Response for combination of PV-10 autolytic immunotherapy and immune checkpoint blockade in stage III cutaneous melanoma

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Melanoma Bridge 2022
December 1st – 3rd, 2022, Naples, Italy

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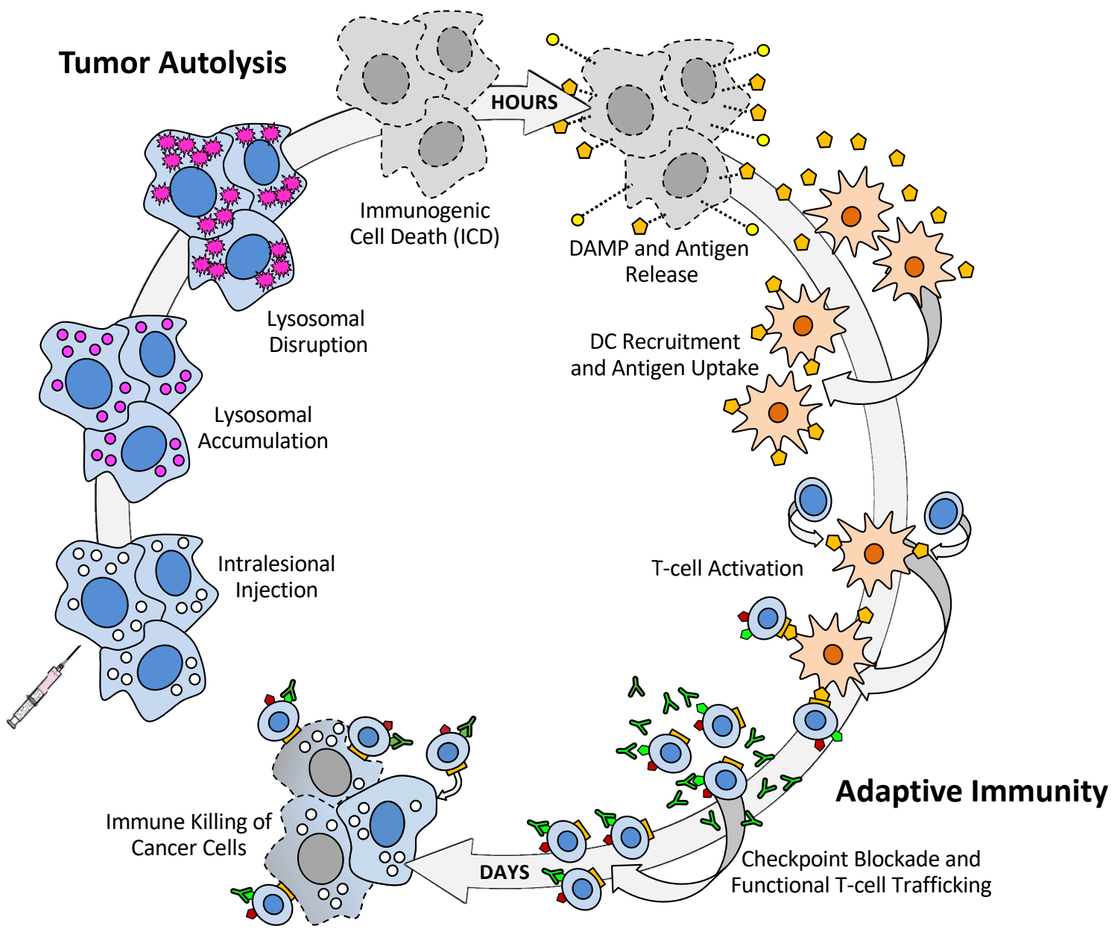
Introduction and Background

PV-10 (10% rose bengal sodium for injection) is a small molecule autolytic immunotherapy in development for solid tumors [1-6]. In both the single-agent (SA) setting and in combination with immune checkpoint blockade, intralesional injection can induce immunogenic cell death and tumor-specific reactivity in circulating T cells [6-10]. PV-10 is currently the subject of a Phase 1b/2 study in combination with immune checkpoint blockade (CB) in patients with advanced cutaneous melanoma (NCT02557321).



The present work is predicated on the following:

- In the SA setting, PV-10 has exhibited a high rate of complete response of injected lesions (56% CR in Stage III patients) [11] but a lower rate of response in non-injected lesions (26% CR in designated, non-injected bystander lesions) [2].
- Single-agent CB appears to exhibit a rate of overall response in Stage III (M0) patients (26% CR) [12] similar to that of PV-10 in non-injected bystander lesions; this rate for SA-CB may be lower than that achieved with SA-CB in M1a and M1b patients [13].
- Initial combination data for PV-10 and CB (pembrolizumab) in a predominantly Stage IV study population have shown potential for significant combinational interaction [6,14].

Here, we assess response of PV-10 and CB in a cohort of Stage III, CB-naïve patients.

Materials and Methods

Participants in study NCT02557321 must have at least 1 injectable lesion, at least 1 measurable target lesion (TL), and be candidates for pembrolizumab. Patients receive combination treatment q3w for up to 5 cycles, followed by pembrolizumab alone q3w (up to 24 months total duration); patients may receive PV-10 PRN beyond the initial combination treatment course per investigator discretion. The primary endpoint is safety and tolerability, with objective response rate (ORR) and progression-free survival (PFS) as key secondary endpoints (assessed via RECIST 1.1 after 15 weeks, then q12w). Immune correlative assessments are being performed on a subgroup of patients.

Patients

Initial results from an exploratory subpopulation of patients in the main study cohort and a dedicated expansion cohort of Stage III CB-naive patients (6 patients total) are presented. Demographic and baseline characteristics of these patients are:

- Age: median 73.5 years (range 68-82)
- Gender: 50% male, 50% female
- Race: 100% white
- Geographic Region: 100% USA
- AJCC Stage: 50% Stage IIIB, 50% Stage IIIC
- BRAF V600E: 83% wild-type, 17% unknown
- Baseline Disease Burden: median 8 melanoma lesions (range 2-18)
- Baseline Target Disease Burden: median 2.5 cm SLD (range 1.0-11.0)

All patients had previously received standard primary excision, with half undergoing sentinel node biopsy. Two patients had modest elevation of LDH (1.1xULN).

Safety

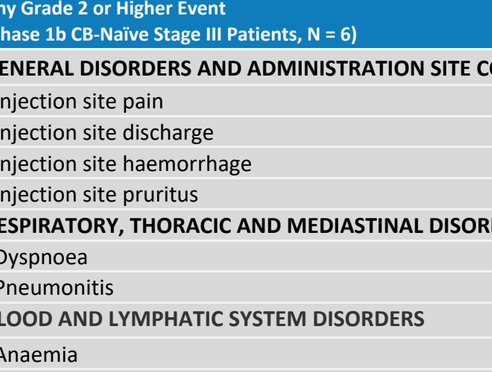
Treatment-Emergent Adverse Events (TEAEs) were consistent with established patterns of both study drugs, with no evidence of significant overlap. These results are consistent with prior observations for the combination in CB-naïve and CB-refractory patients [6,15].

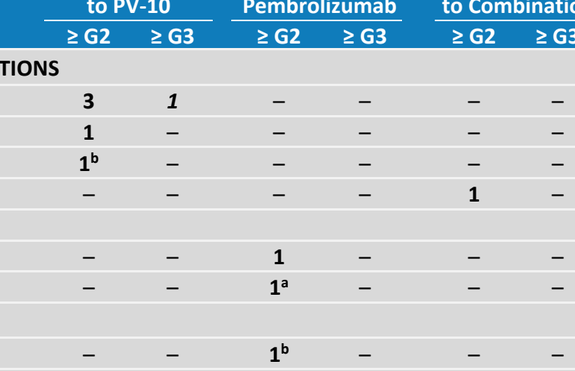
Treatment-Emergent Adverse Events (TEAEs) Any Grade 2 or Higher Event (Phase 1b CB-Naïve Stage III Patients, N = 6)	TEAEs Related to PV-10		TEAEs Related to Pembrolizumab		TEAEs Related to Combination	
	≥ G2	≥ G3	≥ G2	≥ G3	≥ G2	≥ G3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Injection site pain	**3**	***1***	–	–	–	–
Injection site discharge	**1**	–	–	–	–	–
Injection site haemorrhage	**1**[b]	–	–	–	–	–
Injection site pruritus	–	–	–	–	**1**	–
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Dyspnoea	–	–	**1**	–	–	–
Pneumonitis	–	–	**1**[a]	–	–	–
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Anaemia	–	–	**1**[b]	–	–	–
ENDOCRINE DISORDERS						
Immune-mediated thyroiditis	–	–	**1**	–	–	–
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Rash maculo-papular	–	–	**1**[b]	–	–	–
VASCULAR DISORDERS						
Contusion	–	–	**1**	–	–	–

AEs coded using MedDRA v25.1 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 subject experiencing Grade 3 injection site pain.
[a] Event led to permanent discontinuation of study treatment.
[b] Event led to temporary discontinuation of study treatment.

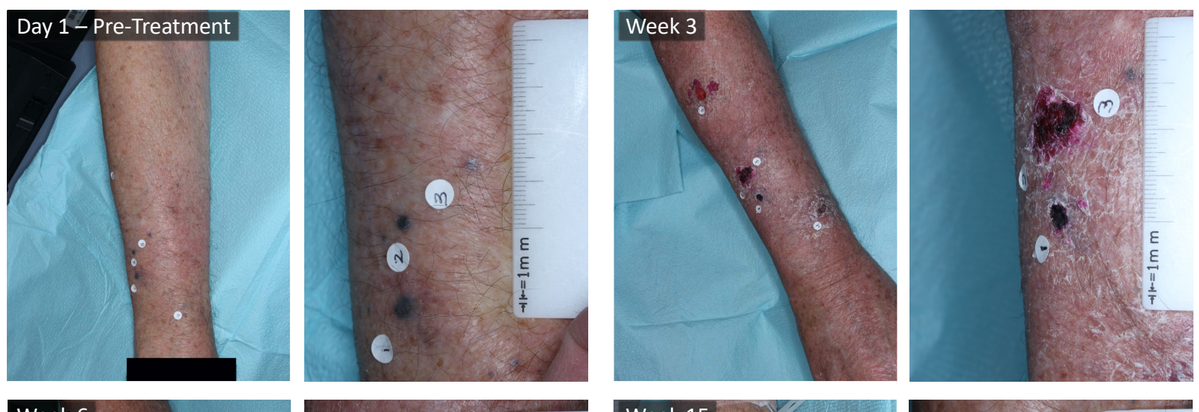
Response and Survival

As of the data cutoff (11 Nov 2022), PFS was not reached within the 24 month study interval. ORR by RECIST was 83%: 3 patients achieved CR (50%), 2 PR (33%), and 1 PD (17%). Complete responses were rapid and durable, reached within the first 15 weeks by 2 responders and within 27 weeks by the third, and were ongoing after 18-38 months of study follow-up. All complete responders remained alive at the data cutoff.

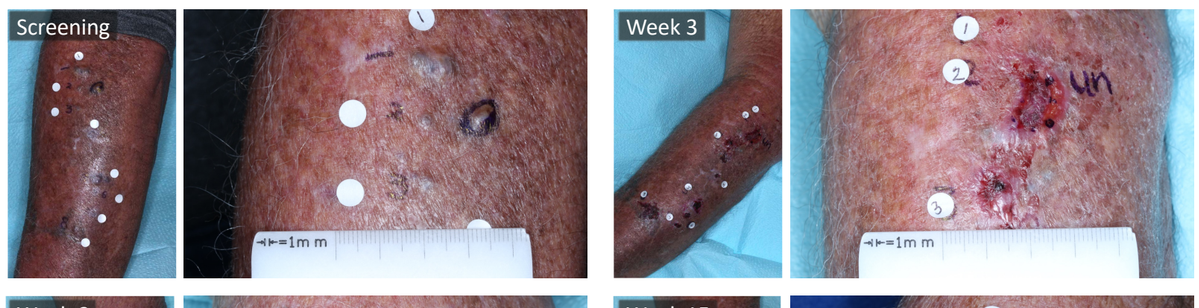




Clinical Examples

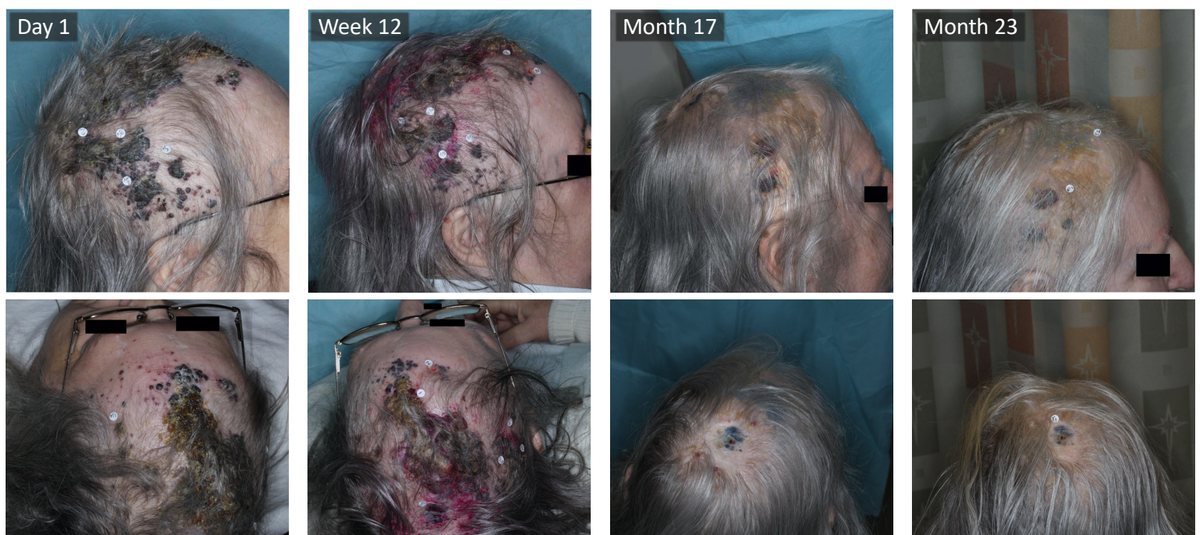


Subject 0504. Male, age 73, Stage IIIC BRAF WT, with 18 lesions of upper extremity at baseline. Five lesions injected in 4 cycles (10 total PV-10 injections), resulting in a PR at first RECIST assessment (15 weeks) and a durable CR at second RECIST assessment (27 weeks), with response ongoing at 18 months. Subject exhibited mild vitiligo locoregionally to several PV-10 injection sites.



Subject 0411. Male, age 74, Stage IIIB BRAF UNK, with 8 lesions of upper extremity at baseline. All lesions injected in 5 cycles (26 total PV-10 injections), resulting in a CR at first RECIST assessment (15 weeks), with continued response after 34 months.

Subject 0424. Female, age 73, Stage IIIB BRAF WT, with 7 lesions of lower extremity at baseline. Two lesions injected on Day 1 (subject declined further PV-10 due to procedural discomfort). PR at first RECIST assessment (15 weeks), with local progression of non-injected lesion leading to study discontinuation at Week 22. Subject expired at month 9 from pneumonia.



Subject 0111. Female, age 68, Stage IIIC BRAF WT, with extensive involvement of the scalp at baseline. Three lesions injected at first cycle (subject declined further PV-10 due to procedural discomfort). PR at first RECIST assessment (15 weeks), with gradual improvement throughout remainder of study interval. Subject expired at month 36 from melanoma.

Correlative Assessments

Correlative assessments showed increased T cell reactivity to HLA-matched tumor that preceded a durable CR in 1 of 2 CR patients evaluated for this biomarker. Similar immune upregulation has been shown with single-agent PV-10 in Stage III CB-naive patients [8] and for PV-10 and pembrolizumab in CB-refractory patients [16].

- **Subject 0409** (female, age 80, Stage IIIB BRAF WT, with lower extremity disease) achieved a durable CR within 15 weeks after a single injection cycle of PV-10; at one week after initiation of PV-10 + pembrolizumab she exhibited significant peripheral blood T cell reactivity against one of two HLA-matched tumor lines tested.
- **Subject 0411** (photos shown above) achieved a durable CR within 15 weeks upon repeat intervention with PV-10; T cell reactivity was not observed upon testing against a single HLA-matched tumor line.
- **Subject 0424** (photos shown above) achieved a PR after a single intervention with PV-10; T cell reactivity was not observed upon testing against multiple HLA-matched tumor lines.

Conclusions

Encouraging response and a non-overlapping safety profile support further evaluation of the combination in this population, which has previously exhibited suboptimal response to single-agent CB, via a contemplated multi-center Phase 2 randomized controlled trial of PV-10 and investigator's choice of standard care single-agent CB versus investigator's choice of standard care single-agent CB for first-line treatment of Stage III cutaneous melanoma.

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.** Wachter et al., SMR 2021. **12.** Nan Tie et al., J Immunother Cancer 2020; 8: e000440. **13.** Ribas et al., LBA9000, ASCO 2014. **14.** Schmidt, Semim Immunopathol 2019; 41: 21. **15.** Zager et al., SMR 2021. **16.** Zager et al., ESMO 2020.