Abstract #B79

Phase 1/2 Trial of the Novel Hsp90 Inhibitor, IPI-504, in Patients with Relapsed and/or Refractory Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC) Stratified by EGFR Mutation Status

L. Sequist*, P. Janne**, J. Sweeney, J. Walker, D. Grayzel, T. Lynch*

*Massachusetts General Hospital Cancer Center, Boston, MA USA; **Dana-Farber Cancer Institute, Boston, MA USA; Infinity Pharmaceuticals, Cambridge, MA USA

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Abstract

Introduction: Inhibition of the Heat Shock Protein 90 (Hsp90) chaperone protein results in selective destruction of the mutated epidermal growth factor receptor (EGFR) kinase in human non-small cell lung cancer (NSCLC) cell lines, including those resistant to tyrosine kinase inhibitors (TKIs). We designed a Phase 1/2 trial of IPI-504, a water-soluble Hsp90 inhibitor, for patients (pts) with advanced NSCLC who had received prior TKI therapy.

Methods: Pts with Stage IIIb (with malignant effusion) or Stage IV NSCLC who had received prior therapy with an EGFR TKI (e.g., gefitinib or erlotinib) for ≥12 weeks, and had available tissue for EGFR mutation analysis were eligible for treatment. The goal of the Phase 1 portion was to evaluate the safety and maximum tolerated dose (MTD) of IPI-504 in pts with advanced NSCLC. Once dose-escalation is completed, the Phase 2 portion will begin with a goal of determining the potential anti-tumor activity of IPI-504 in NSCLC pts, stratified by EGFR mutation status. Pts received IPI-504, IV in 250 cc of normal saline over 30 min, twice weekly on a four-week cycle. Subjects were evaluated for clinical benefit and radiographic improvement or stabilization by RECIST. Pharmacokinetic profiling of IPI-504 and its major active metabolites (17-AAG and 17-AG) was also performed on all pts.

Results: Twelve pts with NSCLC have been entered at 3 dose levels of IPI-504 (150 mg/m² [n=3], 225 mg/m² [n=4], 300 mg/m² [n=5]). To date, 11 patients have data available (9 women, 2 men; average age 63.6 years; 9 positive for EGFR mutation [exon 19 or exon 21]; avg. # prior therapies 3.7 [range 1-6]). All pts completed at least 1 cycle and 9 of 11 pts were evaluable. No objective responses have been observed yet; however, 7 pts had Stable Disease including 1 pt on therapy for >27 weeks (7 cycles). IPI-504 has been well-tolerated to date. Two DLTs (Grade 3 AST elevation [reversible] and Grade 3 fatigue [reversible]) were observed at 300 mg/m², establishing the MTD at 225 mg/m² administered twice weekly for 4 weeks. Of the 4 evaluable pts who underwent PET, 2 had Stable Disease and 2 had Partial Response by EORTC criteria.

Conclusion: Targeting Hsp90 represents a novel therapeutic strategy in advanced or metastatic NSCLC patients who are heavily pre-treated and have failed prior therapy with TKIs. IPI-504 has been well-tolerated overall with establishment of the MTD, and encouraging preliminary biological activity has been observed with the occurrence of extended stable disease.

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 (such as EGFR, AKT, Her-2, Bcr-Abl, PDGFR-α, and c-Kit) are oncoproteins (Maloney) 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 200 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 which has been observed in human clinical trials. (Ge; Demetri 2006)
- IPI-504 is being studied in several different clinical trials. Data recently presented has shown that the compound is well-tolerated and shows promising evidence of biological activity in a Phase I clinical trial in patients with metastatic, imatinib and sunitinib-resistant GIST. (Demetri 2007)

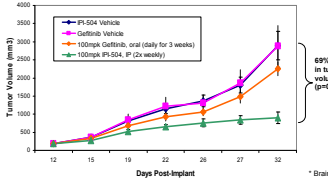
Figure 1. IPI-504
Aqueous solubility >200 mg/mL
Formulation: aqueous solution

Rationale for IPI-504 in NSCLC

- Epidermal growth factor receptor (EGFR) plays a critical role in the pathogenesis of NSCLC. Activating mutations in EGFR lead to increased response and likely increased survival after treatment with EGFR TKIs. (Lynch, Paez, Han, Mitsudomi)
- Although erlotinib or gefitinib have been shown to be effective treatment for NSCLC in certain sub-populations of patients, acquired resistance ultimately develops.
  - One molecular mechanism of acquired resistance is the emergence of the exon 20 T790M mutation in EGFR. (Kobayashi, Pao)
  - Another molecular mechanism of acquired resistance is the amplification of c-Met. (Engelman)
- Both EGFR and c-Met are client proteins of Hsp90 and are highly sensitive to IPI-504. Mutant EGFR associates with Hsp90 and is rapidly degraded after inhibition of Hsp90 with ansamycin-based inhibitors. (Shimamura) In addition, IPI-504 has demonstrated potent cytotoxicity in NSCLC cell lines containing upregulation of c-Met. (Webb, Park)
- Treatment of mutant EGFR containing NSCLC cell lines with Hsp90 inhibitors leads to a loss of downstream EGFR signaling and induction of apoptosis. The findings are observed irrespective of whether the mutant EGFR contains acquired resistance mutations (e.g. T790M). (Shimamura)
- A strong scientific rationale and significant unmet medical need support the evaluation of IPI-504 in patients with relapsed and/or refractory Stage IIIB or Stage IV NSCLC.

Preclinical data

Figure 2. IPI-504 Reduces Tumor Volume In Murine Xenograft (NCI-H1975 (L858R/T790M)) Model.*

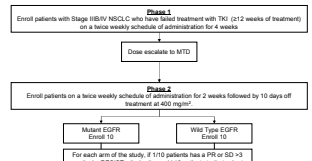


* Brain et al.

Methods

- Patients with Stage IIIb (with malignant effusion) or Stage IV NSCLC who had received prior therapy with an EGFR TKI (e.g., gefitinib or erlotinib) for ≥12 weeks were eligible
- Primary objective for the Phase 1 portion of the study:
  - To determine the safety and tolerability of IPI-504 and identify a recommended Phase 2 dose for future clinical trials
- 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)
  - All AEs graded using the NCI-CTCAE v3.0
- All patients had known EGFR mutational analysis
  - For patients with unknown EGFR status, mutational analysis was performed by Genzyme diagnostics or any CLIA certified laboratory
- Response was assessed using RECIST criteria
  - Cycle 1: Initial assessment at baseline and then at 4 weeks
  - Additional cycles: Approximately every 8 weeks
- Exploratory PET imaging assessments to detect evidence of biologic activity
- Pharmacokinetic data for IPI-504 and its primary active metabolites 17-AAG and 17-AG were collected
- Administration of IPI-504
  - IPI-504 is manufactured as a sterile lyophilized powder
  - IPI-504 is administered in 250 cc of normal saline
  - Drug is administered as an intravenous infusion over 30 minutes by either peripheral or central venous access

Study Schematic



Results

Patient Characteristics

Patients, n	**11**
Average Age (years)	**63.6**
Gender, n **Male** **Female**	 **2** **9**
Performance Status, n **ECOG – 0** **ECOG – 1**	 **2** **9**
EGFR status (10 evaluable), n **EGFR mutation** **EGFR wild type**	 **9** **1**
Average Number of Prior Therapies	**3.7**
Average Time Since NSCLC Diagnosis (years)	**2.8**
Stage at Screening, n **Stage IIIb** **Stage IV**	 **0** **11**

Mutational Status and Prior Therapies

Patient No.	Mutational Status	Prior Therapies
1	Exon 21,L861Q	whole brain radiation, gefitinib, erlotinib, radiosurgery boost
2	Exon 19, E746_A750del5	RLL resection, LLL resection, gefitinib, erlotinib, HKI-272
3	Exon 19, E746_A750del5 and Exon 20, T790M	carboplatin/paclitaxel/TLK-286, right hemispheric radiotherapy, erlotinib, bevacizumab, lumbosacral spine (L4 to S4) radiotherapy
4	Exon 19, E746_A750del	gefitinib
5	Negative	LLL lobectomy, cisplatin/docetaxel, vinorelbine, erlotinib
6	Exon 21, L858R	carboplatin/paclitaxel, pemetrexed/oxaliplatin/bevacizumab, erlotinib, HKI-272, gemcitabine, left hilum/left upper lobe mass radiotherapy
7	Exon 19, E746_S752delinsV	gefitinib, bortezomib, carboplatin/gemcitabine
8	Exon 21, L858R	wedge resection, gefitinib
9	Not yet available	carboplatin/paclitaxel, erlotinib
10	Exon 21, L861Q	whole pelvis radiation, erlotinib, carboplatin/paclitaxel/bevacizumab, erlotinib, pemetrexed, whole brain radiation, vinorelbine
11	Exon 19, Deletion	right bilobectomy (middle and upper lobes) with lymphadenectomy, gefitinib/sorafenib, erlotinib

All Adverse Events Regardless of Attribution Occurring in 2 or More Patients, by Grade (All Cycles; All Dose Groups)

System Organ Class	Preferred Term	Number of Patients (n, %) (N=11) Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal Disorders	**Diarrhea**	**3 (27.3)**	**1 (9.1)**	-	-
General Disorders and Administration Site Conditions	**Asthenia**	**1 (9.1)**	**1 (9.1)**	-	-
	Fatigue	**2 (18.2)**	**4 (36.4)**	**2 (18.2)**	-
	Infusion related reaction	**2 (18.2)**	-	-	-
	Infusion site irritation	**2 (18.2)**	-	-	-
	Infusion site pain	**3 (27.3)**	-	-	-
	Edema peripheral	**3 (27.3)**	-	-	-
Metabolism and Nutrition Disorders	**Dehydration**	**1 (9.1)**	**1 (9.1)**	-	-
	Hypokalemia	**1 (9.1)**	-	**1 (9.1)**	-
	Hypophosphatemia		**1 (9.1)**	**1 (9.1)**	-
Musculoskeletal and Connective Tissue Disorders	**Back pain**	**4 (36.4)**	-	-	-
	Myalgia	**2 (18.2)**	**1 (9.1)**	-	-
Nervous System Disorders	**Headache**	**3 (27.3)**	**1 (9.1)**	-	-
	Peripheral sensory neuropathy	**2 (18.2)**	-	-	-
Psychiatric Disorders	**Insomnia**	**2 (18.2)**	-	**1 (9.1)**	-
Respiratory, Thoracic and Mediastinal Disorders	**Nasal congestion**	**2 (18.2)**	-	-	-
	Postnasal drip	**2 (18.2)**	-	-	-
	Wheezing	**2 (18.2)**	**1 (9.1)**	-	-
Skin and Subcutaneous Tissue Disorders	**Rash**	**2 (18.2)**	-	-	-
Vascular Disorders	**Poor venous access**	**2 (18.2)**	-	-	-

Note: Severity grading for adverse events: Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening

Dose-Limiting Toxicities

Dose Group	IPI-504 (mg/m²)	No. of Patients	Dose-Limiting Toxicities (No. of patients)
1	150	3	None observed
2	225	4	None observed
3	300	5	Grade 3 AST elevation (1)* Grade 3 fatigue (1)*

* Reversible

Duration of Treatment

Dose Group	IPI-504 (mg/m²)	No. of Patients	Best Response by RECIST	No. Cycles per patient
1	150	3	SD, SD, PD	1, 7^, 2
2	225	4	PD, SD, SD, n/a	1, 1, 1, 1
3	300	5	SD, SD, SD, n/a, n/a	1, 1, 3, 1, 1

^ Patient still receiving therapy
n/a = not available, central radiographic assessment pending

Patient Narrative

Patient No. 2 is a 62-year old woman with Stage IV adenocarcinoma with BAC features. She was initially diagnosed with Stage I disease in 1997 and underwent surgical resection. In 2002 she had a relapse presenting as tiny bilateral pulmonary metastases. She was asymptomatic and was followed with close surveillance but no active therapy until 2004. In 2004, progressive disease mandated therapy and gefitinib was begun; she had a partial response. After the discovery of EGFR mutations, her tumor was examined and an EGFR mutation was confirmed (Exon 19, E746_A750del5). She remained on gefitinib for 17 months. She subsequently progressed and was treated with erlotinib which resulted in stable disease for 4.5 months. At progression she was treated with HKI-272, an experimental TKI, which resulted in SD for 15 weeks.

After having progressed on treatment with 3 different TKIs, the patient was enrolled in this study and has been receiving IPI-504 twice weekly at the 150 mg/m2 dose level. She has had a response of SD for >27 weeks and is currently receiving her seventh cycle of treatment with IPI-504.

Figure 3. Percent Change in the Sum of Longest Diameter for Target Lesions at Cycle 1.

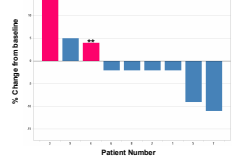


Figure 4. Percent Change in the Sum of SUVmax for Target Lesions at Cycle 1.

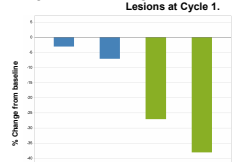
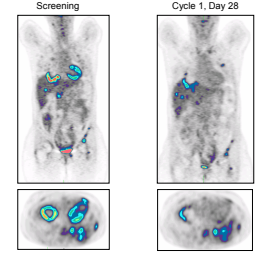


Figure 5. ^{18}FDG-PET for Patient Number 3. Patient received 150 mg/m² of IPI-504.



Dose and Schedule Amendment for Phase 2

- The treatment schedule for the Phase 2 portion of the study will be replaced with a schedule of twice weekly dose administration for 2 weeks followed by 10 days off treatment.
  - Investigators observed that patients have had significant difficulty with the time commitment and inconvenience of twice weekly intravenous dose administration without a drug holiday.
  - The 10-days off treatment will be more convenient for patients and is not predicted to adversely affect the potential for clinical benefit when compared to uninterrupted treatment.
- The recommended dose and schedule of 400 mg/m² for 2 weeks followed by 10 days off treatment was determined in two Phase 1 studies conducted in patients with metastatic refractory GIST and in relapsed, refractory Multiple Myeloma.
  - Importantly, the total dose of IPI-504 that a patient may receive over a course of therapy will be greater using the intermittent treatment schedule at 400 mg/m² compared to an uninterrupted schedule at 225 mg/m².

Conclusions

- The primary objective of the Phase 1 portion of the study has been met. The MTD for twice-weekly IV administration of IPI-504 without interruption is 225 mg/m².
  - DLTs of Grade 3 AST elevation and Grade 3 fatigue were observed at 300 mg/m², establishing the MTD at 225 mg/m².
- In general, IPI-504 has been well-tolerated in patients with NSCLC up to doses of 225 mg/m². IPI-504 also appears to be well-tolerated in the patient who is receiving her 7th cycle of treatment.
- In this Phase 1 study there is promising early evidence of biologic activity of IPI-504 in this heavily pre-treated patient population with Stage IV NSCLC:
  - 7/9 evaluable patients had a best response of Stable Disease (SD).
  - One of these patients, who had progressed after receiving treatment with 3 different tyrosine kinase inhibitors, has Stable Disease for >27 weeks and received IPI-504 for 7 cycles with treatment ongoing.
  - In addition, exploratory evaluation with PET scanning revealed that of the 4 evaluable patients who underwent PET, 2 had SD and 2 PRs by EORTC criteria.
- The Phase 2 component of the study will now begin on an amended dose and schedule of 400 mg/m² for 2 weeks followed by 10 days off treatment.
- These data, along with previously reported data in patients with advanced, metastatic GIST, support further studies of IPI-504 in a broad range of clinical indications. Additional Phase 2 clinical trials are under development.

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