

A single arm Phase 2 trial of IPI-504 in patients with castration resistant prostate cancer



Oh WK, Stadler WM, Srinivas S, Chu F, Bublely G, Quigley M, Goddard J, Dunbar J, Grayzel D, Ross RW

Dana-Farber Cancer Institute, Boston MA; University of Chicago, Chicago IL; Stanford University, Stanford CA; San Bernardino Urological, San Bernardino CA; Beth Israel Deaconess Medical Center, Boston MA; Infinity Pharmaceuticals, Cambridge MA

Abstract

Background: IPI-504 (retaspimycin hydrochloride) is a potent, water-soluble heat shock protein 90 (Hsp90) inhibitor. IPI-504 induces the degradation of the androgen receptor, AR, and HER-2 in PC cell lines and significantly reduces tumor growth in murine CRPC xenograft models. This study evaluated the clinical activity and safety of IPI-504 in men with CRPC.

Methods: We conducted a single arm trial of IPI-504 in two groups of men with CRPC – Group A (patients who had received no prior cytotoxic chemotherapy for CRPC) and Group B (patients who experienced disease progression during or within 60 days after at least two cycles of docetaxel-based chemotherapy). IPI-504 at a dose of 400 mg/m² was administered intravenously on days 1, 4, 8 and 11 of a 21-day cycle. The trial was designed to expand if at least one PSA or radiographic response was noted in either cohort. Pharmacokinetic samples were collected following the first dose and safety was assessed throughout.

Results: A total of 19 patients were enrolled (4 in Group A and 15 in Group B), with a median age of 64 years (range 49-79). Patients had an average of 4.8 prior systemic treatments. Group B patients had an average of 1.6 prior chemotherapy regimens. Median PSA at study entry was 41 ng/ml (range 5–100) for Group A patients and 305 ng/ml (range 45–4823) for Group B patients. All Group B patients had bony metastatic disease, and 66% had measurable soft tissue or visceral metastases. No PSA or RECIST responses were observed, however one Group A patient has remained on trial for 5 cycles with a PSA decline of 48% from baseline. Serious adverse events were observed in Group B, including one patient with Grade 5 hepatic failure and one patient with Grade 5 ketoacidosis.

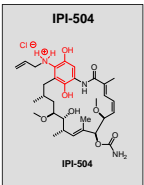
Conclusions: Hsp90 inhibition with IPI-504 given as a single agent had a minimal effect on PSA or tumor burden. Further evaluation of IPI-504 as a single agent in this patient population is not warranted at this time.

Background

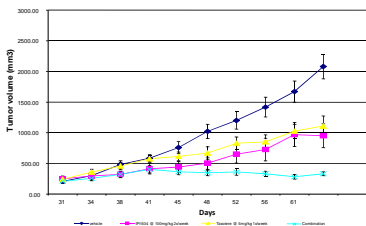
Hsp90 is a protein chaperone responsible for the proper folding, function, and stability of various “client” proteins. Many of these client proteins, either in their wild type or mutant form, are oncoproteins that play a key role in the pathogenesis of many different cancers.

IPI-504 is a novel, potent, selective, and water-soluble heat shock protein 90 (Hsp90) inhibitor. IPI-504 exists as a hydrochloride salt which is soluble in water in excess of 250 mg/ml.

The biologic and anti-neoplastic effects of IPI-504 have been demonstrated in multiple human xenograft and murine orthotopic models of cancer. IPI-504 inter-converts with 17-AAG and exists in a pH and enzyme-mediated dynamic redox equilibrium in humans.

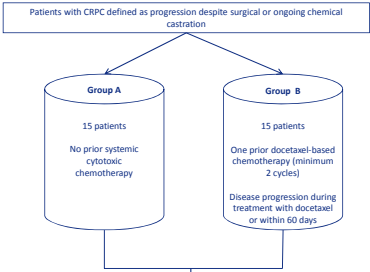


IPI-504 delays growth in PC-3 xenograft



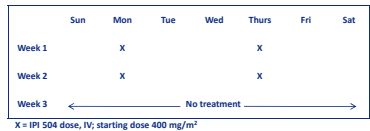
Methods

Study design



If 1 or more patients achieve a PSA response or RECIST response then an additional 10 patients will be added to that cohort

Treatment schema



Results

Baseline characteristics

	Group A (n=4)	Group B (n=15)
Age, years (median)	68.5	60.0
≤ 6	0%	13.3%
7	25.0%	33.3%
8-10	75.0%	46.7%
Measurable disease at baseline	75.0%	60.0%
Bone metastasis at baseline	75.0%	100%
Median PSA at baseline (range)	41.8 ng/ml (5-104.2)	317.8 ng/ml (25.7-4823.0)

Prior treatment

	Group A (n=4)	Group B (n=15)
Prior prostatectomy	0	13.0%
Prior prostate radiation	75.0%	20.0%
Median number of prior hormonal therapies (range)	6 (4-11)	3 (1-15)
Median number of prior chemotherapy treatments (range)	N/A	2 (1-8)
Median number of months since last docetaxel treatment (range)	N/A	5 (1-27)
Median number of months since last chemotherapy (range)	N/A	3 (1-27)

All adverse events experienced by > 10% of patients on study (n = 19)

Event	Grade (% n)					Total (% n)
	1-2	3	4	5		
Any AE	36.8%, 7	26.3%, 5	15.8%, 3	10.5%, 2	89.5%, 17	
Fatigue	21.1%, 4	5.3%, 1	0%, 0	0%, 0	26.3%, 5	
Nausea	21.1%, 4	5.3%, 1	0%, 0	0%, 0	26.3%, 5	
Diarrhea	15.8%, 3	5.3%, 1	0%, 0	0%, 0	21.1%, 4	
Anorexia	15.8%, 3	5.3%, 1	0%, 0	0%, 0	21.1%, 4	
Arthralgia	21.1%, 4	0%, 0	0%, 0	0%, 0	21.1%, 4	
Constipation	15.8%, 3	0%, 0	0%, 0	0%, 0	15.8%, 3	
Infusion site pain	15.8%, 3	0%, 0	0%, 0	0%, 0	15.8%, 3	
Dehydration	0%, 0	15.8%, 3	0%, 0	0%, 0	15.8%, 3	
Anemia	10.5%, 2	5.3%, 1	0%, 0	0%, 0	15.8%, 3	

Reason for study discontinuation

Reason	Group A (n=4)	Group B (n=15)
Progressive disease	0	3
Adverse event/Death	0	7
Consent withdrawn/other	3	5
Still on study	1	0

After an unplanned interim analysis revealed no clinically meaningful effects on PSA and occurrence of the two deaths on study, new accrual to the trial was halted

All patients on-trial were dose-reduced to 300 mg/m². Many of the ongoing patients withdrew from the study.

Results

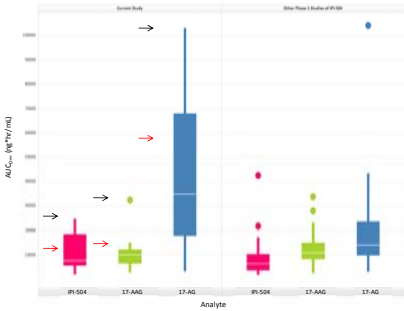
Safety narratives

There were two deaths on study, both in patients from Group B – one from hepatic failure and one from hyperglycemic ketoacidosis.

Hepatic failure: This patient was a 57-year-old male with extensive bone and liver metastases and a history of spinal cord compression. The patient's PSA at study entry was 568.10 ng/ml. Prior to beginning treatment with IPI-504, the patient's LFTs were notable for AST 49 U/L and an alkaline phosphatase of 129 U/L (both Grade 1) with an albumin of 2.9 g/dL. During the course of Cycle 1, the patient's AST, ALT and alkaline phosphatase rose gradually to a peak of an AST of 118 U/L (Grade 2), but returned to baseline prior to Cycle 2 Dose 1. On the day of scheduled treatment with Cycle 2, Dose 2, the patient's laboratory results revealed an AST of 339 U/L (Grade 3), which, according to the protocol, should have resulted in holding the dose. Nevertheless, IPI-504 was administered to the patient prior to the investigator's review of the laboratory results. The next day, the patient presented to the emergency room complaining of abdominal pain, nausea/vomiting and diarrhea. The patient's LFTs were elevated and he was coagulopathic, with an AST of 1089 U/L, an ALT of 2164 U/L, an alkaline phosphatase of 661 U/L, a prothrombin count of 92 K/mL, PT of 31 s and PTT of 139.1 s. A head CT, obtained to evaluate the patient's change in mental status, revealed a cerebral hemorrhage. The patient expired the day after presenting to the emergency room. The investigator determined that the cause of death was hepatic failure related to IPI-504.

Hyperglycemic ketoacidosis: This patient was a 60-year-old man with metastases to his bones and intra-abdominal lymph nodes. He had a history of hepatitis C and elevated glucose levels during steroid treatment. After his first dose of IPI-504 400 mg/m², the patient complained of nausea and 10/10 back pain. Prior to his second dose he was premedicated with dexamethasone, and was sent home on a dose of 4 mg BID. Two days later he experienced confusion, dyspnea, thirst, and polyuria for which he was hospitalized. He was found to be hyperglycemic with ketoacidosis, and also had Grade 4 hypotension requiring multiple pressors. The patient subsequently developed multi-system organ failure, Grade 4 pancreatitis, and Grade 3 liver dysfunction. Hyperglycemia persisted despite intravenous insulin. The ketoacidosis and lactic acidosis worsened, and the patient developed disseminated intravascular coagulation with gastrointestinal hemorrhage, and two days later. The investigator determined the cause of death as hyperglycemia with ketoacidosis, related to IPI-504. Several studies were performed to better understand the etiology of this insulin-refractory hyperglycemic ketoacidosis, including assessing the patient for circulating antibodies to insulin and the insulin receptor as well as assessing for mutations in his insulin receptor, but none of these investigations were positive.

Pharmacokinetics



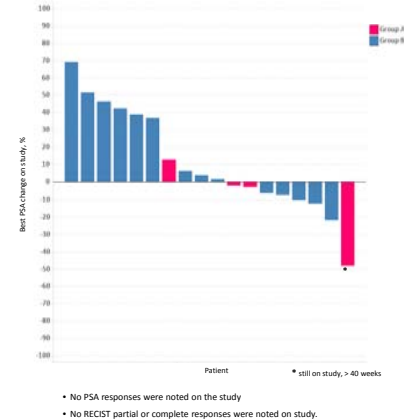
Plasma was analyzed for IPI-504 and its two major metabolite - 17-allylamino-17-demethoxygeldanamycin (17-AAG) and 17-amino-17-demethoxygeldanamycin (17-AG)

The boxes represent the 1st to 3rd quartiles

The white line is the median value

The arrows note the AUC for the two patients on this trial who died

Efficacy - PSA waterfall plot



No PSA responses were noted on the study

No RECIST partial or complete responses were noted on study.

Conclusions

IPI-504 as a single agent has no demonstrated efficacy in the treatment of CRPC. Studies of Hsp90 inhibition in prostate cancer should be conducted with care, given the lack of activity and the toxicity of Hsp90 inhibition in this patient population.

The exposure to IPI-504 and its metabolites in this patient population is markedly variable, particularly for 17-AG, an active metabolite.

Work is ongoing to understand if this heterogeneity is related to castration, concomitant medications, or other baseline or metabolic characteristics of this population

In contrast to studies of IPI-504 in multiple myeloma, sarcoma, and lung cancer, IPI-504 was less well tolerated in this patient population, with two unexpected patient deaths.

Analyses are being performed to understand the relationship between the increased toxicity and the association between the AUC, C_{max} and clearance of IPI-504 and its metabolites in this patient population

Acknowledgements

All the patients and their families who participated in this study

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