Metabolic complete responses in metastatic uveal melanoma patients treated with image-guided injection of PV-10

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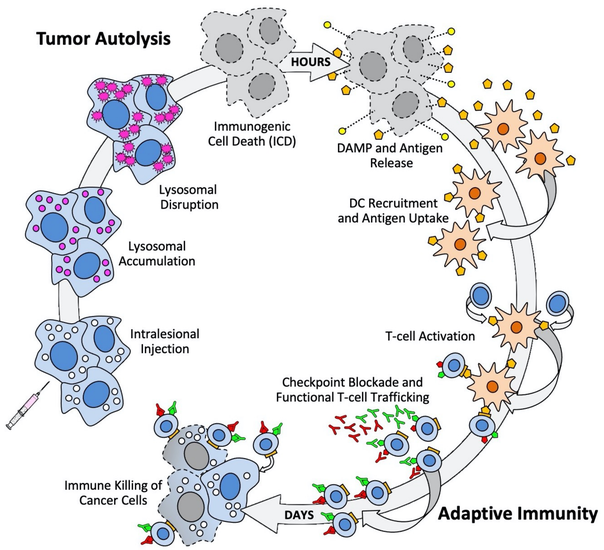
Background

Rose bengal disodium (PV-10) is a small molecule oncolytic immunotherapy in clinical development for treatment of solid tumors [1-4]. 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 [5-8]. Adaptive immunity can be enhanced through combination with immune checkpoint blockade (CB) [4,8].



Traditional CT imaging can underestimate the degree of anti-cancer treatment effect due to reliance on morphological changes of visualized tumors. In contrast, PET imaging offers information on metabolic activity using a positron-emitting radiolabeled agent (e.g. FDG) but is less sensitive to changes in tumor size. FDG-PET images acquired, co-registered, and superimposed on CT images (PET-CT) allow spatial detection of anti-cancer activity. Moreover, FDG-PET-CT can provide information regarding anti-tumor immune responses in patients receiving immunotherapy.

Response assessment of injected lesion response by RECIST and 2D EASL [9] criteria allows evaluation of PV-10 treatment effect and may provide early prognostic evidence of potential clinical benefits of metabolic complete response (mCR) and overall survival (OS).

Methods

PV-10-LC-01 (NCT00986661) is an open-label Phase 1 study evaluating the safety, tolerability, and preliminary efficacy of intralesional PV-10 in patients with solid tumors metastatic to the liver. PV-10 is administered percutaneously to 1-3 designated hepatic tumors 1.0-4.9 cm in diameter. Response assessments are performed at Day 28, then every 3 months. Patients with additional injectable tumors may receive further PV-10 after Day 28. Here we describe the experience in a cohort of patients with metastatic uveal melanoma (mUM). Eligible patients could receive standard of care CB during or after PV-10 treatment.

Patient Characteristics

All patients had at least 1 injectable hepatic metastasis; approximately half had additional extra-hepatic disease. Seven patients underwent PET-CT during the study; 4 achieved mCR (including 2 patients with extensive extra-hepatic disease). mCR patients were similar to the general study population, with the exception of a lower overall M-category, and received similar study treatment.

Table 1. Patient characteristics and study treatment

Category	All Patients (N)	mCR Patients (N)
No. Patients	23	4
Age, median (range)	64 (32–80)	68 (56–70)
Gender		
Male	12	2
Female	11	2
M-category		
M1a (largest diameter ≤ 3.0 cm)	14	4
M1b (largest diameter 3.1–8.0 cm)	8	0
M1c (largest diameter ≥ 8.1 cm)	1	0
Sites of metastatic disease		
Hepatic only	12	2
Hepatic + extra-hepatic	11	2
Prior lines of therapy		
0	10	2
1	11	1
2+	2	1
Prior treatment		
Immunotherapy	12	2
No immunotherapy	11	2
Study treatment		
PV-10 only	6	1
PV-10 + PD-1	6	0
PV-10 + PD-1 + CTLA-4	11	3
PV-10 treatment cycles, median (range)	2.0 (1–6)	1.5 (1–3)
Lesions injected, median (range)	2.0 (1–11)	2.0 (1–3)

Lesion response

Equivalent response patterns were observed when injected lesions were assessed via CT using RECIST and 2D EASL criteria. Patients achieving mCR generally exhibited stabilization or regression of their injected lesions, but did not achieve CR by CT, with maximum response developing gradually.

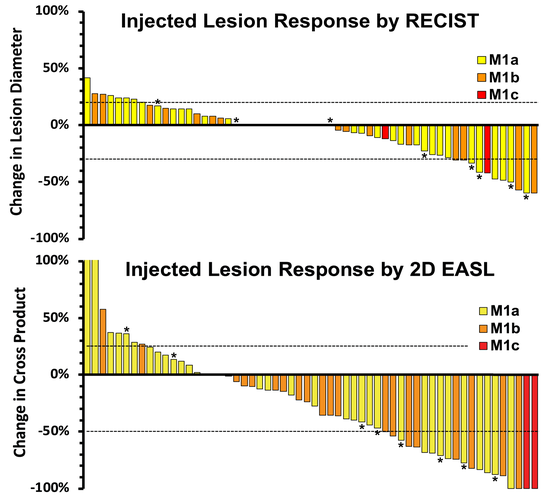


Fig. 1 Change in injected lesion diameter (RECIST) and two dimensional viable cross product (2D EASL). Asterisks indicate response of lesions in patients achieving mCR. Dashed horizontal lines denote response thresholds for the respective assessment criteria.

Best Overall Response (Injected Lesions)	RECIST	2D EASL
No. Lesions Evaluated	59	58*
Objective responses	11 (19%)	20 (34%)
Complete response	0 (0%)	4 (7%)
Partial response	11 (19%)	16 (28%)
Stable disease	39 (66%)	30 (52%)
Progressive disease	9 (15%)	8 (14%)

* One lesion was not evaluable by 2D EASL due to a baseline cross product of zero.

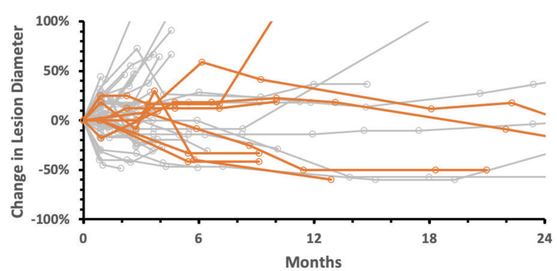
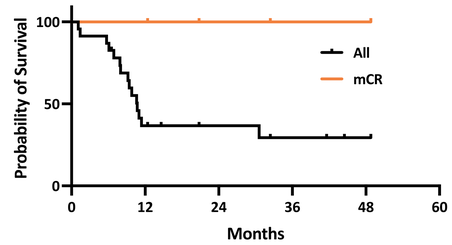


Fig. 2 Change in injected lesion diameter (RECIST); orange lines illustrate patients achieving mCR compared to the general study population (grey bars).

Survival

Median OS was 10.7 months (range 1.1 to 48.8+ months) from initiation of PV-10 treatment; OS from the onset of metastatic disease was 16.9 months (range 2.7 to 72.2+ months).

All four patients achieving mCR were alive at data cutoff (range 12.4+ to 48.8+ months from initiation of PV-10 treatment).



Safety

Acceptable safety was observed with no mortality or permanent Grade 3 or higher morbidity attributed to study treatment.

Conclusions

- PV-10 can induce mCR in both injected (adscopal) and non-injected (abscopal) lesions.
- mCR suggests immunogenic cell death in mUM patients with liver metastases.
- CT response assessment may underestimate the effect of PV-10 in injected tumors; 2D EASL is more sensitive than RECIST to changes in injected lesions, but both are less sensitive than PET-CT.
- Translational research is underway to elucidate the molecular basis for mCR responders vs non-responders.

References

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