More Than Minimal Risk Consent and HIPAA Form

Principal Investigator	Malcolm Mattes, MD
Department	Radiation Oncology
Protocol Number	WVU010516
Study Title	Use of Response-Adapted Hypofractionated Radiation Therapy to Potentiate a Systemic Immune Response to Checkpoint Inhibitors in Non-Small Cell Lung Cancer
Co-Investigator(s)	Patrick Ma, MD, Geraldine Jacobson, MD, Tim Eubank, PhD, Mohammed Almubarak, MD, Aaron Provenzano, DO, Matthew Smolkin, MD, HCLD, Gary Marano, MD; Mohammad Shaikh, MD; Ann Morris, MD; Todd Tenenholz, MD
Sponsor	WVU Cancer Institute Mary Babb Randolph Cancer Center / WV Clinical and Translational Institute

Contact Persons

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In the event you experience any side effects or injury related to this research, you should contact Dr. Mattes at (304) 598-4706. (After hours, contact the Radiation Oncology Doctor on call at (304-598-4000). If you have any questions, concerns, or complaints about this research, you can contact Dr. Mattes (304)-598-4706.

For information regarding your rights as a research subject, to discuss problems, concerns, or suggestions related to the research, to obtain information or offer input about the research, contact the Office of Research Compliance at (304) 293-7073.

In addition if you would like to discuss problems, concerns, have suggestions related to research, or would like to offer input about the research, contact the Office of Research Integrity and Compliance at 304-293-7073.

Introduction

You, _____, have been asked to participate in this research study, which has been explained to you by _____. This study is being

conducted by Dr. Malcolm Mattes in the Department of Radiation Oncology at West Virginia University with funding provided by the West Virginia Clinical and Translational Science Institute.

Purpose(s) of the Study

It has been explained to you that you have metastatic (Stage IV) non-small cell lung cancer (NSCLC), for which your medical oncologist has recommended a checkpoint inhibitor immunotherapy agent (e.g. Nivolumab, Pembrolizumab, or Atezolizumab) as the standard treatment. You have been invited to participate in this research study, which involves the additional use of radiation therapy in combination with this immunotherapy medication, in order to determine whether the radiation may improve your cancer's response to immunotherapy and to learn more about your disease. Radiation is commonly used as a standard of care treatment of lung cancer but is considered the investigational component of this study because it will be used in a specific context (with immunotherapy) in an attempt to improve your condition. WVU expects to enroll approximately 35 subjects to participate in this study.

Description of Procedures

All patients enrolled in this study will receive at least one course of the investigational radiation therapy. The initial course of radiation therapy will be given shortly after study enrollment: The radiation may be given either at the same time as the start of immunotherapy or during ongoing immunotherapy. After the radiation is given, you will undergo a standard of care imaging evaluation using CT or PET/CT every 2-4 months, and if you are found to have anything less than a complete or partial response, subsequent course(s) of radiation therapy will be recommended for you as part of this study. Each radiation therapy course will be comprised of five or fewer fractions (treatments) per targeted site of cancer over 3-10 days. The dose of radiation used will vary depending on the location and physical properties of the targeted tumor, but only doses that are considered within standard of care will be utilized. The investigators expect that you will continue to follow-up in the radiation oncology department to discuss any subsequent treatment recommendations for the duration of time that you are pursuing active treatment for your malignancy, or at least for 12 months after the date of documented progression of disease on immunotherapy. Throughout the course of this study your immunotherapy will be managed in a standard fashion by your medical oncologist. If immunotherapy is to be discontinued due to either disease progression or intolerable side effects, a final course of radiation therapy is likely to be recommended prior to starting any alternative systemic therapy agent. The duration of immune therapy administration and the number of courses of radiation therapy that you receive will be dependent upon your response to prior treatment. There is no specific maximum number of cycles of immune therapy that will be recommended if you continue to respond to treatment, or courses of radiation therapy if you continue to have stable disease on imaging.

Prior to the first course of radiation therapy, at the time of the first follow-up imaging study, and at the time of further changes in your cancer's response to treatment on imaging, you will be asked for a blood sample of approximately 6 teaspoons in volume (4 tubes) to help correlate the biological effects of treatment to your cancer's response and any side effects that you may be experiencing. The specific tests to be obtained from the blood sample include flow cytometry to evaluate levels of circulating immune cells (CD4+, CD8+ and Treg T-cell subsets, and iNOS+/CD80+ macrophages), ELISA to evaluate levels of cytokines (HGF, TGF-β) and chemokines (CCL2, CXCL9, CXCL10, and CXCL11), and next generation sequencing (genetic testing) of the T-cell receptor to evaluate for changes in the immune-repertoire (i-repertoire). The samples for genetic testing may need to be sent to vendors or collaborators outside of the

WVU Cancer Institute for analysis, and if this is the case strict compliance to HIPAA policy will be followed in order to maintain your privacy and confidentiality. We recommend but do not require you to agree to these additional blood tests if you want to take part in this study.

_____ Yes, I agree to the above blood samples.

_____ No, I do not agree to the above blood samples.

You will also be asked to fill out a questionnaire every 3 months for up to 12 months to assess your quality of life during therapy. This questionnaire will take approximately 10 minutes to complete. Your answers are important to help researchers understand how the treatments you are undergoing affects you. We encourage you to answer all of the questions but you may skip any questions that you prefer not to answer. You will have the opportunity to see the questionnaire before signing this consent form.

There are anticipated circumstances under which your participation may be terminated by the investigator without regard to your consent, particularly if your physician determines that continuing treatment is not in your best interest. You may also withdraw from the study at any time.

Risks and Discomforts

Radiation therapy can have side effects, which rarely (but possibly) can be life-threatening. Temporary short-term side effects are common whereas permanent long-term side effects are rare. The most common temporary short-term side effect from this type of radiation therapy is fatigue, which can occur in the weeks to months after treatment. This can occasionally be accompanied by decreased appetite, changes in taste, or weight loss. Since radiation is a focal, localized treatment to a specific targeted tumor, the likelihood of all other side effects is dependent on the part of the body that is treated. The expected side effects from the specific radiation therapy you will undergo will be discussed with your radiation oncologist prior to treatment. These other occasional side effects from radiotherapy could include:

	Acute/Short-Term/Temporary	**Chronic/Long-Term/Permanent**
Skin	redness, dryness, darkening, itching, peeling, tenderness, hair loss	thickening, firmness, discoloration, hair loss
Bone	decreased blood counts	fracture, pain
Nerves	electrical sensation	pain, loss of strength, numbness, tingling, paralysis
Lymphatics	swelling	lymphedema
Brain	fatigue, brain swelling, headaches, nausea, vomiting, dizziness, drowsiness, altered taste or smell	loss of strength, numbness, tingling, paralysis
Lungs	cough, shortness of breath, bleeding	cough, shortness of breath, bleeding, decreased lung capacity
Heart	chest pain, pericarditis, abnormal rhythm	chest pain, heart attack, heart failure, pericarditis
Esophagus	difficulty swallowing, painful swallowing food sticking, heartburn, nausea, vomiting, decreased appetite,	stricture, obstruction, perforation, fistula, bleeding, chest pain
Stomach/ Bowel	nausea, vomiting, fatigue, diarrhea, cramping, decreased appetite	stricture, obstruction, perforation, bleeding, abdominal pain, ulceration

Liver	nausea, vomiting, fatigue, diarrhea	decreased liver function, ascites, cirrhosis, encephalopathy, bleeding
Rectum	spasm, frequent bowel movements	ulceration, bleeding
Bladder	burning/pain with urination, increased frequency, urinary urgency	decreased bladder capacity, bladder spasms, bleeding

Available evidence does not suggest that the combination of radiation therapy with immunotherapy leads to increased rates of toxicity or unexpected side effects. However, you should be aware that it is possible that unknown side effects may arise due to the combination of radiation therapy and immunotherapy in this study. Radiation therapy may also involve risks to an unborn child. For this reason, women who are pregnant will not be accepted in this study. If you are a woman who could become pregnant, you will not be allowed to participate in this study until you have had a pregnancy test and the test has indicated that you are not pregnant. You must use a medically approved method of birth control while you are on this study. Men who are able to father a child should never have unprotected sex with a woman of childbearing potential while in this study because radiation therapy may cause genetic damage to semen or sperm.

Radiation: The amount of radiation (x-rays and scans to assess your disease) that you are exposed to in this study is considered standard of care for your disease. The risks of these procedures will be explained to you by your doctor and staff involved in your care. Risks from radiation exposure are cumulative (they increase) over time.

In addition, having blood drawn may cause bruising, bleeding, or in rare cases infection. Having contrast agents for imaging tests may impair your kidney function.

Immunotherapy agents have their own set of expected side effects, as detailed below.

	Nivolumab	**Pembrolizumab**	**Atezolizumab**
Common	Fatigue Decreased appetite Generalized weakness	Fatigue Decreased appetite Nausea Rash	Fatigue Decreased appetite Lung inflammation Fever
Occasional	Nausea Diarrhea Joint inflammation Fever Lung inflammation Rash	Diarrhea Decreased thyroid hormone levels Increased thyroid hormone levels Lung inflammation Generalized weakness Anemia Mouth/Lip Sores	Nausea Diarrhea Joint inflammation Insomnia Lung Infection Generalized weakness
Rare	Mouth/Lip Sores Muscle inflammation Colon inflammation Anemia Peripheral Neuropathy Decreased white blood cell count Hair Loss Liver inflammation	Hair loss Decreased white blood cell count Colon inflammation Severe rash (skin blistering/ulceration) Pancreas inflammation Decreased adrenal hormone levels Muscle inflammation Liver inflammation Diabetes Mellitus	Myalgia Hair loss Pneumonia Decreased thyroid hormone levels Peripheral neuropathy Neutropenia Muscle inflammation

Alternatives

You do not have to participate in this study. Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time.

Refusal to participate or withdrawal will involve no penalty to you and will not affect your future care, or your employee status, if applicable, at West Virginia University.

In the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether or not to continue your participation.

Alternatives that could be considered in your case include undergoing immunotherapy alone as prescribed by your medical oncologist or taking part in an alternative clinical trial.

Benefits

Possible benefits that may result from your participation include the improvement of your health, but since it is not known whether the addition of radiation therapy to immunotherapy will be effective in your case, it is possible that you may not receive any benefit or your condition may worsen. The knowledge gained from this study may eventually benefit others.

Financial Considerations

You may wish to consult your insurance carrier prior to entering this study. With the exception of special correlative blood tests, which will be paid for by the study sponsor, all other treatments, tests, and procedures you will undergo as part of this study will be billed to your insurance company (e.g. doctor visits, radiation treatments, immunotherapy, imaging tests, and standard bloodwork). The portion of these costs that you will be responsible for personally will depend on your agreement with your insurance provider. No treatments will be undertaken by your physicians unless authorization is received by your insurance provider. There may be some additional expenses related to this study, such as transportation, parking, or meals. There are no special fees for participating in this study, and you will not be paid for participating in this study.

There is no money set aside to help treat you if you get hurt or sick in this study. The study doctor and WVUMedicine or its partners do not have special funds to pay for research study injuries if they occur.

Voluntary Compensation

If you are injured as a result of this research, treatment will be available. Responsibility for this treatment will be borne by you and/or your insurance company. In the event that you are physically injured as a result of participating in this research, care will be available. You will, however, be responsible for the charges for the care. There is no commitment to provide any compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact the investigator, Dr. Malcolm Mattes at 304-598-4706 if you are injured or for further information.

Patient Travel Reimbursement.

Travel reimbursement may be offered to patients on trial. Due to the limited travel funds available, travel reimbursement will be reviewed on case by case basis by the principal investigator.

Confidentiality

Any information about you that is obtained as a result of your participation in this research will be kept as confidential as legally possible. Your research records and test results, just like hospital records, may be subpoenaed by court order or may be inspected by the study sponsor or federal regulatory authorities (including the FDA if applicable) without your additional consent.

In addition, there are certain instances where the researcher is legally required to give information to the appropriate authorities. These would include mandatory reporting of infectious diseases, mandatory reporting of information about behavior that is imminently dangerous to your child or to others, such as suicide, child abuse, etc.

In any publications that result from this research, neither your name nor any information from which you might be identified will be published without your consent.

HIPAA

We know that information about you and your health is private. We are dedicated to protecting the privacy of that information. Because of this promise, we must get your written authorization (permission) before we may use or disclose your protected health information or share it with others for research purposes. You can decide to sign or not to sign this authorization section. However, if you choose not to sign this authorization, you will not be able to take part in the research study. Whatever choice you make about this research study will not have an effect on your access to medical care.

Persons/Organizations Providing the Information

Patient/West Virginia University Medicine

Persons/Organizations Receiving the Information

- The research site(s) carrying out this study. This includes UHA or UHA Affiliated, WVU, WVU Medicine, or the covered entities under the purview of West Virginia University, collaborating institutions, affiliate institutions, and component institutions. It also includes each site's research staff and medical staff.
- Health care providers who provide services to you as part of this research study.
- Laboratories and other people and groups that look into your health information as part of this study in agreement with the study protocol.
- The United State Department of Health and Human Services (which includes the National Institutes of Health (NIH), Food and Drug Administration (FDA)) and other groups that have the right to use the information as required by law.

- The members and staff of any Institutional Review Board (IRB) that oversees this research study.
- West Virginia University Office of Research Compliance and Office of Sponsored Programs.
- West Virginia University Clinical Trials Research Unit.

The Following Information Will Be Used

Information from your existing medical records and new information about you that is created or collected during the study such as: history and physicals, clinic visit notes, nursing and staff notes, laboratory results, x-rays, EKG results, demographic data, pulmonary tests, imaging scans and study forms.

The Information is Being Disclosed for the Following Reasons

- Review of your data for quality assurance purposes
- Publication of study results (without identifying you)
- Other research purposes such as reviewing the safety or effectiveness of the study drug and other products or therapies; conducting performance reviews of the study drug; evaluating other products or therapies for patients; developing a better understanding of disease; improving the design of future clinical trials

You May Cancel this Authorization at Any Time by Writing to the Principal Investigator

Malcolm Mattes, MD
West Virginia University School of Medicine
Department of Radiation Oncology
1 Medical Center Drive, PO Box 9234
Morgantown, WV 26506

If you cancel this authorization, any information that was collected already for this study cannot be withdrawn. Once information is disclosed, according to this authorization, the recipient may re-disclose it and then the information may no longer be protected by federal regulations.

You have a right to see and make copies of your medical records. You will not be able to see or copy your records related to the study until the sponsor has completed all work related to the study. At that time you may ask to see the study doctor's files related to your participation in the study and have the study doctor correct any information about you that is wrong.

This authorization will expire at the end of the study unless you cancel it before that time.

Voluntary Participation

Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time.

Refusal to participate or withdrawal will involve no penalty to you. Refusal to participate or withdrawal will not affect your future care, or your employee status at West Virginia University.
In the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether or not to continue your participation.

You have been given the opportunity to ask questions about the research, and you have received answers concerning areas you did not understand.

Upon signing this form, you will receive a copy.

I willingly consent to participate in this research.

Signature of Subject or Subject's Legal Representative	Printed Name	Date	Time

The participant has had the opportunity to have questions addressed. The participant willingly agrees to be in the study.

Signature of Investigator or Co-Investigator	Printed Name	Date	Time