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2007 ASCO Annual Meeting | Chicago, Illinois | June 2007

## Abstract

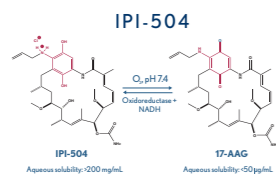
**Introduction:** Prior work from our team has demonstrated that inhibition of the Hsp90 chaperone protein results in selective destruction of the mutated Kit kinase in molecularly-characterized human GIST cell lines. This novel strategy is associated with antitumor activity in cells harboring mutations which confer resistance to small molecule tyrosine kinase inhibitors (TKIs). 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 TKI therapy.

**Methods:** Patients (pts) with metastatic GIST were eligible for study entry following failure of prior TKI therapy such as imatinib and sunitinib. Patients received IPI-504, infused in 250 cc of normal saline over 30 minutes IV, on one of two schedules: Schedule A – days 1, 4, 8 and 11 of a 21-day cycle; Schedule B – twice weekly on a 21-day cycle. Serial monitoring with <sup>18</sup>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.

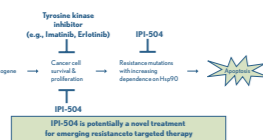
**Results:** To date in this ongoing trial, 21 GIST pts have been enrolled at 5 dose levels on Schedule A (90 [n=6], 150 [3], 225 [3], 300 [3], 400 [6] mg/m<sup>2</sup> IPI-504). The maximum tolerated dose has not been reached, and enrollment is ongoing. On Schedule A, one DLT was observed in each of the 1<sup>st</sup> and 5<sup>th</sup> dose levels. SUV<sub>max</sub> quantification of PET imaging as a biomarker demonstrates decreased tumor <sup>18</sup>FDG activity in 12/18 (66%) patients on Schedule A. Reactivation of tumor FDG uptake by PET was seen during the planned 10-day breaks in IPI-504 administration with reinduction of decreased tumor FDG avidity upon re-treatment with IPI-504. On Schedule A, although no RECIST-defined disease responses were noted, stable disease has allowed 7/21 (33%) pts to continue on study treatment for 5 or more cycles. To date 7 pts have been enrolled at 2 dose levels on Schedule B (150 [n=3], 225 [n=4] mg/m<sup>2</sup> IPI-504). On Schedule B, one patient experienced a DLT of nausea (Grade 3) and the cohort has been expanded to 6 pts.

**Conclusion:** Targeting Hsp90 represents a novel therapeutic strategy in GIST resistant to TKIs, 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<sup>2</sup>. 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 continuously administered twice-weekly administration (without “drug holiday”) was initiated (“Schedule B”). Further studies of IPI-504 in a broad range of clinical applications is warranted based on these data.

## Introduction

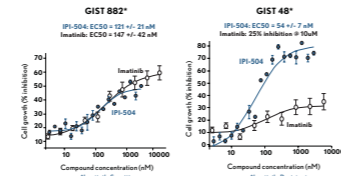


## TARGETING SPECIFIC ONCOGENIC Hsp90 CLIENT PROTEINS

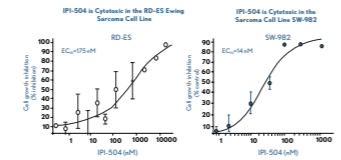


## Preclinical Data

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



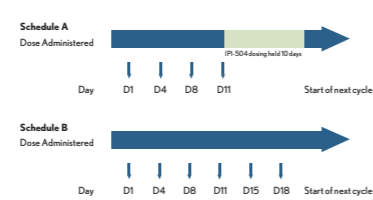
### Soft Tissue Sarcoma Preclinical Data



## Methods

- Conventional “3+3” modified Fibonacci 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
- 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
- Cardiac Monitoring
  - During the trial EKGs are obtained in triplicate to evaluate the potential impact on QTc or cardiac toxicity
- 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 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



### IPI-504 Dose Levels

Group	Dose (mg/m <sup>2</sup> )	Patients Treated Schedule A	Patients Treated Schedule B	Escalation over previous dose
1	90	6	–	–
2	150	3	3	66%
3	225	3	4	50%
4	300	3	–	33%
5	400	6	–	33%
6	500	–	–	25%

## Results

Average age (yrs)	55.5
Gender	Male 16/ Female 10
Performance status	ECOG - 0 ECOG - 1
Average years since GIST diagnosis	5.5
# Patients having progressed on prior TKI therapy:	Imatinib (%) 23/23 (100%) Sunitinib (%) 22/23 (96%)
Average number of prior therapies per patient (range)	2.6 (1-6)

### Past Therapy Responses

	Best Response		Initial TTP (months)	
	Imatinib	Sunitinib	Imatinib	Sunitinib
Complete Response	25	12		
Partial Response	14	13		
Stable Disease	14	6		
Progressive Disease	31	3		
Stable Disease	58	2		
Partial Response	19	14		
Stable Disease	24	3		
Progressive Disease	6	6		
Stable Disease	39	8		
Stable Disease	12	2		
Stable Disease	28	8		
Stable Disease	12	2		
Stable Disease	6	6		
Stable Disease	8	7		
Stable Disease	20	3		
Stable Disease	34	2		
Stable Disease	13	4		
Stable Disease	–	12		
Progressive Disease	3	26		
Progressive Disease	4	9		
Progressive Disease	1	12		
Progressive Disease	–	1		
Progressive Disease	4	50		

### Related Adverse Events (All Cycles)

System Organ Class	Preferred Term	Grade	Number of Subjects (N=24)			
			Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders	Anaemia		1(4.2%)	–	–	–
Cardiac disorders	Arrhythmias		–	–	–	–
	Sinus tachycardia		3(12.5%)	–	–	–
Eye disorders	Subconjunctival haemorrhage		1(4.2%)	–	–	–
	Nausea		1(4.2%)	1(4.2%)	–	–
Gastrointestinal disorders	Taste disorders		1(4.2%)	–	–	–
	Fatigue		6(25.0%)	2(8.3%)	–	–
General disorders and administration site conditions	Injection site pain		6(25.0%)	1(4.2%)	–	–
	Injection site irritation		2(8.3%)	–	–	–
Investigations	Aspartate aminotransferase increased		–	–	1(4.2%)	–
	Blood alkaline phosphatase increased		–	2(8.3%)	–	–
Metabolism and nutrition disorders	Blood potassium decreased		1(4.2%)	–	–	–
	Urine colour abnormal		–	–	1(4.2%)	–
Musculoskeletal and connective tissue disorders	Arthralgia		2(8.3%)	–	–	–
	Back pain		1(4.2%)	–	–	–
Nervous system disorders	Muscle spasms		1(4.2%)	–	–	–
	Headache		3(12.5%)	–	–	–
Skin and subcutaneous tissue disorders	Hyperhidrosis		–	–	1(4.2%)	–
	Pruritus		–	–	–	1(4.2%)

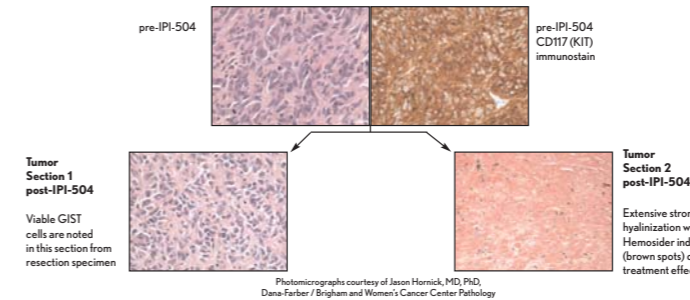
\* refer to ASCO GI 2007 presentation for details

### Duration of Treatment

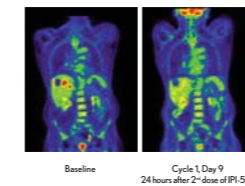
Schedule	IPI-504 (mg/m <sup>2</sup> )	# of Patients	Best Response by RECIST	# Cycles per patient
A	90	6	SD, PD, PD, SD, SD, SD	3, 2, 1, 1, 3, 5
A	150	3	SD, PD, SD	8, 2, 2
A	225	3	SD, SD, SD	5, 7, 3
A	300	3	SD, PD, SD	5, 2, 6
A	400	6	SD, n/e, SD, SD, SD, SD	3, n/e, 5, 3, 4, 4
B	150	3	SD, SD, SD	2, 1, 3
B	225	4	SD, n/e, n/e, n/e	1, 1, 1, 1*

\* Still receiving treatment due to toxicity

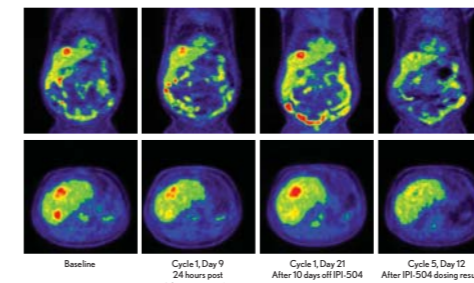
### Histopathology of GIST lesions Before and After IPI-504 Treatment Pt received 225 mg/m<sup>2</sup> of IPI-504



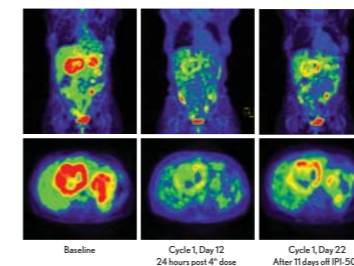
### Serial <sup>18</sup>FDG-PET images for patient following failure of Imatinib and Sunitinib Pt received 90 mg/m<sup>2</sup> of IPI-504



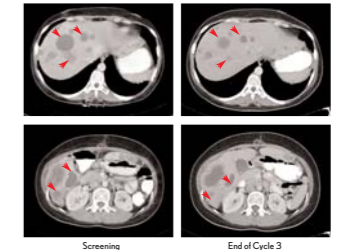
### Serial <sup>18</sup>FDG-PET images of patient following failure of Imatinib, Sunitinib and combination Imatinib + Nilotinib Pt received 225 mg/m<sup>2</sup> of IPI-504



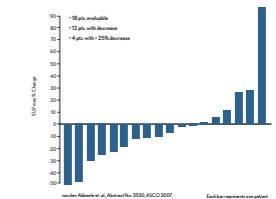
### Serial <sup>18</sup>FDG-PET images of patient following failure of Imatinib, Sunitinib, AMG 706 and combination Gefitinib + Calcitriol Pt received 400 mg/m<sup>2</sup> of IPI-504



### CT for patient following failure of Imatinib and Sunitinib Pt received 400 mg/m<sup>2</sup> of IPI-504



### SUV<sub>max</sub> % Change Results (Day 8-11)



## Conclusions

- In this Phase I study there is promising early evidence of biologic activity of IPI-504 in advanced metastatic GIST patients resistant to TKI therapy.
  - A decrease in FDG avidity on PET scanning, as measured by SUV<sub>max</sub>, has been seen in 12/18 (66%) patients on Schedule A. PET responses have been observed at all IPI-504 dose levels studied.
  - 7/21 (33%) patients, on Schedule A, received IPI-504 for 5 or more cycles, with one patient receiving 8 cycles.
  - 3/4 (75%) patients, on Schedule B, had a qualitative decrease in FDG avidity.
  - Correlative histologic changes and evidence of CT response to treatment have occurred.
- In patients with advanced GIST treated with IPI-504 on Schedule A, a “PET flare” phenomenon has been observed during the “drug holiday” period of 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).
- IPI-504 has been well-tolerated up to doses of 400 mg/m<sup>2</sup> on Schedule A. 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 either Schedule A or B.
- Further studies of IPI-504 in a broad range of clinical applications is warranted based on these data.
- Additional in vitro data has demonstrated that IPI-504 is potentially cytotoxic in additional STS cell lines. The protocol has been amended to include treatment of metastatic STS patients whose disease is not amenable to cure with conventional multimodality therapies.
- These data support the role of Hsp90 inhibition in overcoming resistance to TKIs in this heavily pre-treated patient population with metastatic GIST.

## ACKNOWLEDGEMENTS

- We are deeply grateful to all the patients who participated in this study, as well as the families who supported them
- Ludwig Trust for Cancer Research
- The GIST Cancer Research Foundation
- The dedicated team of expert research nurses, study coordinators and nurse practitioners, including: David Flanagan, Conor Devine, Amy Potter, Brianne O'Sullivan, and Rebecca Levy

## REFERENCES

Bauer S, Hubert C, Heinrich MC, Cohen P, Bertagnoli M, Demetri GD, Fletcher J. *KIT* hyperactivation in imatinib-resistant GIST: Implications for salvage therapies. ASCO (2005) Abstract #9034. • Ge J, Normant E, Porter J, Ali J, Dembski M, Gao Y, Georges A, Grenier L, Pak R, Patterson J, Saylor J, Tibbitts T, Tong J, Adams J, Palombella V. Design, synthesis, and biological evaluation of hydroquinone derivatives of 17-amino-17-demethoxygeldanamycin as potent, water-soluble inhibitors of Hsp90. J Med Chem (2006) 49, 4606-4615 • van den Abbeele AD, Badawi RD, Manola J, Morgan JA, Desai J, Kazanovicz A, St. Armand M, Baum C, Demetri GD. Effects of cessation of imatinib mesylate (IM) therapy in patients (pts) with IM-refractory gastrointestinal stromal tumors (GIST) as visualized by FDG-PET scanning. Proc Am Assoc Clin Oncology (2004) Abstract 3012. • van den Abbeele AD, Melnitsky Y, de Vries D, Manola J, Dileo P, Tetrault R, Baum C, Badawi R, Demetri G. Imaging kinase target inhibition with SU11248 by FDG-PET in patients (pts) with imatinib-resistant gastrointestinal stromal tumors (GIST). Proc Am Assoc Clin Oncology (2005) Abstract 9006. • Dileo P, van den Abbeele AD, Manola J, Desai J, Morgan JA, George S, St. Armand MW, Baum C, Demetri GD. Qualitative assessment of <sup>18</sup>FDG-PET correlates with clinical benefit in patients (pts) with imatinib mesylate (IM)-resistant GIST treated with the multi-targeted tyrosine kinase inhibitor SU11248. Proc Am Assoc Clin Oncology (2005) Abstract 8.