PHASE I/II STUDY OF PCI-27483, A COAGULATION FACTOR VIIA (FVIIA) INHIBITOR, IN ADVANCED PANCREATIC CANCER PATIENTS RECEIVING TREATMENT WITH GEMCITABINE

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UPDATED ABSTRACT

Background: PCI-27483 is a selective inhibitor of FVIIa, a serine protease activated by interaction with tissue factor (TF). TF upregulation in tumor cells correlates with angiogenesis and a worsened prognosis. Hydrolysis of protease activated receptors by the TF:FVIIa complex induces upregulation of IL-8 and VEGF. PCI-27483 inhibited the growth of human pancreatic tumors in animal models at doses resulting in a 2.5x to 3.0x change in prothrombin time. PK/INR relationships from a Phase I study in healthy volunteers were used to select initial doses of PCI-27483 for the current study.

Methods: Patients (pts) with locally advanced or metastatic pancreatic cancer, ECOG performance status 0-1, and normal coagulation were enrolled. All pts in Phase I and II receive gemcitabine as a 30-min IV infusion at a dose of 1000 mg/m^2 on 3 out of every 4 wks. PCI-27483 is administered twice daily by SC injection. In Phase I, doses of PCI-27483 were intra-patient escalated (0.8 to 1.2 to 1.5 mg/kg) over 4 to 8 wks. The targeted peak INR, measured 2 h postdose, was 3.0. In Phase II, pts are being randomized to a control arm to receive gemcitabine only or to a PCI-27483 arm to receive gemcitabine plus PCI-27483. Phase I pts receiving 80% of planned doses during the first 8 wks were considered evaluable. Spiral CT scans are performed at 8-wk intervals. Study endpoints: adverse event profile, progression-free survival, venous thromboembolic events and overall survival.

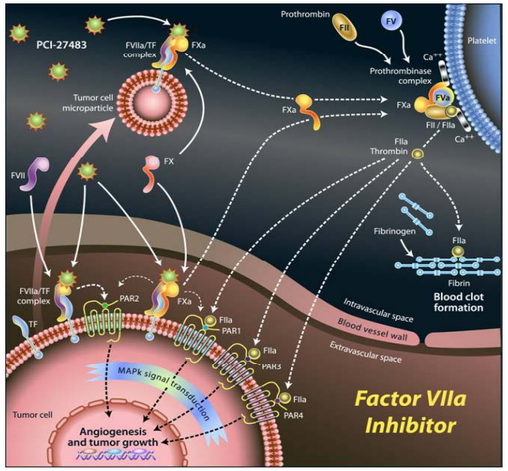
Results: Phase I - 8 pts enrolled, 5 pts evaluable. Highest dose of PCI-27483 achieved was 0.8 mg/kg for 2 pts, 1.2 mg/kg for 3 pts and 1.5 mg/kg for 3 pts. Hematologic toxicity: grade 3 neutropenia (n=1), anemia (n=2), and thrombocytopenia (n=1). Other grade 3 toxicities: elevated INR (n = 4) and hypokalemia (n=1). Dose-level-specific mean 2-h INR values were 2.1 at 0.8 mg/kg (CV=13%; n=7), 3.2 at 1.2 mg/kg (CV=36%; n=5) and 2.9 at 1.5 mg/kg (CV=13%; n=3). No VTEs occurred. Radiologic evaluations of 5 evaluable pts: 5 with stable disease at 16 wks (1st pt SD for 56 wks).

Conclusions: PCI-27483 is well tolerated at doses up to 1.5 mg/kg bid with gemcitabine 1,000 mg/m^2. Sustained SDs occurred and INRs were generally within the expected range. The randomized Phase II study is ongoing at a dose of 1.2 mg/kg bid.

INTRODUCTION

- PCI-27483 is a highly selective and potent small-molecule inhibitor of Factor VIIa.
- Factor VII , which is normally produced by the liver and present in the systemic circulation, becomes activated upon interaction with tissue factor (TF), a cell surface glycoprotein (Figure 1).
- Proteolytic hydrolysis of protease activated receptor 2 (PAR2) by the TF:FVIIa complex induces intracellular signaling pathways that lead to the expression of CXCL1, VEGF, and IL-8.[1,2,3] Most epithelial cancers express PAR2 as an upstream activator of promigratory pathways.
- TF expression occurs early in pancreatic neoplastic transformation and is associated with increased VEGF expression and increased microvessel density. Patients with pancreatic cancer are at increased risk of venous thromboembolic events (VTE) related to high TF expression.[4]
- The TF:FVIIa complex is not inhibited by low-molecular weight heparin (LMWH).
- Treatment with gemcitabine is currently a standard therapy for locally advanced or metastatic pancreatic cancer. Median duration of progression-free survival for patients receiving gemcitabine alone in most recently reported clinical studies has typically been 2.6 to 4.3 months (11.2 to 18.5 weeks).[5,6,7,8]
- In a study conducted in healthy volunteers, subcutaneous administration of PCI-27483 at doses of 0.2, 0.8 and 2.0 mg/kg was associated with a dose- and plasma concentration-dependent increase in the International Normalized Ratio (INR).
- PCI-27483, but not LMWH dalteparin, demonstrated anti-tumor growth activity in a human pancreatic tumor xenograft model (BxPC3) at doses associated with prothrombin times 2.5 to 3X baseline values.[9,10]

Figure 1: Proposed Mechanism of Action



METHODS

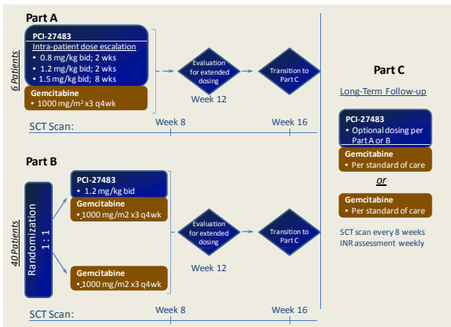
Study Objective – Phase I

- To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of PCI-27483 when administered by subcutaneous injection in patients receiving a standard regimen of gemcitabine.

Study Design

- Phase I (Parts A and C): open-label, intra-patient dose escalation of PCI-27483 in patients receiving gemcitabine (Figure 2). Results from Phase I (Parts A and C) are presented here.
- Phase II (Parts B and C): open-label randomized portion of the study in patients receiving gemcitabine with or without PCI-27483 (Figure 2). Phase II portion of the study is on-going.

Figure 2: Study Design



Treatment

- PCI-27483 administered by subcutaneous injection twice daily (bid) at a dose of 0.8, 1.2, or 1.5 mg/kg with dose reduction in the event of 2 consecutive INR values > 3.5.
- PCI-27483 dosed for 12 weeks (Part A) with the option to continue past 12 weeks (Part C at Week 16).
- Gemcitabine was administered at a dosage of 1000 mg/m^2 as a 30-minute infusion once weekly during 3 out of every 4 weeks.

End Points

Primary Endpoint

- Adverse event profile

Secondary Endpoints

- Pharmacokinetic assessment of PCI-27483 and gemcitabine (C_{max}, T_{max}, $t_{1/2}$, and AUC)

Exploratory Endpoints

- Progression free-survival
- Incidence of thromboembolic complications and associated circulating levels of TF

Main Eligibility Criteria of Phase I Portion of the Study

Inclusion

- Adults with metastatic or locally advanced ductal adenocarcinoma of the pancreas. Diagnosis of metastatic disease ≤ 4 months prior to enrollment.
- Disease measurable using RECIST criteria and determined by spiral CT scan.
- Eastern Cooperative Oncology Group (ECOG) performance score ≤ 1.
- Normal baseline coagulation laboratory values.

Exclusion

- History of brain metastases or evidence of intra-cranial hemorrhage based on head CT scan.
- Bilirubin ≥ 3.0 mg/dL, hemoglobin < 8.0 g/dL, platelet count < 100,000/µL.

Assessments

Pharmacokinetics/Pharmacodynamics

- Blood samples for assessment of plasma drug levels and INR were collected predose and 2, 6 and 9-12 h after first dose on Day 1 as well as predose and 2 h postdose on Days 15, 29, and 57.

Disease Assessment

- Spiral CT scans every 8 weeks.

Definition of Evaluable Patients for Phase I

- Patients receiving 80% of scheduled doses during the first 8 weeks of treatment were considered evaluable. Non-evaluable patients could be replaced.

RESULTS

- A total of 8 patients were enrolled in the Phase I (Part A) portion of the study (6 enrolled initially plus 2 replacements). Five patients in Phase I were considered evaluable.
- Patient demographics are shown in Table 1.

Table 1: Patient Baseline Characteristics and Disease Characteristics for Phase I

Characteristics	N = 8
Gender	
Male	4
Female	4
Median age, years (range)	61.5 (55-80)
ECOG performance status, n	
0	3
1	5
Extent of disease	
Locally advanced	2
Metastatic	6

- Two patients had had prior Whipple's resection, one of whom had adjuvant chemo-radiotherapy.
- Four patients had serum bilirubin > 1.3 mg/dL prior to treatment with study drug.

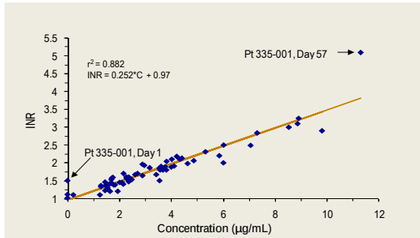
Intra-Patient Dose Escalation

- Patients were eligible for dose escalation after 2-week treatment periods at 0.8 mg/kg or 1.2 mg/kg if platelet count ≥ 65 x 10^3/µL, absolute neutrophil count ≥ 1.25 x 10^3/µL, and hemoglobin ≥ 8.0 g/dL.
- Two of 8 patients did not dose escalate above 0.8 mg/kg (1 discontinued due to GI bleed at Week 1; 1 withdrew consent at Week 4).
- Per protocol, 3 patients dose escalated no higher than 1.2 mg/kg due to peak INR values greater than 2.79.

Pharmacokinetics and Pharmacodynamics

- At all dose levels, INR values correlated with systemic exposure to PCI-27483 (Figure 3).
- Patient 335-001 had an elevated INR at study start and PCI-27483 induced an accentuated response on study day 57.

Figure 3: Plasma Concentrations of PCI-27483 vs. INR



- At a dose of 1.2 mg/kg bid, the targeted peak and trough INR values of 3 and 2, respectively, were achieved at steady state (Table 2).

Table 2: Steady-State Peak and Trough INR Values by Dose Level

	Dose (BID)		
	0.8 mg/kg	1.2 mg/kg	1.5 mg/kg
Peak INR (2 hours postdose)			
Mean	2.11	3.16	2.92
CV	12.7%	35.7%	13.4%
n	7	5	3
Trough INR (12 hours postdose)			
Mean	1.61	2.25	Not evaluated
CV	18.6%	27.2%	–
n	7	4	–

Safety

- Elevated INR (>3.5) necessitating dose reduction was the most frequent grade 3, PCI-27483-related adverse event. There were no grade 4 adverse events.
- The combination regimen of PCI-27483 (0.8 to 1.5 mg/kg bid) and gemcitabine (1,000 mg/m^2 x3 q4wk) was well tolerated with a relatively low incidence of grade 3 adverse events (Table 4).
- One patient in Phase I (no. 319-002) complained of nausea and dizziness upon standing after 3 doses of PCI-27483 at 0.8 mg/kg. On the 5th day of dosing, treatment with PCI-27483 was discontinued due to suspected GI bleeding (Hgb = 4.4 g/dL; INR = 2.16; stool guaiac positive), and patient was transfused with packed RBCs and FFP. The day after transfusions and cessation of dosing, patient no longer complained of nausea; Hgb = 7.3; INR =1.46. At 3 days post-dosing, patient was stable; Hgb = 10.1 g/dL; INR = 1.17. Patient had a positive hemoccult stool test prior to the start of dosing.

RESULTS

Table 3: Adverse Events Attributed to Treatment with PCI-27483 in > 1 of 8 Patients in Phase I

Adverse Event	Highest Grade (n)				All Grades (n)
	1	2	3	4	
All AEs	2	1	5	0	8
Injection site reaction (hematoma, irritation)	6	0	0	0	6
Hemorrhage (epistaxis, hemorrhoidal, gastrointestinal)	2	2	1[a]	0	5
Increased INR[b]	0	0	4	0	4
Contusion	2	0	0	0	2
Decreased Hemoglobin (anemia)	0	1	1[a]	0	2
Rash	2	0	0	0	2

[a] Patient with pre-existing positive test for occult blood in stool.
[b] Patients with INR values >3.5 had PCI-27483 dose reduced per formula: New Dose = Dose x [2.25 ÷(INR-1)].

Table 4: Adverse Events Irrespective of Relatedness Reported in > 2 of 8 Patients in Phase I

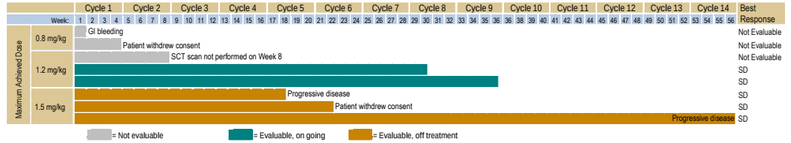
Adverse Event	Highest Grade				All Grades (n)
	1	2	3	4	
Hemorrhage	3	2	1	0	6
Rash	5	1	0	0	6
Injection site reaction	6	0	0	0	6
Diarrhea, constipation	0	5	0	0	5
Increased INR	0	0	4	0	4
Alopecia	3	0	0	0	3
Fatigue	1	2	0	0	3
Decreased hemoglobin (anemia)	0	1	2	0	3
Decreased platelets (thrombocytopenia)	0	2	1	0	3
Vomiting	2	1	0	0	3

- Grade 3 adverse events not presented in Table 4 include neutropenia (n=1), hypokalemia (n=1), duodenal stenosis (n=1), sepsis (n=1), femur fracture (n=1).

Time on Treatment and Thromboembolism

- All 5 patients considered evaluable had stable disease at Week 12 and opted for extended treatment with PCI-27483.
- Among the 5 evaluable patients, 3 have been treated with PCI-27483 for 30 weeks or more, 1 had disease progression at Week 18 and 1 withdrew consent at Week 22 (Figure 4).
- None of the patients receiving PCI-27483 experienced a thromboembolic event.

Figure 4: Patients by maximum achieved dose, treatment duration, and best overall response



CONCLUSIONS

- Twice daily subcutaneous administration of PCI-27483 at 0.8 and 1.2 mg/kg bid was associated with dose- and plasma concentration-dependent increases in INR values.
- PCI-27483 is well tolerated at doses up to 1.5 mg/kg bid.
- Targeted peak and trough INR values (3 and 2, respectively) were achieved, on average, at a PCI-27483 dose of 1.2 mg/kg bid.
- Among the 5 patients in Phase I considered evaluable (>80% of scheduled doses in first 8 weeks), 3 have a progression free survival ≥ 30 weeks (7 months).
- The dose of PCI-27483 selected for Phase II portion of this study is 1.2 mg/kg bid.

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DISCLOSURES

David Loury and Ahmed Hamdy are employees of Pharmacyclics, Inc.