Overcoming Resistance to Small Molecule Kinase Inhibitors (SMKIs) Through Inhibition of Heat Shock Protein 90 (Hsp90) Chaperone Function in Patients with Metastatic GIST: Preliminary Results of a Phase I Trial of IPI-504, a Water-Soluble Hsp90 Inhibitor

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Abstract #570

Abstract

Introduction: Prior work from our team has demonstrated that inhibition of the Hsp90 chaperone protein results in selective destruction of the mutated Kit kinase in human GIST cell lines that have been molecularly-characterized. This novel strategy is associated with antitumor activity in cells harboring mutations which confer resistance to small molecule tyrosine kinase inhibitors (SMKIs). To translate this into clinical testing, we are performing a Phase I trial of IPI-504, a water-soluble inhibitor of Hsp90, in patients with metastatic GIST following failure of SMKI therapy.

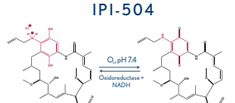
Methods: Patients (pts) with metastatic GIST were eligible for study entry following failure of prior SMKI therapy such as imatinib and sunitinib. Patients received IPI-504, infused in 250 cc of normal saline over 30 minutes IV, on days 1, 4, 8 and 11 of a 21-day cycle. Serial monitoring with ^{18}FDG-PET imaging at baseline, day 11, and day 21, CT scans at baseline and day 21, as well as PK profiling of IPI-504, 17-AAG and its major active metabolite and 17-AG, was performed on all pts.

Results: To date in this ongoing trial, 20 GIST pts have been enrolled at 5 dose levels (90 [n=6], 150 [3], 225 [3], 300 [3], 400 [5] mg/m^2 IPI-504). A DLT occurred at 90 mg/m^2 with one pt having an asymptomatic grade 3 lipase elevation. The cohort was expanded to 6 pts with no further DLTs observed. The protocol was subsequently amended so that asymptomatic lipase elevation in the absence of any clinical signs or symptoms of pancreatitis was removed from the DLT definition. A DLT was also observed at the 400 mg/m^2 dose level (intra-cranial hemorrhage) in a patient with significantly advanced metastatic disease and baseline elevated PT and PTT secondary to multiple liver metastases. This cohort has been expanded to 6 patients and evaluation of this dose level is ongoing. No other DLTs or Grade 3-4 adverse events possibly related to drug administration have been observed. PET imaging as a biomarker demonstrates decreased tumor ^{18}FDG avidity in 1/6, 1/3, 3/3, 1/3 and 1/2 pts at the respective dose levels. Although no RECIST-defined disease responses were noted, stable disease has allowed 6/15 pts to continue on study treatment for 5 or more cycles.

Conclusion: Targeting Hsp90 represents a novel therapeutic strategy in GIST resistant to SMKIs, and the clinical evaluation of IPI-504 is ongoing to define the tolerability, MTD and clinical and biological activity of IPI-504 in this setting. Results to date demonstrate that IPI-504 is well-tolerated at doses up to 400 mg/m^2. The activity of IPI-504 in decreasing FDG avidity of GIST lesions is promising. In addition, a "PET flare" phenomenon has been observed during the "drug holiday" period off IPI-504 administration. This is similar to the "PET flare" in GIST patients noted following withdrawal of imatinib or sunitinib administered on an intermittent treatment schedule and suggests a drug-dependent PET response. Based on these data, a new schedule of twice-weekly administration (without "drug holiday") is planned. Further studies of IPI-504 in a broad range of clinical indications driven by aberrant kinase signaling is warranted based on these data.

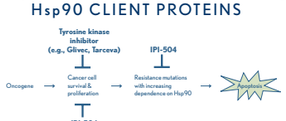
Introduction

IPI-504



* Porter, et al J Med Chem 2006 vol 49(15):4606

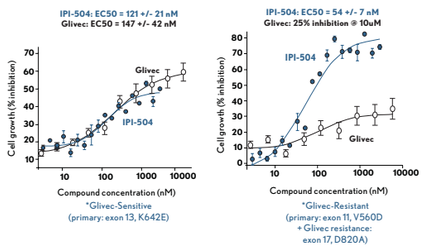
TARGETING SPECIFIC ONCOGENIC Hsp90 CLIENT PROTEINS



IPI-504 is a novel treatment for emerging resistance to targeted therapy

Preclinical Data

Glivec-resistant GIST cells are more sensitive to inhibition with IPI-504



*Glivec-Sensitive (primary: exon 13, K642E)

*Glivec-Resistant (primary: exon 11, V560D + Glivec resistance: exon 17, D820A)

Methods

- Conventional "3+3" modified Fibonnaci study design
- Standard definition of dose limiting toxicity (Grade 4 hematologic toxicities, Grade 3 non-hematologic toxicities in first cycle of treatment), excluding asymptomatic/non-clinically significant lipase elevation
- IPI-504 administered intravenously to patients on Days 1, 4, 8 and 11 of a 21- day cycle
- Response is assessed using RECIST criteria and qualitative assessment of PET imaging PET scans are obtained serially at 3 points during the first cycle
  - -Baseline, once between Days 4-11, and again at the end of the 3-week cycle after drug holiday (Day 21)
- Cardiac Monitoring
  - -During the trial EKGs are obtained in triplicate to evaluate the potential for cardiac toxicity
  - -EKGs are obtained on all patients at the following time points:
    - •Cycle 1 Day 1: Baseline, 5 minutes, 60 minutes and 360 minutes post infusion
    - •Cycle 1 Days 4, 8 and 11: Baseline and 5 minutes post infusion
    - •Cycle 1 Day 21: Baseline
    - •All other days of dose administration: Baseline and 5 minutes post infusion
- Administration of IPI-504
  - -IPI-504 is manufactured as a sterile lyophilized powder
  - -Reconstituted into 250 cc of normal saline
  - -Drug is then infused over 30 minutes by either peripheral or central venous access
- The primary objectives of the study are to determine the safety and tolerability of IPI-504 and identify a recommended Phase II dose for future clinical trials

Schedule of Administration = 21 days

Dose Escalation

Group	Dose (mg/m^2)	Patients Treated	Escalation over previous dose
1	90	6	n/a
2	150	3	66%
3	225	3	50%
4	300	3	33%
5	400	5	33%
6	500	n/a	25%

Results

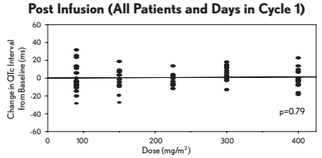
Patient Characteristics

Average age (yrs)	53.5
Gender	M - 14, F - 6
Performance status ECOG - 0 ECOG - 1	 9 patients 11 patients
Average years since GIST diagnosis	4.7
# Patients having progressed on prior SMKI therapy: Gleevec (%) Sutent (%)	 20/20 (100%) 19/20 (95%)
Average number of prior therapies per patient (range)	2.65 (1-6)

Dose Limiting Toxicities

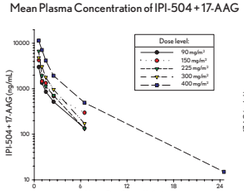
- Pt 001 is a 58 year-old man with a history of metastatic GIST originally diagnosed in 1999. He was enrolled at the 90 mg/m^2 dose level and was found to have Grade 3 asymptomatic lipase elevation after his first dose administration. The patient reported no symptoms, a normal amylase level and all other laboratory values were WNL. As per protocol, the following dose was withheld. The pt continued to receive IPI-504 for 3 additional cycles without any evidence of clinical toxicity. The protocol was amended so that asymptomatic lipase elevation in the absence of any clinical signs or symptoms of pancreatitis was removed from the DLT definition.
- Pt 019 is a 60-year old woman with a history of metastatic GIST originally diagnosed in 1998. She was enrolled at the 400 mg/m^2 dose level with baseline Grade 1 PT and PTT prolongation secondary to her multiple hepatic metastases. Concomitant medications of note include naprosyn 375 mg PO BID and Excedrin® prn (includes active ingredients: 250 mg aspirin, 250 mg acetaminophen). On July 17th the pt reported a progressively worsening headache and took numerous Excedrin® several times over the next 24 hrs. Left visual field changes and declining mental status were noted on July 18th when a head CT revealed an intra-cranial hemorrhage. Pt was admitted to the Neurology Intensive Care Unit. After extensive discussions with her family, it was agreed that she should receive comfort measures only given the progressive and symptomatic nature of her underlying malignancy. The pt died shortly thereafter.
- No other DLTs or Grade 3-4 adverse events possibly related to drug have been observed.
- No DLTs or Grade 3-4 cardiac toxicities observed, no evidence of QTc prolongation (1,810 EKGs evaluated).

No Observable Change in QTc Interval from Baseline to 5 minutes Post Infusion (All Patients and Days in Cycle 1)

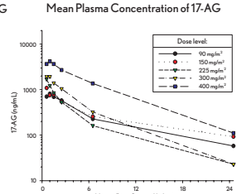


PHARMACOKINETIC DATA

Mean Plasma Concentration of IPI-504 + 17-AAG

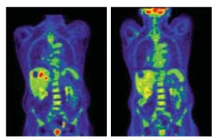


Mean Plasma Concentration of 17-AG



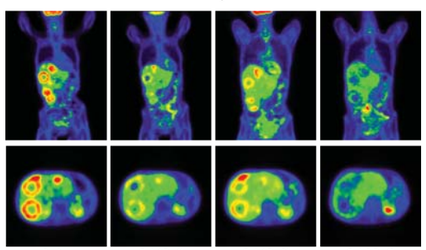
EVIDENCE OF BIOLOGIC ACTIVITY

^{18}FDG-PET for Pt 006 following Failure of Glivec and Sutent Pt received 90 mg/m^2 of IPI-504



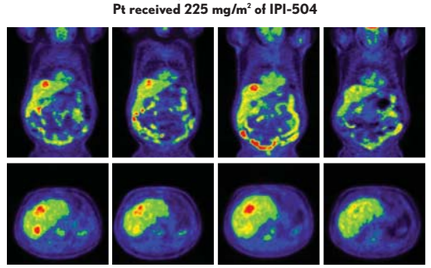
Baseline | Cycle 1, Day 9, 24 hours after 2nd dose of IPI-504

^{18}FDG-PET for Patient 007 following failure of Glivec, Sutent and AMN-107 Pt received 150 mg/m^2 of IPI-504



Baseline | Cycle 1, Day 11, 72 hours post 3rd dose of IPI-504 | Cycle 1, Day 21, After 10 days off treatment | Cycle 3, Day 12, After treatment re-initiated

^{18}FDG-PET for Patient 011 following failure of Glivec, Sutent and Glivec/AMN-107 Pt received 225 mg/m^2 of IPI-504



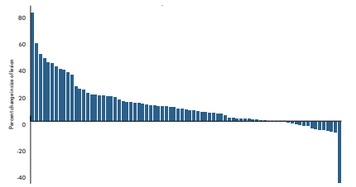
Baseline | Cycle 1, Day 9, 24 hours post 2nd dose of IPI-504 | Cycle 1, Day 21, After 10 days off treatment | Cycle 5, Day 12, After treatment re-initiated

Duration of Treatment

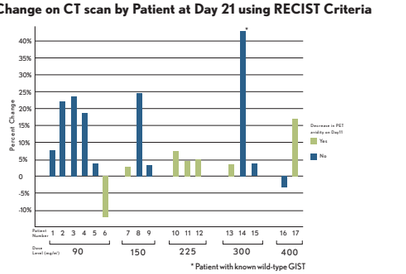
Dose Level	IPI-504 (mg/m^2)	# of Patients	Best Response by RECIST	# Cycles per patient
1	90	6	SD, PD, PD SD, SD, SD	3, 2, 1, 1, 3, 5
2	150	3	SD, PD, SD	8, 2, 2
3	225	3	SD, SD, SD	5, 7, 3
4	300	3	SD, PD, SD	5, 2, 6*
5	400	5	SD, n/e, SD, TETA, TETA	4, n/e, 3*, TETA*, TETA*

* Patient still receiving therapy at time of presentation
* n/e = not evaluable; TETA = Too early to assess

% Change on CT scan for All Lesions at Day 21 using RECIST Criteria



% Change on CT scan by Patient at Day 21 using RECIST Criteria



* Patient with known wild-type GIST

Conclusions

- **In this Phase I study there is promising early evidence of biologic activity of IPI-504 in advanced metastatic GIST patients resistant to SMKI therapy.**
  - **-A decrease in FDG avidity on PET scanning has been seen in 7/17 (41%) patients. PET responses have been observed at all IPI-504 dose levels studied.**
  - **-6/15 (40%) patients received IPI-504 for 5 or more cycles.**
- **In patients with advanced GIST, a "PET flare" phenomenon has been observed during the "drug holiday" period off IPI-504 administration. This is similar to the "PET flare" in GIST patients noted following withdrawal of imatinib or sunitinib administered on an intermittent treatment schedule and suggests a drug-dependent PET response (van den Abbeele, Dileo).**
  - **-Based on these data, a new schedule of twice-weekly continuous administration (without "drug holiday") is planned.**
- IPI-504 has been well-tolerated up to doses of 400 mg/m^2. In the limited number of patients who have received 5 or more cycles of treatment the drug appears to be equally well-tolerated.
- The Maximum Tolerated Dose of IPI-504 has not yet been identified on the current 21- day schedule of administration.
- Pharmacokinetic data demonstrate dose proportionality for IPI-504, its inter-conversion product 17-AAG and its primary active metabolite 17-AG.
- Further studies of IPI-504 in a broad range of clinical indications driven by aberrant kinase signaling is warranted based on these data.
- **These data support the role of Hsp90 inhibition in overcoming resistance to SMKIs in this heavily pre-treated patient population with metastatic GIST.**

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