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

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CONTRACTING ORGANIZATION: Mayo Clinic

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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

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5b. GRANT NUMBER

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6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

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.
Five patients have been enrolled in the study. They completed treatment per protocol and continue the follow up. None of the treated patients experienced side effects. With the first 3 patients we have completed the first dose level, and two patients have been treated by dose 2 level. Accrual of the third patient into dose 2 is ongoing.
So far out of 5 treated patients two died to cancer progression. Others are undergoing follow up. A few additional patients are under evaluation for eligibility at this time.

15. SUBJECT TERMS
Neurofibromatosis 1, Malignant Peripheral Nerve Sheath Tumor(MPNST), MV-NIS, Oncolytic Virus, Measles Virus

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	10	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98) Prescribed by ANSI Std. Z39.18

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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?

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 stuff 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. Five patients treated per protocol, completed first dose level.
8. Two patients are on the study at second dose level and another patient is being evaluated for eligibility.
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.

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

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

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?

Nothing to report

What was the impact on other disciplines?

Nothing to report

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 3x10^8 and dose Level 3 to be 1x10^10. 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.

First dose level is completed. Second dose level is in progress. Due to initial administration delay of opening study we requested a one year extension of funding. Request was submitted in August 2019.

In addition to slow accrual, the study was temporarily discontinued due to COVID19 and enrollment of subjects was halted. Therefore we requested a 2nd year extension to complete the study.

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 subjects 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.

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**

Journal publications.

Nothing to report

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

Nothing to repost

Other publications, conference papers and presentations.

Nothing to report

- **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 Picket
Project role: study coordinator
Person months worked: 2
Contribution to projects: coordination of study procedures
Funding support: this award

Name: Jaclynn Wessling
Project role: study coordinator
Person months worked: 13.5
Contribution to projects: coordination of study procedures
Funding support: this award

Name: Jodi Klocke
Project role: study coordinator
Person months worked: 8
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: