¹⁸

Pharmacokinetic data from this study are consistent with a previous study conducted in patients with relapsed or refractory multiple myeloma that demonstrated approximately equal exposure to IPI-504 and 17-AAG following IPI-504 administration. Furthermore, exposure to 17-AG as a major metabolite is consistent with preclinical studies in mice¹⁹ and previously conducted clinical studies with 17-AAG.^{15-17,20}

While the association between increased exposure and the 2 patient deaths on study is notable, the relationship between exposure and safety has not been fully defined for IPI-504, 17-AAG, or 17-AG. In vitro studies have demonstrated the cytochrome P450 3A4 (CYP3A4) enzyme is involved in the metabolism of IPI-504;¹⁹ **Error! Bookmark not defined.** however, neither of these two patients was receiving concurrent potent CYP3A4 inhibitors or inducers which could have altered the exposure to IPI-504, 17-AAG, or 17-AG.

Patients progressing despite castrate levels of serum testosterone often respond to inhibitors of adrenal androgens or androgen receptor (AR) binders. These clinical observations are bolstered by studies demonstrating persistently elevated intraprostatic androgen concentrations despite castration, upregulation of genes involved in androgen synthesis in metastatic samples compared to primary prostate tumors, and frequent AR amplifications in CRPC.^{21,22} Studies of the androgen-axis in CRPC have demonstrated significant activity with more potent and selective inhibitors of androgen signaling, confirming that AR remains a key therapeutic target for this clinical state.^{23,24} Other important pathways in CRPC, supported by preclinical studies, include upregulation of the PI3K/Akt/mTOR pathway due primarily to loss of *PTEN*, and signaling through the epidermal growth factor family

receptors through amplifications of *HER2*.²⁵⁻²⁷ Given that AR, Akt, and Her-2 are all client proteins for Hsp90, inhibition of Hsp90 in CRPC represents an attractive strategy for disrupting several vital pathways in CRPC simultaneously. Indeed, preclinical studies with a variety of Hsp90 inhibitors, including IPI-504, have demonstrated antitumor activity in prostate cancer xenografts along with a concomitant decline in client protein expression,^{1,28} providing further support for the clinical development of this novel class of agents in CRPC.

To our knowledge, this is the first clinical trial exploring a water soluble Hsp90 inhibitor in patients with CRPC. Similar to other studies exploring Hsp90 inhibition in prostate cancer, negligible antitumor activity was observed. The lack of apparent clinical benefit in this small sampling of CRPC patients does not warrant the risk associated with administration of IPI-504 400 mg/m² twice weekly for 2 weeks each cycle in this patient population. However, if a cancer patient population were identified in which clinical benefit could be achieved, the observed profile may be acceptable with appropriate monitoring for and management of known toxicities.

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Figure 1.
Post-treatment changes in PSA. Waterfall plot demonstrating maximum post-treatment PSA changes in individual patients treated with IPI-504.

Table 1
Baseline Demographics of Enrolled and Treated Patients

Demographic	Statistic/Parameter	Group A (N=4)	Group B (N=15)
Age (years)	Mean (SD)	70.5 (2.5)	61.8 (2.2)
	Median	68.5	60.0
	Min, Max	67, 78	49, 74
Age Category [n(%)]	40-65	0	9 (60.0)
	> 65	4 (100.0)	6 (40.0)
	Missing	0	0
Race [n(%)]	White	4 (100.0)	12 (80.0)
	Black or Afr. Am.	0	2 (13.3)
	Asian	0	1 (6.7)
Weight (kg)	Mean (SD)	93.0 (3.3)	79.6 (3.1)
	Median	94.10	80.70
	Min, Max	84.0, 99.7	59.7, 103.0

Table 2
Summary of Treatment Emergent Adverse Events (TEAEs) in at least 2 Patients (10%)

Treatment-Emergent Adverse Events	Patients [n (%)]	
	Any TEAE*	TEAE (Grade $\geq$ 3)
Nausea	9 (47)	1 (5)
Diarrhea	8 (42)	1 (5)
Fatigue	6 (32)	1 (5)
Anorexia	5 (26)	1 (5)
Arthralgia	5 (26)	0
Dehydration	4 (21)	3 (16)
Pain in Extremity	4 (21)	0
Infusion Site Pain	4 (21)	0
Constipation	4 (21)	0
Vomiting	4 (21)	1 (5)
Anemia	4 (21)	1 (5)
Musculoskeletal Pain	3 (16)	0
Pyrexia	3 (16)	0
Myalgia	3 (16)	0
Hyponatremia	2 (11)	2 (11)
ALT Increased	2 (11)	1 (5)
Anxiety	2 (11)	0
AST Increased	2 (11)	2 (11)
Back Pain	2 (11)	1 (5)
Headache	2 (11)	0
Hypokalemia	2 (11)	0
Pneumonia	2 (11)	2 (11)

* Including TEAEs Grade $\geq$ 3 and Serious TEAEs.

Table 3
Pharmacokinetic Parameters

Drug and Metabolite	Pharmacokinetic Parameter					
	AUC _∞ (ng•h/mL)	C _{max} (ng/mL)	T _{max} (h)	T _{1/2} (h)	CL (L/h)	V _{ss} (L)
IPI-504	11712 (7595)	7800 (4227)	0.58 (0.55, 1.02)	2.27 (2.81)	97.9 (65.3)	208 (124)
17-AAG	9847 (3551)	7038 (2497)	0.58 (0.55, 1.02)	1.38 (1.23)	Not Done	Not Done
17-AG	45320 (25514)	6086 (3061)	0.97 (0.58, 2.17)	5.19 (1.57)	Not Done	Not Done

Note: All PK parameters are presented as mean (SD) except Tmax (median [range]). Definitions: AUC_∞, Area under the plasma concentration time curve extrapolated to infinity; C_{max}, maximum plasma drug concentration; T_{max}, time to maximum concentration in plasma; T_{1/2}, half-life; CL, clearance; V_{ss}, steady-state volume of distribution