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

PRINCIPAL INVESTIGATOR: Karen Kelly, MD

CONTRACTING ORGANIZATION: University of California, Davis
Sacramento, CA 95817-2229

REPORT DATE: October 29, 2018

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
OCT 2018	Annual	30 Sep 2017 – 29 Sep 2018

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
W81XWH-15-2-0063

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

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Karen Kelly MD, Arta Monjazeb MD PhD, Megan Daly MD, Lt. Col. David Eastham, MD, MPH

E-Mail: karkelly@ucdavis.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

University Of California, Davis
1850 Research Park Dr, Ste 300
Davis CA 95618-6134

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

Table of Contents

Page

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 3 (N=5). All patients were from UC Davis. In dose level 3, two patients were replaced. Once patient withdrew consent and the other patient was replaced due to patient/MD choice for grade 2 LFTs of unclear etiology after cycle 2. No patients in dose

level 3 experienced a DLT (see tables below). Two patients have completed six cycles of treatment. No other grade 3 toxicities reported.

No patient on dose level 1 has progressed 18+mos; 16+ mos and 6+mo from initial treatment but one patient died of unrelated causes. No patient on dose level 2 has progressed 18+ mos; 16+ mos and 6+ mos from initial treatment.

Worst Toxicity Grade Per Patient Regardless of Attribution		
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	N/A
004	Grade 1	Grade 1
005	Grade 1	Grade 2 Hypothyroidism (Cycle 6)
006	Grade 1	Grade 2 Nausea (Cycle 4)
007	Grade 3 Lichenoid dermatitis (drug rash - Cycle 2)	N/A
008	Grade 2 Lymphopenia (Cycle 1 & 3) & Grade 2 Maculopapular Rash (Cycle 3)	Grade 2 Nausea, Anorexia, Lymphopenia (Cycle 5)
009	Grade 2 Dyspnea (Cycle 3)	Grade 2 Dyspnea (Cycle 3)
010	Grade 2 Lymphopenia (Cycles 1 & 3)	Grade 1
011	Grade 1 (Only 2 Cycles)	N/A
012	Grade 2 Lymphopenia (Cycle 3)	Grade 1
013	Grade 2 Lymphopenia (Cycle 3)	Grade 1
014	Grade 3 (Only 1 Cycle)	N/A
015	Grade 2 Hyperthyroidism (Cycle 3)	Grade 2 Hyperthyroidism (Cycle 3)

Adverse Event (Possible, Probably or Definitely Related)	**Any Grades**	**Grade 3+**
Alkaline phosphatase increased	2	0
Anemia	16	0
Anorexia	3	0
Aspartate aminotransferase increased	2	0
Blood bilirubin increased	2	0
Chest wall pain	1	0
Diarrhea	4	0
Dizziness	2	0
Dry skin	1	0
Dyspnea	4	0
Edema limbs	1	0
Endocrine disorders - Other, Decreased TSH level	1	0
Endocrine disorders - Other, Elevated TSH	1	0
Fatigue	5	0
General disorders and administration site conditions - Other, Generalized Edema	2	0
Generalized muscle weakness	1	0

Headache	1	0
Hepatobiliary disorders - Other, Hepatitis (drug induced liver injury)	1	0
Hyperglycemia	1	0
Hyperkalemia	2	0
Hyperthyroidism	1	0
Hyponatremia	1	0
Hypothyroidism	1	0
Lymphocyte count increased	26	4
Malaise	1	0
Myalgia	1	0
Nausea	3	0
Neck pain	1	0
Neutrophil count decreased	1	0
Non-cardiac chest pain	1	0
Peripheral sensory neuropathy	1	0
Platelet count decreased	5	0
Pneumonitis	2	0
Productive cough	2	0
Rash maculopapular	5	0
Skin and subcutaneous tissue disorders - Other, Lichenoid dermatitis with eosinophils	1	1
Skin and subcutaneous tissue disorders - Other, Rash NOS	1	0
Urinary frequency	1	0
White blood cell decreased	7	0

Twenty six patients have been prescreened during this grant year, 25 from UC Davis and 1 from Cedars Sinai. Nine patients were enrolled. The reasons for screen failures included no available slot (6), incorrect tumor stage (3), comorbidities (3), surgical resection (2), patient declined (2) and lymphoma (1).

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

Dr. Daly, the junior investigator of this trial, will be the overall PI for the upcoming SWOG/NRG trial S1914 - A randomized phase III trial of SBRT with or without atezolizumab.

How were the results disseminated to the communities of interest?

We are having discussion regarding submitting the data to ASCO 2019 or the WCLC 2019.

4. IMPACT:

The data has led to an NCI National Clinical Trials Network (NCTN) sponsored randomized phase III trial.

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

We have entered into the expansion phase of the trial and do not anticipate accrual problems.

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 is actively recruiting patients and has enrolled five patients during the reporting period and 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 four patients during the reporting period 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 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 for this study 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:	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) 01/01/18-02/28/19 .12 calendar
Oregon Health & Science University/SWOG subcontract
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

Megan Daly
None

Arta Monjazeb
None

David Eastham
None

Amin Mirhadi
None

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