Initial Results from a Phase 1b Study of PV-10 and anti-PD-1 in Melanoma Refractory to Checkpoint Inhibition

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Updated Abstract and Background

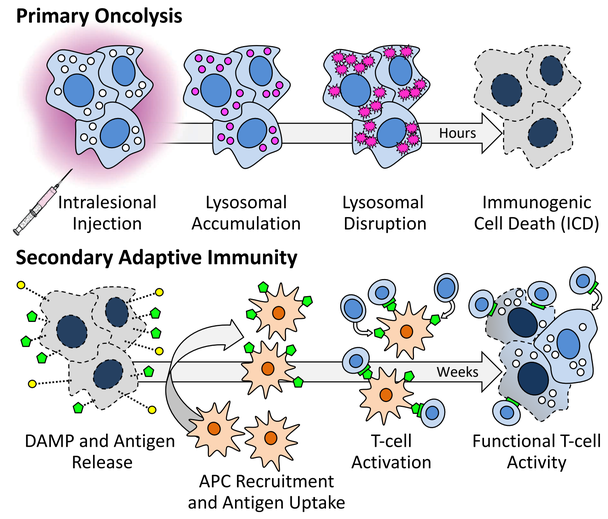
PV-10 (10% rose bengal disodium for injection) is a small molecule oncolytic immunotherapy in development for solid tumors; intralesional injection can yield immunogenic cell death and induce tumor-specific reactivity in circulating T cells [1-4]. It has been administered as a single agent to 130 cutaneous melanoma patients (pts) in phase 1 and 2 and 197 pts with cutaneous malignancies under expanded access [5-8].

Study PV-10-MM-1201 (**NCT02557321**) is a phase 1b/2 study of PV-10 in combination with anti-PD-1 (pembrolizumab) for pts with advanced cutaneous melanoma; pts must have at least 1 injectable lesion and be candidates for pembrolizumab. The combination is administered q3w for 5 cycles followed by pembrolizumab alone for up to 24 months; the primary endpoint is safety and tolerability with objective response rate and progression free survival key secondary endpoints (assessed by RECIST 1.1 after 5 cycles then q12w). Correlative assessments are being performed on a subgroup of pts.

Accrual into an expansion cohort of pts relapsed or failing to achieve an objective response on checkpoint inhibition (CI) began in Dec 2018; this extends an exploratory group of CI-refractory pts enrolled into the main cohort of the study. Ten pts (1 Stage IIID, 4 M1a, 1 M1b, 3 M1c and 1 M1d; median age 77, range 54-90) refractory to CI (3 refractory to CTLA-4, 4 to PD-1 and 5 to CTLA-4 + PD-1) have commenced study treatment. Adverse events have been consistent with established patterns for each drug. Among this initial group, 4 pts withdrew due to progression during combination treatment; 2 pts (IIID and M1a, respectively) achieved a best overall response of PR, 2 pts (M1a and M1c) achieved SD and 2 pts were not evaluated. Five pts have completed correlative assessment: post-PV-10 serum exhibited elevation of High Mobility Group Box 1 (HMGB1), a Damage Associated Molecular Pattern (DAMP) associated with activation of dendritic cells.

Acceptable safety and tolerability have been observed, and enrollment is ongoing. Initial correlative results for this highly refractory population are consistent with prior evidence of immune activation by PV-10 in CI-naïve pts (both as single-agent and in combination with pembrolizumab) [2,9].

Small Molecule Oncolytic Immunotherapy



- Functional T cell Activity in Peripheral Blood of Melanoma Patients [2]
- Induction of Functional T cells Boosts Activity of Checkpoint Inhibition in Murine Melanoma Models [4]

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.** Thompson et al., Melanoma Research 2008; 18: 405. **6.** Thompson et al., Annals Surg Oncol 2015; 22: 2135. **7.** Lippey et al., J Surg Oncol 2016; 114: 380. **8.** Foote et al., J Surg Oncol 2017; 115: 891. **9.** Agarwala et al., J Clin Oncol 2019; 37 (suppl; abstr 9559).

Study Participants and Results

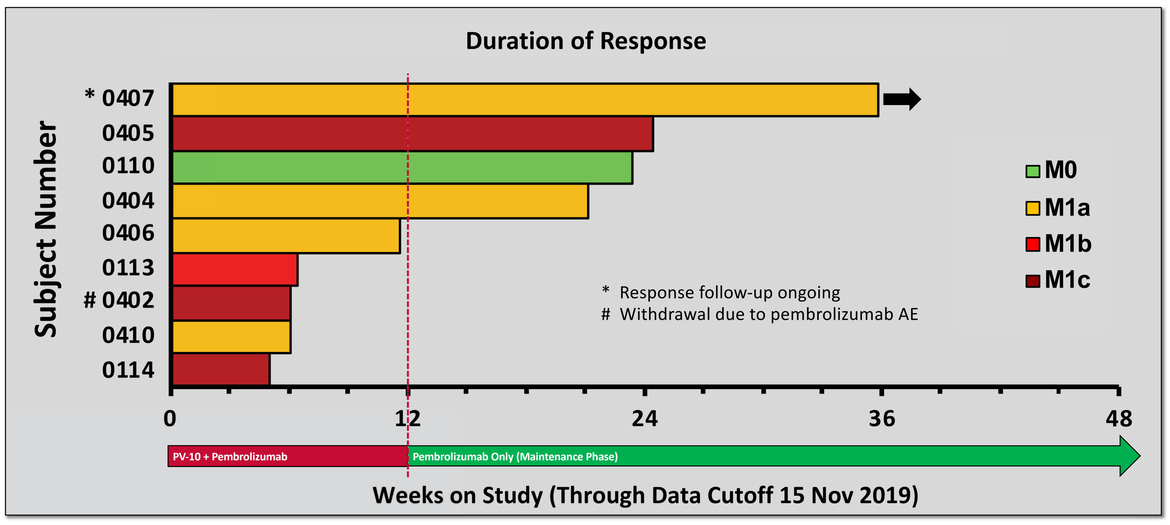
Subject Characteristics
(Phase 1b CI-Refractory ITT Population, N = 10)

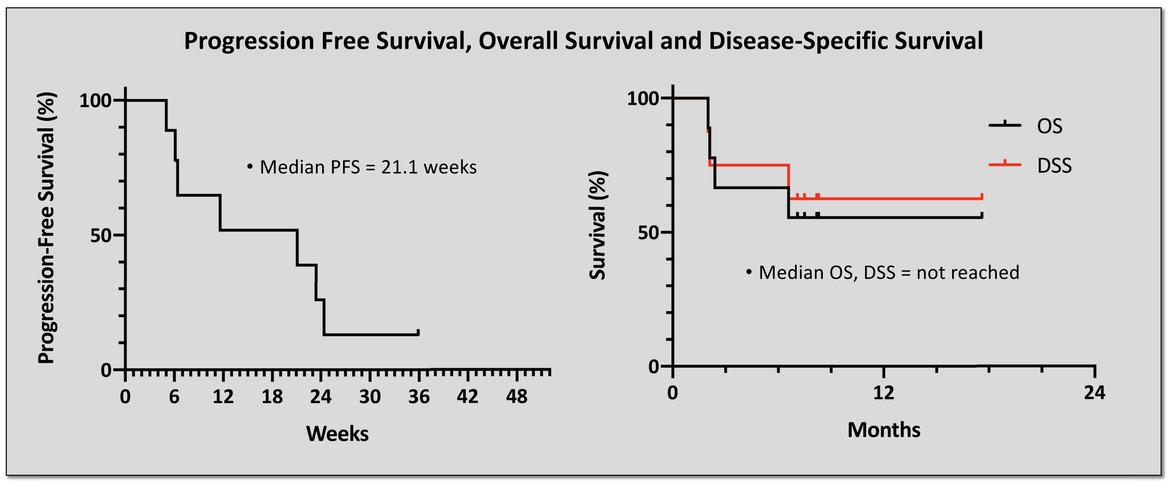
ID / Age / Gender	Stage	CUT/SQ Lesions [a]	Location(s) of Target Lesions	Site(s) of Non-Target Lesions	Prior Therapy	BORR
0110 / 90 / F	IIID	5	Scalp (x2)	Scalp	Ni	PR
0407 / 71 / F	M1a	2	ALN	ALN	Ipi+Nivo	PR
0404 / 77 / F	M1a	4	Torso (x2)	Torso (x2), LE	Ipi+Nivo, Chemo	SD
0406 / 65 / M	M1a	3	UE (x2), ALN	--	Ipi	PD
0410 / 77 / M	M1a	2	UE, Torso	--	Nivo, Ipi+Pem, Nivo, Chemo, XRT	PD
0113 / 77 / F	M1b	8	Chest Wall (SQ), Adrenal, Pelvic LN, Ing LN	Lung, Torso	Ipi+Pem, DAB-MEK	PD
0405 / 64 / M	M1c	1	Chest Wall, Spleen	Lung	XRT, Ipi+Nivo	SD
0114 / 77 / M	M1c	20	Axilla (x2), Chest Wall (SQ), Neck, Liver	Liver, Lung	Peg-IFN, Pem, XRT	PD
0402 / 79 / M	M1c	2	Axilla, Flank, Lung, Liver, Peritoneum	Peritoneum, Retroaortic LN, Lung	Adjuv Vaccine, XRT, Ipi	NEV (AE)[b]
0601 / 54 / M	M1d	13	Scalp (x3)	Bone (vertebral)	Nivo	NEV[c]

Abbreviations: AE, adverse event; ALN, axillary lymph node; CI, checkpoint inhibition; Ing, inguinal; LE, lower extremity; LN, lymph node; Ipi, ipilimumab; ITT, intent-to-treat; N, number; NEV, not evaluated; Nivo, nivolumab; Pem, pembrolizumab; SQ, subcutaneous; UE, upper extremity; XRT, radiotherapy.

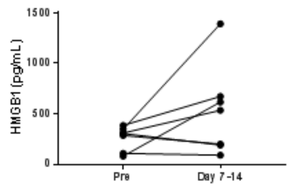
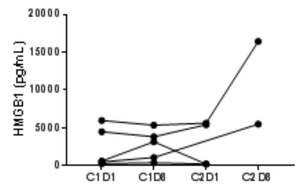
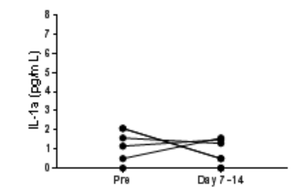
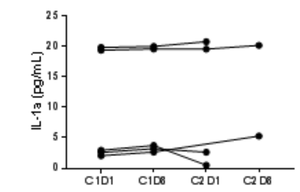
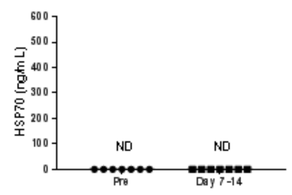
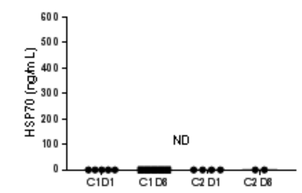
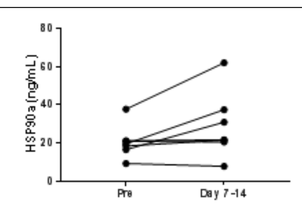
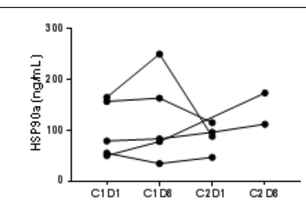
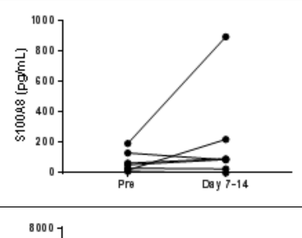
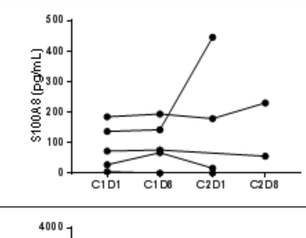
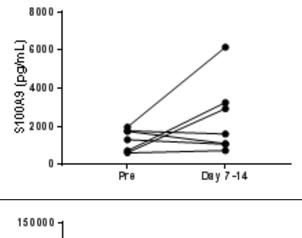
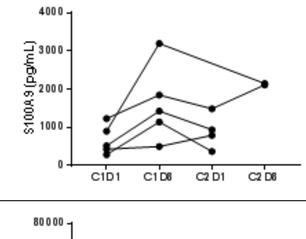
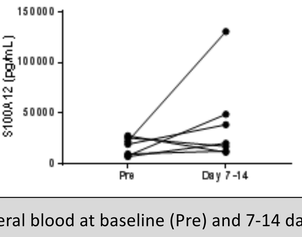
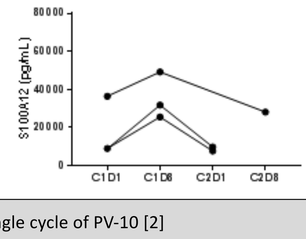
[a] Subjects had a median of 3.5 injectable lesions (range 1 – 20).
[b] Subject 0402 withdrew due to AE (myasthenia gravis) attributed to pembrolizumab.
[c] Subject 0601 (M1d, prior treated/resolved brain metastasis) on study treatment, not yet evaluated.

- ITT population is all subjects receiving at least one dose of PV-10 and pembrolizumab
- All subjects had measurable Target Lesions assigned at baseline and were followed per RECIST 1.1
- PV-10 was injected to cutaneous, subcutaneous, nodal and soft tissue lesions
- PV-10 was limited to 5 cycles
- Half of subjects were refractory to multiple lines of CI





- Approximately half of subjects exhibited early RECIST progression during combination treatment leading to short PFS
- Overall survival and disease-specific survival not reached (three subjects died from disease progression)
  - RECIST may not be optimal criteria for assessing immunotherapy response in CI-refractory patients

DAMP	PV-10 (Single-Agent) [a]	PV-10 + Pembrolizumab [b]
HMGB1		
IL-1a		
HSP70		
HSP90a		
S100A8		
S100A9		
S100A12		

[a] DAMPs measured in peripheral blood at baseline (Pre) and 7-14 days after single cycle of PV-10 [2]
[b] DAMPs measured in peripheral blood at baseline (C1D1) and 7 (C1D8) and 21 days (C2D1) after start of first cycle of PV-10 + pembrolizumab, and 7 days (C2D8) after start of second cycle of PV-10 + pembrolizumab

Conclusions

- Established AE profiles of each study drug were maintained
- Approximately half of subjects exhibited clinical benefit upon minimal intervention with PV-10
- CI-refractory pts exhibit a DAMP profile similar to CI-naïve patients receiving PV-10 alone
  - PV-10 can serve as an oncolytic immunotherapy in CI-refractory patients