

# Use of PI-88, A novel heparanase inhibitor, as adjunct therapy in post-resection hepatocellular carcinoma: a large randomised phase II clinical trial.

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## INTRODUCTION

**PI-88 (sulfated monophosphorylated mannose oligosaccharide) is a novel, first in class, mimetic of heparan sulfate.**

**Mechanism of Action** – PI-88 was developed as an antagonist of heparan sulfate interaction with angiogenic growth factors (VEGF, FGF-1 and FGF-2) and as an inhibitor of heparanase that cleaves heparan sulfate (HS) in the extracellular matrix (ECM), Fig. 1. Maintenance of the ECM integrity is the key to preventing tumor growth. Cleavage of HS by heparanase disrupts the ECM leading to the release of growth factors (eg. VEGF, FGF-1 and FGF-2) which in turn promote tumor growth.

**Tumor Models** – PI-88 has been tested in the following preclinical tumor models: 13762 MAT tumors in Fischer Rats<sup>1</sup>, BCI tumors in Dark Agouti rats, 4TI mammary tumors in Balb/c mice, B16F1 and B16F10 tumors in C57Bl/6J mice, Lewis lung carcinoma model in mice, Human tumor xenografts in nude mice, RIP1-Tag2 transgenic mouse model<sup>2</sup>, murine models of human myeloid leukaemias<sup>3</sup> and combination studies. PI-88 efficacy has been observed with various cytotoxic drugs in several of the models above.

## Preclinical GLP Toxicology Studies Completed to Date –

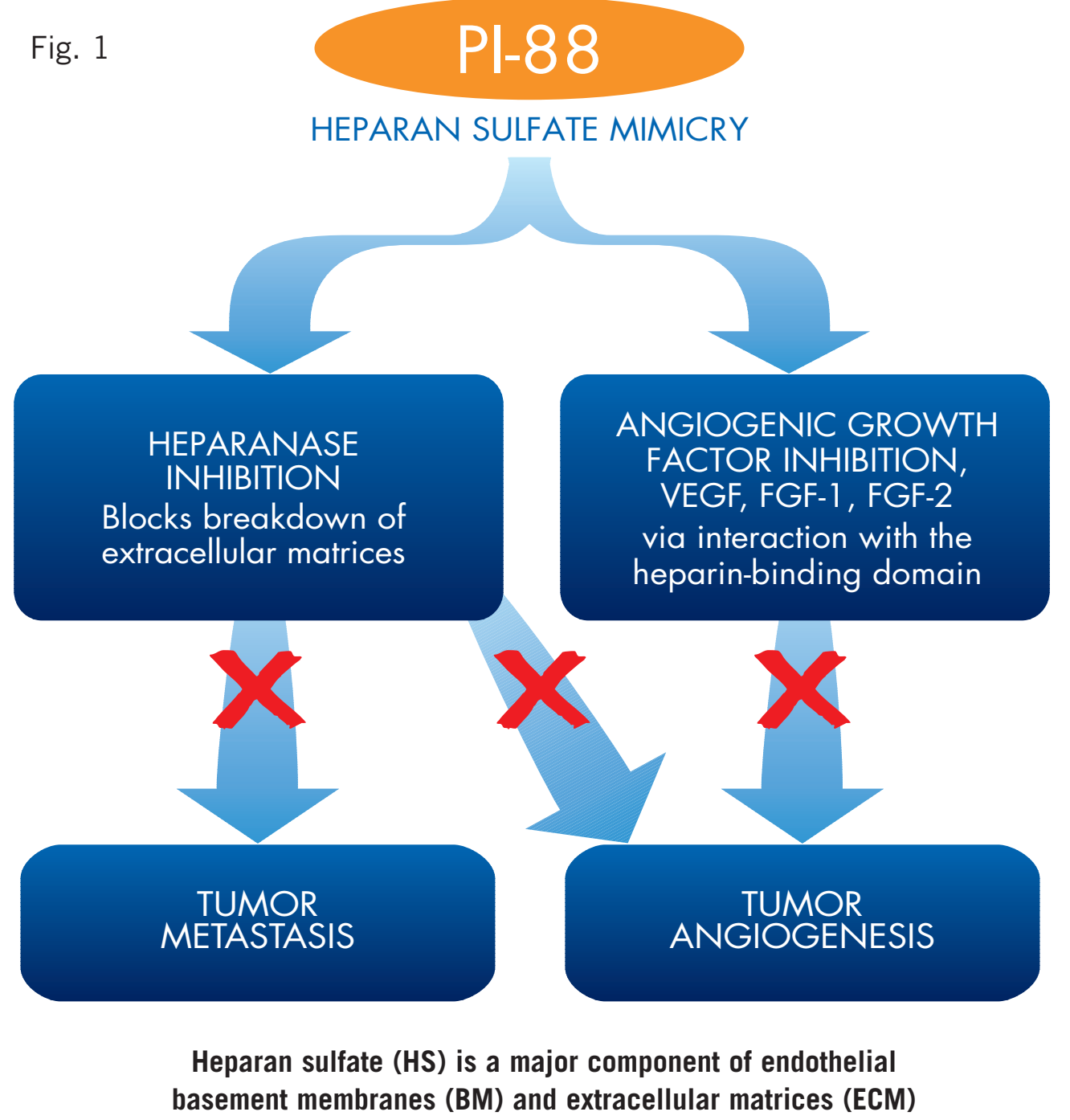
- Acute IV toxicity in rats
- Local SC tolerance in rats
- Cardiovascular safety study in dogs
- Repeated-dose studies in rats and cynomolgus monkeys – (2-4 weeks IV, 4-13 weeks SC)
- Teratology studies in rats and rabbits
- Genetic toxicity studies *in vitro* and *in vivo*

PI-88 safety has been assessed in rats and cynomolgus monkeys with minimal toxicity. Anticoagulation (prolongation of activated partial thromboplastin time (APTT)), was observed in a few cases.

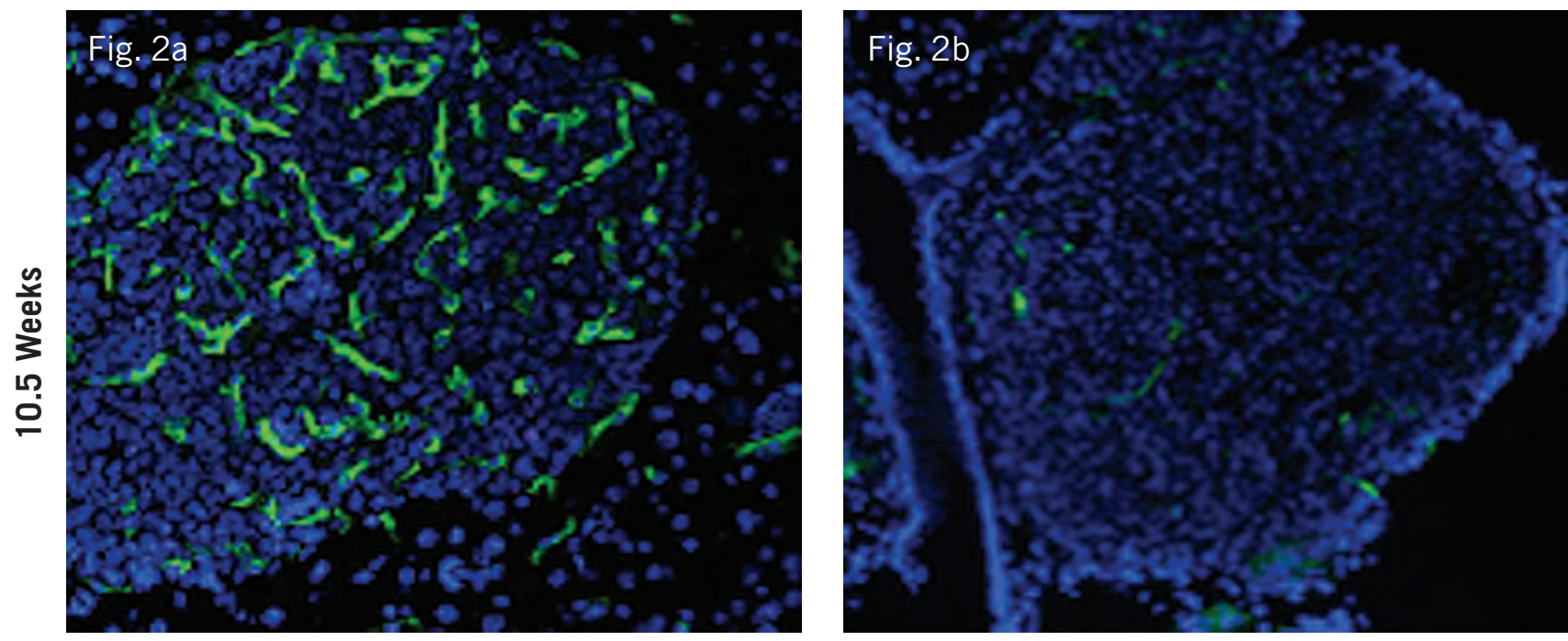
**Clinical Trials Completed** – Six phase I and two phase II clinical trials have been completed to date under an IND and the current ongoing phase II trials are as follows: Post resection hepatocellular carcinoma, advanced NSCLC in combination with docetaxel, metastatic melanoma in combination with dacarbazine and androgen-independent prostate cancer in combination with docetaxel.

<sup>1</sup>Parish et al., *Cancer Research*, 1999, 59, 3433  
<sup>2</sup>Joyce et al., *Oncogene*, 2005, 24 (25):4037-51; Erratum in: *Oncogene*, 200524(25):4163,  
<sup>3</sup>Inversen et al., *Leukemia*, 2002, 40, 376

## PI-88 – WELL DOCUMENTED MODE OF ACTION

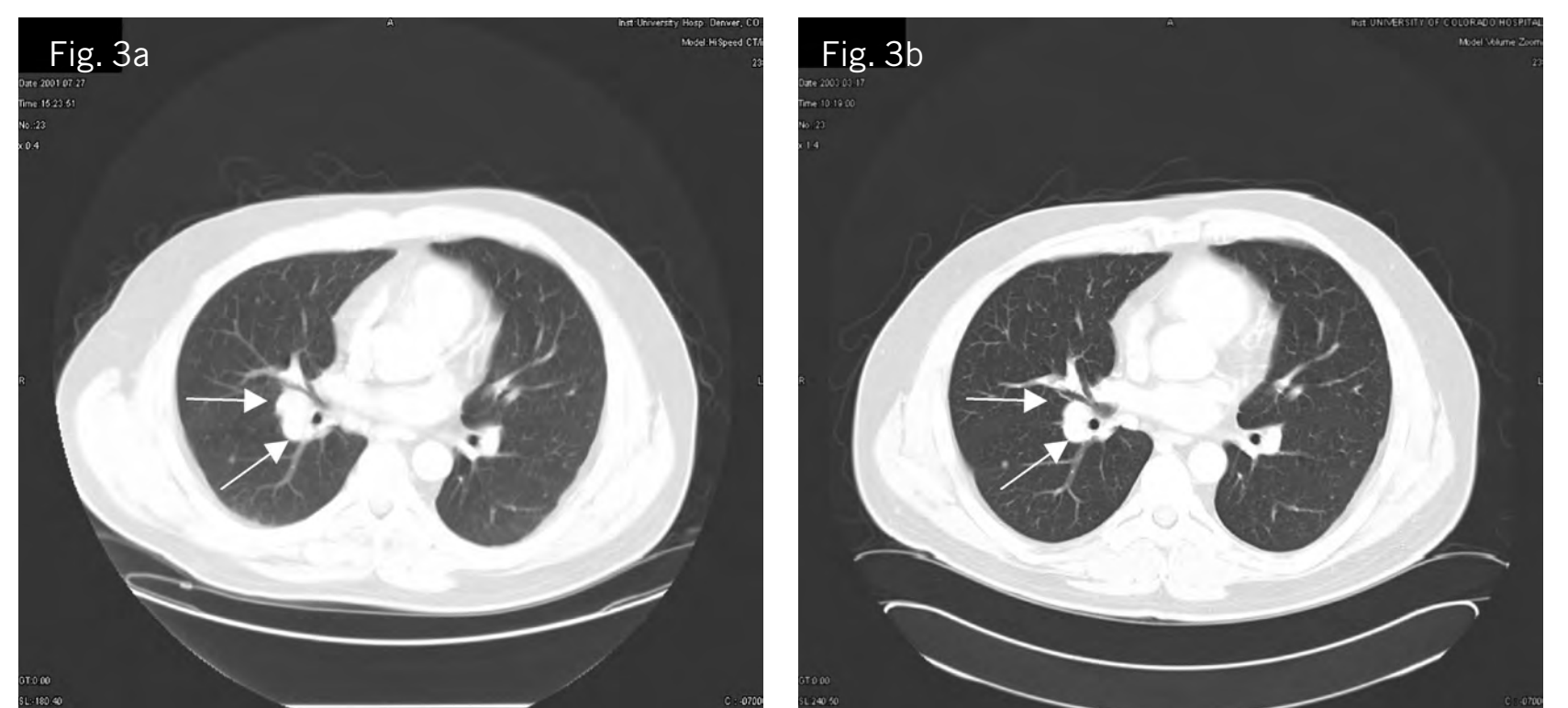


## PI-88 INHIBITS ANGIOGENESIS IN RIP1-TAG2 MODEL OF PANCREATIC ISLET CELL CARCINOGENESIS



Rip1-Tag2 mice at intervention stage perfused with FITC-lectin to visualise modification of vasculature by PI-88  
 Joyce et al., *Oncogene*, 2005, 24 (25):4037-51; Erratum in: *Oncogene*, 200524(25):4163

## CT SCAN DEMONSTRATING PARTIAL RESPONSE



Partial response in melanoma patient #102 after 22 months. PI-88 received for 59 cycles (55 months) in a Phase I study. Top arrows – tumor; bottom arrows – vasculature.

## KEY COMPLETED PI-88 TRIALS UNDER US FDA GUIDELINES

Study	Phase	Treatment	Key Points
IV infusion in healthy volunteers	Phase Ia	Escalating single doses as a 2-h IV infusion	<ul style="list-style-type: none"> <li>24 healthy male adults recruited</li> <li>Short term safety and pharmacokinetic data obtained</li> <li>Doses of up to 180 mg were well tolerated</li> </ul>
IV infusion in cancer patients	Phase Ib	Dose escalation by continuous IV infusion	<ul style="list-style-type: none"> <li>14 pts recruited with advanced malignancies</li> <li>2 cases of GR3 thrombocytopenia, platelets recovered following cessation of treatment</li> </ul>
Alternative IV dosage regimen in cancer patients	Phase Ib	Dose escalation by IV infusion for 4 days with 7 day follow up period	<ul style="list-style-type: none"> <li>9 pts recruited with median age of 46 years</li> <li>DLT – 1 case of GR3 serum ALT</li> <li>Repeat cycles at 2 week intervals</li> </ul>
SC injection in healthy volunteers	Phase I	Dose escalation by SC administration and comparison with IV infusion	<ul style="list-style-type: none"> <li>Healthy male volunteers</li> <li>Measurement of SC bioavailability via a two-way crossover design</li> <li>Determined 95% bioavailability by SC administration</li> </ul>
Self administered SC in advanced cancer patients	Phase I	Dose escalation for 4 days every fortnight and 4 days every week	<ul style="list-style-type: none"> <li>42 pts recruited (25 male) with median age of 55 years</li> <li>MTD 250 mg/day 4 days every 7 days</li> <li>38 evaluable pts, 1 PR, 14 SD for 3 months or longer (39.4% disease control)</li> <li>2 pts still on PI-88 treatment for 47 and 55 months respectively</li> </ul>
Self administered SC with docetaxel in patients with advanced malignancies	Phase I	Dose escalation PI-88 and docetaxel	<ul style="list-style-type: none"> <li>16 pts recruited</li> <li>Established MTD for PI-88 in combination with docetaxel, 250 mg/day, 4 days per week</li> <li>No DLT</li> </ul>
Self administered SC in multiple myeloma patients	Phase II	PI-88 dose determined via doubling APTT levels	<ul style="list-style-type: none"> <li>Paraprotein marker study – 19 patients recruited</li> <li>Disease stabilization – 41% of pts evaluable for 8 weeks or longer</li> </ul>
Self administered SC in advanced melanoma patients	Phase II	250 mg/day 4 days in every 7	<ul style="list-style-type: none"> <li>44 pts recruited</li> <li>9 months median survival led to initiation of first line trial in combination with DTIC</li> <li>11pts with SD at end of C2, 1 PR and 5 SD at the end of cycle 4</li> </ul>

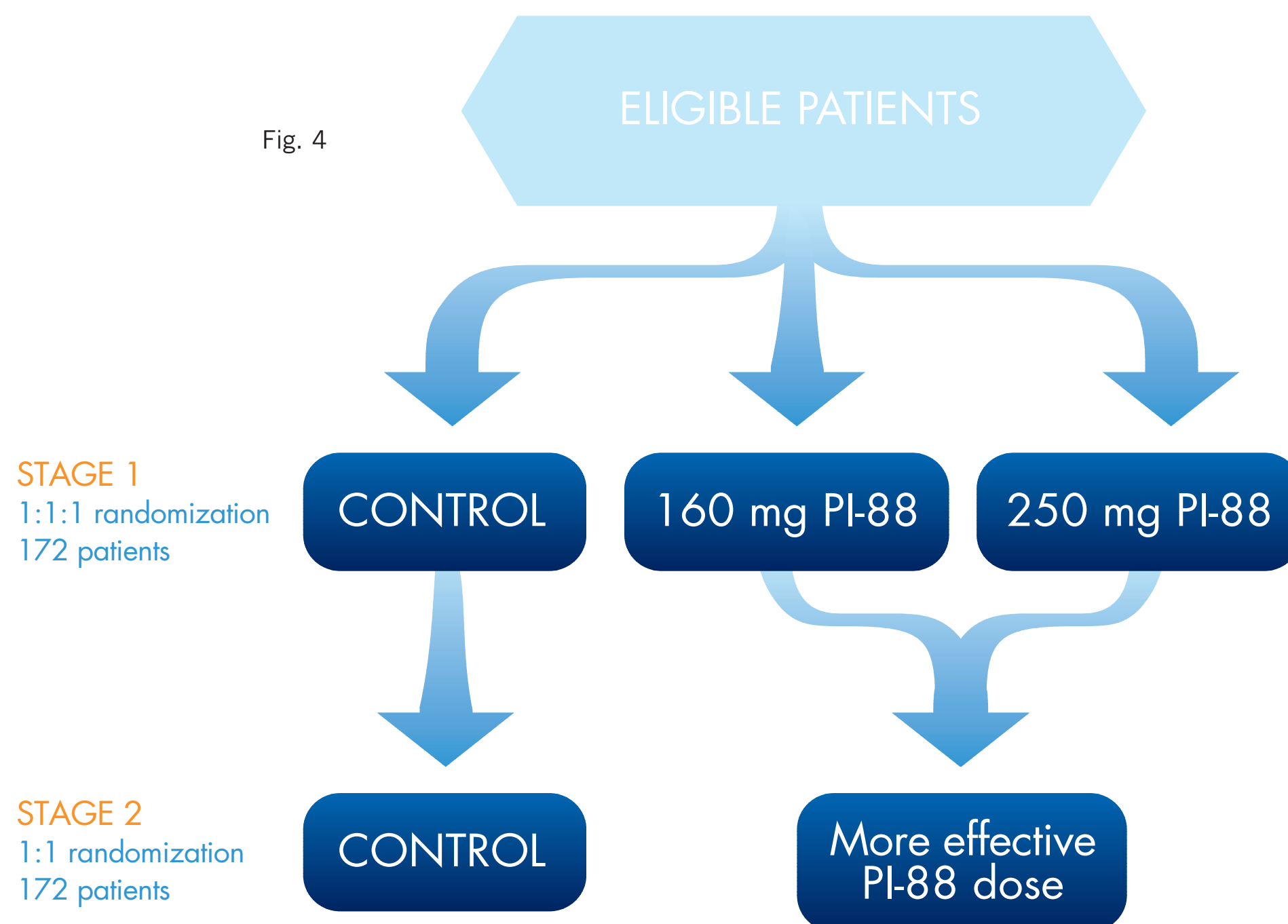
## PI-88 CURRENT TRIALS UNDER IND

Study	Treatment	Key Points
Primary liver cancer (Post resection hepatocellular carcinoma)	3-arm study: 2 dose levels of PI-88 and control	<ul style="list-style-type: none"> <li>Trial commenced July 2004</li> <li>Approx. 343 pts to be recruited</li> <li>172 pts recruited to date for stage 1</li> </ul>
NSCLC second line treatment	2-arm study: Combined therapy Taxotere® (docetaxel) with and without self administration of PI-88	<ul style="list-style-type: none"> <li>Trial commenced February 2004</li> <li>100 pts to be recruited</li> <li>94 pts recruited to date, completion of recruitment expected by the end of Q1 CY06</li> </ul>
Metastatic melanoma first-line treatment	2-arm study: Combined therapy DTIC (dacarbazine), with and without self administration of PI-88	<ul style="list-style-type: none"> <li>Trial commenced May 2005</li> <li>Up to 118 pts to be recruited</li> <li>Dose escalation lead-in safety study. Randomized stage will assess the benefit of the addition of PI-88</li> </ul>
Androgen-independent prostate cancer	2-arm study: Self administration of PI-88 combined with Taxotere® (docetaxel)	<ul style="list-style-type: none"> <li>Trial commenced in August 2005</li> <li>90 pts to be recruited</li> <li>Dose escalation lead-in safety study</li> <li>Randomized stage will assess combination at two different dose regimens in combination with Taxotere®</li> </ul>

## HEPATOCELLULAR CARCINOMA (HCC) AND PI-88

- HCC is the fifth most common neoplasm worldwide and causes the third largest number of cancer deaths with over half a million new cases per year worldwide.<sup>1</sup>
- HCC is the leading cause of cancer related death in Taiwan.<sup>2</sup>
- HCC is rarely cured and recurs frequently after regional therapy or transplantation.
- For 60% of pts, HCC recurs after 12 months following surgery.<sup>3</sup>
- This randomised Phase II study will assess the efficacy and safety of PI-88 treatment for patients with HCC following hepatectomy.
- Study commenced July 04 and patients have been recruited at six sites in Taiwan.
- 172 patients have been recruited completing the first stage of the trial.
- Following analysis of stage one, 172 patients will be recruited in the second stage.

## HCC CLINICAL TRIAL PROTOCOL



### PRIMARY EFFICACY ENDPOINT

- Tumor non-recurrence rate within 48 weeks

### SECONDARY EFFICACY ENDPOINTS

- Time to first recurrence and survival rate

STAGE 1: 3-arm design comparing the control group to two dose levels of PI-88 (160mg and 250 mg)

STAGE 2: 2-arm design comparing the control group to the more effective dose of PI-88 from stage one

PI-88 is administered by SC injection 4 consecutive days per week for the first 3 weeks in each 4 week cycle for up to 9 cycles (36 weeks) with a 12 week follow up period

## CONCLUSION

- Based on the importance of heparan sulfates in angiogenesis and metastasis, PI-88 was developed as an antagonist of heparan sulfate interaction to block activity of angiogenic growth factors (VEGF, FGF-1 and FGF-2) and as an inhibitor of heparanase to block heparan sulfate cleavage from the ECM.
- PI-88 blocks angiogenesis, tumor growth and metastasis in a variety of tumor models.
- The results of the preclinical and clinical studies indicate that PI-88 is generally well tolerated.
- To date 388 patients and healthy volunteers have received PI-88.
- Six phase I trials and two phase II trials have been completed. Four phase II trials are ongoing.
- Evidence of clinical benefit has been observed with multiple cancers.
- The current phase II HCC trial has recruited 172 patients to date completing stage one.
- Stage two is scheduled to commence in early 2007.
- The evidence of benefit seen to date combined with the very acceptable safety profile of PI-88 warrant further clinical trial investigation.

<sup>1</sup>Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: GLOBOCAN 2000. *Int J Cancer* 2001;94:153-156.  
<sup>2</sup>DOH. The leading cause of cancer related death in Taiwan area in year 2001. [http://www.doh.gov.tw/statistic/data/boarddocuments/90\\_10.xls](http://www.doh.gov.tw/statistic/data/boarddocuments/90_10.xls). (in Chinese)  
<sup>3</sup>Portolani et al., *Annals of Surgery*, Volume 243, No. 2, Feb 2006.