**Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver**

Paul Goldfarb, MD; James Lyon, MD; Russell Low, MD; Eric Wacher, PhD; Kathleen McMillan, PhD; Alexander Rosemurgy, MD FACS; and Sanjiv S. Agarwala, MD

Sheng Oncology Associates, San Diego, CA USA; Sheng HealthCare, San Diego, CA USA; Protienda Biopharmaceuticals, Inc., Kansas City, TN USA; and the American Association for Cancer Research, San Francisco, CA USA

**Abstract**

Background: Intralesional PV-10, a 10% solution of rose bengal, has recently demonstrated high rates of complete response and durable local control in metastatic melanoma [1]. The current Phase 1 study is assessing safety, pharmacokinetics, and preliminary efficacy of PV-10 in subjects with non-resectable hepatocellular carcinoma (HCC) or cancer metastatic to the liver (NCT 00886655).

Methods: Subjects having at least one liver tumor ≥1 cm in diameter are administered a single percutaneous intralesional injection of PV-10 to one target lesion at dose of 0.25 to 0.50 ml per cm3 lesion volume. Plasma concentrations of PV-10 from 1 hour to 28 days after injection are measured. Radiologic assessments of the injected Target Lesion are performed to determine response over initial 28 day and long-term 3-6 month periods. Serum levels of potential liver injury markers are measured, and adverse events recorded.

Results: In an initial study cohort, six subjects received PV-10. Significant adverse events were limited to injection site and photosensitivity reactions, and resolved without sequelae. All injected tumors were stable in size at 28 days, and 4 of 6 had long-term assessment. 2 had partial response, for a long-term tumor-specific objective response rate of 50%. PV-10 plasma levels decreased rapidly in a bi-exponential pattern, with initial and terminal half-phases of 4.5 and 100 hours, respectively. Elevated liver enzymes levels subside within a week of treatment.

Conclusions: Preliminary efficacy in treatment of liver tumors with PV-10 was observed. Toxicity was transient, and treatment had acceptable tolerability. The study is continuing at three study centers with two expansion cohorts to assess response in hepatocellular carcinoma and other cancers metastatic to the liver.


**Background**

PV-10 is a sterile, non-pyrogenic solution of Rose Bengal (D10%) for intralesional injection.

- **Small molecule** Fluorescein derivative analogous to Gomori (1882)
- **Prior human use of D10**
  - IV hepatic diagnostic
  - Topical ophthalmic diagnostic
- **Established safety history**
  - Not metabolized
  - Short circulating half-life (ca 30 min)
  - Extravasation via bile
- **Radiopaque with prolonged retention in tumors**

**Primary Ablative Mechanism**

- **Intravascular Injection**
- **Lysosomal Accumulation**
- **Lysosomal Disruption**
- **Autolytic Cell Death**

**Secondary Immunologic Activation**

- **Antigen Release**
- **APC Uptake**
- **T-cell Activation**
- **Bystander Tumor Regression**

**Phase 1 Patients**

- **6 Male, 7 Female, median age 60 years (Range 51 - 89)***
- **Hepatocellular Carcinoma – 6 patients; TCC tumors**
- **Metastases to Liver – 7 patients: 3 colorectal mets (CRL), 2 non-small cell lung (NSCL), 2 melanoma (Mel), 1 ovarian (Ov)**
- **Injection:**
  - 3 HCC; median diameter 1.6 cm (range 0.8 – 3.9 cm)
  - 1 Injected CR: 2.5 cm
  - 1 Injected NSCL: 1.4 x 2.4 cm
  - 1 Injected Mel: 1.1 x 1.9 cm
  - 1 Injected Ov: 1.4 cm
  - One HCC and one Mel patient with multiple tumors enrolled twice to allow sequential treatment of additional tumors

**Pharmacokinetics and Liver Enzymes**

- **RB extravesions rapidly cleared with prolonged retention in tumor**
- **PK samples from initial 6 participants over 28 days following 1st injection**
- **PB clearance (extravesion followed by tumor deposit):**
  - Cmax 29.500 mg/mL
  - t1/2 10.35 hr
  - Area 0.2007 hr^-1
  - t1/2 4.5 hours
  - 100 hours (2-3 days)
- **SAUC++/+ 89.3%**
- **SAUC–/+ 7.0%**
- **Rapid clearance consistent with observed safety profile of PV-10**
- **Systemic uptake and clearance compare favorably with other photodynamic agents**
- **Local relax to < 5% of Cmax, within 7 days, making cumulative plasma levels unlikely upon repeat treatment at intervals of 1 week or greater**

**Pharmacokinetics**

**Subject Populations**

**Toxicity**

**Summary and Conclusions**

- **Study Ongoing at Three Centers in the USA**
  - Expansion Cohort 1: Additional HCC and Liver Metastases
  - 26 Subjects, Single Treatment, Re-enrolled for Multiple Courses
  - Expansion Cohort 2: HCC Patients on Sorafenib
  - PO-156 (locoregional) vs. -154 (systemic)
  - Objective Response Observed in Injected Tumors
  - Toxicity was Transient

**Upcoming:** Asia/Pacific Phase 1b/2 Combination Study for HCC
  - SAT: SC + PV-10
  - RET: SC + PV-10

**Subject 0005 (HCC)**

- **ALT**
- **AST**
- **GCT**
- **Bil**

**Clinical Trials**

**Phase I Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver**

**Phase II Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver**

**Phase III Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver**

**Phase IV Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver**

**Safety and Efficacy of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver**

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