A Phase I Trial of Intratumoral PVSRIPO in Patients with Unresectable Treatment Refractory Melanoma

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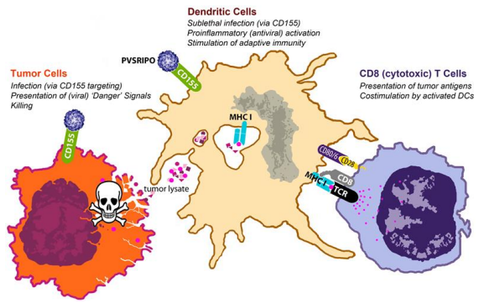
Introduction

- While immune checkpoint inhibitors (ICI) have revolutionized oncology, the majority of patients never respond (primary resistance) and up to 40% acquire resistance to therapy[1-4]
- PVSRIPO is a unique intratumoral immunotherapy (IT) being developed to treat multiple solid tumors as monotherapy or in combination with ICI, with the potential to enhance or rekindle ICI activity[5]
- PVSRIPO is derived from the type 1 Sabin polio vaccine, genetically engineered for enhanced safety and immunogenicity[5]
- PVSRIPO works by direct damage and killing of cancer cells in injected tumors and by engagement of the innate and adaptive immune systems. This unique mechanism of action results in sustained antitumor immunity and may help target lesions if they return[5]
- PVSRIPO is distinguished from other viral ITs by its well-defined target, the poliovirus receptor (CD155), which is expressed on most solid tumor cells, including melanoma and glioblastoma, and antigen-presenting cells (APCs; macrophage and dendritic cells)[5,6]
- Upon entry into the cell via CD155, PVSRIPO causes a lethal infection of cancer cells and a potent, type 1 interferon (IFN) dominant activation of tumor-associated APCs. PVSRIPO-mediated type-1 IFN inflammation in APCs generates tumor antigen-specific T cell-mediated immunity (**Figure 1**)[5]
  - This is augmented by anti-poliovirus-specific memory CD4 T cell recall response recognizing the PVSRIPO challenge[7]
- Animal models show that combination therapy with PVSRIPO and anti-PD-1/PD-L1 therapy may lead to a greater anti-tumor response than either agent alone, warranting further clinical investigation[8]

Figure 1. PVSRIPO Mechanism of Action



APC, antigen-presenting cell; DC, dendritic cell; MHC I, major histocompatibility complex-I; TCR, T-cell receptor.

Objectives

- To characterize the safety, tolerability, efficacy, and immune response of intratumoral PVSRIPO in patients with recurrent, unresectable melanoma

Methods

- *Study Design*
  - This phase 1 modified 3+3 dose escalation trial (NCT03712358) enrolled at least three patients into four separate cohorts (Cohorts 0-3); N=12
  - Cohort 0: PVSRIPO ($1x10^8$ tissue culture infectious dose 50% [$TCID_{50}$]) into 1 lesion on study day (d) 1; Cohort 1: PVSRIPO into 1 lesion on d 1 and a 2nd lesion on d 21; Cohort 2: PVSRIPO into 3 separate lesions 21 d apart; Cohort 3: PVSRIPO into one lesion 3 times, 21 d apart
  - A dose limiting toxicity (DLT) was defined as any Grade (G) 4 or higher toxicity that was possibly, probably, or definitely related to PVSRIPO (with the exception of vitiligo)
- *Patients*
  - Eligibility criteria included:
    - Unresectable, recurrent, histologically confirmed, American Joint Committee on Cancer stage IIIB, IIIC, or IV with an Eastern Cooperative Oncology Group performance status <2
    - Failure of ≥1 anti-PD-1-based regimen; patients with *BRAF*^{V600} mutations also failed ≥1 BRAF-targeted therapy
    - Prior vaccination with a positive serum anti-poliovirus titer; all patients received a booster anti-poliovirus vaccine (IPOL®, Sanofi-Pasteur) 1-6 weeks prior to intratumoral injection of PVSRIPO
    - Presence of injectable melanoma lesions (number dependent on cohort), defined as cutaneous, subcutaneous (SC), or nodal lesion ≥ 10 mm in longest diameter
  - Patients with life expectancy <6 months, clinically active cerebral or bone metastases (mets), and >3 visceral mets (exclusive of nodal mets associated with visceral organs) were excluded
- *Assessments*
  - Adverse events (AEs) were reported using the Common Terminology Criteria for Adverse Events version 4
  - Stool samples for assessment of viral shedding were collected from patients at multiple timepoints after PVSRIPO injections
  - Tumor response was determined using the immune-related response criteria (irRC); lesion measurements were performed via imaging and/or physical exam on study days 0, 21, 42, and 84[9]

Results

Patients

- A total of 12 adult patients were enrolled. Median age was 68.9 (range, 38-81) years and 8 (66.7%) patients were male; all patients were white (non-Hispanic or Latino). See **Table 1** for a summary of key baseline characteristics of PVSRIPO-treated patients
- 67% of patients had ≥5 lesions
- All results are as of data cutoff (July 2020)

Safety

- All treatment-emergent adverse events (TEAEs) were G 1 or 2; the most common TEAE was pruritus (58% of patients; **Table 2**)
  - No serious AEs or DLTs were reported
  - Except for one case each of G 1 hot flash and fatigue, all TEAEs considered related to PVSRIPO were localized to the injection site or adjacent areas (**Table 2**)
  - No viral shedding was identified in the stool of treated patients

Table 1. Patient Characteristics and Treatment Response

Patient Number	Baseline Demography				Follow-Up
	Baseline Stage	Prior Tx (earliest to most recent)	Anti-PD-1 Resistance[a]	Additional Therapies after PVSRIPO	Progression-free After Additional Therapy?[b]
Cohort 0: Single lesion injected at baseline/day 0					
1	IV, M1a	Nivo, T-VEC	Primary	Ipi/nivo and maintenance nivo	Yes[c]
2	IV, M1b	Pembro, T-VEC, ipi/nivo, IA, pembro	Primary	Pembro, radiation, binimetinib	No
3	IIIC	Vemurafenib, ipi/nivo	Inadequate Exposure[d]	Ipi/nivo and maintenance nivo, radiation, T-VEC, IA plus pembro	No
Cohort 1: 2 total lesions injected; 1 at baseline/day 0; 1 on day 21					
4	IV, M1a	>10 therapies, including encorafenib/ binimetinib, pembro, IL-2, and T-VEC	Secondary	Encorafenib, IA plus pembro, binimetinib, paclitaxel	No
5	IIIC[e]	Pembro, T-VEC, IA/pembro, dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib	Secondary	Pembro	Yes
6	IIIC[e]	Nivo, T-VEC, ipi/ nivo, radiation	Primary	Nivo, IA	No
Cohort 2: 3 total lesions injected; 1 at baseline/day 0, 1 on day 21, 1 on day 42					
7	IV, M1b	Ipi/nivo and IA/pembro	Secondary	Pembro, T-VEC	No
8	IV, M1a	Nivo and pembro	Primary	Pembro	Yes
9	IIIB[e]	Nivo	Primary	Nivo	Yes
Cohort 3: Single lesion injected 3 times; once at baseline/day 0; 2nd time on day 21, 3rd time on day 42					
10	IIIC	Ipi/nivo and nivo	Secondary	Nivo	No
11	IV, M1a	Nivo	Primary	Nivo	Yes
12	IIIC[e]	Pembro	Primary	None	Yes

[a]Definitions of primary and secondary PD-1 resistance based on SITC Immunotherapy Resistance Task Force recommendation.[1] [b]As of data cutoff. [c]After follow-on therapy, biopsy of two cutaneous lesions showed no viable tumor. Patient 1 has unbiopsied stable disease in the lymph node basin and stable cutaneous/SC disease. [d]Patient had inadequate exposure to determine type of anti-PD-1 resistance given rapid disease progression. [e]In-transit disease. IA, investigational agent; ipi, ipilimumab; Tx, treatment; mos, months; nivo, nivolumab pembro, pembrolizumab.

Results

Table 2. TEAE Summary[a]

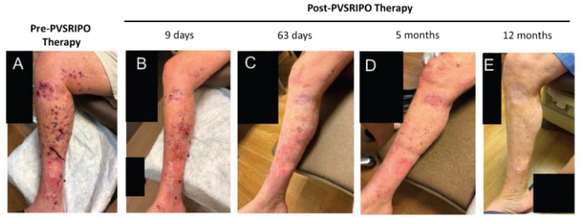
	TEAE (N=12)			Related TEAE[b] (N=12)		
	Grade 1	Grade 2	Overall	Grade 1	Grade 2	Overall
Any TEAE, n (%)	12 (100.0)	5 (41.7)	12 (100.0)	10 (83.3)	0	10 (83.3)
Pruritus skin	7 (58.3)	0	7 (58.3)	6 (50.0)	0	6 (50.0)
Erythema	5 (41.7)	0	5 (41.7)	4 (33.3)	0	4 (33.3)
Bruising	2 (16.7)	0	2 (16.7)	1 (8.3)	0	1 (8.3)
Erythema non injected lesion	1 (8.3)	0	1 (8.3)	1 (8.3)	0	1 (8.3)
Fatigue	1 (8.3)	0	1 (8.3)	1 (8.3)	0	1 (8.3)
Hot flashes	1 (8.3)	0	1 (8.3)	1 (8.3)	0	1 (8.3)
Injection site itching	1 (8.3)	0	1 (8.3)	1 (8.3)	0	1 (8.3)
Lesion discoloration	1 (8.3)	0	1 (8.3)	1 (8.3)	0	1 (8.3)
Pruritus generalized	1 (8.3)	0	1 (8.3)	1 (8.3)	0	1 (8.3)
Skin infection	0	1 (8.3)	1 (8.3)	0	1 (8.3)	1 (8.3)
Tingling	1 (8.3)	0	1 (8.3)	1 (8.3)	0	1 (8.3)
Anorexia	1 (8.3)	2 (16.7)	3 (25.0)	0	0	0
Constipation	3 (25)	0	3 (25.0)	0	0	0

[a]TEAEs occurring in 3 or more patients and all treatment-related TEAEs are shown; [b]Includes TEAEs possibly, probably, or definitely related to PVSRIPO treatment. TEAE, treatment-emergent adverse event.

Treatment Response

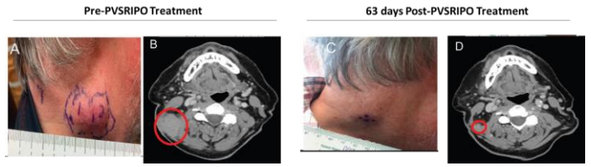
- Imaging of lesions in select PVSRIPO-treated patients prior to and following administration are shown in **Figures 2-3**

Figure 2. Lesions in Patient 9 Prior to PVSRIPO Administration/Baseline (**A**) and Post-PVSRIPO Therapy (**B-E**)



Patient 9 presented with Stage IIIB in-transit melanoma (**2A**). PVSRIPO therapy was initiated 15 days following last anti-PD-1 treatment. Lesion regression apparent 9-days post-PVSRIPO therapy (**2B**); day 63 biopsy (**2C**) demonstrated a pCR (defined as the absence of viable tumor) in injected and non-injected lesions. At least 12 months post-PVSRIPO therapy, patient had scattered, flat, pigmented, stable lesions remaining, consistent with pCR (**2D-E**). Subsequent therapies are detailed in **Table 1** and timing of therapy prior to PVSRIPO is shown in **Table 3.**
pCR, complete pathologic response.

Figure 3. Lesions in Patient 8 (**A-B**) Prior to PVSRIPO and (**B-C**) 63 Days Post-PVSRIPO Administration



3A: SC lesions to be injected outlined in purple; red circles: SC lesions in **3B** and **3D**.
Patient 8 presented with dermal mets and nodal disease. Received nivo (3 doses) followed by pembro (3 doses), with clinical progression (**3A-B**). At day 63, >75% reduction noted in all index lesions (**3C-D**). irPR confirmed via CT scan 3 weeks later. Given residual disease, patient taken off study before 4-week confirmation to resume systemic therapy; patient subsequently received pembro (4 doses) and remains progression free 12 months post-PVSRIPO therapy.
CT, computed tomography; irPR, immune-related partial response; mets, metastases; nivo, nivolumab; pembro, pembrolizumab; SC, subcutaneous.

Results

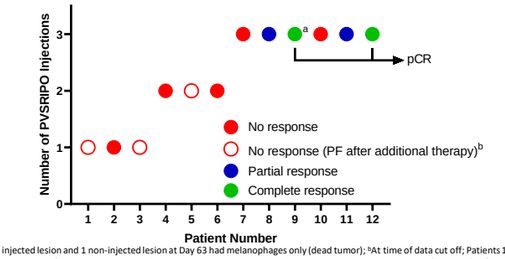
- Among the 12 treated patients, 4 (33%) met criteria for overall response rate (ORR) per irRC (**Table 3, Figure 5**), including 4/6 (66%) who received 3 injections (**Table 1, Figure 5**)
  - pCR was observed in 2 of 4 (50%) patients with in-transit disease (**Table 1**; **Figures 2-3**)

Table 3. PVSRIPO Anti-Tumor Response Relative to ICI Administration and Post-Study Disease Status

Time since anti-PD-1 relative to PVSRIPO	ORR per irRC % (n/N)	Proportion treated with ICI post-PVSRIPO % (n/N)	Progression-free post PVSRIPO alone or PVSRIPO followed by ICI % (n/N)	Median duration of follow-up (months)[a]
≤30 days	60% (3/5)	80% (4/5)	60% (3/5)	10
>30 days	14% (1/7)	86% (6/7)	43% (3/7)	16
Overall	33% (4/12)	83% (10/12)	50% (6/12)	12

[a]As of data cut off.
ICI, immune checkpoint inhibitor; irRC, immune-related response criteria; ORR, overall response rate; PD-1, programmed death-receptor 1.

Figure 5. Results Summary by Number of PVSRIPO Injections



[a]Biopsy on 1 injected lesion and 1 non-injected lesion at Day 63 had melanophages only (dead tumor); [b]At time of data cut off; Patients 1, 3 (for 9 months), and 5 were PF after receiving additional anti-PD-1 therapy; patients 1 and 3 in combination with ipilimumab (patient 1's 1st exposure), following PVSRIPO therapy (see **Table 1**). pCR, pathological complete response; PF, progression free.

- Overall PVSRIPO response, and response relative to time since prior anti-PD-1 exposure, is summarized in **Table 3**
  - Following study completion/PVSRIPO therapy, the majority of patients were rechallenged with a previously received ICI/regimen (10/12 patients [83%]) or new ICI/regimen (11/12 patients [92%]; **Table 1**)
  - 6/12 patients (50%) at the data cutoff remained progression free

Conclusions

- Intratumoral PVSRIPO therapy was well tolerated
  - All TEAE were low Grade (1 or 2) and the majority were localized to treated lesions
- There was no evidence of viral shedding in stool or disease related to viral origin
  - Anti-poliovirus immunity and CD155 targeting likely restricts viral spread and off-target/systemic immune related AEs
- Anti-tumor responses were noted in injected and non-injected lesions (ie, abscopal response**; Figure 2**)
- Response after PVSRIPO/subsequent ICI therapy was noted in patients with resistant disease, warranting further investigation
  - The anti-tumor response may correlate to the number of PVSRIPO injections and recent ICI therapy, which suggests synergy with combination therapy, given half-life of agents
- An amendment exploring higher PVSRIPO dose levels is ongoing and a phase 2 study with and without anti-PD-1 therapy in the refractory melanoma population is initiating (NCT04577807)

References

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Disclosures

As relevant to the current study, **DMB, MG,** and **SN** have a financial interest in Istari Oncology, Inc.; Duke University (Licensor of PVSRIPO) has a financial interest in Istari Oncology, Inc. (Licensee of PVSRIPO).

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