Results from a Checkpoint Inhibition-Naïve Cohort of Patients in a Phase 1b Study of PV-10 and anti-PD-1 in Advanced Melanoma

Sanjiv S Agarwala [1], Merrick Ross [2], Jonathan S Zager [3], Keisuke Shirai [4], Richard Essner [5], Bernard M Smithers [6], Victoria Atkinson [6] and Eric Wachter [7]

[1] Temple University, Philadelphia, PA USA; [2] MD Anderson Cancer Center, Houston, TX USA; [3] Moffitt Cancer Center, Tampa, FL USA; [4] Dartmouth-Hitchcock Medical Center, Lebanon, NH USA; [5] John Wayne Cancer Center, Santa Monica, CA USA; [6] Princess Alexandra Hospital, Brisbane, QLD AUS and [7] Provectus Biopharmaceuticals, Inc., Knoxville, TN USA

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For additional information:
info@pvct.com

Updated Abstract and Background

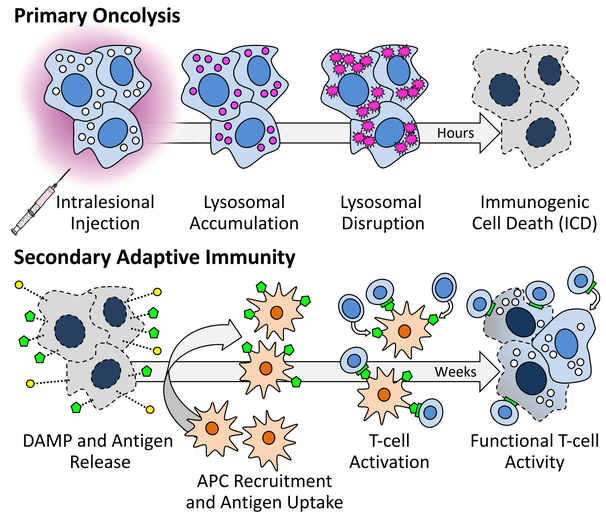
PV-10 (10% rose bengal disodium for injection) is a small molecule oncolytic immunotherapy in development for solid tumors; intralesional injection can yield immunogenic cell death and induce tumor-specific reactivity in circulating T cells [1-4]. It has been administered as a single agent to 130 cutaneous 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. Eligibility for the main cohort of Phase 1b required pts to have at least 1 injectable lesion, be naïve to checkpoint inhibition (CI), and be candidates for pembrolizumab. The combination was 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 (ORR) and progression-free survival (PFS) key secondary endpoints (assessed by RECIST 1.1 after 5 cycles then q12w).

Full accrual of the main cohort was reached in April 2018, with 21 CI-naïve pts (2 IIIC/IIID, 8 M1a, 7 M1b, 4 M1c; median age 69 years, range 28-82) receiving at least 1 dose of PV-10 and pembrolizumab (2 pts with prior CI treatment enrolled in the main cohort are not included here). Treatment-Emergent Adverse Events were consistent with established patterns for each drug, principally Grade 1-2 injection site reactions attributed to PV-10 and Grade 1-3 immune-mediated reactions attributed to pembrolizumab, with no significant overlap or unexpected toxicities. Among the mostly Stage IV population a best overall response of CR has been achieved (as of November 2019) by 10% of pts (1 each M1a and M1b), 57% of pts have achieved PR (including all M1c pts); PFS was 11.7 months with 95% overall survival (OS) and 100% disease-specific survival (DSS) at 12 months. Response assessment is ongoing for 4 pts.

The primary endpoint for phase 1b was met, with acceptable safety and tolerability and no unexpected safety issues identified. Two phase 1b expansion cohorts (24 pts each) are enrolling pts refractory to prior CI and pts with in-transit or satellite disease.

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.

Study Participants and Results

Subject Characteristics
(Phase 1b Main Cohort CI-Naïve ITT Population, N = 21)

ID / Age / Gender	Stage	CUT/SQ Lesions [a]	Location(s) of Target Lesions	Site(s) of Non-Target Lesions
0111 / 68 / F	IIIC	8	Scalp (x2)	Scalp
0501 / 82 / M	IIIC	15	UE (x2)	LNs
0106 / 78 / M	M1a	1	LE (x2)	LE
0108 / 82 / F	M1a	2	UE (x2)	UE
0109 / 60 / M	M1a	1	Chest (x2), ALN	ALN and Skin
0202 / 52 /M	M1a	1	Chest Wall	Chest Wall and ALN
0204 / 28 / M	M1a	TNC	Jaw, UE	Scalp, Face, Neck, Torso, UE, ALN
0205 / 50 / F [b]	M1a	3	Chest Wall	Back
0207 / 44 / M	M1a	1	Infraclavicular (SQ)	Subcutaneous
0209 / 66 / M	M1a	2	Back, UE	Spinal Muscle and LN, Back
0102 / 47 / M [c]	M1b	4	Scalp	Lung
0104 / 79 / M [c]	M1b	3	LE	Bilateral Lung
0107 / 68 / M	M1b	1	Flank (SQ)	Lung
0203 / 76 / M	M1b	2	LE (x2)	Lower Extremity and Lung
0206 / 73 / M	M1b	1	UE	Lung
0401 / 70 / M [d]	M1b	1	Shoulder, Lung, Liver	Liver and Lung
0502 / 47 / M	M1b	2	Head, Lung	Lung and Hilar LN
0101 / 81 / M	M1c	3	SQ (x2), ALN	Liver and Lung
0105 / 69 / M	M1c	4	UE, R Axilla, Liver (x2)	Bone, Liver and Lung
0112 / 80 / M	M1c	1	Scalp, Liver (x2)	Liver
0403 / 78 / M	M1c	TNC	Shoulder (x2), Clavicle, Bladder (x2)	Bladder and Bone

Abbreviations: ALN, axillary lymph node; CI, checkpoint inhibition; CUT, cutaneous; LE, lower extremity; LN, lymph node; ITT, intent-to-treat; N, number; SQ, subcutaneous; TNC, too numerous to count; UE, upper extremity.

[a] Subjects had a median of 2.0 injectable lesions (range 1 – 15); Subjects 0204 and 0403 excluded from calculation (TNC).
[b] Subject 0205 previously treated with dabrafenib and trametinib.
[c] Subjects 0102 and 0104 previously treated with pegylated interferon alfa-2b.
[d] Subject 0401 previous treated with doxorubicin and olaratumab.

- 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
- PV-10 injection to cutaneous and subcutaneous lesions (not to nodal or visceral lesions)
- PV-10 was limited to 5 cycles in main cohort

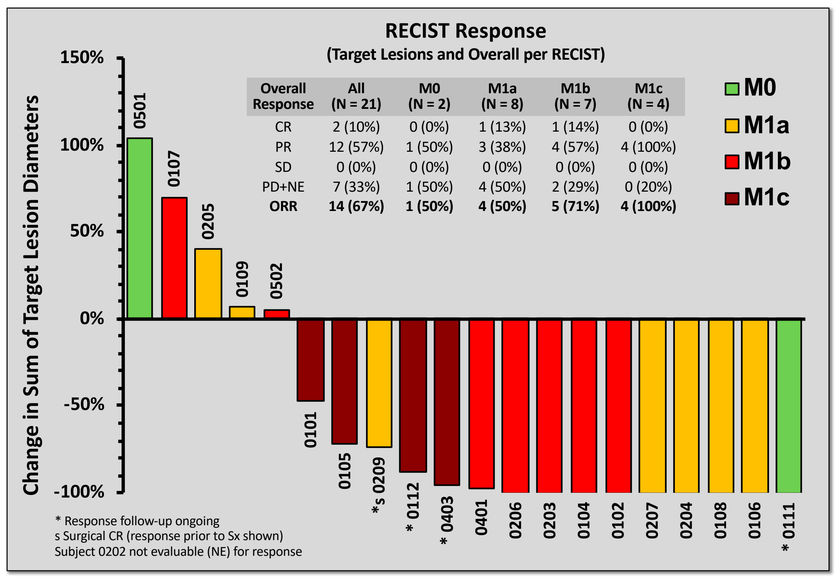
Treatment-Emergent Adverse Events (TEAEs)
Occurring in >1 Subject, or Any Grade 3 or Higher
(Phase 1b Main Cohort CI-Naïve ITT Population, N = 21)

	TEAEs Related to PV-10		TEAEs Related to Pembrolizumab		TEAEs Related to Combination	
	All	≥ G3	All	≥ G3	All	≥ G3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Injection site pain	16	***1***	0	0	0	0
Injection site discharge	6	0	0	0	0	0
Injection site oedema	6	0	0	0	0	0
Injection site photosensitivity reaction	5	0	0	0	0	0
Injection site discolouration	4	0	0	0	0	0
Injection site pruritus	2	0	0	0	2	0
Injection site erythema	2	0	0	0	1	0
Injection site ulcer	3	0	0	0	0	0
Injection site haemorrhage	2	0	0	0	0	0
Fatigue	0	0	10	0	1	0
Influenza like illness	0	0	1	0	1	0
Pyrexia	0	0	1	0	1	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
Eschar	2	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Pruritus	0	0	4	***1***	0	0
Rash	0	0	4	0	0	0
Rash maculo-papular	0	0	3	0	0	0
METABOLISM AND NUTRITION DISORDERS						
Hypothyroidism	0	0	6	0	0	0
Hyperthyroidism	0	0	4	0	0	0
Hyperglycaemia	0	0	2	***1***	0	0
IMMUNE SYSTEM DISORDERS						
Pemphigoid	0	0	1	***1***	0	0
Psoriasis	0	0	1	***1***	0	0
GASTROINTESTINAL DISORDERS						
Diarrhoea	0	0	4	0	0	0
Dry mouth	0	0	2	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Arthralgia	0	0	6	0	0	0
Neck pain	0	0	2	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Dyspnoea	0	0	3	0	0	0
INVESTIGATIONS						
Lymphocyte count decreased	0	0	1	***1***	0	0

AEs coded using MedDRA v21.1 for system organ class (SOC) and preferred term (PT).
Subjects with more than one occurrence of the same AE are counted once based on maximum severity.
All AEs deemed at least possibly related to PV-10 were Grade 1 or 2 except for a single occurrence of Grade 3 injection site pain.
All Grade 3 or higher AEs deemed at least possibly related to pembrolizumab were Grade 3.
All AEs deemed at least possibly related to the combination were Grade 1 except for a single occurrence of Grade 2 increase in TSH.

- Treatment Emergent Adverse Events (TEAEs) consistent with established single-agent patterns
- No unexpected toxicities or significant overlapping toxicity

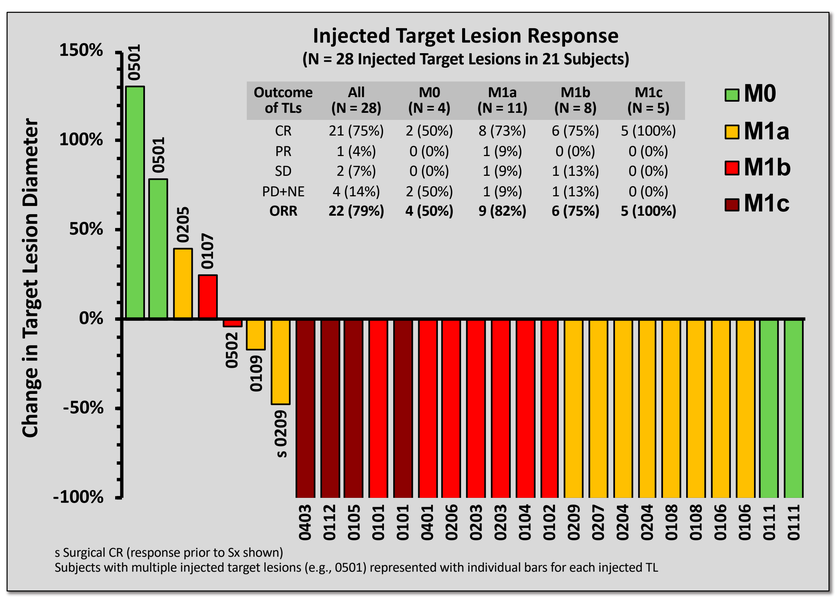
RECIST Response
(Target Lesions and Overall per RECIST)



Overall Response	All (N = 21)	M0 (N = 2)	M1a (N = 8)	M1b (N = 7)	M1c (N = 4)
CR	2 (10%)	0 (0%)	1 (13%)	1 (14%)	0 (0%)
PR	12 (57%)	1 (50%)	3 (38%)	4 (57%)	4 (100%)
SD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PD+NE	7 (33%)	1 (50%)	4 (50%)	2 (29%)	0 (20%)
ORR	**14 (67%)**	**1 (50%)**	**4 (50%)**	**5 (71%)**	**4 (100%)**

* Response follow-up ongoing
s Surgical CR (response prior to Sx shown)
Subject 0202 not evaluable (NE) for response

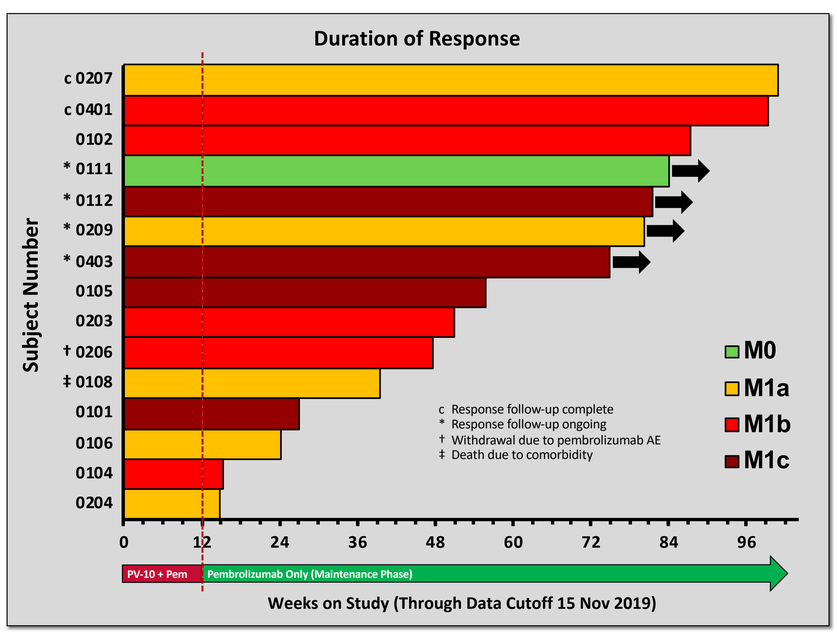
Injected Target Lesion Response
(N = 28 Injected Target Lesions in 21 Subjects)



Outcome of TLs	All (N = 28)	M0 (N = 4)	M1a (N = 11)	M1b (N = 8)	M1c (N = 5)
CR	21 (75%)	2 (50%)	8 (73%)	6 (75%)	5 (100%)
PR	1 (4%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)
SD	2 (7%)	0 (0%)	1 (9%)	1 (13%)	0 (0%)
PD+NE	4 (14%)	2 (50%)	1 (9%)	1 (13%)	0 (0%)
ORR	**22 (79%)**	**4 (50%)**	**9 (82%)**	**6 (75%)**	**5 (100%)**

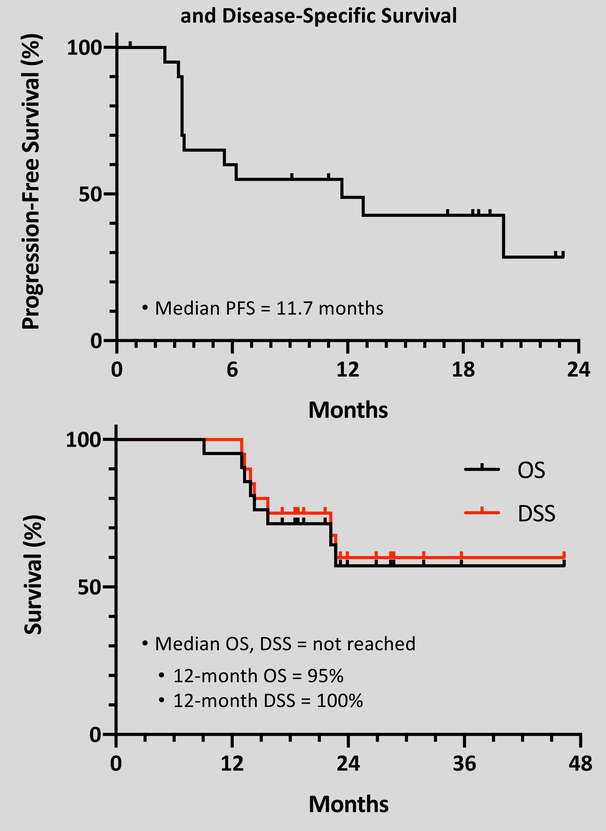
s Surgical CR (response prior to Sx shown)
Subjects with multiple injected target lesions (e.g., 0501) represented with individual bars for each injected TL

Duration of Response



- Subjects received a median of 5.0 cycles of PV-10 (mean 3.8, range 1 – 5)
- Subjects received a median of 5.0 injections of PV-10 (mean 11.7, range 1 – 82)

Progression Free Survival, Overall Survival and Disease-Specific Survival



Study	Stage IV Pts N	CR	PR	ORR	PFS (months)	OS (12 mon)
PV-10 + Pembrolizumab (current study)	21	90%	10%	57%	67%	11.7 [a]	95%
Talimogene Laherparepvec + Pembrolizumab [b]	21	62%	24%	33%	57%	>12	
SD-101 + Pembrolizumab (single injection/cycle) [c]	41	80%	10%	39%	49%	4.2	92%
SD-101 + Pembrolizumab (four injections/cycle) [c]	45	78%	18%	58%	76%	NR	96%
Pembrolizumab Single Agent [d,e]	556	97%	6%	28%	34%	4.1-5.5	85%
Nivolumab Single-Agent [f]	210	NR	8%	32%	40%	5.1	73%
Nivolumab + Ipilimumab [g,h]	95	89%	22%	37%	59%	>12	85%

[a] Estimate through data cutoff Nov 2019. [b] Long et al., ASCO 2016 (abstract 9568). [c] Milhem et al., ASCO 2019 (abstract 9534).
[d] Robert et al., NEJM 2015; 372: 2521. [e] Schachter et al., Lancet 2017; 390: 1853. [f] Robert et al., NEJM 2015; 372: 320.
[g] Postow et al., NEJM 2015; 372: 2006. [h] Larkin et al., NEJM 2019; 381: 1535.

Conclusions

- Adverse events consistent with established patterns for each drug, principally Grade 1-2 injection site reactions attributed to PV-10 and Grade 1-3 immune-mediated reactions attributed to pembrolizumab, no significant overlap or unexpected toxicities
- Response rate (10% CR, 67% ORR) and durability of response (PFS estimated at 11.7 months) superior to either therapy alone, and consistent across all disease stages in a patient population with substantial uninjected disease burden
- Clinical benefit observed upon minimal intervention with PV-10 (limited to 5 or fewer cycles); additional PV-10 treatment may increase response rate and durability of clinical outcome
- Two Phase 1b Expansion Cohorts (24 pts each) have been opened to patients with (a) CI-refractory melanoma and (b) in-transit or satellite disease