

AWARD NUMBER: W81XWH-15-1-0115

TITLE: Phase I Trial of Intratumoral Administration of NIS-Expressing Strain of Measles Virus in Unresectable or Recurrent Malignant Peripheral Nerve Sheath Tumor

PRINCIPAL INVESTIGATOR: Dusica Babovic-Vuksanovic, MD

CONTRACTING ORGANIZATION: Mayo Clinic, Rochester, MN

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Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES				
14. ABSTRACT <p>Study approved by Mayo IRB on April 18, 2016, and by USAMRMC/ORP/HRPO on May 6, 2016. All study staff completed IRB training. Dose volume charts have been developed to facilitate pharmacy orders. Study opened for enrollment on May 17, 2016. Study coordinators identified and assigned to the study by Mayo Clinic Cancer Center.</p> <p>Eight patients have been enrolled in the study and 7 received study drug per protocol One patient withdrew from the study after enrollment and others completed treatment per protocol and the follow up. None of the treated patients experienced side effects. Three patients completed treatment at the first dose level, and three patients have been treated by dose 2 level. We enrolled and treated two patients into dose level 3, one of these patients withdrew after enrollment and another completed treatment and follow up per protocol Accrual of additional patients into dose 3 level is ongoing. A few additional patients are under evaluation for eligibility at this time. We anticipate next patient to be treated in November 2023, currently undergoing standard oncology therapy.</p> <p>So far out of 7 treated patients 6 experienced tumor progression. None of patients experienced side effects and there was no documented viral shedding, so we did not reach dose limiting toxicity at the level 1 and 2 dosing.</p> <p>Nuclear imaging documented presence of viral particles 8 days after MV-NIS intratumoral injections and tumor biopsies were positive for viral DNA, but imaging and DNA studies were negative on later timepoints.</p>				
15. SUBJECT TERMS Neurofibromatosis 1, Malignant Peripheral Nerve Sheath Tumor (MPNST), MV-NIS, Oncolytic Virus, Measles Virus				
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1. INTRODUCTION:

Malignant peripheral nerve sheath tumors (MPNST) is the major complication contributing to early mortality and overall decrease in life expectancy in Neurofibromatosis 1 patients. Oncolytic viruses can selectively infect and destroy tumor cells. Our preliminary data confirm that MPNST cells are highly susceptible to MV-NIS. We are conducting Phase I clinical trial to determine safety of intratumoral administration of MV-NIS. Protocol includes MV-NIS injections under ultrasound or CT guidance, *in vivo* monitoring of distribution and kinetics of virus using SPEC/CT or planar gamma camera imaging after TC-99m administration and assessing changes in tumor size by using WHO criteria. Our correlate studies will explore the time course of viral gene expression, virus elimination and humoral and cellular immune response to the injected virus.

2. KEYWORDS:

Neurofibromatosis 1, malignant peripheral nerve sheath tumor (MPNST), MV-NIS, oncolytic virus, measles virus

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Prepare Protocol for Phase I Clinical Trial --completed
Major Task 2: Coordinate Study Staff for Clinical Trial I--completed
Major Task 2: Conduct Phase I Clinical Trial---study open and recruitment in progress
Major Task 3: Perform Correlate Studies
Subtask 1: Evaluate virus incorporation and persistence in MPNST after injection
Subtask 2: Assess viremia and viral shedding

What was accomplished under these goals?

Patient accrual, treatment and correlate studies are ongoing

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Data will be presented to communities of interest when accrual and data analysis are complete. We plan to present data at the national NF conference and to publish data in one of oncology journals.

What do you plan to do during the next reporting period to accomplish the goal?

Continue patient accrual and procedures per protocol

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Data from this study will contribute to understanding the impact of oncolytic viral therapy in treatment of MPNST and potentially other NF1-related tumors

What was the impact on other disciplines?

Nothing to report

1. Received Mayo IRB approval on 04/18/2016.
2. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, US Army, and USAMRMC human subjects protection requirements. Approval Received on May 6, 2016.
3. All staff completed IRB training.
4. Developed drug dose volume chart to facilitate pharmacy orders once patients start enrolling.
5. Study opened for patient enrollment on May 17, 2016 to Mayo Clinic in Rochester.
6. Study coordinators identified and assigned to the study by Mayo Cancer Center.
7. Seven patients treated per protocol, completed first and second dose levels.
8. One patient is treated by a dose level 3 another patient is anticipated to start evaluation for eligibility next month.
9. Third annual report submitted to Mayo Clinic IRB and HRPO and received approval.
10. The fourth annual report was submitted to Mayo Clinic IRB and approved on December 5, 2019. It was also submitted to HRPO and approved on April 14, 2020.
11. The fifth annual report was submitted to Mayo Clinic IRB and approved on December 4, 2020. It was also submitted to HRPO and approved on January 14, 2021.
12. Request for third extension without funds was submitted on August 11, 2021.
13. The sixth annual report was submitted to Mayo Clinic IRB and approved on November 2, 2022. It was also submitted to HRPO and approved on January 9, 2023.
14. We requested a 5th year NCE (submitted in July 2023).

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:**Changes in approach and reasons for change**

We did not observe toxicity at the dose Level 1. Other studies with same agent did not show toxicity on the higher dose levels. Since positive effect with the tumor shrinkage was observed on the higher dose level, we have modified the protocol to change dose Level 2 to 3×10^8 and dose Level 3 to be 1×10^{10} . The modification was approved by IRB on December 1, 2017.

Actual or anticipated problems or delays and actions or plans to resolve them

The study is now open and actively recruiting eligible patients, however, the IRB approval was longer than anticipated due to administrative delays.

The slow accrual was caused by rarity of MPNST and the fact that the study is the phase 1, such that patients were referred to us in final stages of disease when many do not meet inclusion criteria. In addition, the study was temporarily discontinued due to COVID-19 and enrollment of subjects was halted. Therefore we requested a 5th year extension to complete the study. Request was submitted in July 2023.

We introduced several changes in order to improve accrual, including budgeting some of patient expenses related to travel and lodging, adding new investigators who will contribute to selection of eligible patients and advertising our study within and outside of the institution.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**Significant changes in use or care of human subjects**

Received Mayo IRB approval on 04/18/2016.

The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, US Army, and USAMRMC human subject protection requirements. Approval Received on May 6, 2016.

Third annual IRB progress report approved by Mayo IRB 12/14/2018.

We are preparing the fourth annual IRB progress report to submit to Mayo Clinic IRB due 12/20/2019.

The fourth annual IRB progress report was approved on December 5, 2019.

The fifth annual IRB progress report was approved on December 1, 2020.

The sixth annual IRB progress report was approved on November 15, 2021.

The seventh annual IRB progress report was approved on November 2, 2022.

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**
Report only the major publication(s) resulting from the work under this award.

Journal publications.

Nothing to report

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Study design and ongoing procedures were presented at the NF symposiums in 2020 and 2021

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Dusica Babovic-Vuksanovic
Project role: PI
Person months worked: 34
Contribution to projects: submitted quarterly reviews, coordinated activities needed for study opening for accrual
Funding support: this award

Name: Scott Okuno
Project role: co-PI
Person months worked: 26
Contribution to projects: patient accrual
Funding support: this award

Name: Jennifer Pickett
Project role: study coordinator
Person months worked: 2
Contribution to projects: coordination of study procedures
Funding support: this award

Name: Jordan E. Meyers
Project role: study coordinator
Person months worked: 13.5
Contribution to projects: coordination of study procedures
Funding support: this award

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: