PV-10 and anti-PD-1 in cutaneous melanoma refractory to checkpoint blockade

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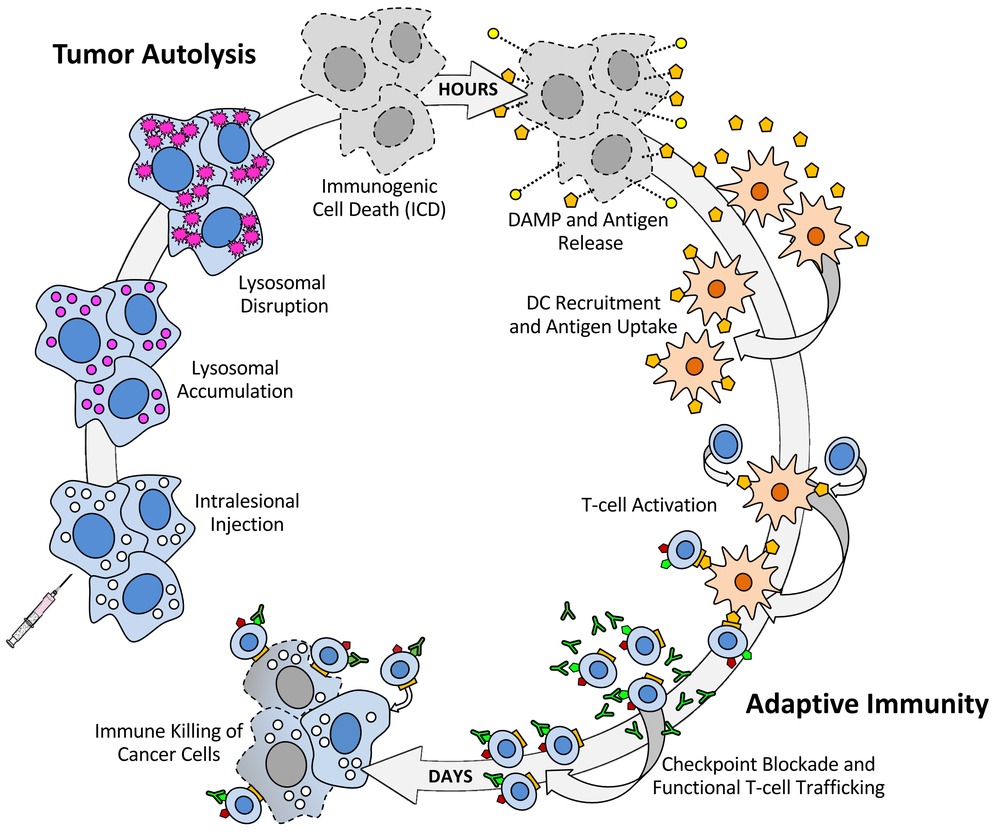
Introduction and Background

PV-10 (10% rose bengal sodium for injection) is a small molecule autolytic immunotherapy in development for solid tumors [1-6]; intralesional injection can induce immunogenic cell death and tumor-specific reactivity in circulating T cells that can synergistically augment immune checkpoint blockade (CB) [6-11].



A phase 1b/2 study (**NCT02557321**) is evaluating PV-10 in combination with systemic anti-PD-1 (pembrolizumab, "pembro") in patients (pts) with at least 1 injectable lesion. The combination is administered q3w for 5 cycles, followed by pembrolizumab alone q3w for up to 24 months; additional PV-10 cycles may be administered to remaining injectable disease after cycle 5. The primary endpoint is safety and tolerability; objective response rate (ORR) is a key secondary endpoint; exploratory immune correlative assessments are being performed on a subset of pts.

1. Thompson et al., Melanoma Res 2008; 18: 405. **2.** Thompson et al., Annals Surg Oncol 2015; 22: 2135. **3.** Lippey et al., J Surg Oncol 2016; 114: 380. **4.** Foote et al., J Surg Oncol 2017; 115: 891. **5.** Thompson et al., Melanoma Res 2021; 31: 232. **6.** Agarwala et al., ESMO 2020. **7.** Wachter et al., Proceedings of SPIE 2002; 4620: 143. **8.** Liu et al., Oncotarget 2016; 7: 37893. **9.** Qin et al., Cell Death and Disease 2017; 8: e2584. **10.** Liu et al., PLoS ONE 2018; 13: e0196033. **11.** Pilon-Thomas et al., BMC Cancer 2021; 21: 756.

Study Participants

Between mid-2017 and the abstract deadline, 22 pts (15 male, 7 female; 3 AJCC Stage IIIB-IIIC, 8 M1a, 4 M1b, 4 M1c, 3 M1d; median age 72 yrs, range 28-90) refractory to at least one prior line of checkpoint blockade were enrolled at 3 sites in phase 1b:

- 2 pts were refractory to CTLA-4
- 7 pts were refractory to PD-1
- 13 pts were refractory to CTLA-4 and PD-1

All had ≥1 prior resection; 9 were refractory to XRT, 7 to chemotherapy, and 4 to BRAF-MEK inhibition.

Safety

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.

Treatment-Emergent Adverse Events (TEAEs) Occurring in >1 Subject, or Any Grade 3 or Higher (Phase 1b CB-Refractory Safety Population, N = 22)	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***	–	–	–	–
Injection site oedema	**11**	–	–	–	–	–
Injection site erythema	**8**	–	–	–	–	–
Injection site pruritus	**8**	–	–	–	–	–
Injection site discharge	**6**	–	–	–	–	–
Injection site discolouration	**5**	–	–	–	–	–
Injection site vesicles	**5**	–	–	–	–	–
Injection site photosensitivity reaction	**3**	–	–	–	–	–
Injection site ulcer	**3**	–	–	–	–	–
Fatigue	–	–	**11**	–	–	–
Chills	–	–	**3**	–	–	–
Oedema peripheral	–	–	**1**	–	**1**	–
Hot flush	–	–	–	–	**2**	–
EYE DISORDERS						
Periorbital oedema	**1**	***1***	–	–	–	–
Vision blurred	–	–	**1**	–	**1**	–
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Rash maculo-papular	–	–	**4**	–	–	–
Pruritus	–	–	**2**	–	**1**	–
METABOLISM AND NUTRITION DISORDERS						
Hyperglycaemia	–	–	**3**	–	–	–
Decreased appetite	–	–	**2**	–	–	–
IMMUNE SYSTEM DISORDERS						
Myasthenia gravis	–	–	**1**	***1***	–	–
GASTROINTESTINAL DISORDERS						
Diarrhoea	–	–	**3**	–	–	–
Nausea	–	–	**3**	–	–	–
Vomiting	–	–	**3**	–	–	–
Constipation	–	–	**2**	–	–	–
Abdominal pain	–	–	**1**	–	**1**	–
INVESTIGATIONS						
Alanine aminotransferase increased	–	–	**3**	***1***	–	–
Aspartate aminotransferase increased	–	–	**2**	***1***	–	–
Blood alkaline phosphatase increased	–	–	**2**	–	–	–
Lipase increased	–	–	**2**	***1***	–	–
Lymphocyte count decreased	–	–	**2**	–	–	–
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Back pain	–	–	**1**	***1***	–	–

AEs coded using MedDRA v24.1 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 subjects experiencing Grade 3 periorbital oedema and injection site pain.
Grade 3 or higher AEs deemed at least possibly related to pembrolizumab were single subjects experiencing: Grade 3 alanine aminotransferase increase, aspartate aminotransferase increase, and back pain; 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.

Clinical Response

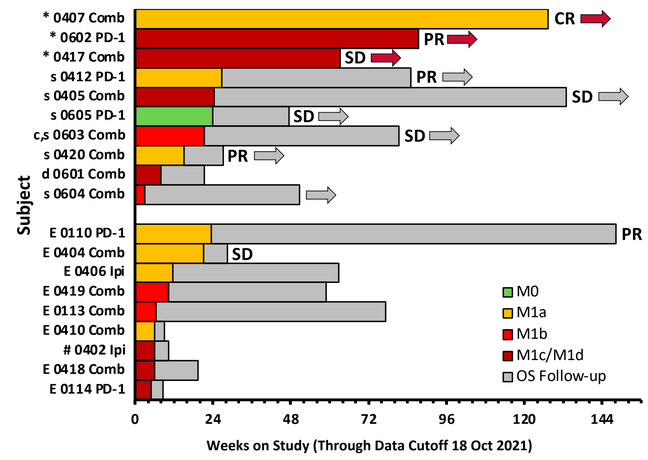
Nineteen pts were evaluable for overall response by RECIST: 1 pt achieved CR (M1a), 4 PR (3 M1a and M1d) (26% ORR), and 5 SD (IIIC, M1a, M1b, and 2 M1c) (53% disease control rate).

BOR by RECIST 1.1 (CB-Refractory Population)	Evaluable Participants (N = 19)	Prior PD-1 (N = 6)	Prior CTLA-4 (N = 1)	Prior CTLA-4 + PD-1 (N = 12)
Complete Response (CR)	1 (5%)	0	0	1
Partial Response (PR)	4 (21%)	3	0	1
Stable Disease (SD)	5 (26%)	1	0	4
Progressive Disease (PD)	9 (36%)	2	1	6
ORR (CR + PR)	5 (26%)	3	0	2
DCR (CR + PR + SD)†	10 (53%)	4	0	6

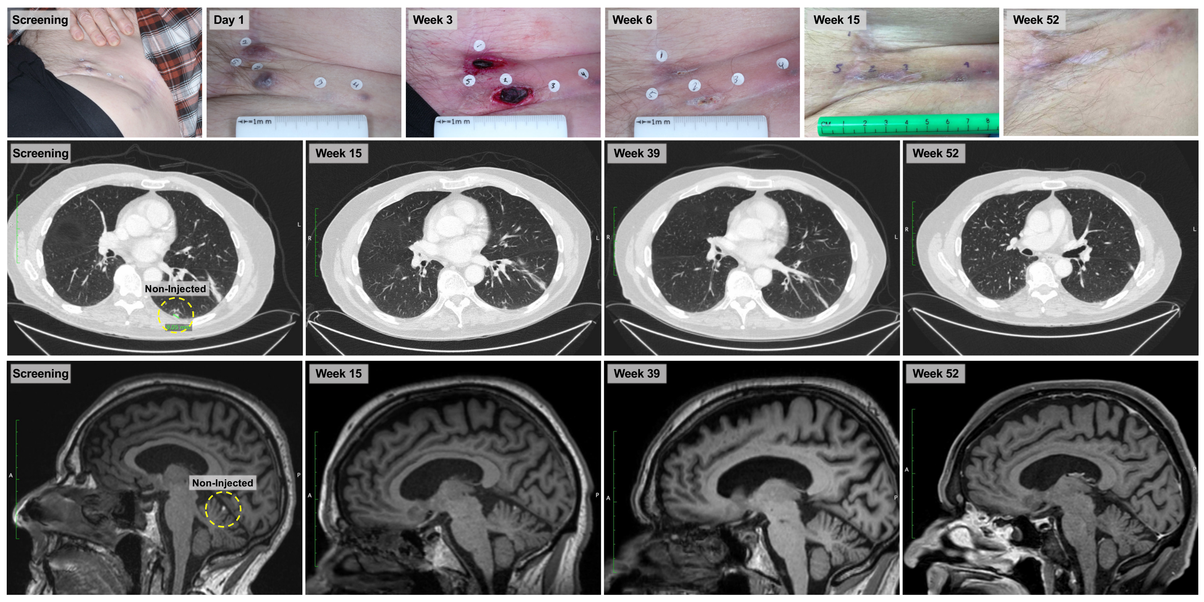
† DCR = disease control rate (CR + PR + SD)

As of the data cutoff date:

- Median PFS estimated at 4.9 months
- Median OS estimated at 34.1 months
- 36% of subjects had expired from melanoma



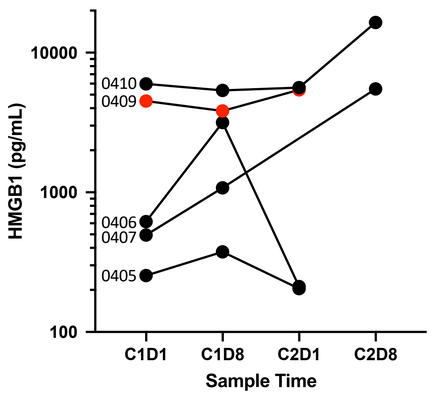
* = Study treatment ongoing
s = Survival follow-up ongoing
c = Discontinued due to co-morbidity (SCC)
d = Requested discontinuation / LTF
E = Expired (disease progression)
# = Expired (AE)



Subject 0602: Male age 74, M1d (N3: in-transit metastasis with metastatic nodes) refractory to BRAF-MEK, PD-1, and 20 Gy XRT to cerebellum; baseline metastases in right inguinal lymph nodes, lung, and cerebellum. Five injectable SQ metastases of the left front lower quadrant received 9 cycles of PV-10 over a period of 5 months. Complete response of all injected SQ lesions and non-injected nodes by week 27, with complete to near-complete resolution of all visceral metastases evident by week 52. RECIST response of PR is ongoing at 87 weeks.

Immune Correlative Assessments

Initial correlative assessments demonstrated increased HMGB1, a Damage Associated Molecular Pattern (DAMP) molecule associated with activation of dendritic cells, in post-PV-10 serum from 2 of 4 CB-refractory pts; additionally, 2 pts refractory to CTLA-1 and PD-1 exhibited enhanced T cell reactivity to HLA-matched melanoma cell lines that preceded a durable CR (M1a) and a durable SD (M1c).

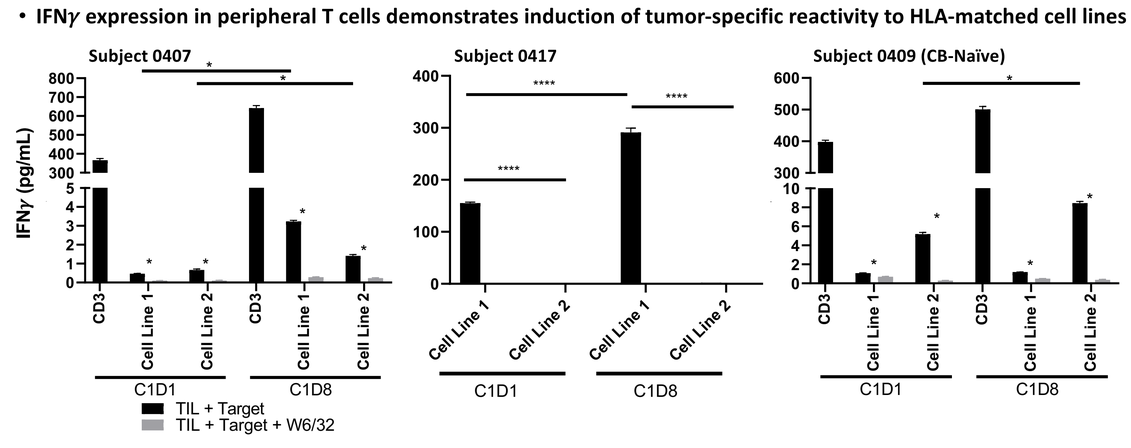


- **Increases in HMGB1 consistent with pattern in CB-naïve patients**

Subject 0405 : M1c (refractory to CTLA-4+PD-1, achieved durable SD)
Subject 0406 : M1a (refractory to CTLA-4, rapid PD)
Subject 0407 : M1a (refractory to CTLA-4+PD-1, achieved durable CR)
Subject 0409 : IIIB (CB-naïve enrolled to EC2, achieved durable CR)
Subject 0410 : M1a (refractory to CTLA-4+PD-1, rapid PD)
Subject 0417 : M1c (refractory to CTLA4+PD-1, achieved durable SD)

C1D1 = start of PV-10 + pembro study treatment / first treatment cycle
C1D8 = 1 wk after start of first treatment cycle
C2D1 = 3 wks after start of study treatment / start of second treatment cycle
C2D8 = 4 wks after start of study treatment / 1 wk after start of second treatment cycle

- **IFNγ expression in peripheral T cells demonstrates induction of 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 (internal control)
- CB-refractory pt 0407 and CB-naïve pt 0409 exhibited significant reactivity after 1st cycle of PV-10 + pembro consistent with clinical outcome (CR)
- CB-refractory pt 0417 (M1c) exhibited significant reactivity after 1st cycle of PV-10 + pembro and achieved durable SD
- This reactivity is equivalent to that observed in CB-naïve melanoma pts treated with single-agent PV-10 [8] and substantiates a common immune-mediated mechanism of action of PV-10 in both CB-naïve [6] and CB-refractory pts in the single-agent and combination settings

Conclusions

- Encouraging response, durability, and safety outcomes to date support expanded enrollment
- Pharmacodynamic assessments substantiate a common immune-mediated mechanism of PV-10 in CB-refractory and CB-naïve patients
- PV-10 can restore activity of checkpoint blockade in CB-refractory patients