SAFETY AND EFFICACY OF NEOADJUVANT INTRAVESICAL ONCOLYTIC MV-NIS IN PATIENTS WITH UROTHELIAL CARCINOMA

¹Tanner Miest, ²Bradley Leibovich, ³Stephen Bardot, ²Paul Young, ²Stephen Boorjian, ⁴Mark Gonzalgo, ²Loren Herrera-Hernandez, ²Matthew Tollefson, ²Jeffrey Karnes, ²Paige Nichols, ²Tessa Kroeninger, ³Rachel Graham, ⁴Carole Lahana, ⁵Monica Reckner, ²Alysha Newsom, ⁶Nandakumar Packiriswamy, ⁷Janice Anoka, ²Kah Whye Peng, ⁷Erol Wiegert, ⁷Alice Bexon, ⁶Shruthi Naik*. ¹University of Texas and Mayo Clinic, Houston, TX, USA; ²Mayo Clinic, Rochester, MN, USA; ³Ochsner Clinic, New Orleans, LA, USA; ⁴University of Miami, Miami, FL, USA; ⁵Vyriad, Inc., Rochester, MN, USA; ⁶Mayo Clinic and Vyriad Inc., Rochester, MN, USA; ⁷Vyriad Inc., Rochester, MN, USA

Background Bladder cancer is a leading cause of cancer death in the United States.¹ The histology in > 90% of cases is urothelial carcinoma (UC). Tumors may present either as non-muscle-invasive (NMIBC) or muscle-invasive disease (MIBC). Current standard of care for patients with high risk NMIBC includes transurethral resection of bladder tumor (TURBT) followed by intravesical immunotherapy with Bacillus Calmette-Guerin (BCG).² Meanwhile, patients with BCG unresponsive NMIBC or MIBC are recommended to undergo radical cystectomy (RC), which adversely impacts quality of life and is associated with significant morbidity.³ MV-NIS is an investigational oncolytic measles virus with an excellent clinical safety profile.⁴ This ongoing phase I clinical study is designed to test the safety, efficacy and identify the recommended phase 2 dose (RP2D) of intravesical MV-NIS in patients with NMIBC or MIBC who are scheduled for RC and not eligible for neoadjuvant chemotherapy.

Methods Bladder UC patients were evaluated for eligibility and provided informed consent prior to enrolling. To date 8 patients have been enrolled: 4 to the single dose safety cohort, and 4 to the multi-dose expansion cohort. Patients were administered intravesical $\sim 1 \times 10^9$ TCID₅₀ MV-NIS once at least 1 week prior to RC (safety cohort), or twice at 4 and 2 weeks prior to RC (expansion cohort). Patients were closely monitored during the 2-hour instillation period. Tumor specimens from the pre-treatment TURBT and post-treatment RC were analyzed to determine pre- and post-treatment pathological stage and evaluate tumor killing and immune cell infiltrate.

Results Intravesical MV-NIS treatment was well tolerated in all patients. Only a single Adverse Event (AE) attributable to MV-NIS treatment (Grade 1 hematuria). AEs Grade>2 were related to post-surgical complications. Tumor pathology findings are summarized in table 1. Tumor downstaging was observed in 4 of 8 patients. Among 4 patients in the expansion cohort, 2 had no residual disease (pT0). Central assessment of RC tissues showed significant inflammatory infiltrate in all treated bladder specimens. Detailed analyses are ongoing to characterize MV infection and immune infiltrate in bladder tissue

Conclusions The higher-than-expected rate of tumor downstaging and pT0 pathology, paired with the significant immune infiltrate observed in post-treatment bladder tissue, provide compelling evidence that intravesical MV-NIS has clinical activity against UC. These results support the use of two doses of $\sim 1 \times 10^9$ TCID₅₀ as the RP2D in future clinical studies for BCG unresponsive NMIBC or MIBC patients. MV-NIS induced inflammation may act synergistically with checkpoint blockade therapies.

Abstract 422 Table 1 Pre-treatment (TURBT) and post-treatment (RC) pathology

	PID	TURBT pathology (local)	RC pathology (central)
SINGLE DOSE COHORT	201-001	MIBC: High grade pT3	High grade pT3: Significant inflammatory infiltrate (lamina propria): eosinophils, monocytes/macrophages, T-cells. Necrosis present in normal and tumor tissue.
	201-002	NMIBC: High grade pTis	pT0 – No residual disease. Significant inflammatory infiltrate (lamina propria): neutrophils, eosinophils, monocytes/macrophages, T-cells, plasma cells.
	208-003	MIBC: High grade pT2 with <25% glandular diff.	High grade pT3 with glandular differentiation. Significant inflammatory infiltrate including neutrophils, eosinophils, T-cells and plasma cells.
	201-004	MIBC: High grade pT2	High grade pTis – Disease downstaging. Significant inflammatory infiltrate including neutrophils, eosinophils, T-cells, plasma cells. Necrosis present.
TWO DOSE	201-005	NMIBC: High grade pT1	pT0 – No residual disease. Significant inflammatory infiltrate (lamina propria): T-cells.
	201-006	MIBC: High grade pT2	pT0 – No residual disease. Significant inflammatory infiltrate (predominantly T-cell lymphocytes and plasma cells).
	201-007	NMIBC: High grade pTis	pTis – significant inflammatory infiltrate (predominantly T-cells). Necrosis is absent.
	201-008	MIBC: High grade pT3	Persistent pT3 disease with squamous differentiation. Significant inflammatory infiltrate (predominantly lymphocytes) – neutrophils, eosinophils, B- and T-cells, monocytes/macrophages.

Trial Registration NCT03171493

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Ethics Approval Approval was received from the Institutional Review boards (IRBs) at all clinical sites including Mayo Clinic (#17–004167); Ochsner Health (#2020 060); and University of Miami (#20200174). All study participants are required to review and sign an IRB approved informed consent before taking part in the clinical trial.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.422>