Oncolytic Immunotherapy of Hepatic Tumors with Intralesional Rose Bengal Disodium

Poster ID 509
SIR 2020 Annual Scientific Meeting
29 March – 2 April 2020

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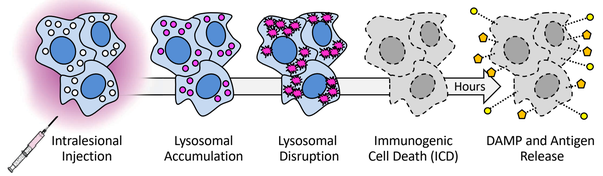
Background

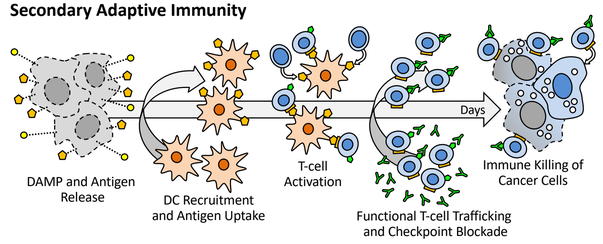
PV-10 (10% GMP rose bengal disodium for injection) is a radiopaque, small molecule, oncolytic immunotherapy in clinical development for solid tumors; intralesional (IL) injection can yield autolytic, immunogenic cell death (ICD) and tumor-specific reactivity in circulating T cells against treatment-refractory and immunologically-cold tumors [1-5]. It has been administered as a single agent to over 300 cutaneous melanoma subjects in Phase 1-3 testing and under expanded access [6-10], and is under investigation in combination with immune checkpoint blockade (CB) in over 30 subjects with advanced metastatic melanoma [11].

PV-10 is also under investigation for percutaneous administration, both as a single agent and with CB, to hepatic tumors (e.g., hepatocellular carcinoma and metastatic colorectal carcinoma, metastatic uveal melanoma, and metastatic neuroendocrine tumors) [12-13].

Primary Tumor Autolysis



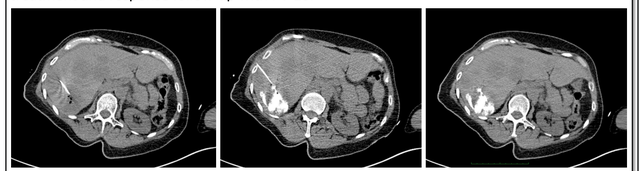
Secondary Adaptive Immunity



Methods

Multicenter, open-label, Phase 1 basket study PV-10-LC-01 (**NCT00986661**) is evaluating safety, tolerability, and preliminary efficacy of IL PV-10 in up to 78 subjects with non-resectable hepatocellular carcinoma (HCC) or other cancers metastatic to the liver. PV-10 is patent on CT or ultrasound (US) and in this study is administered percutaneously under image guidance to 1–3 hepatic tumors 1.0–4.9 cm in diameter. Response assessments (CT, MR, and/or PET) are performed at day 28, then q12w. Subjects with additional injectable disease may receive further PV-10 after day 28. Modified RECIST [14] and European Association of the Study of the Liver (2D-EASL) [15] methods are used to evaluate response of injected lesions; 2D-EASL measures only viable tumor tissue.

Rose bengal (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein) is radiopaque, facilitating treatment and response follow-up with PV-10.



Subject 0304 (mCRC) with extensive hepatic disease. Single 4 cm lesion injected once with 15 mL PV-10 via 19 Ga Chiba needle.

1. Wachter et al., Proceedings of SPIE 2002; 4620: 143. **2.** Liu et al., Oncotarget 2016; 7: 37893. **3.** Qin et al., Cell Death and Disease 2017; 8: e2584. **4.** Liu et al., PLoS ONE 2018; 13: e0196033. **5.** Swift et al., Onco Targets Ther. 2019; 12:1293. **6.** Thompson et al., Melanoma Res 2008; 18: 405. **7.** Thompson et al., Annals Surg Oncol 2015; 22: 2135. **8.** Lippey et al., J Surg Oncol 2016; 114: 380. **9.** Foote et al., J Surg Oncol 2017; 115: 891. **10.** Read et al., J Surg Oncol 2018; 117: 579. **11.** Agarwala et al., ASCO 2019 (abstract 9559). **12.** Patel et al., ISOO Biennial Conference 2019. **13.** Price et al., ASCO 2019 (abstract 4102). **14.** Therasse et al., JNCI 2000; 92: 205. **15.** Riaz et al., J Hepatol. 2011; 54: 695. **16.** Augsburger et al., Am J Ophthalmol 2009; 148: 119. **17.** Piulats et al., ESMO 2018 (abstract 1247PD). **18.** Pelster et al., ASCO 2019 (abstract 9522).

Patient Characteristics

At interim analysis (February 2020 data cutoff), 32 subjects (14 male, 18 female; median age 66, range 32-89) had received PV-10 into one or more hepatic tumors:

- HCC (7 subjects)
- colorectal carcinoma (mCRC, 6 subjects)
- uveal melanoma (mUM, 13 subjects)
- lung carcinoma (2 subjects)
- cutaneous melanoma (1 subject)
- breast carcinoma (1 subject)
- ovarian adenocarcinoma (1 subject)
- pancreatobiliary adenocarcinoma (1 subject)

Safety

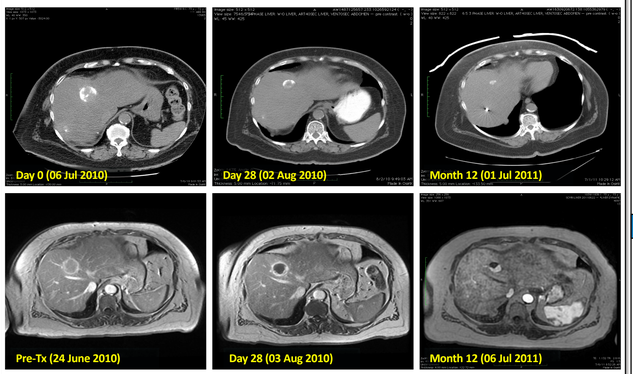
PV-10 exhibited acceptable safety on percutaneous injection to 49 lesions (46 treatment procedures, one lesion injected twice). Treatment-emergent serious adverse events attributed to PV-10 were observed in 6 subjects. Five subjects experienced transient CTCAE Grade 3 events that resolved without sequelae:

- diaphragmatic injury (1 subject)
- photosensitivity reaction (1 subject)
- lethargy (1 subject)
- hypoxia (1 subject)
- hypertension (1 subject)

One subject (subject 0101, age 89 with an 8.9 cm HCC) experienced Grade 5 thrombus (leading to reduction in allowed tumor size).

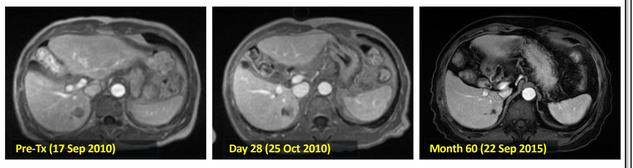
Radiologic Assessment

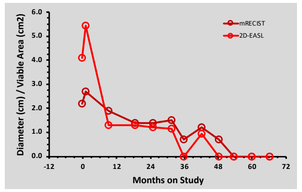
Focal necrosis of injected lesions is evident on CT and MR.



Subject 0001 (HCC) with two lesions (3.4 cm and 3.8 cm) injected 3 months apart (via 20 and 21 Ga Chiba needles). Injection of second lesion (7.2 mL PV-10) illustrates prolonged local retention (non-contrast CT at 12 months). MR illustrates central hypodense region with peripheral enhancement at Day 28 (SD by mRECIST, PR by 2D-EASL) with further regression at 12 months.

By emphasizing viable tumor tissue, 2D-EASL may be a better early predictor of response.





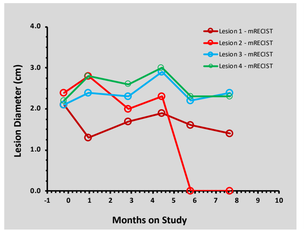
Subject 0005 (HCC, above and left) with complex tumor (2.6 x 2.3 cm having hypervascular and hypovascular regions) injected once with 4.6 mL PV-10 via 22 Ga Chiba needle. Apparent pseudo-progression evident by CT at Day 28 assessment (mRECIST and 2D-EASL), with marked decrease in viable tumor evident by 2D-EASL at month 3. On longer-term assessment, mRECIST tracks 2D-EASL but lags as a predictor of outcome. Subject achieved NED at month 54.

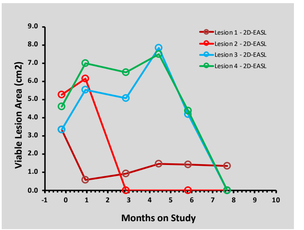
Treatment Pattern and Response Characteristics: HCC

Subject demographics, disease burden, and outcome. All subjects received single-agent PV-10.

Subject	Disease Status / Treatment History	Study Therapy	Therapy Post PV-10	Lesion Response [1] mRECIST / 2D-EASL	Overall Status
0005 M 68	2 tu, HBV and CIR	1 cycle to 1 tu	Nexavar for chest wall, adrenal mets (30 mos)	-100% / -100%	Alive (112 mos, NED)
0001 F 71	3 tu / Lobectomy, RFA	2 cycles to 2 tu		-11% / -30% -25% / -23%	Alive (58 mos, LTF)
0209 M 63	≥ 12 tu, HCV and CIR	3 cycles to 4 tu		-38% / -83% -100% / -100% -24% / -100% -23% / -100%	Alive (11.4 mos)
0004 F 73	4 tu, HCV, CIR, PHT / RFA, TACE	1 cycle to 1 tu	TACE	+28% / ND	Alive (11.0 mos, LTF)
0008 F 66	3 tu, HCV, CIR, PHT / TACE	1 cycle to 1 tu	^{90}Y Embolization	+2% / -67%	Expired (DP, 11.1 mos)
0007 M 67	1 tu 4.5 cm Penetrating Diaphragm	1 cycle to 1 tu		-3% / ND	Expired (Cardiac Comorbidity, 3.4 mos)
0101 F 89	1 tu 8.9 cm	1 cycle to 1 tu		ND / ND	Expired (SAE, suspected thromboembolism)

Abbreviations: CIR, cirrhosis; DP, disease progression; HBV, hepatitis B virus; HCV, hepatitis C virus; LTF, lost to follow-up; ND, not done; NED, no evidence of disease; PHT, portal hypertension; RFA, radiofrequency ablation; SAE, serious adverse event; TACE, transarterial chemoembolization; tu, hepatic tumor. [1] Injected lesion response assessment by CT.





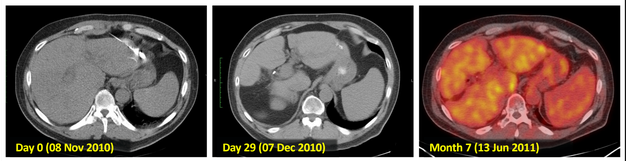
Subject 0209 (HCC), four lesions injected in three cycles (Lesion 1 at month 0, Lesion 2 at month 1, Lesions 3 and 4 at month 5). Follow-up ongoing at data cutoff. Depth of response emphasized by 2D-EASL.

Treatment Pattern and Response Characteristics: mCRC

Subject demographics, disease burden, and outcome. Most subjects had extensive metastatic disease and multiple prior lines of therapy. All subjects received single-agent PV-10.

Subject	Disease Status / Treatment History	Study Therapy	Therapy Post PV-10	Lesion Response [1] mRECIST / 2D-EASL	Overall Status
0006 M 61	3 tu + extensive Ab mets / FOLFOX, CPT 11/Avastin, Camptosar, Erbitux	1 cycle to 1 tu	Cyberknife of non-injected hepatic lesions	-25% / ND [2]	Alive (97 mos, NED, LTF)
0010 F 53	3 tu / FOLFOX, Avastin, Irinotecan, Partial Hepatectomy	1 cycle to 1 tu		-10% / -89%	Alive (14.5 mos, LTF)
0009 M 85	Numerous Metabolically Active Hepatic tu / Colon Resection	1 cycle to 1 tu	Avastin, 5-FU, Fusilev	-20% / -100%	Expired (47 mos, NED)
0204 F 67	2 tu / RFA, FOLFOX, Hepatic Lobectomy	1 cycle to 1 tu	Resection	+5% / +24%	Expired (DP, 27 mos)
0304 F 59	Extensive Hepatic Dz / None	1 cycle to 1 tu	Capecitabine	+34% / -89%	Expired (DP, 5.3 mos)
0206 F 67	≥ 6 tu / FOLFOX, FOLFIRI, ZALTRAP, Regorafenib	1 cycle to 1 tu		+32% / +49%	Expired (DP, 3.0 mos)

Abbreviations: Ab, abdominal; DP, disease progression; Dz, disease; LTF, lost to follow-up; ND, not done; NED, no evidence of disease; NR, not recorded; RFA, radiofrequency ablation; tu, hepatic tumor. [1] Injected lesion response assessment by CT. [2] CR of injected hepatic lesion observed at month 4, overall NED at month 57 after gradual regression of metastatic disease.



Subject 0006 (mCRC), single 2.5 cm lesion injected once with 4.1 mL PV-10 via 19 Ga Chiba needle. Fused PET-CT at month 7 illustrates retention of PV-10 and no definite, definable active metastasis.

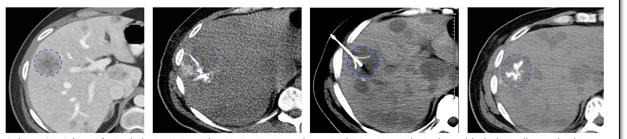
Treatment Pattern and Response Characteristics: mUM

Subject demographics, disease burden, and outcome. Most subjects received PV-10 in combination with emerging standard of care CB (anti-PD-1 ± anti-CTLA-4); five subjects were refractory to prior CB.

All subjects are being followed for overall survival (OS); potential survival benefit is critical in this population with historical OS of approximately 12 months [16] and 56-66% 1-yr OS with anti-PD-1 + anti-CTLA-4 checkpoint blockade [17-18].

Subject	Disease Status / Treatment History	Study Therapy [1]	Overall Status
0401 F 69	2 hepatic tu	2 cycles to 2 tu + Ipi-Nivo	Alive (22.7 mos)
0404 F 46	Multiple hepatic tu	2 cycles to 2 tu + Ipi-Nivo	Alive (19.3 mos)
0407 F 63	2 hepatic tu + ex-hepatic mets / Ipi + Nivo	2 cycles to 2 tu + Nivo	Alive (15.6 mos)
0408 F 60	2 hepatic tu + ex-hepatic mets	2 cycles to 2 tu + Autologous T cells + Pem	Alive (9.6 mos)
0409 M 54	Multiple hepatic tu	2 cycles to 3 tu + TIL + Ipi-Nivo	Alive (6.9 mos)
0410 F 56	Multiple hepatic tu + ex-hepatic mets / Pem and ^{90}Y refractory	1 cycle to 2 tu + Ipi-Nivo	Alive (6.6 mos)
0412 M 32	5 hepatic tu + ex-hepatic mets	2 cycles to 2 tu + Ipi-Nivo	Alive (5.8 mos)
0413 M 66	Multiple hepatic tu + ex-hepatic mets / immunoembolization and ^{90}Y refractory	1 cycle to 1 tu + Ipi-Nivo	Alive (5.4 mos)
0411 M 75	Multiple hepatic tu + ex-hepatic mets / Nivo refractory	4 cycles to 4 tu + Ipi-Nivo	Alive (5.3 mos)
0414 M 71	1 hepatic tu	1 cycle to 1 tu + Ipi-Nivo	Alive (4.6 mos)
0402 F 64	2 hepatic tu / adjuvant Ipi and Ipi+Nivo	1 cycle to 1 tu + Nivo	Expired (DP, 11.4 mos)
0406 F 61	1 hepatic tu	1 cycle to 1 tu + hepatic embolization	Expired (DP, 7.9 mos)
0210 M 81	>6 tu / Ipi and Pem refractory	2 cycles to 2 tu + hepatic embolization	Expired (DP, 6.9 mos)

Abbreviations: DP, disease progression; Ipi, ipilimumab; Ipi-Nivo, combination ipilimumab and nivolumab; Nivo, nivolumab; Pem, pembrolizumab; TIL, tumor infiltrating lymphocyte therapy; tu, hepatic tumor. [1] Number of injection cycles and number of hepatic tumors injected with PV-10; concomitant therapy listed when applicable.

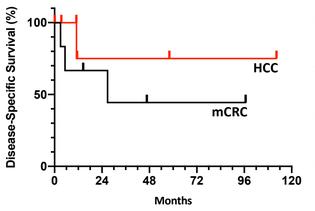


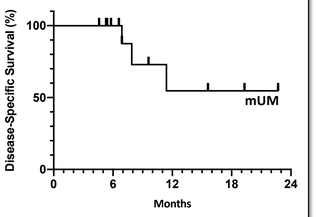
Subject 0412 (mUM), single lesion injected twice in repeat cycles. Initial injection with single end-holed needle resulted in extravasation and heterogeneous IL distribution of PV-10. Repeat injection with multi-pronged needle yielded improved retention and more uniform distribution within the injected tumor.

Survival Characteristics

Median disease-specific survival (DSS) was not reached for HCC subjects (0.1–112+ months) and estimated at 26.8 months for mCRC subjects (range 3.0–97+ months); subjects with the longest DSS in both groups were alive with no evidence of disease at last follow-up.

DSS was not reached for mUM subjects after limited initial follow-up (<24 months).





Conclusions

- Percutaneous IL PV-10 exhibited acceptable safety and tolerability with encouraging evidence of activity.
- Direct imaging of injected drug using CT or US allows immediate assessment of procedure.
- PV-10 is compatible with standard end-holed needles, multi-port infusion needles, and multi-pronged needles.
- Enrollment is ongoing to allow further investigation into combination with immune checkpoint blockade, including:
  - HCC patients that are candidates for CB (anti-PD-1).
  - mUM patients that are candidates for combination CB (anti-CTLA-4 + anti-PD-1)
- A companion study is assessing PV-10 in neuroendocrine tumors metastatic to the liver (**NCT02693067**).