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

Paul Goldfarb, MD, Russell Low, MD, James Lyon, MD, Sanjiv S. Agarwala, MD, Alexander Rosemurgy, MD FACS, and Eric A. Wachtler, PhD

Sharp Clinical Oncology Research, San Diego, CA USA1, St. Luke’s Hospital and Health Network and Temple University, Bethlehem, PA USA2, Florida Hospital Tampa, Tampa, FL USA3, and Proventus Biopharmaceuticals, Inc., Knoxville, TN USA4

Abstract

BACKGROUND: IntralAxional 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 patients with non-resectable hepatocellular carcinoma (HCC) or cancer metastatic to the liver (NCT 00986661).

METHOD: Subjects having at least one liver tumor ≥1 cm are administered a single percutaneous intralAxional injection of PV-10 to one Target Lesion at dose of 0.25 or 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 9-15 months 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 of 4 that 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 phase half-lives of 4.5 and 100 hours, respectively. Elevated liver enzymes levels subsided 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 expansions 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 disodium (10% RB) for intralAxional injection
• Small molecule Fluorescein derivative attributed to Gnehm (1882)
• Prior human use of RB
  • IV hepatic diagnostic, 131I radiolabeled RB: Robengatop®
  • Topical ophthalmic diagnostic: Rosettes® and Minims®
• Established safety history
  • Not metabolized
  • Short circulatory half-life (ca 30 min)
  • Excretion via bile
• Radiopaque with prolonged retention in tumor

Primary Ablative Mechanism [2]

IntralAxional Injection
Lysosomal Accumulation
Lysosomal Disruption
Autolytic Cell Death

Secondary Immunologic Activation [3]

Antigen Release
APC Uptake
T-cell Activation
Bystander Tumor Regression

Phase 1 Patients

• 6 Male, 7 Female, median age 68 years (range 51 – 89)
• Hepatocellular Carcinoma – 6 patients
• Metastases to Liver – 7 patients: 3 colorectal mets (CRLM), 2 non-small cell lung (NSCL), 2 melanoma (Mel), 1 ovarian (Ova)
• Injected HCCs: median diameter 3.8 cm (range 1.9 – 9.0 cm)
• Injected CRLM: 2.5 cm
• Injected NSCL: 3.2 – 3.6 cm
• Injected Mel: 1.1 – 1.9 cm
• Injected Ova: 1.4 cm
• One HCC and one Mel patient with multiple tumors enrolled twice to allow sequential treatment of additional tumors

Example Response

Subject 0001, female, age 71
3.4 cm HCC lesion injected once with 5.1 mL PV-10
(second 3.8 cm HCC lesion injected once with 7.2 mL PV-10 3 months later)

CT Follow-up

MRI Follow-up

4 Months (26 June 2016)

4 Months (30 Aug 2016)

Outcome

Subject / Demographics / Disease / Status
Subject 0001 / Female, age 71 / Hep / Alive (with disease, 51 mos)
Subject 0002 / Female, age 73 / HCC [Hep], Colon, Portal Hypertension / Expired (DF, 48 mos)
Subject 0003 / Male, age 88 / HCC [Hep] and (Chronic Kidney Disease) / Alive (54 mos)
Subject 0004 / Male, age 65 / Mel / Alive (54 mos)
Subject 0005 / Male, age 67 / HCC / Expired (Cardiac Compromise, 2 mos)

10 of 13 patients alive after up to 54 months follow-up
• 1 death due to cardiac morbidity
• 1 death due to SAE (BP yst, Carcinoid) 60, 8.0 cm HCC, possible thromboembolism
• No long-term AEs

PV-10 Pharmacokinetics

Subject 0001

Subject 0002

Subject 0003

Subject 0004

Subject 0005

Dose (mg/kg)

Elapsed time (hr)

Liver Enzymes

Transit Elevation of Transaminases
• Samples at screening and 1, 2, 3, 7, 14, 28 and 174 days after injection
• Marked elevation of ALT / AST upon ablation
• Return to baseline within 7-14 days
• Similar trends reported for EiOH attributed to “technical success” of ablation

Summary and Conclusions

• Study Ongoing at Three Centers in the USA
• Expansion Cohort 1 – Additional HCC and Liver Metastases
• 24 Subjects, Single Treatment, Re-enroll for Multiple Lesions
• Expansion Cohort 2 – HCC Patients on Sorafenib
• PV-10 Dose Elevation (n = 6 Subjects)
• Objective Response Observed in Injected Tumors
• Toxicity was Transient

Upcoming: Asia/Pacific Phase 1b/2 Combination Study for HCC
• SAT: SOC + PV-10
• BCT: SOC + PV-10