A phase 1b study of rose bengal disodium and anti-PD-1 in metastatic cutaneous melanoma: results in patients naïve to immune checkpoint blockade

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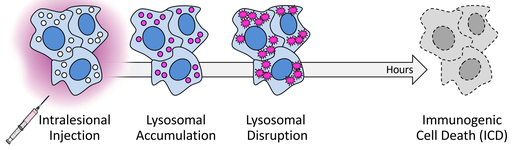
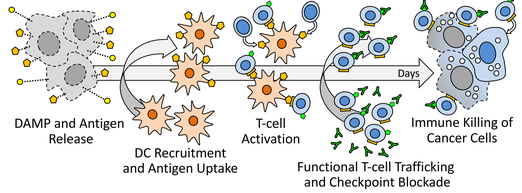
Background, Methods, and Study Participants

PV-10 (10% rose bengal disodium for injection) is a small molecule autolytic immunotherapy in development for solid tumors [1-5]; intralesional (IL) injection can yield immunogenic cell death and induce tumor-specific reactivity in circulating T cells. Functional T cell response may be enhanced through combination with immune checkpoint blockade (CB). The investigational drug product is undergoing clinical development for solid tumors (e.g., cutaneous melanoma, metastatic uveal melanoma, metastatic neuroendocrine tumors, and hepatocellular carcinoma) [6-9].

Primary Tumor Autolysis



Secondary Adaptive Immunity



PV-10-MM-1201 (**NCT02557321**) is a phase 1b/2 study of IL PV-10 in combination with systemic anti-PD-1 (pembrolizumab, "pembro") for patients (pts) with advanced cutaneous melanoma. Eligibility for the main cohort of Phase 1b required pts to have at least 1 injectable lesion, be CB-naïve, and be candidates for pembro. The combination was administered q3w for 5 cycles followed by pembro alone q3w for up to 24 months. The primary endpoint was safety and tolerability, with objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) as key secondary endpoints (assessed by RECIST 1.1 after 15 weeks then q12w).

Full accrual of the main cohort was reached in April 2018 and final response assessments were completed in April 2020, with 21 CB-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 pembro. Pts had a median of 2.0 cutaneous/subcutaneous lesions (range 1 – 15; subjects 0204 and 0403 with baseline disease burden too numerous to count (TNC) were excluded from this calculation). Long-term survival follow-up is ongoing.

1. Wachter et al., SPIE 4620, 143, 2002 (lysosomal accumulation and rupture in tissue culture)
2. Thompson et al., Mel Res 18, 405, 2008 (phase 1 study of PV-10 in metastatic melanoma)
3. Toomey et al., PLoS One 8, e68561, 2013 (tumor-specific immune response in mice)
4. Liu et al., Oncotarget 7, 37893, 2016 (DAMPs, DC recruitment/activation, T-cell activation in mouse and man)
5. Qin et al., Cell Death and Disease 8, e2584, 2017 (immunogenic cell death in colon cancer)
6. Thompson et al., J Surg Oncol 22, 2135, 2015 (phase 2 study of PV-10 in metastatic melanoma)
7. Foote et al., J Surg Oncol 115, 891, 2017 (phase 2 study of PV-10 and hypofractionated radiation in metastatic melanoma)
8. Price et al., ASCO 2019, abstract 4102 (phase 1 study of percutaneous PV-10 in metastatic neuroendocrine tumors)
9. Patel et al., SIR 2020, poster ID 509 (phase 1 basket study of percutaneous PV-10 in hepatic tumors)
10. Schmidt, Semin Immunopathol 41, 21, 2019 (combination strategies using PD-1 inhibitors to treat cancer)
11. Agarwala et al., Melanoma Bridge 2018 (patterns of response for combination of PV-10 and checkpoint inhibition)
12. Ribas et al., ASCO 2014, abstract LBA9000 (efficacy and safety of pembrolizumab in 411 patients with melanoma)
13. Zager et al., ESMO Virtual Congress 2020, presentation 1123P (PV-10 + pembrolizumab in checkpoint-refractory cutaneous melanoma)

Exposure and Safety

Participants could receive up to 5 cycles of PV-10 to their cutaneous and/or subcutaneous lesions q3w during the first 12 weeks of the study interval. PV-10 exposure is summarized below.

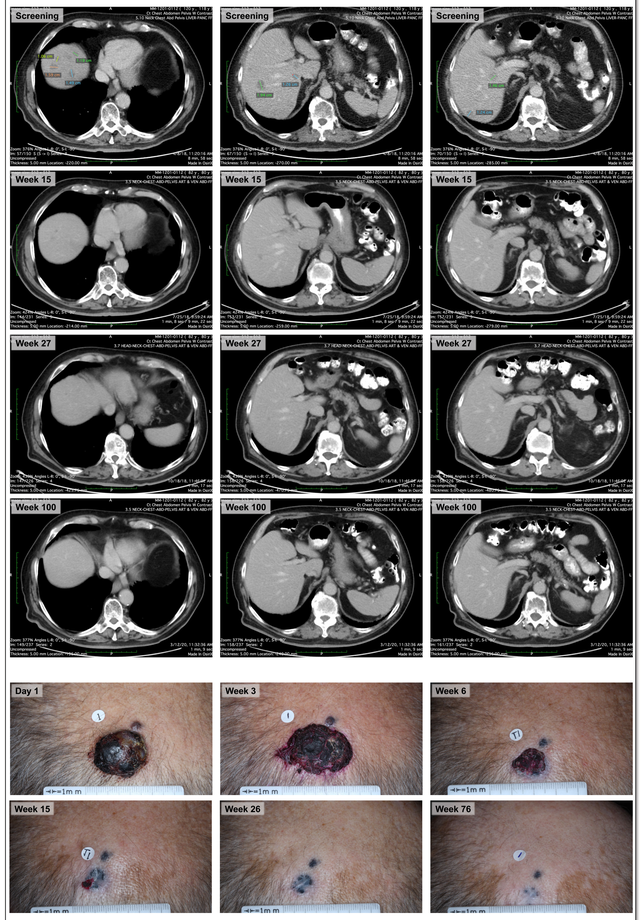
PV-10 Dose Exposure (Phase 1b Main Cohort CB-Naïve ITT Population, N = 21)	Median	Mean	Range
Lesions Injected	2.0	3.1	1 – 21
Total Injections	5.0	11.6	1 – 82
Injection Cycles	4.0	3.7	1 – 5
Dose per Injection Cycle	1.9 mL	4.8 mL	0.15 – 15 mL

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 pembro, with no significant overlap or unexpected toxicities.

Treatment-Emergent Adverse Events (TEAEs) Occurring in >1 Subject, or Any Grade 3 or Higher (Phase 1b Main Cohort CB-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	17	***1***	0	0	0	0
Injection site discharge	7	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	3	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	5	***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	3	***1***	0	0
Hypophosphatemia	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	7	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	2	***1***	0	0
Alanine aminotransferase increased	0	0	2	0	0	0

AEs coded using MedDRA v23.0 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 subject experiencing 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 subject experiencing Grade 2 increase in TSH.

Example Clinical Response

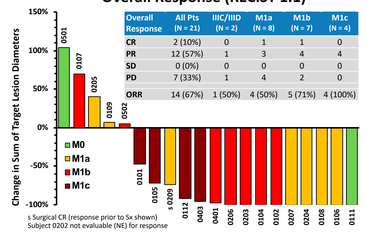


Subject 0112: Male age 80, M1c (N0) with multifocal hepatic metastases and cutaneous scalp metastases. Subject received 3 injections of PV-10 to a single scalp lesion during initial 12 weeks of study interval. **Upper panel:** CT at screening (first row); 15 weeks (second row); 27 weeks (third row); and 100 weeks (fourth row). Subject exhibited ≥21 hepatic metastases ≥ 1 cm at screening (median diameter 1.28 cm, SLD 29.1 cm); at 100 weeks 2 hepatic metastases remained (median diameter 0.55 cm, SLD = 1.1 cm). **Lower panel:** clinical photographs of injected scalp lesion over treatment and follow-up; residual pigmented tissue stable over final 18 months of study interval.

Response and Survival

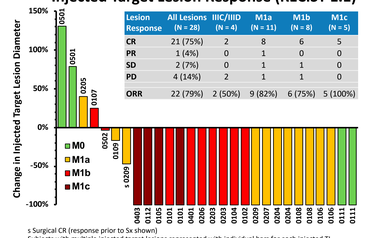
Among this predominantly Stage IV population, an ORR of 67% was achieved (10% CR, 57% PR. Median PFS was estimated at 11.7 months. Median OS was not reached.

Overall Response (RECIST 1.1)



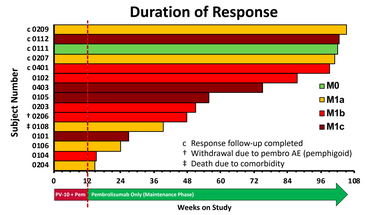
Overall Response	All Pts (N = 21)	IIIC/IIID (N = 2)	M1a (N = 8)	M1b (N = 7)	M1c (N = 4)
CR	2 (10%)	0	1	1	0
PR	12 (57%)	1	3	4	4
SD	0 (0%)	0	0	0	0
PD	7 (33%)	1	4	2	0
ORR	14 (67%)	1 (50%)	4 (50%)	5 (71%)	4 (100%)

Injected Target Lesion Response (RECIST 1.1)

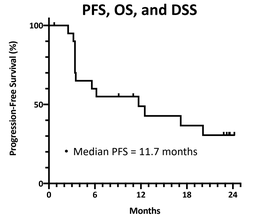


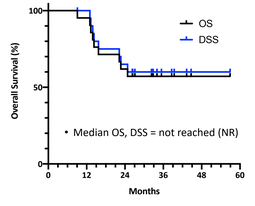
Lesion Response	All Lesions (N = 28)	IIIC/IIID (N = 4)	M1a (N = 11)	M1b (N = 8)	M1c (N = 5)
CR	21 (75%)	2	8	6	5
PR	1 (4%)	0	1	0	0
SD	2 (7%)	0	1	1	0
PD	4 (14%)	2	1	1	0
ORR	22 (79%)	2 (50%)	9 (82%)	6 (75%)	5 (100%)

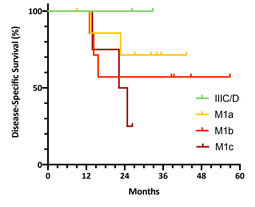
Duration of Response



PFS, OS, and DSS







Survival	All Pts (N = 21)	IIIC/IIID (N = 2)	M1a (N = 8)	M1b (N = 7)	M1c (N = 4)
DSS (median)	NR	NR	NR	NR	23.5 mo
OS (12 mo)	95%	100%	86%	100%	100%
OS (24 mo)	62%	100%	71%	57%	50%
DSS (12 mo)	100%	100%	100%	100%	100%
DSS (24 mo)	65%	100%	71%	57%	50%

Bliss independence and combinational interaction (Z) [10] for Stage IV CB-naïve pts:

		$ORR_{PV\text{-}10+Pembro} - (ORR_{PV\text{-}10} + ORR_{Pembro} - ORR_{PV\text{-}10} \times ORR_{Pembro})$		
$Z_{Patient\text{-}level}$ = 0.25 (25%)	68%	11% [11]	36% [12] [a]	4%
$Z_{Lesion\text{-}level}$ = 0.35 (35%)	83%	19% [11]	36% [12] [a,b]	7%

[a] Estimated based on 37% ORR in 35 M1a pts, 50% in 62 M1b pts, and 32% in 213 M1c pts.
[b] Estimated assuming uniform response of all disease burden for systemic therapy (Eisenhauer et al., Eur J Cancer 45, 228, 2009).

Conclusions

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 CB [13] or with in-transit/satellite disease.

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