Percutaneous Rose Bengal as an Oncolytic Immunotherapy for Hepatic Metastases

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Abstract (Updated)

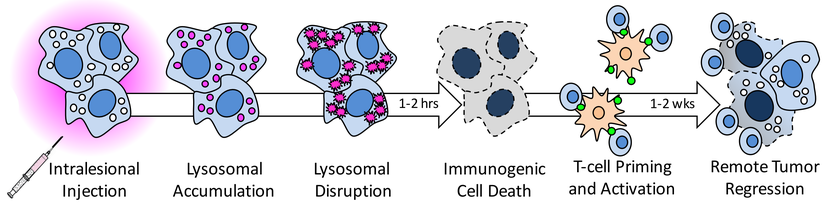
PURPOSE: PV-10 (10% rose bengal disodium for injection) is a small molecule investigational oncolytic immunotherapy that can yield high rates of complete response and durable local control in cutaneous metastatic melanoma. Ablation of injected tumors may elicit a tumor-specific T cell response that can lead to regression of uninjected disease. A Phase 1 study to assess safety, pharmacokinetics, and preliminary efficacy of percutaneous PV-10 in patients with non-resectable hepatocellular carcinoma (HCC) or other cancer metastatic to the liver is underway (NCT00986661).

MATERIALS AND METHODS: Subjects having at least one liver tumor ≥ 1 cm receive a single intralesional (IL) injection of PV-10 to a designated Target Lesion at 0.25 or 0.50 mL per cm^3 lesion volume. Plasma concentrations of PV-10 from 1 hour to 28 days after injection are measured. Radiologic assessments are performed to determine response over initial 28-day and longer-term 9-15 month follow-up intervals. Serum levels of potential liver injury biomarkers are measured, and adverse events recorded. Subjects with multiple tumors may receive sequential injection of additional tumors upon completion of the initial 28-day assessment.

RESULTS: An initial 6 subjects received PV-10 in two sequential dose-escalation cohorts, with an additional 12 subjects receiving PV-10 at the higher dose level. Overall, 12 of 18 subjects had metastatic disease, including 5 with metastatic colorectal carcinoma (mCRC). Significant adverse events were observed in 4 of 18 subjects, consisting of single incidents of injection site reaction, photosensitivity reaction and lethargy that resolved without sequelae, while 1 elderly patient with an 8.9 cm HCC lesion experienced an apparent fatal thrombus. PV-10 levels in plasma decreased rapidly in a bi-exponential manner, and elevated liver enzyme levels observed immediately after ablation subsided within a week. At last follow-up, 4 of 5 mCRC patients remained alive 9-73 months after receiving PV-10, including one having no evidence of disease at 73 months; the fifth, with multifocal disease, expired from disease progression at 3 months.

CONCLUSIONS: Preliminary safety and efficacy endpoints for treatment of liver tumors were met. Toxicity was generally transient, and the investigational treatment had acceptable tolerability. The study is continuing to accrue at 4 study centers in the USA in two expansion cohorts to extend assessment of safety and therapeutic activity in multiple hepatic tumor types.

Oncolytic Immunotherapy

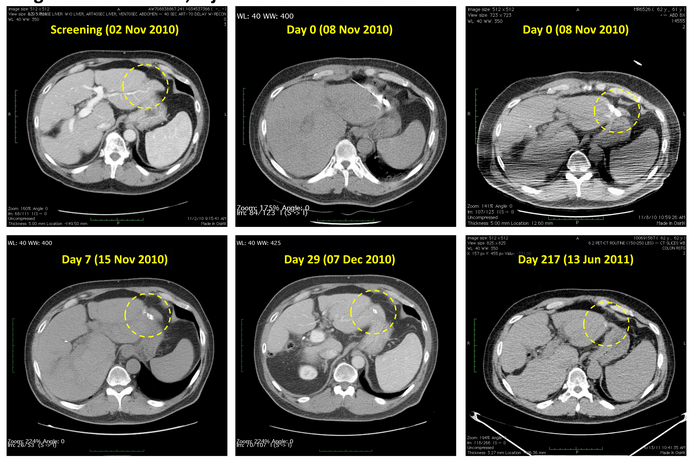


- **Consistent response observed in multiple tumor models (e.g., melanoma, HCC, colon, breast, pancreatic)**

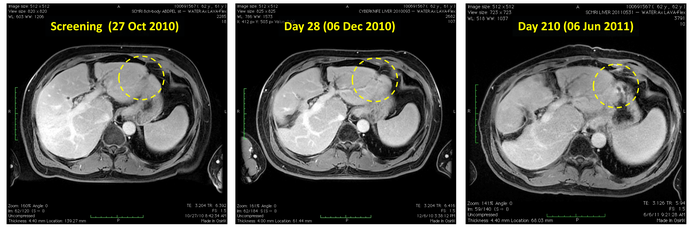
• Wachter et al., SPIE 2002; 4620: 143 (lysosomal accumulation and tumor cell disruption in tissue culture)
• Liu et al., Oncotarget 2016; 7: 37893 (murine and human T-cell activation and tumor microenvironment)
• Qin et al., Cell Death and Disease 2017; 8: e2584 (immunogenic cell death in murine and human colon cancer)

Clinical Example – Subject 0006 / mCRC

Target Lesion: 2.5 cm, injected once with 4.1 mL PV-10

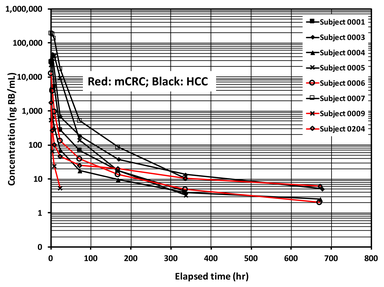


Target Lesion

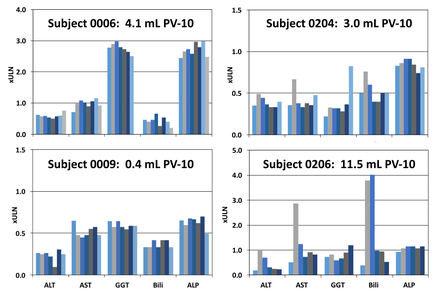


Bystander Lesions

Pharmacokinetics, Liver Enzymes and Long-Term Outcome



Rapid Primary Clearance of Extravasate



Transient Elevation of LFTs May be Observed

Subject	Disease and History	Survival Status
0006 M 61	mCRC (3 tu + Extensive Abdominal Mets, FOLFOX, Avastin, Erbitux)	Alive (NED, 73 mon)
0204 F 67	mCRC (2 tu, RFA, FOLFOX, Liver Resections)	Alive (24 mon)
0009 M 85	mCRC (Numerous Metabolically Active Hepatic tu)	Alive (18 mon)**
0010 F 53	mCRC (3 tu, FOLFOX, Avastin, Irinotecan, Partial Hepatectomy)	Alive (9 mon)
0206 F 67	mCRC (≥ 6 tu, FOLFOX, FOLFIRI, ZALTRAP, Regorafinib)	Expired (DP, 3 mon)
0005 M 68	HCC (2 tu + Chest Wall and Adrenal Mets, HepB and Cirrhosis)	Alive (NED, 75 mon)
0001 F 71	HCC (3 tu, Lobectomy, RFA)*	Alive (with Disease, 58 mon, lost to follow-up)
0004 F 73	HCC (4 tu, HepC, Cirrhosis, Portal Hypertension, RFA, TACE)	Expired (DP, 48 mon)
0008 F 66	HCC (3 tu, HepC, Cirrhosis, Portal Hypertension, TACE)	Expired (DP, 12 mon)
0007 M 67	HCC (1 tu Penetrating Diaphragm)	Expired (Cardiac Comorbidity, 2 mon)
0101 F 89	HCC (1 tu 8.9 cm)	Expired (SAE, suspected thromboembolism)
0203 M 69	Lung (≥ 4 tu, Nivo, SNX-5422 and Carbo/Paclitaxel)	Expired (DP, 12 mon)
0202 M 83	Lung (≥ 6 tu, Carbo/Abraxane)	Expired (DP, 4 mon)
0205 M 83	Pancreatic (2 tu)	Alive (12 mon)
0102 F 53	Melanoma (≥ 4 tu + Lung Mets, Hepatitis, Biochemo, Nivo + Ipi)*	Expired (DP, 18 mon)
0201 F 51	Ovarian (≥ 35 tu, Carbo/Paclitaxel)	Expired (DP, 15 mon)

* 2 lesions treated with PV-10 (requiring re-enrollment under separate subject number)
** commenced Avastin, 5-FU and Fusilev two months after PV-10

Conclusions

INTRAHEPATIC ONCOLYTIC IMMUNOTHERAPY with **PV-10**

- Readily imaged drug delivery due to radiopacity of PV-10
- Immunogenic cell death and tumor-specific activation potential
- Intriguing long-term survival despite grim prognosis for metastatic colorectal cancer

This basket study is designed to demonstrate safety and relevance of PV-10 for design of future randomized studies