Patterns of Response for Combination of PV-10 Oncolytic Immunotherapy and Checkpoint Inhibition

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Extended Abstract and Background

Background

PV-10 (rose bengal disodium) is the first small molecule oncolytic immunotherapy in development for solid tumors. Intralesional injection of PV-10 can yield immunogenic cell death and stimulate tumor-specific reactivity in circulating T-cells [1-4]. PV-10 has been administered as a single agent to 130 cutaneous melanoma patients in Phase 1 and 2 and 180 patients under expanded access, and is currently the subject of a Phase 1b/2 study in combination with systemic immune checkpoint inhibition (CI) for patients with advanced melanoma [5-9].

Materials and Methods

Study PV-10-MM-1201 (**NCT02557321**), an international, multicenter, open-label, sequential phase study, is assessing safety and efficacy of PV-10 in combination with anti-PD-1 therapy (pembrolizumab). Patients must have at least 1 injectable lesion, at least 1 measurable target lesion (TL), and be candidates for pembrolizumab. In the Phase 1b portion of the study, patients receive combination treatment during the induction phase (q3w for 5 cycles) and then pembrolizumab alone in the maintenance phase (total duration of up to 24 months); the primary endpoint is safety and tolerability with objective response rate (ORR) and progression-free survival as key secondary endpoints (assessed via RECIST 1.1 after 15 weeks then q12w).

Results

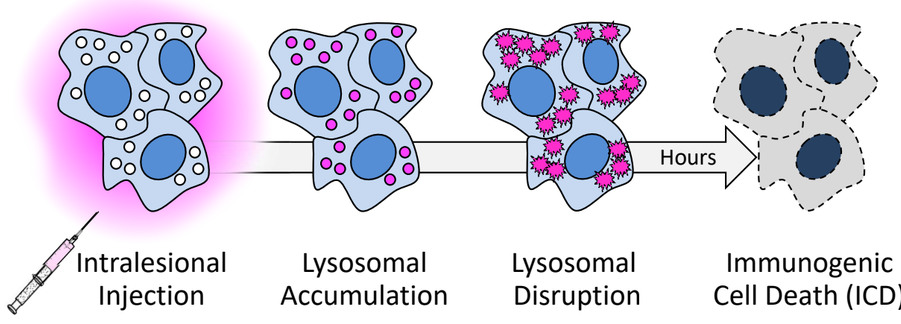
An initial Phase 1b cohort of predominantly CI-naïve subjects reached full accrual in April 2018 (Main Cohort), with an intent-to-treat (ITT) population of 20 Stage IV and 3 Stage IIIC/IIID patients (median age 70 years, range 28-90) receiving at least 1 dose of PV-10 and pembrolizumab. All Treatment-Emergent Adverse Events (TEAEs) were consistent with established patterns for both drugs, with no significant overlap of AEs or unexpected toxicities. All disease stages exhibited response after minimal PV-10 intervention (median of 4 cycles of PV-10, range 1 – 5; median of 5 injections of PV-10 per patient, range 1 – 82), with 9% complete response (CR) and 65% ORR (overall per RECIST) as of a 1 Nov 2018 data cutoff. Response of injected target lesions (77% CR and 80% ORR across all disease stages) was higher than historical data for single-agent PV-10 (46% CR and 53% ORR across all disease stages, **NCT00521053**)[6]. Although data on the combination for treatment of Stage III (M0) disease is currently limited, the response rate of injected target lesions was also higher for M0 disease in the Phase 1b Main Cohort than that observed in single-agent use: 67% CR (4 of 6 lesions) vs 54% CR (214 of 395 lesions).

Conclusion

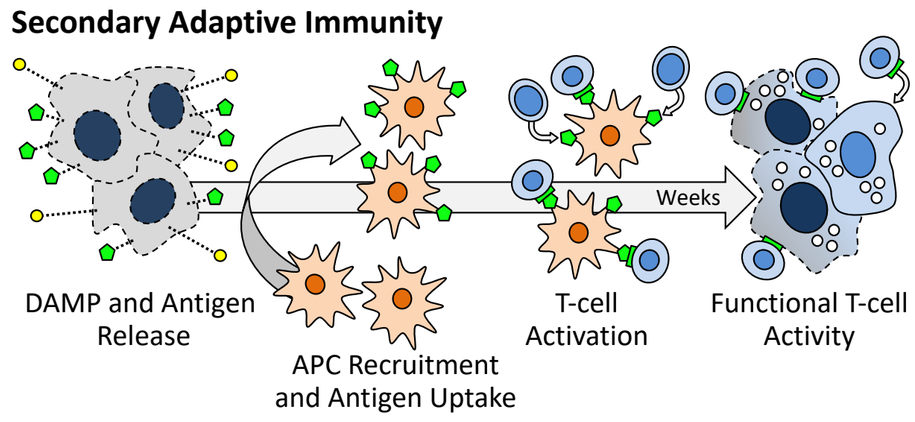
Robust response was observed in injected and non-injected lesions across all disease stages. A first expansion cohort in the Phase 1b portion of the study is accruing CI-refractory patients to further characterize response in this emergent population. Systemic therapy with CI is now recommended in the USA for Stage III patients with satellite or in-transit disease [10], but the KEYNOTE-001 study demonstrated lower overall response in M0 vs M1 patients [11] and for subcutaneous vs visceral lesions [12]. To address this population, a second Phase 1b expansion cohort directed to patients with satellite or in-transit disease will be opened in early-2019.

Small Molecule Oncolytic Immunotherapy

Primary Oncolysis



Secondary Adaptive Immunity



- Functional T cell Activation in Peripheral Blood of Melanoma Patients [2]
- Immunologic Priming of PV-10 Complementary to Checkpoint Inhibition in Murine Melanoma Models [4]

1. Wachter et al., Proceedings of SPIE 2002; 4620: 143. **2.** Liu et al., Oncotarget 2016; 7: 37893. **3.** Qin et al., Cell Death and Disease 2017; 8: e2584. **4.** Liu et al., PLoS ONE 2018; 13: e0196033. **5.** Thompson et al., Melanoma Res 2008; 18: 405. **6.** Thompson et al., Annals Surg Oncol 2015; 22: 2135. **7.** Lippey et al., J Surg Oncol 2016; 114: 380. **8.** Foote et al., J Surg Oncol 2017; 115: 891. **9.** Agarwala et al., SMR 2018. **10.** NCCN Guidelines for Cutaneous Melanoma, Ver 1.2019. **11.** Ribas et al., LBA9000, ASCO 2014. **12.** Lee et al., Pigment Cell Melanoma Res 2018; 31: 404.

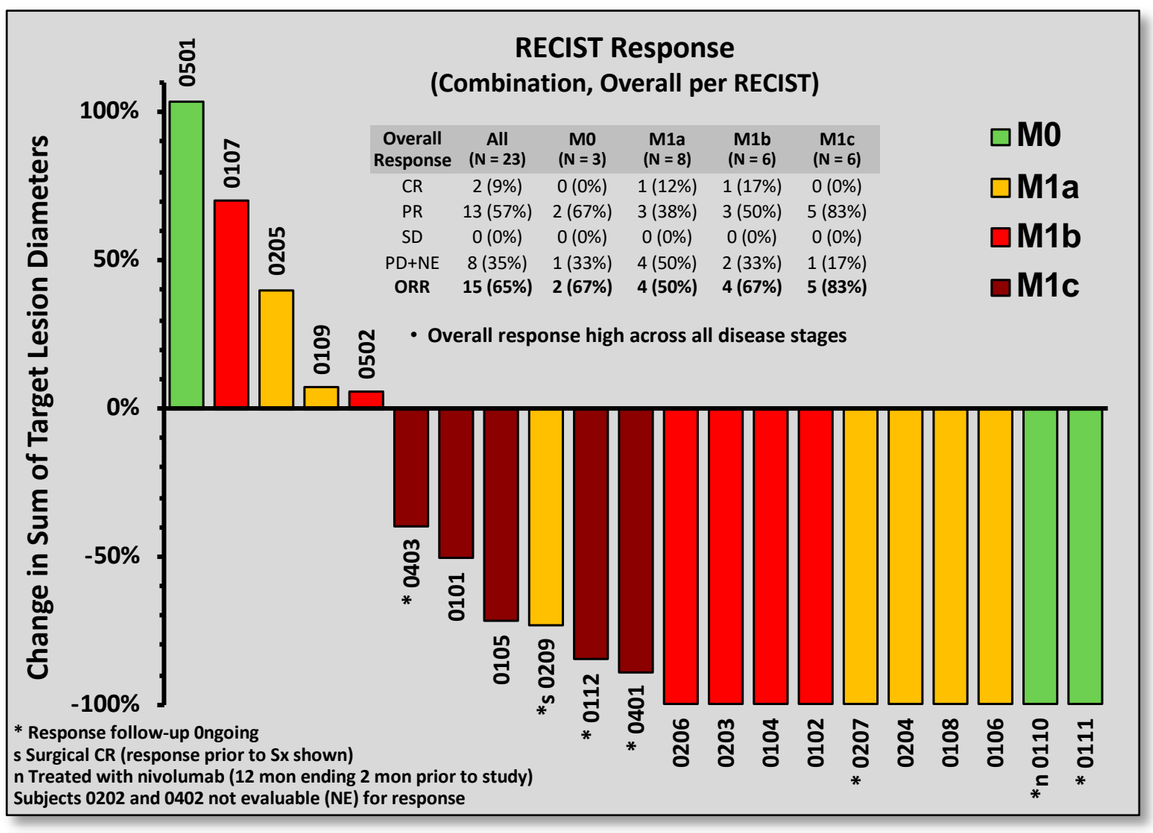
Study Participants and Interim Clinical Data

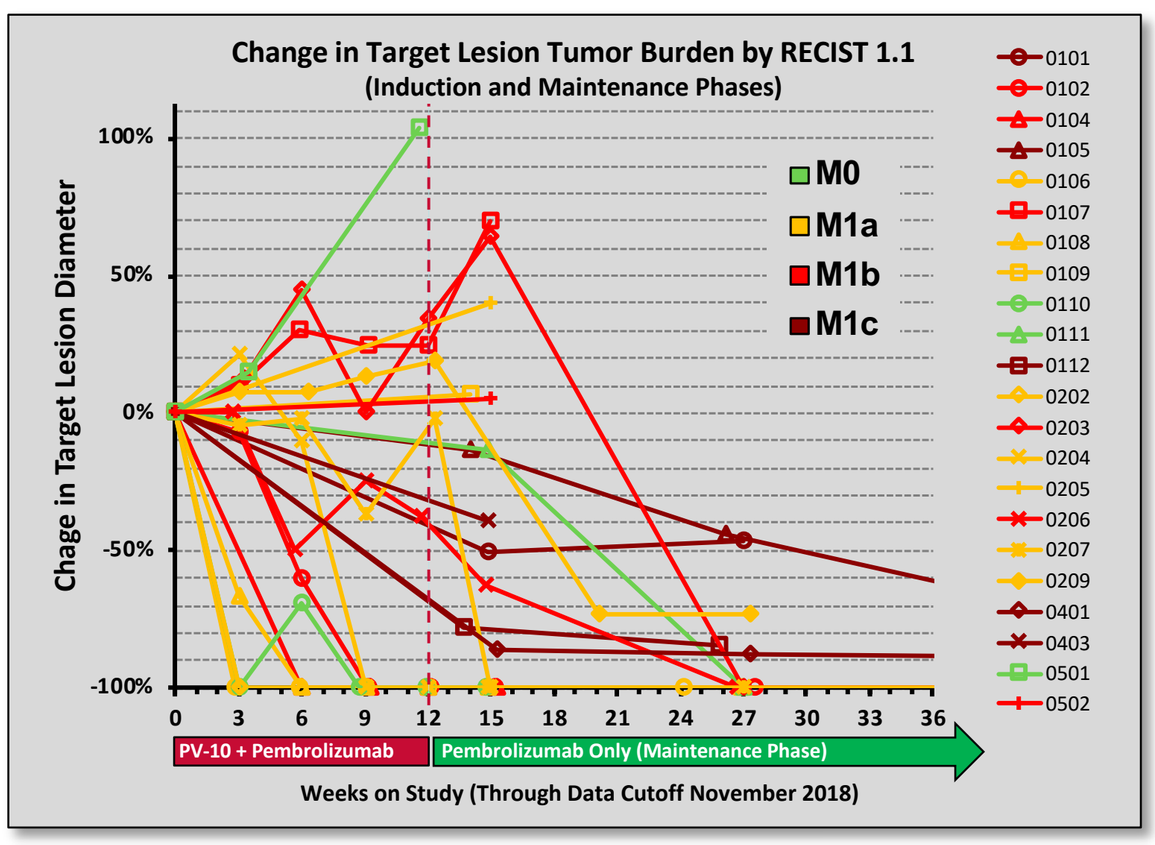
Baseline Characteristics
(Phase 1b Main Cohort ITT Population, N = 23)

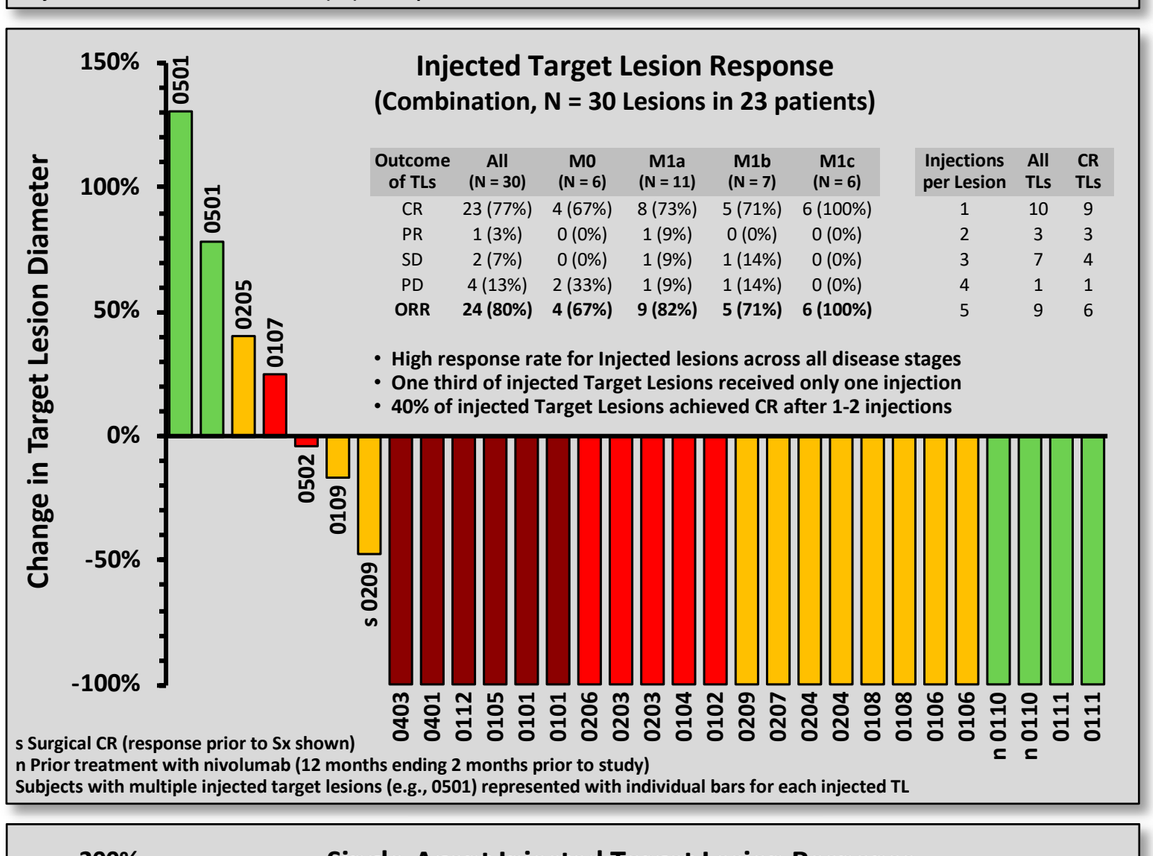
Gender	Male	19 (83%)
	Female	4 (17%)
Age	Median (Range)	70.0 (28 – 90)
AJCC Disease Stage	M0 (IIIC/IIID)	3 (13%)
	IV M1a	8 (35%)
	IV M1b	6 (26%)
	IV M1c	6 (26%)
Number of Cutaneous / Subcutaneous Lesions	Median (Range)	2.0 (1 – 15) [a]
Prior Therapy	Checkpoint Inhibition	2 (9%) [b]
	Other Immunotherapy	3 (13%) [c]
	Targeted Therapy	1 (4%) [d]
	Chemotherapy	1 (4%) [e]
	Radiotherapy	2 (9%)
	Surgery	23 (100%)

[a] Subjects 0204 and 0403 with baseline disease burden too numerous to count (TNC) are excluded from calculation.
[b] Subjects 0110 and 0402 enrolled under waiver for prior treatment with nivolumab and ipilimumab, respectively.
[c] Subjects 0102 and 0104 previously treated with pegylated interferon alfa-2b; subject 0402 previously treated with adjuvant vaccine.
[d] Subject 0205 previously treated with dabrafenib and trametinib.
[e] Subject 0401 previous treated with doxorubicin and olaratumab.

- PV-10 injection to cutaneous and subcutaneous lesions (not nodal or visceral lesions)
- Phase 1b Main Cohort eligibility restricted to checkpoint inhibitor-naïve patients
- Subjects had substantial systemic disease burden in addition to their injectable lesions







- PV-10 induction phase can
  - Rapidly reduce tumor burden (77% CR in injected lesions) with minimal PV-10 intervention
  - Enhance checkpoint inhibition (CI) activity (synergy consistent with PV-10 mechanism)
- The combination may convey superior response rates than either therapy alone
- Promising responses observed in a sparse population of Stage III and CI-refractory patients; dedicated expansion cohorts will explore potential utility in these important groups