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

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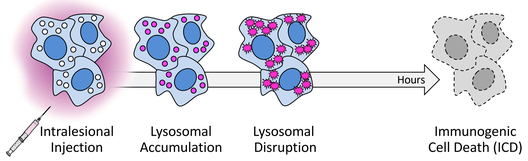
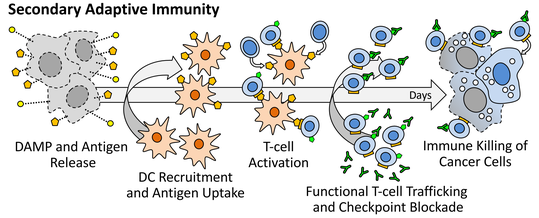
Background, Methods, and Study Participants

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; pts must have at least 1 injectable lesion and be candidates for pembro. The combination is administered q3w for 5 cycles followed by pembro alone q3w for up to 24 months. The primary endpoint is safety and tolerability, with objective response rate (ORR) and progression-free survival (PFS) as key secondary endpoints (assessed by RECIST 1.1 after 15 weeks then q12w). Immune correlative assessments are being performed on a subgroup of pts.

We report initial results of a first expansion cohort (EC1) of up to 24 melanoma pts refractory to CB, an indication with unmet clinical need. As of a data cutoff of 28 Aug 2020, 15 pts had enrolled and initiated study treatment in EC1 (1 Stage IIIC, 1 IIID, 4 M1a, 2 M1b, 5 M1c, 2 M1d; median age 74 years, range 28-90) and had one or more prior lines of CB (2 pts were refractory to CTLA-4, 4 to PD-1 and 9 to CTLA-4 and PD-1); in addition, all pts had one or more prior resection, while 6 had were refractory to radiotherapy, 4 to chemotherapy and 3 to BRAF-MEK inhibition.

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. Agarwala et al., ESMO Virtual Congress 2020, presentation 1125P (PV-10 + pembrolizumab in checkpoint-naive cutaneous melanoma)

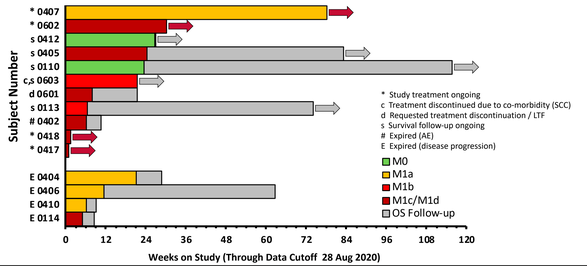
Safety and RECIST Response

All pts receiving at least one dose of study medication are included in the safety population for EC1. Treatment-Emergent Adverse Events in this population 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. This profile is similar to that observed in CB-naïve patients in the main cohort of the study [10].

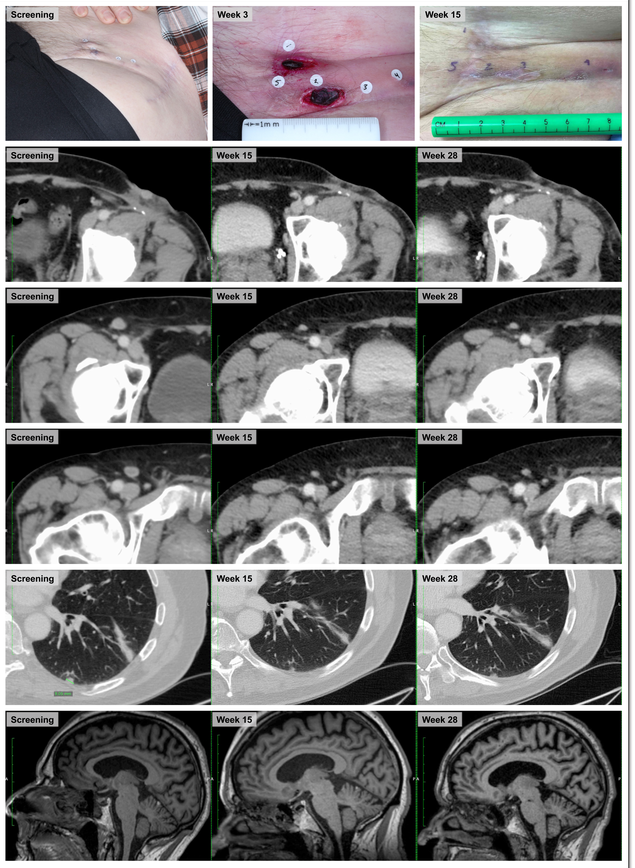
Treatment-Emergent Adverse Events (TEAEs) Occurring in >1 Subject, or Any Grade 3 or Higher (Phase 1b CB-Refractory Safety Population, N = 15)	TEAEs Related to PV-10		TEAEs Related to Pembrolizumab		TEAEs Related to Combination	
	All	≥ G3	All	≥ G3	All	≥ G3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Injection site pain	8	0	0	0	0	0
Injection site oedema	5	0	0	0	0	0
Injection site discharge	4	0	0	0	0	0
Injection site erythema	4	0	0	0	0	0
Injection site pruritus	4	0	0	0	0	0
Injection site ulcer	2	0	0	0	0	0
Injection site vesicles	2	0	0	0	0	0
Fatigue	0	0	6	0	0	0
Oedema peripheral	0	0	1	0	1	0
EYE DISORDERS						
Periorbital oedema	1	***1***	0	0	0	0
Vision blurred	0	0	1	0	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Rash maculo-papular	0	0	3	0	0	0
METABOLISM AND NUTRITION DISORDERS						
Hyperglycaemia	0	0	2	0	0	0
IMMUNE SYSTEM DISORDERS						
Myasthenia gravis	0	0	1	***1***	0	0
GASTROINTESTINAL DISORDERS						
Constipation	0	0	2	0	0	0
Vomiting	0	0	2	0	0	0
INVESTIGATIONS						
Alanine aminotransferase increased	0	0	2	***1***	0	0
Aspartate aminotransferase increased	0	0	2	***1***	0	0
Lymphocyte count decreased	0	0	2	0	0	0
Lipase increased	0	0	1	***1***	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 periorbital oedema.
Grade 3 or higher AEs deemed at least possibly related to pembrolizumab were single subjects experiencing: Grade 3 alanine aminotransferase increase and aspartate aminotransferase increase; Grade 4 lipase increase; and Grade 5 myasthenia gravis.
All AEs deemed at least possibly related to the combination were Grade 1 or 2.
One subject discontinued study participation due to a TEAE: 0402 withdrew due to myasthenia gravis attributed to pembrolizumab.

As of the data cutoff date, 11 pts in EC1 were evaluable for response by RECIST, with a 36% ORR in this initial group consisting of 1 CR (M1a) and 3 PRs (IIIC, IIID, and M1d pts); 3 pts (M1a, M1b, and M1c) achieved SD for a disease control rate of 64%.



Example Clinical Response

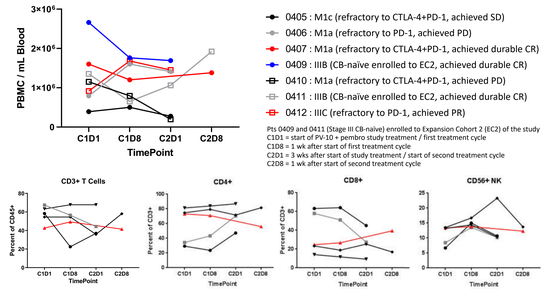


Subject 0602: Male age 74, M1d (N3: in-transit or satellite metastasis with metastatic nodes) refractory to BRAF-MEK, PD-1, and 2 Gy XRT to cerebellum; baseline metastases in right inguinal lymph nodes, lung, and cerebellum; 5 injectable SQ metastases of the left front lower quadrant. Subject received 9 cycles of PV-10 to his injectable SQ lesions over a period of 5 months (median dose 0.32 mL PV-10 per cycle, range 0.15-2.46 mL per cycle). RECIST PR as of the data cutoff date, with complete response of target lesions and regression in all metastatic sites. **Top row:** clinical photographs of injected SQ lesions at screening, week 3 (after first cycle of PV-10), and week 15. **Second row:** CT of injected SQ lesions at screening, week 15, and week 28. **Third and fourth rows:** CT of non-injected inguinal nodes. **Fifth row:** CT of non-injected lung metastasis. **Bottom row:** MRI (T1) of one of two metastases of the cerebellum. Subject remains in response follow-up.

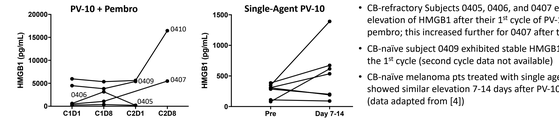
Correlative Assessments

Five CB-refractory pts have completed correlative assessment: 2 of these pts exhibited increased High Mobility Group Box 1 (HMGB1), a Damage Associated Molecular Pattern (DAMP) molecule associated with activation of dendritic cells, in post-PV-10 serum; and 1 pt (0407 with M1a disease refractory to CTLA-4 and PD-1) also exhibited increased T cell reactivity to HLA-matched tumor 7 days after initiation of PV-10 treatment that preceded achieving a durable CR. Two CB-naïve pts enrolled into a second expansion cohort (EC2) have completed these same assessments.

- **PBMCs Isolated from Patient Blood Exhibit No Clear Trend in Absolute Counts or Subpopulations**

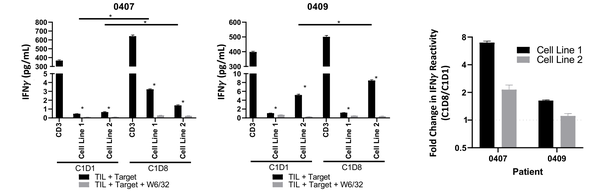


- **HMGB1 Isolated from Patient Plasma Exhibits Trends Comparable to Single-Agent PV-10 in CB-Naïve Pts**



- CB-refractory Subjects 0405, 0406, and 0407 exhibited elevation of HMGB1 after their 1st cycle of PV-10 + pembro; this increased further for 0407 after the 2nd cycle
- CB-naïve subject 0409 exhibited stable HMGB1 through the 1st cycle (second cycle data not available)
- CB-naïve melanoma pts treated with single agent PV-10 showed similar elevation 7-14 days after PV-10 treatment (data adapted from [4])

- **IFNγ Expression in Patient Peripheral T Cells Demonstrates Tumor-Specific Reactivity to HLA-Matched Cell Lines**



- Patient T cells purified from isolated PBMCs and co-cultured with HLA-matched melanoma cell lines for 24 hrs
- MHC-I specific reactivity blocked with W6/32 antibody
- CB-refractory pt 0407 and CB-naïve pt 0409 exhibited significant reactivity after 1st cycle of PV-10 + pembro consistent with clinical outcome (CR)
- This reactivity is equivalent to that observed in CB-naïve melanoma pts treated with single-agent PV-10 [4] and substantiates a common immune-mediated mechanism of action of PV-10 in both CB-naïve [10] and CB-refractory pts

Conclusions

Acceptable safety and tolerability were observed, supporting ongoing enrollment. Pharmacodynamic assessments substantiate the immune-mediated mechanism of action of PV-10 in a CB-refractory population.

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