Consent Date: Approval Period 9/12/2023-6/11/2024; Stamped effective 9/12/2023

Official Title of Study: A Phase I Trial of MR-Guided Dose-Escalated Hypofractionated Adaptive Radiation Therapy and Immunotherapy in Primary Metastatic or Very Locally Advanced Patients With Head and Neck Cancer

NCT04477759

EFFECTIVE

9/12/2023

MCW IRB

Medical College of Wisconsin
INTRODUCTION TO THE INFORMED CONSENT

IIT-AWAN-NIH-DEHART: A Phase I Study of MR-Guided Dose-Escalated Hypofractionated Adaptive Radiation Therapy and Immunotherapy in Primary Metastatic or Very Locally Advanced Patients with Head and Neck Cancer

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Definitions

Magnetic Resonance-guided Radiation Therapy (MRgRT) – a new way of administering radiation therapy by using MRI scans to determine how your cancer is changing throughout your treatment. It is considered investigational in this study because it has not been approved by the FDA for treatment of your type of cancer.

Hypofractionated – radiation therapy that is given in a smaller number of fractions (visits) but with a higher dose of radiation compared to standard radiation therapy.

Atezolizumab – an immunotherapy drug administered with radiation therapy. Atezolizumab is considered investigational in this study because it has not been approved by the FDA for treatment of your type of cancer.

Dynamic Contract Enhancement (DCE) MRI – imaging that allows your study doctor to see greater detail about your tumor, including the blood vessels going into and out of your tumor. Researchers believe that blood vessels surrounding a tumor help feed a tumor to allow it to survive and grow.

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Purpose

This project is being done to test an experimental treatment for your HNSCC. This study will use a new way of administering radiation therapy for HNSCC called Magnetic Resonance-guided Radiation Therapy (MRgRT).

Length

You will be in this research project for about 14 months, from the time of Screening through Follow-up visits.

Procedures

All subjects in this study will receive the same treatment: MRgRT combined with Atezolizumab immunotherapy. You will receive radiation therapy over 15 visits, given 5 days a week for 3 weeks.

List of visits:

- Screening Visit(s)
  - Total Number: approx. 1-3
  - Total Time: approx. 6-10 hours
- Pre-Treatment Visits
  - Total Number: approx. 1-2
  - Total Time: approx. 4-8 hours
- Treatment Visits
  - Total Number: 15
  - Total Time: approx. 4-6 hours each
- Follow-up Visits
  - Total Number: approx. 20-25
  - Total Time: approx. 2-4 hours each

Procedures that will occur at various visits:

Invasive Procedures

- Blood collection for routine laboratory tests and pregnancy test
- Atezolizumab administration, via IV infusion

Non-invasive Procedures

- Radiation therapy
- Physical exam and vital signs
- Performance assessment
- Tumor assessments by PET/CT and MRI
- Questionnaires

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

Radiation Therapy risks:

- Dry mouth
- Loss of taste buds
- Thick saliva
- A skin burn that looks like a sunburn
- Fatigue
- Pain requiring numbing or pain medicine
- Unable to eat requiring a feeding tube
- IV fluids for dehydration
- Scar tissue in neck
- Difficulty opening your mouth
- Swallowing difficulty with big bites and dry food
- HSV1/HSV2 reactivation (oral soreness, blisters, rash)

Atezolizumab risks:

- Fatigue
- Joint pain (arthralgia)
- Lack of energy (asthenia)
- Decreased appetite
- Diarrhea
- Shortness of breath (dyspnea)
- Urinary tract infection
- Cough
- Itching of the skin
- Nausea
- Fever
- Rash
- Vomiting
- Muscle and bone pain
- HSV1/HSV2 reactivation (oral soreness, blisters, rash)

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

1. Joining a different project
2. Routine care for this condition
3. Getting no treatment for this condition

If you have more questions about this project at any time, you can call Musaddiq Awan, MD at 414-805-6700.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research because you have head and neck squamous cell carcinoma (HNSCC).

A total of about 18 people are expected to participate in this research the Medical College of Wisconsin/Froedtert Hospital.

The Director of the project is Musaddiq Awan, MD in the Department of Radiation Oncology. A research team works with Dr. Awan. You can ask who these people are.

This project is funded by a grant from the National Institutes of Health (NIH).

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you do not agree to join, or if you leave, you will not be penalized or lose any benefits that you had before starting the research project. Even if you join this project, you do not have to stay in it. You may stop at any time. Take as much time as you need to make your choice.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

The purpose of this study is to test an experimental treatment for your HNSCC. This study will use a new way of administering radiation therapy for HNSCC called Magnetic Resonance-guided Radiation Therapy (MRgRT), MRgRT uses weekly MRI scans to track how your cancer changes over the course of treatment. This makes it possible to increase the dose of radiation given to specific areas that need it while reducing the dose of radiation given to specific areas where the tumor is getting smaller. Subjects in this study will also receive the immunotherapy drug Atezolizumab after radiation therapy. Researchers hope that this treatment plan will result in better outcomes and fewer adverse effects compared to standard radiation therapy. This treatment is investigational, meaning it has not been approved by the FDA for the treatment of your cancer.

We don’t know if this study will help you. Your condition may get better but it could stay the same or even get worse. We hope the information from this study will help us develop better treatments for head and neck cancer.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

STUDY TREATMENTS

All subjects in this study will receive the same treatment: MRgRT combined with Atezolizumab immunotherapy.

The radiation therapy will be hypofractionated. This means it will be given in a smaller number of fractions (visits) but with a higher dose of radiation compared to standard radiation therapy. If you participate in this study, you will receive radiation therapy over 15 visits. This will be given 5 days a week for 3 weeks. You will receive a total radiation dose of 50 Gy, 55 Gy, or 60 Gy over the course of treatment, depending on the recommended dosing at the time of your enrollment.

Atezolizumab will be given as an IV infusion over 1 hour for the first dose. You will be monitored during the infusion. A reaction to the infusion is uncommon. However, you should let the infusion staff know if you experience chills, itching, shortness of breath, swelling of your face/lips, or feel like you may pass out. If any of these symptoms occur, you may be given medications, and the infusion may be stopped or slowed until side effects resolve. If you do not experience side effects with your first infusion, subsequent infusions of Atezolizumab may be given over 30 minutes.

The first dose of Atezolizumab will be administered after your radiation therapy. You will receive Atezolizumab every 4-5 weeks. You will be able to receive up to 12 doses of Atezolizumab over the course of 1 year.

STUDY VISITS

The study is divided into 4 periods: Screening, Pre-Treatment, Radiation Therapy Treatment, and Follow-up.

Screening
After you sign the informed consent form, you will have visits with both a radiation oncologist and a medical oncologist. Both doctors will assess your disease, ask you some questions about your health and medications you are taking, and run some tests to determine if you are eligible. If some of the tests were completed recently, they may not have to be repeated for the study. The Screening period will last up to 30 days.

Pre-Treatment
You will have a few preparatory visits that are standard for patients who receive head and neck radiation therapy. Your radiation oncologist will acquire practice MRI images that will help plan where your radiation treatment is delivered. These Pre-Treatment period also include a visit with a speech and language pathologist.

Radiation Therapy Treatment
Your radiation therapy and Atezolizumab treatment will be administered as described above. Your study doctors will monitor your health during these visits. If you experience any adverse reactions to either of the treatments, your treatment plan may be modified or you may be given additional premedications. At the beginning of each week, your radiation therapy plan may be adjusted to account for how your cancer is responding to your treatment.

Follow-Up
The Follow-up period will begin after your radiation therapy is completed and will last up to 1 year. You will continue to come to the clinic for Atezolizumab immunotherapy during this period of the study. Your study doctors will monitor how your cancer continues to respond to treatment.

Follow-up visits take place weekly for the first month after you complete radiation therapy. Then visits will be at 3, 6, 9, and 12 months after the end of your radiation therapy.

STUDY ASSESSMENTS

Screening

You will need to have all or some of the following exams, tests, or procedures to find out if you can be in the study. They may be done even if you do not join the study. If some of the tests were completed recently, they may not have to be repeated.

- Informed consent: Prior to any study-related procedures being performed, you will be required to voluntarily sign and date this consent form.
- Medical history: You will be asked about if you experienced any changes in your health status.
- Medications: You will be asked about any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements.
- Physical examination: You will receive a complete physical examination, including weight and height.
- Vital signs: Your blood pressure, temperature, and heart rate will be checked.
- Blood tests: Blood samples will be collected for:
    - Blood cell counts, blood chemistry, clotting ability, and organ function
    - Pregnancy, if you are a female patient capable of having children
    - For HIV and Hepatitis B infections

      As part of the screening procedures, your blood will be tested for diseases that can be passed on to other people by transfusion, including AIDS (the disease caused by the HIV virus) and Hepatitis B. If certain tests are positive, we will inform you and inform certain government health agencies as required by law. Results of your blood test will be released only to authorized persons as governed by Wisconsin law. A list of persons to be notified and reasons that will cause release of your blood test is available upon request. Results of the blood test will be released to the study team.
- Performance status: An assessment of your overall health and ability to perform daily tasks
- Tumor assessment by CT or PET/CT scan

Pre-Treatment

The following assessments or activities will be performed during the Pre-Treatment visits.

- Medical history: You will be asked about if you experienced any changes in your health status.
- Medications: You will be asked about any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements.

- Radiation planning: Your radiation oncologist will run simulation MRI images in order to plan your treatment.
- Speech and language pathologist visit: A speech and language pathologist will perform a number of baseline evaluations about your speech and your ability to swallow food.
- Questionnaires: You will be asked to complete baseline questionnaires about your overall health and wellbeing. These are MDASI-HN, MDADI, and EAT-10.

Radiation Therapy Treatment

The following assessments or activities will be performed during the Radiation Therapy Treatment visits.

- Medical history: You will be asked about if you experienced any changes in your health status.
- Medications: You will be asked about any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements.
- Physical examination: You will receive a complete physical examination, including weight and height.
- Vital signs: Your blood pressure, temperature, and heart rate will be checked.
- Radiation therapy: You will receive 15 radiation therapy fractions, given 5 days a week for 3 weeks.
- Questionnaires: You will be asked to complete questionnaires about your overall health and wellbeing. These are MDASI-HN, MDADI, and EAT-10.

Follow-up

The following assessments or activities will be performed during the Follow-up period. Not all assessments will be performed at every Follow-up visit.

- Medical history: You will be asked about if you experienced any changes in your health status.
- Medications: You will be asked about any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements.
- Physical examination: You will receive a complete physical examination, including weight and height.
- Vital signs: Your blood pressure, temperature, and heart rate will be checked.
- Atezolizumab treatment: You will receive Atezolizumab immunotherapy every 4-5 weeks for up to 1 year from the beginning of your radiation therapy.
- Vital signs: Your blood pressure, temperature, and heart rate will be checked.
- Blood tests: On days you receive Atezolizumab, blood samples will be collected for:
    - Blood cell counts, blood chemistry, and organ function

- Speech and language pathologist visit: At the visits 3 and 6 months after radiation therapy, a speech and language pathologist will perform a number of evaluations about your speech and your ability to swallow food.
- Questionnaires: You will be asked to complete questionnaires about your overall health and wellbeing. These are MDASI-HN, MDADI, and EAT-10.
- Imaging assessments: You will have a PET/CT and MRI of the head and neck at the visit at 3 months after radiation therapy.

CONSENT FOR ADDITIONAL OPTIONAL PROCEDURES

If you agree, we would like to obtain your consent to perform additional procedures. You do not need to provide consent to these additional procedures to participate in the study.

We would like to perform Dynamic Contract Enhancement MRI (DCE) MRI imaging on the day of fractions 5, 10, and 15 of radiation therapy. DCE MRI imaging allows your study doctor to see greater detail about your tumor, including the blood vessels going into and out of your tumor. Researchers believe that blood vessels surrounding a tumor help feed a tumor to allow it to survive and grow. This DCE MRI imaging would requirement IV placement and injection of gadolinium contrast.

MRI (Magnetic Resonance Imaging) is a way for us to see inside your body. MRI uses a powerful magnet, radio waves and a computer to produce detailed pictures of organs, bones and other internal body structures. For the MRI, you will lie on a table inside a scanner tube for about 30 minutes, while the scanner moves the reading unit over the areas of your body to be scanned.

A liquid containing a gadolinium contrast “dye” will be injected into your vein. This increases the ability of the MRI scan to show certain tissues in the brain or elsewhere in the body.

We would also like to collect tumor tissue samples by research only biopsies. These would occur on the day of your simulation imaging to plan your radiation therapy treatment and on the days of Radiation Therapy Treatment fractions 5 and 15.

In this project, we will do genetic testing on your tumor tissue biospecimens. This will be collected at the visits listed in the “CONSENT FOR ADDITIONAL OPTIONAL PROCEDURES” heading above. Genetic testing will be done because sponsor would like to understand the response of biomarkers to study drug treatment and to understand how the study drugs and underlying disease works.

This genetic testing is for research only. The purpose is not to discover information that could be used to change your medical care, make or change your diagnosis, or advise you on your risk of diseases.

The biospecimens collected for this part of the project will be coded, which means they will be labeled with numbers and/or letters instead of information that could identify you. Only the research team will be able to link the code to you. The sample will also be labeled with date of collection, which could potentially be used to identify you. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized

person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you.

It is against federal law (Genetic Information Nondiscrimination Act, or GINA) for health insurance companies to deny health insurance, or large employers to deny jobs, based on your genetic information. But the same law does not protect your ability to get disability, life, or long-term care insurance.

You will not be given your genetic test results.

Please indicate below if you are willing to undergo DCE MRI imaging and additional tumor biopsies as described above. If you are not willing to agree to this, you are still able to participate in the study.

_____ (Initials) YES, I willingly agree to undergo DCE MRI imaging and additional tumor biopsies as described above.

_____ (Initials) NO, I do NOT agree to undergo DCE MRI imaging and additional tumor biopsies as described above.

B2. HOW LONG WILL I BE IN THE PROJECT?

From the Screening to Follow-up visits, you will be in this research project for about 14 months.

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time, including during the MRI scans. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.

The research doctor can tell you about the effects of stopping, and you and the research doctor can talk about what follow-up care would help you the most.

You might be asked to come back for one more visit to check your health.

The research doctor may take you out of this project at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

B4. ARE THERE ANY SPECIAL INSTRUCTIONS WHILE I AM IN THE PROJECT?

You should not breastfeed a baby while you are receiving Atezolizumab treatment.

You should discuss with your study doctor before you receive any vaccines, including a COVID-19 vaccine. Some types of vaccines are not allowed during the study. Your doctor can tell you which these are.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that you may get an intervention that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from the intervention itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.** In an emergency, call 911.

C2. RISKS OF THE INTERVENTION

The research intervention itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.

RADIATION RISKS

Risks and side effects related to the radiation include those which are:

Likely (20% or greater of the time):

- Dry mouth
- Loss of taste buds
- Thick saliva
- A skin burn that looks like a sunburn
- Fatigue
- Pain requiring numbing or pain medicine

Less Likely (occurs 10-20% of the time):

- Unable to eat requiring a feeding tube
- IV fluids for dehydration
- Scar tissue in neck
- Difficulty opening your mouth
- Swallowing difficulty with big bites and dry food
- HSV1/HSV2 reactivation (oral soreness, blisters, rash)

Rare but serious (2-10% of the time):

- Bleeding or Carotid blowout – leaky blood vessel in your neck that can bleed. A carotid blowout can be fatal.
- Infection
- Non-healing wound
- Mandible necrosis – the jaw bone gets weak or fractures
- Teeth damage/loss
- Permanent feeding tube
- Permanent breathing tube
- Death
- Radiation induced cancer

In addition to radiation therapy you may receive additional radiation from diagnostic procedures to evaluate your condition. The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. However, the additional risk of radiation-induced cancer from these diagnostic procedures is low compared to the risks from the radiation therapy.

ATEZOLIZUMAB RISKS

Atezolizumab is designed to increase the number of immune system cells in your body that can fight cancer. These cells may cause inflammation within the tumor, as well as in normal tissue. Therefore, by taking Atezolizumab, you may develop a condition where there is inflammation against a part of your own body (an autoimmune condition).

SIDE EFFECTS KNOWN TO BE ASSOCIATED WITH ATEZOLIZUMAB

The side effects associated with Atezolizumab are listed below. There may be side effects that are not known at this time.

Side Effects Known to Be Associated with Atezolizumab		
Very common (occurs in more than 10% of patients)	• Fatigue • Joint pain (arthralgia) • Lack of energy (asthenia) • Decreased appetite • Diarrhea • Shortness of breath (dyspnea) • Urinary tract infection • Cough • Back pain	• Itching of the skin (pruritis) • Nausea • Fever • Rash • Vomiting • Muscle and bone pain (myalgia, musculoskeletal pain and bone pain) • Headache • HSV1/HSV2 reactivation (oral soreness, blisters, rash)
Common (occurs in 1%–10% of patients)	• Chills • Difficulty swallowing (dysphagia) • Increase in liver enzymes, which may indicate inflammation of the liver • Allergic reaction or intolerance to medication (hypersensitivity) • Decreased level of potassium in blood (hypokalemia) • Decreased level of sodium in blood (hyponatremia) • Low blood pressure (hypotension) • Underactive thyroid gland (hypothyroidism)	• Inflammation of the intestines (colitis) • Decreased oxygen supply in body resulting in shortness of breath (hypoxia) • Influenza-like symptoms • Infusion-related reaction • Inflammation of the lungs (pneumonitis) • Low platelet count in the blood, which may make you more likely to bruise or bleed (thrombocytopenia) • Inflammation of the liver (hepatitis)

	• Inflammation of the throat and nasal cavities (nasopharyngitis) • Dry skin • Increased blood sugar level (hyperglycemia) • Pain at the back of the throat (oropharyngeal pain)	• Stomach area pain (abdominal pain) • Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine • Immune mediated pericardial disorders may occur. Pericarditis (inflammation of the lining of the heart) may be associated with pericardial effusion (fluid in the lining of the heart), which may progress to cardiac tamponade. Cardiac tamponade puts pressure on the heart and keeps it from filling properly. Symptoms include low blood pressure, shortness of breath, and lightheadedness. If your blood pressure drops too low, cardiac tamponade can be fatal.
Less common but important (occurs in less than 1% of patients)	• Decreased production of hormones by the adrenal glands (adrenal insufficiency) • Diabetes • Overactive thyroid gland (hyperthyroidism) • Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis) • Inflammation of the pituitary gland (hypophysitis) • Inflammation of the heart muscle (myocarditis) or membrane surrounding the heart (pericarditis) • Inflammation of the kidneys (nephritis) • Severe skin or mucosal reactions (severe cutaneous adverse reactions including Stevens-Johnson syndrome and Toxic epidermal necrolysis) • Facial paresis, inability to move the muscles of the face • Myelitis. Inflammation of the spinal cord	• Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome) • Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis) • Inflammation of the pancreas (pancreatitis), including increase in pancreatic enzymes (such as amylase and lipase) • Severe high levels of sugar and acids in the blood or urine (diabetic ketoacidosis) • Inflammation or damage of the muscles (myositis) • Severe immune reactions affecting white blood cell activation causing an overactive immune response including cytokine release syndrome, hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) • Hemophagocytic lymphohistiocytosis, a rare but potentially fatal condition in which certain white blood cells

		(histiocytes and lymphocytes) build up in and damage organs, including the bone marrow, liver, and spleen, and destroy other blood cells

Among the side effects known to be associated with Atezolizumab, Roche and your study doctors would like you to pay more attention to the following:

- Inflammation of the intestines (colitis); symptoms may include diarrhea, blood in stool, and pain in stomach area
- Inflammation of the thyroid glands (hypothyroidism, hyperthyroidism); symptoms may include headaches, fatigue, weight loss, weight gain, change in mood, hair loss, and constipation
- Inflammation of the adrenal glands (adrenal insufficiency); symptoms may include dizziness, irritability, fainting, low blood pressure, skin darkening, and craving of salty foods
- Inflammation of the pituitary gland (hypophysitis); symptoms may include fatigue and headaches that will not go away, increased thirst, increased urination, and changes in vision

  Side effects that may occur at the same time include hypothyroidism and adrenal insufficiency (see above for details).
- Inflammation of the liver (hepatitis); symptoms may include yellowing of skin, pain in stomach area, nausea, vomiting, itching, fatigue, bleeding or bruising under the skin, and dark urine
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis); symptoms may include neck stiffness, headache, fever, chills, vomiting, seizure, irritability, and eye sensitivity to light
- Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis); symptoms may include weakness in the arm and leg muscles, double vision, and difficulties with speech and chewing
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome); symptoms may include tingling in fingers and toes, fatigue, and difficulty walking
- Inflammation of the lungs (pneumonitis); symptoms may include new or worsening cough, shortness of breath, and chest pain
- Inflammation of the heart muscle (myocarditis); symptoms may include shortness of breath, decreased exercise tolerance, fatigue, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
- Reactions associated with infusion (events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, and sudden reddening of the face, neck, or chest

- Inflammation of the pancreas (pancreatitis); symptoms may include abdominal pain, nausea, vomiting, and fever
- Condition of high levels of sugar in the blood (diabetes mellitus); symptoms may include increased thirst, increased hunger, frequent urination, irritability, and fatigue
- Inflammation of the kidneys (nephritis); symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
- Inflammation or damage of the muscles (myositis, myopathies including rhabdomyolysis); symptoms may include muscle pain and weakness, urine with a dark brown or reddish color, nausea, and vomiting
- Severe skin or mucosal reactions (severe cutaneous adverse reactions); symptoms may include itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area

Allergic Reactions

Allergic reactions may occur with Atezolizumab and typically occur while it is being given into your vein or shortly after it has been given. Symptoms could include nausea, vomiting, skin reactions (hives or rash), difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability. If you experience any of these symptoms, your study doctor will interrupt, or even stop, the delivery of Atezolizumab into your vein. Your study doctor may also give you some drugs to treat these symptoms.

SIDE EFFECTS POTENTIALLY ASSOCIATED WITH ATEZOLIZUMAB

The following are side effects that may be associated with Atezolizumab:

- Development of special antibodies to Atezolizumab (proteins made in the body that respond to a substance that is foreign to the body) by your immune system

  If you develop these special antibodies, it may affect your body's ability to respond to Atezolizumab in the future. Blood samples will be drawn to monitor for the development of these antibodies during study treatment and at your treatment discontinuation visit.
- Potential to cause harm to a developing fetus
- Inflammation of the eye (uveitis); symptoms may include eye pain and redness, vision problems, and blurry vision
- Inflammation of the blood vessels that can lead to damage of different organs (vasculitis); symptoms may include fever, fatigue, weight loss, weakness, general aches and pains, rash, headache, lightheadedness, shortness of breath, and numbness
- Breakdown of red blood cells (autoimmune hemolytic anemia); symptoms may include fatigue, fever, lightheadedness, paleness of the skin, yellowing of the skin and/or eyes, weakness, and inability to do physical activity

IMMUNE REACTION

In rare situations, an immune reaction can occur with administration of Atezolizumab. This reaction can cause side effects related to severe inflammation and/or severe infection. Several

organs in your body (for example liver, kidney, lungs, and bone marrow) may become involved, causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Symptoms may include very low blood pressure that does not respond to standard treatment, very high fever, cough, severe shortness of breath requiring oxygen therapy and/or intubation, severe dizziness, confusion, weakness, decreased urination with failure of the kidneys, abnormal liver function, very low blood cell counts, and/or bleeding within the organs.

If you experience any of these symptoms, you should notify your doctor immediately, as you may need immediate treatment and hospitalization. Your study doctor may give you drugs to treat these symptoms.

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Other procedures that are part of the research also involve some risks:

Blood collection
Blood collection may cause some discomfort, bleeding or bruising at the puncture site. A small blood crust or swelling may occur at this site. In rare cases, fainting or local infection may occur. If you feel discomfort during blood collection, please report this to the study doctor or staff at the time.

PET/CT
The risks with a PET/CT scan include:

- Exposure to radiation. The amount of radiation from one PET/CT scan will depend on the area of the body being scanned but is generally about equal to 10 years of background radiation (the amount that you would be exposed to from sunlight and other sources in your everyday life).
- Possible allergic reaction to the contrast dye used to help doctors see the different organs and your cancer better. These scans may involve dyes being injected into one of your veins. There is a risk of allergic reaction to the dye. This reaction may be mild (such as a skin rash or hives) to severe (such as breathing difficulties and shock). There is a risk that the injection of dyes may cause:
    - Pain
    - Swelling
    - Bruising
    - Irritation, or redness at the injection site
    - Feeling faint
    - Infection (rare)

Your study doctor may take steps to prevent these risks from happening. He or she may recommend medications that may help with these side effects. You may be asked to sign a separate consent form for these procedures.

Magnetic Resonance Imaging
MRI scans use a very powerful magnet to stimulate atoms in a person's body. Those atoms will be detected by the scanner to produce an image of the scanned body. Any ferromagnetic metal implant may be displaced or overheat, if you have any such implant you should not have the MRI scans. In addition, you need to lie still in the small half-enclosed space of the machine for a long period of time (30 to 40 minutes) during the MRI, which may make you uncomfortable.

There is no exposure to x-rays or radioactivity during an MRI (Magnetic Resonance Imaging) scan, and the risk of injury is very low. However, MRI is not safe for everyone. Serious injury or death can result if you go into the scanner with certain metal objects in or attached to your body. For example, it is not safe to have an MRI scan if you have a cardiac pacemaker, defibrillator, certain metal or implants in your body or have metal in or near your eye.

The MRI scanner makes loud banging sounds that can cause hearing damage, but with earplugs properly worn, there is no known risk of permanent hearing damage. Rarely, your hearing may be less sensitive for several days after an MRI scan, but if this happens your hearing should return to normal within a few days. Some individuals may feel hot or dizzy during the MRI scan. This varies from person to person. You may feel some discomfort because you are lying still for a long time, or because of the padding used to keep your head from moving. Some people feel anxious being in closed or narrow spaces. The scanner operator will be in constant contact with you, and if you choose, you can be taken out of the scanner quickly. Please alert staff to any concerns during the procedure.

Side effects, such as mild headache, nausea, or burning at the injection site can occur from the gadolinium contrast “dye”. Some people are allergic to gadolinium, experiencing hives and itchy eyes, or very rarely, a bee-sting type of severe allergic reaction (anaphylactic shock). Use of gadolinium may be linked to a rare but sometimes fatal condition (nephrogenic systemic fibrosis or NSF) in people with severe chronic kidney disease or acute kidney problems. Therefore, before you are given this dye for MRI, your risk factors for kidney disease will be reviewed and a blood test will be done to check for kidney disease.

In addition, there may be some unknown or unanticipated risks or discomforts in addition to those specified above because some of the procedures are relatively new and are attempts to advance medical knowledge. Every known precaution will be taken to ensure your personal safety and to minimize discomfort.

Biopsies
Risks associated with biopsies include pain, redness, swelling, bleeding, bruising, draining at the needle site, abnormal wound healing, fever, infection, and allergic reaction to the medication used to perform the biopsy procedure.

Questionnaires
The answers that you give are confidential, but there is always a risk that your answers will be read by people who should not read your personal information. You may also feel uncomfortable answering some of the questions.

Privacy and Confidentiality
Another risk may be loss of confidentiality. Every effort will be made to keep your research records confidential but we cannot guarantee it. Depending on the kind of information being collected, if your research information were accidentally seen, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the project director about whether this could apply to you.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The study team can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative,

legislative, or other proceedings, for example, if there is a court subpoena. The study team will use the Certificate to resist any demands for information that would identify you.

The Certificate cannot be used to resist a demand for information from personnel of the United States federal or state government agency sponsoring the project and that will be used for auditing or program evaluation of agency funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

C4. REPRODUCTIVE RISKS

Risks to subjects who could become pregnant
We do not know if the study drug causes harm to a baby, so we do not want anyone who might be pregnant to enter the project.

You should not become pregnant or nurse a baby while in this project. You must tell the research doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the project.

You may not donate eggs during your participation in the project or for 5 months after stopping the study drugs.

Risks to a subject's partner(s)
If you and your partner(s) are able to become pregnant, one or both of you must use some form of effective birth control, because it is unknown if the study drug could affect a baby. You must tell the research doctor right away if you think your partner is pregnant.

You may not donate sperm during your participation in the project or for 5 months after stopping the study drug.

Birth control methods for all subjects
Check with the research doctor about the birth control methods needed for this project and how long to use them. Some methods might not be good enough for this project. If you are having sex that could lead to pregnancy, you should use two forms of highly effective birth control while you are in this project.

This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy/tubal ligation or vasectomy)
- Limiting sexual activity to a partner who has undergone surgical sterilization
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam

- Use of diaphragm with condoms ("double barrier")

You should continue using birth control for 5 months after stopping the study drug.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

We don't know if this study will help you. Your condition may get better but it could stay the same or even get worse. We hope the information from this study will help us develop better treatments for head and neck cancer.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Most of the medical care that you will receive in this project is considered routine care for your condition and would be recommended whether or not you join the project. Costs for routine care will be billed to you or your insurance carrier. For routine clinical care, you will be responsible for paying any copayment, coinsurance, or deductible that is required by your insurance carrier.

Activities / costs that are part of the project will not be billed to you or your insurance company. These are:

- Atezolizumab supply
- Blood tests for
    - Thyroid function (TSH)
    - Clotting (PT/INR)
    - HIV and Hepatitis B testing
- Costs associated with the videofluoroscopic swallow studies, part of the speech and language pathologist visits
- Collection, processing, and analysis of research specimens (tissue)
- Contrast agent associated with DCE MRI scans

Some insurers will not pay for drugs, tests or hospitalization that are part of research, so check with your insurer before you join this project. If you have questions regarding costs, please contact Dr. Awan.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this project.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.

Your other choices may include:

- Routine care for NSCC
- Joining a different research project

- The procedure or drug offered to you may also be available without being in any research project.

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information about the intervention that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information: Musaddiq Awan, MD, 414-805-6700

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Musaddiq Awan, MD at 414-805-6700.
- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); Versiti, Inc.; Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate- Froedtert Hospital (FH), Inc.; Froedtert Menomonee Falls Hospital; Froedtert West Bend Hospital; Froedtert & The

Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- Past and present medical records
- Records about your study visits and results of tests done during the study
- Records about phone calls made as part of this research
- Research records

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.
If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

The research team may share your information with people who don't work at MCW/Froedtert Hospital. because they planned, pay for, or work with us on this project. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this project, we plan to share information with those doctors, researchers or government representatives working with us on this project at the institutions or companies listed here:

- Florence Healthcare, Inc.
- The pharmaceutical company providing study drug, Genentech, and its research partners;
- Government agencies in the U.S., such as the Food and Drug Administration (FDA), National Cancer Institute (NCI), and National Institutes of Health (NIH);
- Other federal and state agencies, such as the Office of Human Research Protections, (OHRP);
- Others required by law

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information and/or biospecimens, the information and/or biospecimens may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results

of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to Musaddiq Awan, MD at

Department of Radiation Oncology
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee WI 53226

The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we will decide that you cannot continue to be part of the project. We may still use the information we have already collected.

E6. Access to records

You may not be able to see, or copy, your project-related health information until after the project has been completed; otherwise, it could affect the study.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can look up this project by referring to the ClinicalTrials.gov number (NCT04477759) or by asking the research team for a printed copy.

CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Witness, if applicable *please print*	**Signature of Witness**	**Date**
Rationale for Use of Witness ☐ Subject has limited/no literacy ☐ Subject has limited English proficiency ☐ Subject has limited/no vision	☐ Sponsor requirement ☐ Other _____	
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the research team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. The Principal Investigator is responsible and accountable for the research project.*