Lesion-Level Response to Single-Agent PV-10 in Stage III Cutaneous Melanoma

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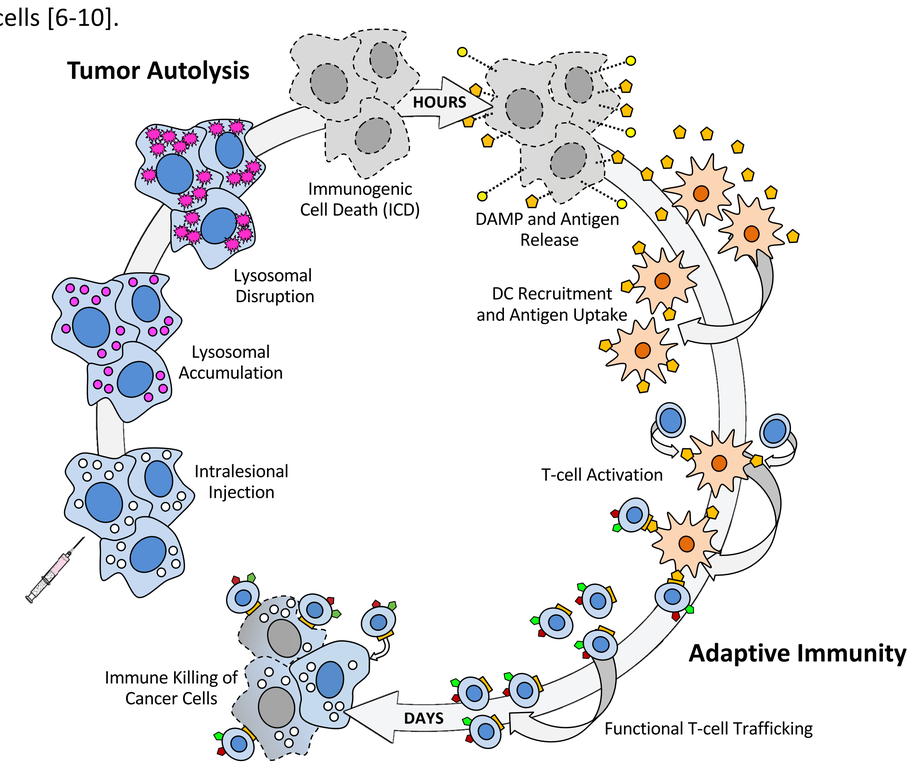
Introduction and Background

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 (inj) can induce immunogenic cell death and tumor-specific reactivity in circulating T cells [6-10].



Assessments

To evaluate SA response in Stage III cutaneous melanoma, a meta-analysis was performed utilizing serial lesion measurement data from 774 lesions in 121 patients (pts) treated at 14 clinical sites between 2007 and 2019 under phase 2, phase 3, and expanded access (EA) protocols (efficacy evaluable population). Data from case report forms and site databases were analyzed for response, survival, and safety. Best response for each lesion was assessed using RECIST thresholds starting ≥8 wks after initial inj to avoid potential interference from local reactions. Time-to-response (TTR) was based on confirmed response starting ≥4 wks after initial inj; time-to-progression (TTP) was based on RECIST thresholds; and time-to-treatment-failure (TTF) was based on evidence of clinically-relevant progressive disease [11].

Clinical response assessment data on an additional cohort of 422 lesions in 57 Stage III EA pts lacking serial lesion measurements were analyzed separately (clinical evaluable population) for comparison with response in the efficacy evaluable population.

Participants

Demographic and baseline characteristics of the efficacy evaluable population are:

- Age: median 71 years (range 33-97)
- Gender: 55.4% male, 44.6% female
- Race: 95.9% white, 0.8% Asian, 3.3% not reported
- Geographic Region: 82.6% USA, 14.0% AUS, 3.3% EU
- Baseline Status: 87.6% in-transit (ITM), 5.8% satellite, 6.6% not classified

Safety

Detailed adverse event (AE) data were collected for a subset of pts (safety population [c]); AEs were predominantly transient, locoregional to the injection site, and mild-to-moderate grade.

Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥ 5% of Patients, or Any Grade 3 or Higher	TEAEs Related to PV-10 [b] (Safety Population, N = 104 [c,d])						
	CTCAE Grade						
System Organ Class / Preferred Term [a]	1	2	3	4	5	Total	%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS							
Injection site pain	40	30	8	0	0	78	75%
Injection site oedema	29	18	0	0	0	47	45%
Injection site discolouration	28	16	0	0	0	44	42%
Injection site vesicles	24	14	1	0	0	39	38%
Injection site pruritus	20	3	0	0	0	23	22%
Injection site erythema	15	3	2	0	0	20	19%
Injection site swelling	13	4	0	0	0	17	16%
Injection site ulcer	12	2	0	0	0	14	13%
Injection site inflammation	3	7	0	0	0	10	10%
Fatigue	6	2	0	0	0	8	8%
Injection site discharge	8	0	0	0	0	8	8%
Injection site infection	5	2	1	0	0	8	8%
Injection site photosensitivity reaction	3	3	0	0	0	6	6%
Injection site cellulitis	0	2	1	0	0	3	3%
Injection site reaction	0	2	1	0	0	3	3%
Injection site necrosis	0	0	1	0	0	1	1%
NERVOUS SYSTEM DISORDERS							
Headache	12	2	0	0	0	14	13%
GASTROINTESTINAL DISORDERS							
Diarrhoea	5	1	0	0	0	6	6%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS							
Photosensitivity reaction	0	0	1	0	0	1	1%

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ITT, intent-to-treat; N, number; TEAE, treatment-emergent adverse events.

[a] System Organ Class and Preferred Term are based on the MedDRA® version 24.0 terminology dictionary. Locoregional adverse events were coded to "injection site" Preferred Terms to differentiate these from systemic events. Participants with more than one occurrence of the same AE are counted once based on maximum severity.

[b] Includes all treatment-emergent adverse events deemed by the investigator to be at least possibly related to PV-10.

[c] Includes all Stage III participants receiving at least one dose of PV-10 under protocol PV-10-MM-02; all Stage III participants at sites in the USA with cutaneous melanoma receiving at least one dose of PV-10 under protocol PV-10-EA-02; and all Stage III participants receiving at least one dose of PV-10 under protocol PV-10-MM-31. Because comprehensive AE data were not provided for participants in AUS receiving PV-10 under protocol PV-10-EA-02 these participants are not included in this summary.

[d] Median age of this safety population was 70 years, range 33-97; there were 61 male and 43 female participants.

Response Characteristics

Objective Response: Overall, in the efficacy evaluable population, 56% of lesions achieved CR after a median of 1 inj (range 1-8); 7% achieved PR (median 2 inj, range 1-10); and 14% achieved SD (median 2 inj, range 1-4). CR and PR were achieved with ≤2 inj in 85% and 81% of responding lesions, respectively. Non-responding lesions exhibited a similar pattern, with progression evident after a median of 1 inj (range 1-9).

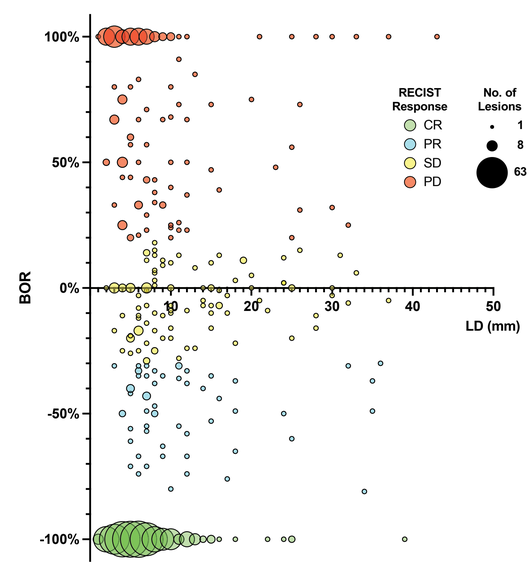
- Consistent objective response was observed across protocols and regions:

Protocol	PV-10-MM-02 (AUS/USA)	PV-10-EA-02 (USA)	PV-10-EA-02 (AUS)	PV-10-MM-31 (USA/EU)	All Studies
Number of Sites	7	4	1	8	14
Number of Stage III Patients	62	28	17	14	121
Number of Stage III Lesions Followed	507	153	77	37	774
CR	300 (59%)	79 (52%)	42 (54%)	16 (43%)	437 (56%)
PR	32 (6%)	14 (9%)	9 (12%)	3 (8%)	58 (7%)
SD	61 (12%)	22 (14%)	14 (18%)	10 (27%)	107 (14%)
PD + NEV	114 (22%)	38 (25%)	12 (16%)	8 (22%)	172 (22%)
ORR (CR + PR)	268 (65%)	95 (61%)	51 (67%)	19 (51%)	495 (64%)
DCR (CR + PR + SD)	316 (78%)	116 (75%)	65 (84%)	29 (78%)	602 (78%)

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

- Lesions in the equivalent clinical evaluable population (N = 422 lesions) exhibited similar objective response: 56% of lesions achieved CR, 9% achieved PR, and 26% achieved SD.

Lesion Diameter: Response as a function of baseline lesion diameter (LD) for the efficacy evaluable population is illustrated as a bubble plot (right): response is color coded by RECIST classification, while the size of each circle is proportional to the number of lesions of a specific size achieving a given response; to simplify presentation, lesions with a best response of 100% or greater increase in diameter, and those classified as NEV, are represented at +100% BOR (top of plot). Consistent with the tabulated data, a bimodal distribution of response is evident, with a majority of lesions achieving CR (-100% BOR in 437 lesions) and the next largest group achieving PD (≥+20% BOR in 172 lesions). Lesions 10 mm or smaller achieved consistently high rates of response (63% CR), evidenced by the cluster of lesions in the lower left corner that achieved CR.

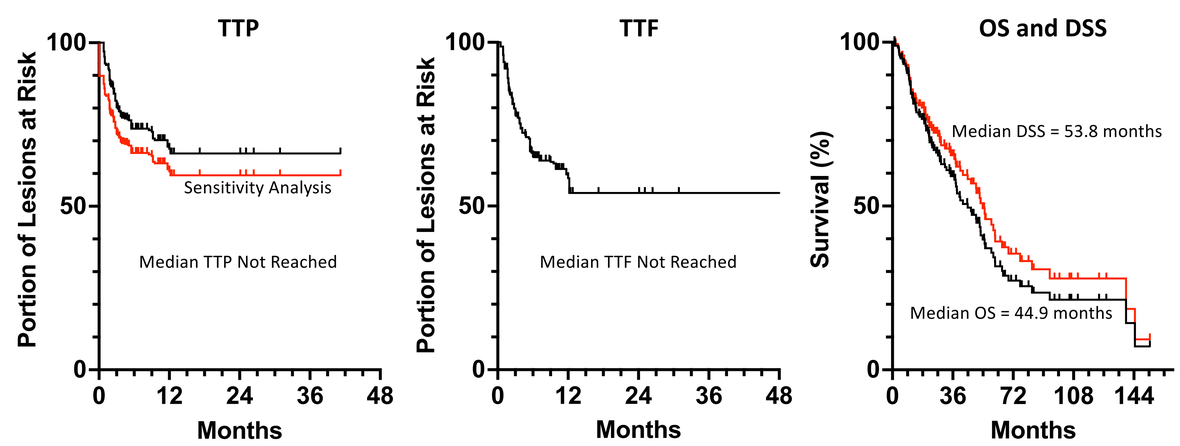


Time-to-response: TTR was calculated for all lesions in the efficacy evaluable population having unambiguous follow-up times (448 out of 495 lesions that achieved an objective response). Median TTR was estimated at 2.4 months, mean TTR was estimated at 2.6 months, range 0.7 to 12.0 months.

Time-to-progression: Kaplan-Meier analysis was used to estimate TTP for all lesions in the efficacy evaluable population for which an objective response outcome could be established (630 out of 701 lesions with temporal response assessment data). Median TTP was not reached (black trace, below). Since this analysis does not include non-evaluable lesions for which progression time was not defined, a sensitivity analysis was conducted, assigning progression to have occurred 1 day (0.03 months) after initiation of study treatment for all non-evaluable lesions, and yielded an identical outcome (not reached, red trace).

Time-to-treatment-failure: Kaplan-Meier analysis was also used to estimate TTF for all lesions in the efficacy evaluable population (701 lesions). Median TTF was not reached.

Overall and Disease-Specific Survival: Kaplan-Meier analysis was also used to estimate OS for 184 pts (including an additional 63 EA pts without lesion-level data); median OS was estimated at 44.9 months (black trace). Median DSS was estimated at 53.8 months (red trace). Survival was calculated from time of initial PV-10 treatment.



Conclusions

- These data demonstrate a favorable risk-benefit profile for minimally invasive single-agent PV-10:
  - consistent response across multiple sites, investigators, regions, protocols, and time;
  - rapid response kinetics;
  - high injected-lesion response rate; and
  - acceptable safety profile.
- These results compare favorably with those reported for products approved for Stage III disease (e.g., oncolytic virus [11] and systemic therapies [12]).
- Single-agent PV-10 has the potential to address a current unmet need as a treatment that is specific to the unique, locoregional characteristics of Stage III cutaneous melanoma [13,14].

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.** Andtbacka et al. J Clin Oncol 2015; 33: 2780. **12.** Nan Tie et al., J Immunother Cancer 2020; 8: e000440. **13.** Read et al., Ann Surg Oncol 2015; 22:475. **14.** Nan Tie et al., ANZ J Surg 2019; 89: 647.