AWARD NUMBER: W81XWH-15-2-0063

TITLE:

A Phase I Trial of an Immune Checkpoint Inhibitor Plus Stereotactic Ablative Radiotherapy in Patients with Inoperable Stage I Non-Small Cell Lung Cancer

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CONTRACTING ORGANIZATION: University of California, Davis
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REPORT DATE: October 2017

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2017	Annual	30 Sep 2016 - 29 Sep 2017

4. TITLE AND SUBTITLE

A Phase I Trial of an Immune Checkpoint Inhibitor plus Stereotactic Ablative Radiotherapy in Patients with Inoperable Stage I Non-Small Cell Lung Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-2-0063

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

6. AUTHOR(S)

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This clinical trial is the first to evaluate the synergy between radiation, a well-known immune modulator, with the novel immune checkpoint inhibitor MPDL3280A (atezolizumab) in early stage inoperable non-small cell lung cancer. The trial is comprised of a traditional 3 + 3 phase I design followed by a dose expansion. We have enrolled 3 patients into dose level 1. Two patients have completed the entire treatment plan and 1 patient is in the 9-week dose limiting time period. The regimen has been well tolerated with no dose limiting toxicities observed in the first two patients. One patient had a partial response and the other patient has stable disease. Interestingly patient #1 had tumor shrinkage after two cycles of low dose MPDL3280A without the radiation. The trial continues as planned.

15. SUBJECT TERMS

None listed

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

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

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1. INTRODUCTION:

Patients with inoperable stage I non-small cell lung cancer are treated with stereotactic ablative radiotherapy (SAR), which is a precise, highly focused radiation technique. Unfortunately, patients with inoperable disease who have been treated with SAR develop recurrences, including the spread of the tumor to new areas of the body (metastases). The chemotherapy often employed to reduce the risk of metastases is not offered to patients with inoperable disease for fear of side effects. As a result, 30% of such patients will die from metastases within 3 years. A new class of drugs called immune checkpoint inhibitors exploit the body's immune system to target and kill tumor cells. The drug used in the proposed trial, MPDL3280A (atezolizumab), blocks signals on tumor cells that allow them to evade the immune system. This study will test whether atezolizumab can be combined with SAR to safely improve outcome. The rationale for this combination is based on the idea that radiation therapy, a well-known mediator of the immune response will partner with the immune checkpoint inhibitor to enhance the body's immune response against tumor cells and promote tumor cell death. The proposed clinical/translational trial seeks to provide the first human evidence for combining SAR with an immune checkpoint inhibitor, with the goal of eradicating subclinical metastatic disease and increase the cure rate for early stage lung cancer in patients who cannot tolerate surgery.

2. KEYWORDS:

Stage I inoperable non-small cell lung cancer, stereotactic ablative radiotherapy, immunotherapy, immune checkpoint inhibitors, MPDL3280A and atezolizumab.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: To conduct a phase I clinical trial of the combination of MPDL3280A plus SAR.

Specific Aim 2: To assess the biological changes of MPDL3280A plus SAR in patient specimens, will not begin until completion of Specific Aim 1.

What was accomplished under these goals?

Specific Aim 1: We have completed Major Tasks 1 and 2 (write the clinical protocol/metric 2 months and completed prior to grant start date of 9/30/15 and navigate the study activation process/metric 2-5 months and completed prior to the grant start date).

We are currently working on Major Task 3 which is enrolling into the dose finding phase of the study (metric 5-20 months). Since the last report we have completed enrollment into dose level 1(N=4) and dose level 2 (N=3). One patient is from the VA system and one patient is from David Grant Medical Center. The remaining patients are from UC Davis.

In dose level 1 the third patient enrolled had to be replaced because she did not complete the DLT period due to travel issues. No patient in dose level 1 or dose level 2 has experienced a DLT (see Tables below). Dose level 3 is scheduled to open November 21, 2017 after the last patient completes the DLT (dose limiting toxicity) period. All patients on dose level 1 have completed six cycles of treatment. One patient had a transient grade 3 lymphopenia. No other grade 3 toxicities have been reported. No patient on dose level 1 has progressed 18+mos; 16+ mos and 6+mo from initial treatment. All patients on dose level 2 are on active treatment and no grade 3 toxicities have occurred.

Worst Toxicity Grade Per Patient		
Patient	DLT period Cycle 1-3	Cycle 4-6
001	Grade 1	Grade 3 lymphopenia (cycle 4)
002	Grade 1	Grade 2 anemia (cycle 6)
003	Grade 1	NA
004	Grade 1	Grade 1
005	Grade 1	Grade 1
006	Grade 1	Grade 1

Adverse Event (Possible, Probably or Definitely Related)	**Any Grades**	**Grade 3+**
Alkaline phosphatase increased	1	0
Anemia	2	0
Blood bilirubin increased	1	0
Dizziness	1	0
Dry skin	1	0
Dyspnea	1	0
Fatigue	2	0
General disorders and administration site conditions-Other-Generalized	2	0
Hyperglycemia	1	0
Hyperkalemia	1	0
Hyperthyroidism	1	0
Hyponatremia	1	0
Lymphocyte count decreased	5	1
Myalgia	1	0
Nausea	1	0
Neck pain	1	0
Platelet count decreased	1	0
Rash maculopapular	1	0
White blood cell decreased	1	0

Fifty-six patients have been prescreened during this grant year, 46 from UC Davis (UCD), 13 from David Grant Medical Center (DGMC) and 3 from Mercy Medical Center (MMC). Many patients did not meet criteria because of a poor performance status, no histological confirmation and other active cancer. Of these, thirteen patients were approached about the trial and 4 enrolled. Reasons for patients not enrolling were 1) they did not meet all the eligibility criteria and 2) they did not want to wait for the next dose level to open.

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

The plan to take this trial to SWOG supported Dr. Daly's selection to participate in the inaugural class of the SWOG Leadership Academy. This 3 year experience prepares young investigators for future leadership roles in the National Clinical Trials Network.

How were the results disseminated to the communities of interest?

N/A

4. IMPACT:

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

N/A

What was the impact on other disciplines?

N/A

What was the impact on technology transfer?

N/A

What was the impact on society beyond science and technology?

N/A

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

No changes have been made

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

As discussed in the quarterly reports, we are in the process of adding Cedars-Sinai (Samuel Oschin Comprehensive Cancer Institute) in Los Angeles, CA as a site to assist us in completing accrual to the trial. The subcontracts were executed on October 27, 2017. The study was submitted to their IRB October 27, 2017. We anticipate site activation in December 2017.

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

Not applicable

Significant changes in use or care of human subjects

Not applicable

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

Publications, conference papers, and presentations

N/A

Website(s) or other Internet site(s)

N/A

Technologies or techniques

N/A

Inventions, patent applications, and/or licenses

N/A

Other Products

N/A

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATOINS

What individuals have worked on the projects?

Name:	Karen Kelly, MD
Project Role:	Principal Investigator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	4

Contribution to Project:	Dr. Kelly has written the protocol, informed consent and developed the case report form and seen these through the scientific, regulatory and contracting processes. Dr. Kelly has conducted the site initiation visit and activated the protocol. Dr. Kelly has treated all patients on the study.
Funding Support:	N/A
Name:	Megan Daly, MD
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID)	Unknown.
Nearest person month worked:	3
Contribution to Project:	Dr. Daly is actively recruiting patients and has enrolled three patients and has treated all patients on the study.
Funding Support:	N/A
Name:	Arta Monjazeb, MD, PhD
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	3
Contribution to Project:	Dr. Monjazeb is actively recruiting patients for the study but is primarily responsible for the translational medicine component of the study.
Funding Support:	N/A
Name:	Lt. Col. James Mitchell, MD – Replaced by Lt. Col David Eastham, MD, MPH
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	3
Contribution to Project:	Dr. Eastham is actively recruiting patients and has enrolled one patient.
Funding Support:	N/A
Name:	Frances Lara, CRC
Project Role:	Clinical Research Coordinator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	3
Contribution to Project:	Ms. Lara assists the investigators in coordinating the screening of patients for the study and maintains this information for the grant. Ms. Lara processes the consent forms for enrolled patients. Ms. Lara monitors the patient's status.
Funding Support:	N/A
Name:	Laura Brennan, NP – Replaced by Paige Woodward, NP
Project Role:	Nurse Practitioner
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	2
Contribution to Project:	Ms. Woodward provides symptom and toxicity management and documentation of toxicities for clinical trial patients.
Funding Support:	N/A
Name:	Nichole Mahaffey, PhD
Project Role:	Data Coordinator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	1
Contribution to Project:	Ms. Mahaffey is responsible for patient registration, confirmation of patient eligibility, and entry of all patient data to the Velos study database for enrolled patients
Funding Support:	N/A

Name:	Leigh Anne Morris
Project Role:	Regulatory Coordinator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	1
Contribution to Project:	Ms. Morris maintains all regulatory documents, prepares and submits protocol and informed consent form amendments, renewals and responses to the IRB, performs SAE reporting, IND submission and reporting and submission of necessary documents to HRPO.
Funding Support:	N/A
Name:	Pawandeep Aujla, PhD
Project Role:	Quality Assurance Manager
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	1
Contribution to Project:	Ms. Aujla is responsible for conduct reviews of clinical research records for data integrity and clinical research compliance. She will report any and all discrepancies to the Principal Investigator, establish a corrective action plan where appropriate, and perform training and follow-up with study personnel when any deficiencies are discovered.
Funding Support:	N/A

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

Karen Kelly

U10CA180888 (Blanke PI/Kelly Subrecipient PI) 03/01/17-02/28/18 2.4 calendar
Oregon Health & Science University/SWOG subcontract $50,767
Lung Cancer Committee, SWOG Network Group Operations Center for the NCTN
Goals: 1) oversee the activities of the Lung Cancer Committee: 2) assist in the development of protocol in the treatment of lung cancer; 3) handle all administrative duties of the Lung Cancer committee.
Role: Chair, Lung Cancer Committee

1 R01 CA211554-01 (Sutcliffe PI) 07/01/17- 06/30/20 .12 calendar
NIH $5,610
First in human study with $^{18}F\alpha_v\beta_6$ targeting peptide
The goal of this proposal is to perform human imaging studies with an ^{18}F-peptide and perform PET imaging.
Role: Co-Investigator

Megan Daly

2R44CA192498-02 (Partain PI) 05/01/16-04/30/18 .6 calendar
NIH/SBIR $9,350
Multi Source E-Beam kV X-Ray Tube for Image-Guided Radiotherapy
The goal of this project is to develop, build, and test a kV x-ray digital tomosynthesis image guided radiotherapy using linac systems.
Role: Co-I

5UM1CA186717-04 (Lara/subcontract PI) 03/01/16-02/28/18 .12 calendar
City of Hope Phase II subaward $5,610
The major goals are to support participation by a consortium of three National Cancer Institute (NCI) Comprehensive Cancer Centers in a consolidated, integrated NCI Experimental Therapeutics-Clinical Trials Network (ET-CTN) to conduct phase II experimental therapeutics clinical trials and to define better approaches to the development of novel anticancer agents that capitalize on the ability to characterize tumors molecularly and find appropriate biomarkers to select patients most likely to respond to specific agents.
Role: Co-Investigator

Arta Monjazeb
P30CA093373-14S4 (deVere White PI) 09/01/16-08/31/18 1.8 calendar
NIH/NCI Cancer Center Support Grant P30 Supplement $39,270
Genomic and Immunologic analysis of Canine High Grade Gliomas, Melanomas, and Osteosarcomas
The goal project is to determine mutational load/neo-antigen burden, mutations in known cancer pathways, and tumor microenvironment immunophenotype of canine malignancies.

U01 CA224166 (Canter/Ragland PI) 09/30/20-08/31/20 .12 calendar
NCI $5,610
Enhancing natural killer immunotherapy with first-in-dog trials of inhaled recombinant IL-15 and super-agonist IL-15 in naturally occurring canine cancers
Role: Co-Investigator

David Eastham
N/A

What other organizations were involved as partners?

Mercy Medical Center Sacramento as a site to identify and refer patients to UC Davis. They will provide standard of care radiation to their patients. This is IRB approved as previously stated.

8. SPECIAL REPORTING REQUIREMENTS

Not Applicable

9. APPENDICES

Not Applicable