LUMINOS-101: Phase 2 Study of PVSRIPO With Pembrolizumab in Recurrent Glioblastoma

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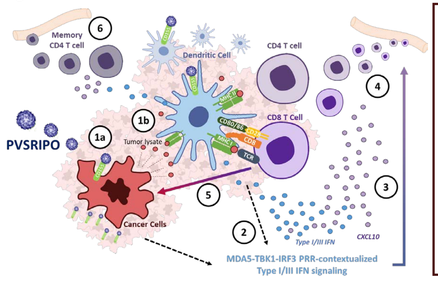
Introduction

- Glioblastoma is an aggressive and debilitating tumor that inevitably recurs despite treatment with currently available therapies[1,2]
  - The prognosis for patients with recurrent glioblastoma (rGBM) is poor, with no highly effective approved therapies[3]
  - GBM displays extensive molecular and cellular heterogeneity as well as substantial subclonal diversity within individual tumors, posing a major therapeutic challenge[4]
- PVSRIPO is a novel intratumoral immunotherapy derived from genetic modifications to the Sabin type 1 attenuated poliovirus (PV) vaccine that engages both the innate and adaptive arms of the immune system[5] (**Figure 1**)
  - PVSRIPO targets the PV receptor, CD155, an emerging immune checkpoint target, expressed on antigen-presenting cells (APCs) and malignant cells of most solid tumors[6,7]
  - Intratumoral PVSRIPO infection results in inflammatory-mediated destruction of tumor cells but non-lethal prolonged infection in APCs, driving type I/III interferon-dominant responses and tumor antigen-specific polyfunctional T-cell responses[8]
  - Additionally, infection with PVSRIPO results in activation of a CD4-mediated polio-specific memory response via prior/boosted vaccination

Figure 1. PVSRIPO Mechanism of Action



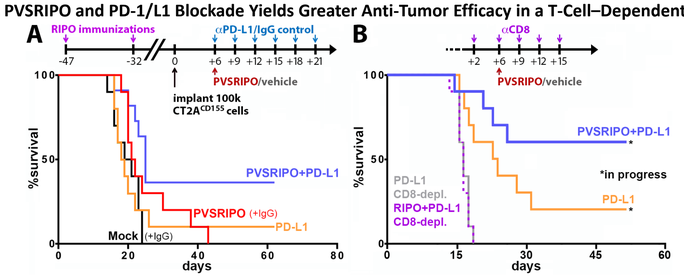
1a PVSRIPO infects and kills CD155-expressing cancer cells
1b PVSRIPO maintains non-lethal, prolonged viral replication in antigen-presenting cells (eg, dendritic cells)
2 PVSRIPO infection of APCs via CD155 induces type I/III IFN dominant responses
3 Sustained type I/III IFN production activates tumor antigen-specific antitumor T-cell responses
4 Increased cytokine production results in recruitment of functional tumor antigen-specific T cells
5 Cancer cells are recognized by T cells and killed by CD8 T cells
6 Active PVSRIPO replication promotes activation and recruitment of polio-specific memory CD4 T cells

APC, antigen presenting cell; IFN, interferon; MHC, major histocompatibility complex; TCR, T-cell receptor.

Trial Rationale

- PVSRIPO-induced type I/III interferon results in upregulation of PD-L1, supporting investigation of PVSRIPO in the context of PD-1/L1 blockade[5]
  - This mechanistic rationale is supported by data in a mouse GBM model, where PVSRIPO and PD-1/L1 blockade led to a greater anti-tumor response than either agent alone[8] (**Figure 2**)
  - While anti-PD-1/L1 therapies have been well tolerated, they have failed to improve outcomes in GBM, alone or in combination with chemo/radiation or bevacizumab therapy, although they have shown promise in the neoadjuvant setting[9-13]
- In an expanded phase 1 dose-finding trial of PVSRIPO, patients with rGBM treated with PVSRIPO showed greater long-term survival (36-60 months: 21%) relative to criteria-matched external controls (36 months: 4%; 60 months: 0)[14]
  - Preliminary results from 4 patients treated with PVSRIPO followed by at least one dose of pembrolizumab under expanded access/compassionate use showed early onset radiographic activity indicative of tumor inflammatory changes, warranting further investigation.

Figure 2. PVSRIPO and PD-1/L1 Blockade Yields Greater Anti-Tumor Efficacy in a T-Cell–Dependent Manner[8]



CT2A murine GBM model. CT2A^{CD155} cells were implanted intracranially on day 0 in CD155 transgenic C57BL/6 mice. Mice received 5x10^7 PFU PVSRIPO via stereotactic intratumoral infusion on day 6; anti-PD-L1 and control (IgG)2A were administered intraperitoneally starting at day 6 as indicated. Survival was determined by body weight loss of >15%. (A) Survival of mice immunized against polio, treated with or without PVSRIPO +/- PD-L1 blockade as indicated. (B) Survival of mice treated as indicated with and without depletion of CD8 T cells. αCD8, anti-CD8; αPD-L1, anti-PD-L1; GBM, glioblastoma; IgG, immunoglobulin G.

Objectives

- Given the mechanistic rationale, the objective of this trial is to evaluate the anti-tumor activity, safety, and tolerability of PVSRIPO followed by pembrolizumab in patients with rGBM in an effort to achieve greater anti-tumor response

Methods

- Following screening (**Table 1**), eligible patients are treated with a single 5x10^7 median tissue culture infectious dose (TCID$_{50}$) intratumoral infusion of PVSRIPO followed by 200 mg intravenous (IV) pembrolizumab 2-4 weeks later and every 3 weeks thereafter, with a maximum planned duration of follow-up up to 24 months (**Table 2** and **Figure 3**)

Table 1. Screening Periods

	Screen 1	Screen 2
Timing	**1 to 6 weeks prior to PVSRIPO infusion**	**Within 7 days of PVSRIPO infusion**
Assessments	• Informed consent • Medical history • IPOL® anti-PV booster vaccination • Safety and research laboratory assessments	• Complete clinical assessments • Radiographic assessments • Safety and research laboratory assessments

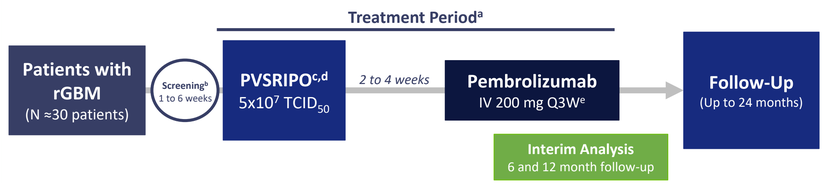
IPOL, poliovirus vaccine inactivated; PV, poliovirus

Table 2. Treatment Schedule and Follow-up Period

	Treatment Period
Baseline (Day 0 or 1)	• Catheter placement and PVSRIPO infusion (5x10^7 TCID$_{50}$) by CED for 6.5 hours
Week 2 to 4	• Initiate pembrolizumab treatment (200 mg IV) given Q3W to a maximum of 24 months
Every 3 to 9 Weeks (schedule dependent on continued pembrolizumab treatment)	• Follow-up visits for clinical, radiographic, laboratory, and research assessments (pembrolizumab administration Q3W)
≥12 Months After Initial PVSRIPO Infusion	• PVSRIPO retreatment is allowed for cPD if infusion-related criteria are met

CED, convection-enhanced delivery; cPD, confirmed progressive disease; IV, intravenous; Q3W, every 3 weeks; TCID$_{50}$, median tissue culture infectious dose.

Figure 3. LUMINOS-101 Study Design



[a]Patients may receive bevacizumab (7.5 mg/kg Q3W) and/or dexamethasone (≤4 mg/day) for symptom control related to peritumoral edema, as needed. [b]Patients receive IPOL® anti-poliovirus booster vaccination. [c]Patients receive intratumoral administration of 5x10^7 TCID$_{50}$ of PVSRIPO by CED. [d]Patients receive PVSRIPO retreatment if cPD ≥12 months from prior infusion. [e]For up to 24 months, permanent discontinuation for toxicity or cPD. CED, convection enhanced delivery; cPD, confirmed disease progression; IV, intravenous; TCID$_{50}$, median tissue culture infectious dose; Q3W, every 3 weeks; rGBM, recurrent glioblastoma.

References

1. Howlader N et al. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020; 2. Stepanenko A et al. *Cancers*. 2018;10(12):492; 3. Sim H et al. *CNS Oncol*. 2018;7(1):51-65; 4. Dirkse A et al. *Nat Comm*. 2019;10:17878; 5. Brown M et al. *Sci Transl Med*. 2017;9(408):eaan4220; 6. Takai Y, et al. *Nat Rev Mol Cell Biol*. 2008;9:603-15; 7. Liu L, et al. *Oncol Rep*. 2021;45:835-845; 8. Brown M, et al. *Nat Comm*. 2021 (in press); 9. Cloughesy T et al. *Nat Med*. 2019;25:477-486; 10. Reardon DA et al. *J Clin Oncol*. 2018;36(15_suppl):2006; 11. de Groot J et al. *Neuro Oncol*. 2020;22:539-49. 12. Lukas RV et al. *J Neurooncol*. 2018;140:317-328; 13. Reardon DA et al. *JAMA Oncol*. 2020;6(7);1003-1010. 14. Desjardins A et al. *N Engl J Med*. 2018;379(2):150-161.

Disclosures

AS: Consultant, Monteris Medical, Surgical Theater; Honoraria, Monteris Medical; Research support, Merck; Travel, Monteris Medical; **ATK, LF, LJ, LM, GN:** Employee, Istari Oncology, Inc.; **MB:** Intellectual property related to this research, which has been licensed to Istari Oncology, Inc.; **RC:** Research support, Novocure, Istari Oncology, Inc., ZioPharm; **AD:** Research support, Istari Oncology, Inc., Triphase Accelerator, Orbus Therapeutics, Symphogen, Celgene/Bristol-Myers Squibb; Stock options, Istari Oncology, Inc.; Patients in partnership with Istari Oncology, Inc.; **HF:** Consultant, Istari Oncology, Inc.; Equity, Istari Oncology, Inc.; **MG:** Financial interest, Istari Oncology, Inc.; **PW:** Research support, Agios, AstraZeneca/Medimmune, BeiGene, Celgene, Eli Lilly, Genentech/Roche, Kazia, MediciNova, Merck, Novartis, Nuvation Bio, Oncoceutics, Vascular Biogenics, VBI Vaccines; Advisory board, Agios, AstraZeneca, Bayer, Boston Pharmaceuticals, CNS Pharmaceuticals, ElevateBio, Immunomic Therapeutics, Imvax, Karyopharm, Merck, Novartis, Nuvation Bio, QED Therapeutics, Vascular Biogenics, VBI Vaccines, Voyager; **RAB, CM, PA, NB, WC, SO, YY:** None.

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In Memoriam

The authors would like to express their sadness at the passing of their friend and colleague, Dr. Dina Randazzo, a beloved and admired neuro-oncologist in the Preston Robert Tisch Brain Tumor Center of Duke University. Dr. Randazzo was a principal investigator for several clinical studies aimed at understanding and treating glioblastoma. We are grateful for her valuable contributions to this and other studies.

Key Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Recurrent supratentorial glioblastoma confirmed via prior histology by the site's neuropathologist or designate and active disease confirmed within 6 weeks of PVSRIPO infusion	• Multifocal disease (>1 enhancing lesion growing >0.5 cm within 3 months of baseline), serious cerebral herniation syndrome, or extensive leptomeningeal, subependymal, or ≥1 cm enhancing disease crossing the midline
• Enhancing lesion ≥1 cm to ≤5.5 cm in all planes and ability to place catheter with tip: o Within the enhancing portion or in the vicinity of enhancement of target lesion (ie, infiltrative disease) o ≥0.5 cm from ventricles o ≥1 cm deep into the brain o ≥0.5 cm from the corpus callosum	• Radiotherapy or treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody within 12 weeks prior to PVSRIPO infusion, or prior discontinuation of any anti-PD-1 or anti-PD-L1 therapy due to toxicity
• Confirmed disease relapse following prior therapies supported by MRI or CT scan	• Prior intratumoral therapy, prior interstitial brachytherapy, implanted chemotherapy or stereotactic radiosurgery or other therapeutics delivered by CED, including prior PVSRIPO
• Failed previous first-line therapy including maximal surgical resection and radiotherapy (plus concomitant chemotherapy followed by maintenance chemotherapy if unknown or unmethylated MGMT promoter methylation status)	• Chemotherapy, anti-VEGF, or TTF therapy ≤1-6 weeks depending on the therapy prior to PVSRIPO infusion
• Karnofsky performance status score ≥70 at screening and baseline	• Systemic immunosuppressive treatments other than low-dose (≤4 mg/day dexamethasone or equivalent acceptable) systemic corticosteroids (eg, methotrexate, chloroquine, azathioprine) within six months of PVSRIPO infusion
• Undergone prior vaccination against PV and received a boost immunization with trivalent IPOL® within 1 to 6 weeks of PVSRIPO administration	• High-dose systemic corticosteroids (>4 mg/day dexamethasone or equivalent) within 2 weeks of PVSRIPO infusion • Severe active comorbidities

CED, convection enhanced delivery; TTF, tumor treating fields.

Study Objectives and Endpoints

- This single-arm study is designed to evaluate the efficacy, safety, and tolerability of PVSRIPO in combination with pembrolizumab in patients with rGBM (**Table 3**)

Table 3. Summary of Efficacy, Safety, and Exploratory Endpoints

Objective	Endpoints
Primary Efficacy	• Objective response rate[a] • Duration of response[b] • Durable radiographic response rate[c]
Primary Safety	• Frequency and severity of TEAEs via CTCAE (v5.0) in patients receiving PVSRIPO and at least one dose of pembrolizumab
Secondary Efficacy	• Disease control rate[d] • Duration of disease control • Overall and landmark survival • PFS[e]
Secondary Safety	• Frequency and severity of TEAEs via CTCAE (v5.0) in patients receiving PVSRIPO only
Exploratory	• Identification of biomarkers of anti-tumor response to PVSRIPO followed by pembrolizumab • Radiographic response via alternative response criteria

Radiographic response via iRANO criteria, unless otherwise noted. [a]Includes patients achieving a complete response or partial response. [b]Time from first response observed until progressive disease or death, whichever comes first. [c]Includes patients with a response that persists for ≥6 months. [d]Includes patients who achieve CR, PR, or durable SD. [e]Per alternative response criteria. cPD, confirmed disease progression; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; iRANO, immunotherapy response assessment for neuro-oncology; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event.

Study Status

- This study began in October 2020, with recruitment planned for approximately 30 patients across up to 10 sites in the United States
- The results of this trial may inform the design of future randomized trials

Registration

- This study is registered at ClinicalTrials.gov (NCT04479241)
- The information presented here is current as of March 2021, pending finalization of any ongoing discussion with FDA
- Please refer to ClinicalTrials.gov or email clinical team for more information at LUMINOS-101@istarioncology.com

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