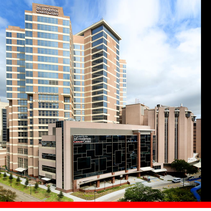

A phase 1 study of percutaneous oncolytic rose bengal disodium for metastatic uveal melanoma patients with hepatic metastases – a single-center cohort summary (#124P)

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Background

Rose bengal disodium (PV-10) is a small molecule oncolytic immunotherapy in clinical development for treatment of solid tumors When administered by intralesional injection, PV-10 can produce an immunogenic cell death that may induce a T-cell mediated immune response against treatment-refractory and immunologically-cold tumors.[1-4] It has been administered as a single agent to over 300 patients with cutaneous melanoma[5-8] and is currently under investigation in combination with anti-PD1.[9] Given this mechanism of action, we investigated treatment of metastatic uveal melanoma with percutaneous hepatic PV-10. The radio-opacity of PV-10 allows for its direct visualization during CT guided injection procedures. This property allows for optimization of injection technique for intratumoral drug delivery.

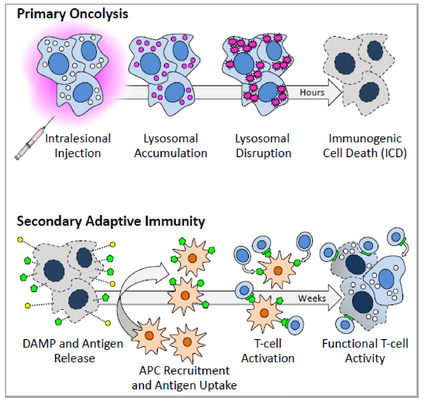

Figure 1. Mechanism of action of PV-10 intralesional injection. PV-10 accumulates in lysosomes of tumor cells. This leads to lysosomal disruption and causes oncolysis. The release of intratumoral damage associated molecular pattern (DAMP) proteins leads to uptake by antigen presenting cells (APC) and recruitment of T cells.

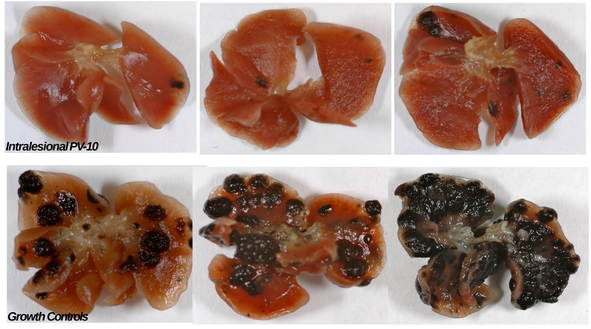

Figure 2. In a murine experiment, melanoma cells were implanted as a solitary dermal tumor and into the lungs via tail vein injection. PV-10 was injected into the dermal tumor 9 days after implantation. Murine lungs harvested 21 days after implantation demonstrate bystander response to dermal PV-10 (top panel) compared to uninjected controls (bottom panel).

Methods

We conducted an open-label Phase 1b study evaluating the safety, tolerability, and efficacy of intralesional PV-10 in a cohort of patients with uveal melanoma metastatic to the liver (NCT00986661). Percutaneous injections of PV-10 are administered to one or more designated hepatic tumor(s) with a maximum sum of diameters ≤4.9 cm and a maximum volume of 15 mL. Response assessments using 2D EASL criteria are performed at Day 28, then every 3 months. Patients with additional injectable tumors may receive further PV-10 after Day 28. Eligible patients may receive standard of care checkpoint blockade immunotherapy during treatment with PV-10. European Association of the Study of the Liver (EASL) guidelines were developed in 2001 and recommend measuring only enhancing tissue in the tumor.[10] EASL response is an early predictor of necrosis at 1-2 months. There have been few reports using EASL tumor response assessment on patients with metastatic melanoma to the liver.

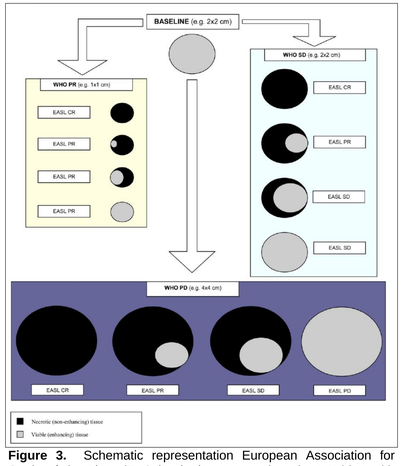

Figure 3. Schematic representation European Association for Study of the Liver (EASL) criteria compared to the World Health Organization (WHO) criteria.[10] WHO guidelines suggest measurement of the whole tumor irrespective of the amount of necrosis (black) whereas EASL criteria utilize measurement of the enhancing tissue only (grey). This figure represents the discordance between the two guidelines.

Table 1. EASL guidelines for assessing hepatic tumor response

CR	100% decrease in amount of enhancing tissue in target lesion(s)
PR	≥50% decrease in amount of enhancing tissue in target lesion(s)
SD	<50% decrease in amount of enhancing tissue in target lesion(s)
PD	>25% increase in amount of enhancing tissue in target lesion(s) and/or New enhancement in previously treated lesions warranting further LRT

Table 2. Baseline demographics

Category	**N** (%)
Patients treated	13 (100)
Age (years)	61 (median)
Gender	
Male	6 (46)
Female	7 (54)
Baseline LDH	
Normal	6 (46)
Elevated	6 (46)
Unknown	1 (8)
Largest tumor diameter	
<3 cm (M1a)	9 (69)
3-8 cm (M1b)	4 (31)
>8 cm (M1c)	0
Prior lines of treatment	
0	8 (62)
1	3 (23)
2	2 (15)
Prior treatment	
Immunotherapy	4 (31)
Liver directed therapy	2 (15)

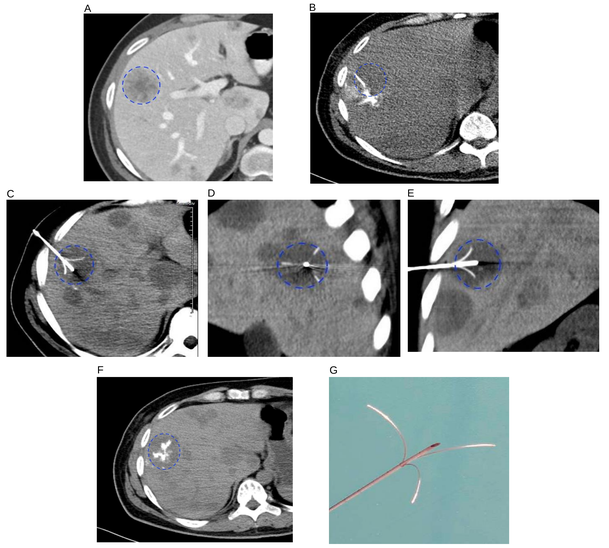

Figure 4. Example of extravasation remedied by change of needle. Panel A shows target tumor in the liver (dashed blue circle). Using a single end holed needle approach, PV-10 extravasated outside the tumor bed (Panel B). Panels C, D, and E show intralesional injection using an alternate multi-pronged needle. Deposition of PV-10 with more intratumoral retention using a multi-pronged needle (Panel F). An example of a Quadra-Fuse™ (Rex Medical, Conshohocken, PA, USA) multi-pronged needle is shown in Panel G.

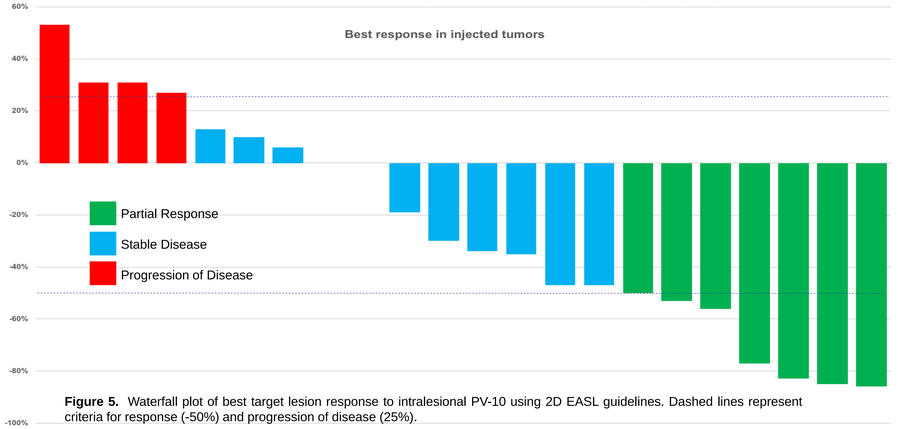

Figure 5. Waterfall plot of best target lesion response to intralesional PV-10 using 2D EASL guidelines. Dashed lines represent criteria for response (-50%) and progression of disease (25%).

Results

- To date, 13 uveal melanoma patients received treatment with intralesional PV-10 to the liver; 6 patients received a second cycle of PV-10; in total, 26 tumors have been injected.
- 9 patients received concomitant standard of care checkpoint blockade.
  - 1 patient entered study on maintenance anti-PD1.
  - 1 patient began anti-PD1 therapy after first dose of PV-10.
  - 7 patients received combination checkpoint blockade after first dose of PV-10.
- Tumor assessments available on 22 injected target lesions:
  - 7 tumors with partial response (32%)
  - 11 tumors with stable disease (50%)
  - 4 tumors with progression of disease (18%)
- Adverse events (AEs) of note were 3 cases of Grade 3/4 transaminitis that resolved to Grade 1 or better within 72 hours.
  - Grade 1 PV-10 related events seen in 1 patient each include: pink stool, pink urine, photosensitivity, injection site pain, and hyperbilirubinemia.
  - Additional AEs such as nausea, headache, myalgias, blurry vision, decreased WBC, and fatigue were attributed to concomitant checkpoint blockade.

Conclusions

- PV-10 as an image-guided percutaneous injection of hepatic metastases in uveal melanoma is well-tolerated.
- Alternate needle selection may overcome high intratumoral pressure and extravasation to obtain optimal drug delivery.
- PV-10 in combination with checkpoint inhibitors demonstrates no additional safety signals.
- Partial responses (32%) and stable disease (50%) have been seen in injected tumors.
- Further follow-up is needed to calculate survival benefit with this approach.

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