Quarterback 22: A Phase II Clinical Trial of Sequential Therapy and De-Intensified Chemoradiotherapy for Locally Advanced HPV Positive Oropharynx Cancer
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STUDY INFORMATION:

Study Title: Quarterback 2b: A Phase II Clinical Trial of Sequential Therapy and De-Intensified Chemoradiotherapy for Locally Advanced HPV Positive Oropharynx Cancer

Study site(s): Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital

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SUMMARY OF THIS RESEARCH STUDY:

This document explains a research study you might be interested in joining. Participation in the study is voluntary. You can agree to join or not. Your decision will not limit your ability to receive care at Mount Sinai. You should only agree to take part if you understand the study and if all of your questions about the research study are answered. If you do join the study, the research team must share any new information with you that may change your mind about taking part.

The purpose of this research study is to establish whether a lower dose radiation therapy is as effective compared to the higher standard dose in study participants with locally advanced HPV+ oropharynx cancer. Oropharynx cancer caused by Human Papilloma Virus or HPVOPC accounts for 60% of oropharynx cancer cases in United States. HPVOPC has better prognosis than participants with HPV negative oropharynx cancer. Even though the survival rate has increased because of chemoradiation therapy (CRT), the long term side effects of radiation therapy are still problematic. In this trial by establishing the efficacy and toxicity of reduced dose of radiotherapy after using chemotherapy as initial treatment for cancer (induction chemotherapy), and comparing it to historical results we can reduce the long term consequences and preserve the high survival rates.

If you choose to take part, you will be asked to attend study visits, perform health tests and take medications as instructed. The study doctor will explain which procedures are being done for research, and which would be done as part of your standard care.

If you choose to take part, the main risks to you are further hearing loss, dry mouth, mouth inflammation and sores and increased susceptibility to yeast infections.

You may benefit from taking part in this research. Some potential benefits may be that by receiving reduced dose of radiation therapy you may experience fewer long term side effects of the therapy compared to standard dose.

Instead of taking part in this research, you may check with your study doctor about the other options to treat your disease.

If you are interested in learning more about this study, please continue to read below.

STUDY PARTICIPATION:

You may qualify to take part in this research study because [you have a squamous (the kind of tissues the cancer develops from) cancer of the oropharynx (tonsil and base of tongue), larynx, nasopharynx, hypopharynx or nasal cavity, or unknown primary; your tumor is found to have HPV in it (HPV+) and has a marker that HPV has caused your cancer (p16+); you have a limited smoking history, and have reasonably good physical health. You also have not had prior chemotherapy or radiation therapy and have not had definitive surgery for your cancer.

Your participation in this research study is expected to last for 3 cycles (each cycle is 21 days) in the induction phase of the study during which time you will receive chemotherapy. If the study doctor determines you have a measurable response then you will continue your participation in this study for an additional 6-7 weeks if the study doctor believes this is in your best interest. You will be followed for up to10 years after completion of study treatment.

There are 65 people expected to take part in this research study at Mount Sinai.

Funds for conducting this research study are provided by Mount Sinai.

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

DESCRIPTION OF WHAT IS INVOLVED:

If you agree to take part in this research study, here is what may be involved:

Before the research starts (screening): After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these

tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures done recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, previous surgery/ treatment, current medications, smoking history and any allergies.
- **European Organization for Research and Treatment of Cancer Core (EORTC) Performance status**, which includes completing questionnaire that will evaluate how you are able to carry on with your usual activities.
- **M.D. Anderson Symptom Inventory-Head and Neck (MDASI-HN),** these questionnaires provide brief measure of symptom distress you experience as a result of your disease or treatment.
- **Xerostomia/Dysphagia assessment questionnaire-** which includes completing a questionnaire that will evaluate your swallowing ability of food with different consistencies.
- **Physical exam,** including vital signs such as blood pressure, heart rate, body temperature, weight and height.
- **Neurological exam,** which includes tests to evaluate function of brain and nervous system
- **ECG, an electrocardiogram**: where you will be asked to lie down while 12 sticky pads are affixed to each of your arms and legs and to your chest. The ECG will last about 10 minutes. An ECG records the electrical activity of the heart and is used to measure how fast and how regular the heart beats, as well as the size and position of the chambers, the presence of any damage to the heart, and the effects of drugs or devices used to regulate the heart (such as a pacemaker). An ECG is painless.
- **An assessment of your tumor** by high resolution CT (Computerized Tomography) scan or MRI (Magnetic Resonance Imaging) or PET Scan (Positive Emission Tomography). In some cases a bone scan may also be required depending on your symptoms. These are x-ray procedures that are used to define normal and abnormal structures in body and to measure the size of your cancer.
- **Clinical assessment** of the tumor will be performed by direct visualization and manual palpation
- **Assessment of any adverse events** that are present
- **Examination under anesthesia (EUA) and biopsy:** With help of a scope your doctor will examine back of your mouth and deeper parts of throat in order to assess the exact extent of disease. This is done in operating room under sedation. Along with proper biopsy, this helps in planning of treatment.
- **HPV and p16 tests-** tumor tissue will be tested for both HPV and p16 antibodies.
- **TNM staging-** with help of information from physical, laboratory, pathology, radiological and surgery reports, your doctor will determine the extent of the tumor (T), whether cancer cells have spread to nearby (regional) lymph nodes (N), and whether distant (to other parts of the body) metastasis (M) has occurred.
- **Urinalysis**: This includes physical, chemical and microscopic examination of urine to assess kidney function.

- **Blood tests:** which will include measurements of:
  - blood chemistry (tests to measure substances in the blood which tell us what is going on in your body) - approximately 2-3tsp (10-15ml) of blood is required
  - Complete blood count (tests to measure cells in blood) - approximately 1 tsp (5ml) of blood is required.
  - Including a pregnancy test if you are a woman of childbearing potential.
  - optional research studies: and additional of 9tsp (46ml) will be collected for optional research studies

If these tests show that you are eligible to participate in the research study, you will begin with induction chemotherapy or Phase 1 treatment regimen. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Induction Chemotherapy or Phase 1

You will come for your clinic visits for induction treatment every 21 days starting on days 1, 22 and 43 (± 2 days). Each initial visit will last for approximately 6-8 hours. Additional visits on days 2, 5, 23, 26, 44, and 47 will last about 2-4 hours.
You will receive Docetaxel, Cisplatin and 5-FUchemotherapy on day 1 during these 3 cycles. If possible, you will have a port-a-Cath placed prior to initiating chemotherapy so that chemotherapy may be given efficiently and completely. Port-a-Cath is a small device that is surgically placed beneath your skin and connected to a vein in your chest through a catheter. If you refuse a port or have an infection that requires removing the port then you will be treated in the inpatient setting or by placing a catheter in large vein in your arm (PICC line).

Docetaxel will be administered on Day 1 every 21 days.

- You will be asked to take dexamethasone 8 mg by mouth twice daily for 6 doses, starting the evening before chemotherapy, plus 10 mg PO or solumedrol 80 mg IV bolus 30-60mins before docetaxel, ranitidine 50 mg IV bolus (or equivalent).
- You will receive infusion of 75mg/m^2 of Docetaxel in 250ml of normal saline over an hour.

Cisplatin will be administered on Day 1 every 21 days.

- You will receive hydration with 1 liter of normal saline containing KCl (20 mEq/L) and MgSO4 (2g/L) followed by
- Furosemide given as 10mg IV bolus and then
- Cisplatin is administered as intravenous infusion over 1-3 hours.
- Mannitol is either mixed with Cisplatin or administered with post cisplatin IV fluids of 1 liter of normal saline.

Fluorouracil (5-FU) will be administered on Days 1, 2, 3 and 4 of Cycles 1, 2 and 3 (every 21 days) (± 2 days) as continuous 24 hour intravenous infusion.

Carboplatin will be administered on Day 1 every 21 days (only as a substitute for Cisplatin)

- You will receive carboplatin as intravenous infusion mixed in normal saline or D5W over 30-45 minutes
- Prehydration is not required

You will be asked to return on Day 2 and Day 5 of each cycle for hydration and on Day 5 you will have the 5-FU infusion disconnected.

- **History and Physical Exam including neurological exam** will be performed the first day of each cycle. You will be asked questions about your general health and specific questions about any problems you may be experiencing and medications you are taking.
- **Blood Tests** including Hematology and chemistry will be performed. Hematology will be performed on Day 1 of each dose and during week 2. Chemistry will be done on Day 1 of each dose and Day 1 and Day 5 of each cycle.
- **Examination under Anesthesia (EUA) -** will be done if necessary to confirm if the tumor had responded by shrinking after completion of chemotherapy (cycle 3, day 21-35).
- **Nasopharyngoscopy/Laryngoscopy:** if no EUA, this test will be done at the end of Cycle 3 and if necessary after Cycle 2. This is routinely done in the clinic with the use of fiber optic scope to visualize airway
- **Clinical assessment** will be performed by direct visualization and manual palpation
- **Assessment of any adverse events** that may have occurred.
- **Questionnaires (EORTC, MDAASI-HN, Xerostomia/Dsyphagia)** will be done on Day 1 of Cycle 1 if not done at screening.
- **Radiological assessment** including CT/MRI of the neck and PET/CT scans will be performed at Week 9, Week 10, or at the completion of Cycle 3.

Chemoradiation Therapy (CRT) or Phase 2:

After three cycles, you will be assessed for clinical, radiographic, and pathologic response to induction chemotherapy before beginning chemoradiation therapy (CRT) or surgery. Participants not completing three cycles of induction chemotherapy for reasons of toxicity, progressive disease, choice, or other medical necessity will be assessed for response and treated with standard Chemoradiation therapy or surgery depending on their primary site and overall medical condition.

If you show response you will be enrolled in phase 2 of the study where you will receive a reduced dose of radiation therapy with weekly Carboplatin. This phase will last for 6 cycles where each cycle will last for 1 week. Your total radiation treatment will consist of 28 treatments and you will receive carboplatin once per week for 6 weeks. Radiation therapy will be administered using a standard Photon Beam (IMRT) or standard Proton Beam (IMPT) technique based on a benefits assessment by the radiation oncologist and insurance approval.

Carboplatin will be administered weekly

- You will receive carboplatin as an intravenous infusion mixed in normal saline or D5W over 30-45 minutes

- Prehydration is not required

Radiation Therapy will be administered 5 days a week with the reduced dose (56 Gy).

- **History and Physical Exam including neurological exam** will be performed weekly where you will be asked questions about your general health and specific questions about any problems you may be experiencing.
- **Blood Tests** including hematology and chemistry will be performed weekly.
- **Xerostomia and Dysphagia assessment questionnaires** will be performed at the beginning and end of CRT.
- **EORTC questionnaires** at the beginning and end of CRT.
- **MDASI-HN questionnaires** at the beginning and end of CRT.
- **Assessment of any adverse events** that may have occurred will be performed at every study visit until resolved or stable will be done weekly.

Reassessment evaluation will take place between 8-16 weeks at the completion of the chemotherapy. You will be assessed as follows:

- **Physical Exam including neurological exam,** will be performed.
- **Nasopharyngoscopy/Laryngoscopy**
- **Xerostomia and Dysphagia assessment questionnaires**
- **CT/MRI of the neck and PET/CT scans** will be performed at 12-16 weeks to assess complete response.
- **Blood Tests** for chemistry will be performed.
- **Optional research studies:** an additional 10 tsp (40ml) of blood for optional research studies will be collected.

Follow up Period:

You will be followed 1-2 months for the first year, every 2-3 months for the second year and then yearly for 5 years after completion of study treatment.

During this period you will have the following:

- **History** will be taken where you will be asked questions about your general health and specific questions about any problems you may be experiencing at weeks 4 and 8.
- **Blood Tests** including hematology and chemistry will be performed at weeks 4 and 8
- **Optional research studies**: an additional of 8 tsp(40ml) of blood will be collected at 3, 6 12 , 24 and 36 months
- **Radiological assessment** which includes PET scan performed at 6, 12, 24 and 36 months after therapy ends.
- **EORTC, MDASI-HN, Xerostomia, Dysphagia assessment questionnaire-** you will be asked to complete questionnaire at 3, 6, 12 and 24 months or in conjunction with follow up visits
- **Assessment of any adverse events** that may have occurred will be performed at every study visit until resolved or stable will be done weekly.

Optional Correlative Studies

In this clinical trial the researchers are investigating reduced radiation therapy in participants with HPVOPC. The purpose of optional studies are to study cancer cells in order to better understand cancer processes, to learn about interaction between cancer cells and immune system, to study distribution and patterns of health-events, health-characteristics, to identify and better understand risk factors associated with cancer, to develop predictive biomarkers(protein in blood to measure presence or severity of disease and effects of treatment) to be examined in a larger prospectively randomized trial. For these tissues, unstained slides, plasma, sera, whole blood DNA, and cells will be collected and stored in the Investigators Laboratory

Genetic Testing

Genetic testing:

Over the past few years, there has been an enormous increase in our knowledge about the important role that hereditary factors (genes) play in a number of diseases. Genes are made up of DNA, which may be found in your blood cells, plasma and tumor tissue. The researchers now have some indication of how the genetic 'makeup' of an individual and an individual's tumor may influence the reaction to a specific drug, both in terms of wanted and unwanted effects. The number of genes the researchers choose to analyze may vary from a few to a very large number of genes depending on how much knowledge is available regarding your disease and the drugs used in this study at the time of the analyses. The researchers may also choose to study the expression of your genes.

Compared to healthy tissue, the genetic material in cancer cells is often altered. The genetic changes in the tumor may influence the reaction to a drug and determine whether the treatment of a particular subject is effective.

The genetic changes in the tumor may result in an increase or decrease in gene activity. These changes can be measured by analysis of the gene products (RNA and proteins). It is possible that analysis of genes and their products may be used in the future to identify those participants that will benefit from the treatment.

In the course of this study, alterations to genes and gene products in your cancer may be analyzed. Furthermore, your heritable genetic make-up may be studied. The research team will not share any results for informational purposes. This study will not provide data involving unrelated diseases or risks to the participant and/or relatives.

If you provide your consent to take part in optional research studies, your whole blood (DNA) will be collected for genetic testing and some of your blood (plasma, serum) and tumor biopsy material will be collected for non-genetic biomarker testing (i.e., not involving DNA or RNA).

The researchers would like to ask your permission to keep specimens (like blood or tissue) collected from you during this study to use them in future research studies. They would also like to know your wishes about how they might use your specimens in future research studies. You should also know

that it is possible that products may someday be developed with the help of your specimens, and there are no plans to share any profits from such products with you.

Your samples will be stored indefinitely or until they are exhausted. The researchers will be using a unique code that does not identify you by name or address. Researchers with access to your samples will not be able to identify you. The code linking the sample to your name would be stored at Mount Sinai and known only to your doctor and a limited number of research personnel at Mount Sinai.

Pregnancy

If you can possibly get pregnant, a blood or urine test for pregnancy will be done before you begin the study.

You cannot be included in the study if you are or become pregnant, as the study involves drugs or investigational treatment that could harm your fetus. You also should not be in the study if you are producing milk to feed a child as the drugs or investigational treatment could harm your baby.

Unless you are at least one year past menopause or have had a successful operation to make pregnancy impossible, you should use effective birth control. Unless you are sexually abstinent (not having genital sex) the recommended methods of birth control are:

- The consistent use of approved hormonal birth control (pill, patches, or rings),
- An intrauterine device (IUD),
- Contraceptive injection (Depo-Provera),
- Double barrier methods (Diaphragm with spermicidal gel or condoms with contraceptive foam),
- Sexual abstinence (no sexual activity),
- Sterilization (a vasectomy, getting tubes tied, or a hysterectomy).

All birth control methods (other than abstinence and sterilization) are only effective if you use them properly, start them at least one month before you begin the research study, and continue using them throughout the research study and for one month after the research study ends. If you are unsure whether the method of birth control you use is approved to use while you are in this study, you should ask the Lead Researcher before you begin the study. If you are less than one-year post-menopausal, you could still become pregnant. If you or your partner becomes pregnant, or may be pregnant, at any time during the study, you must tell a person from the research team immediately. The team may stop the chemotherapy and refer you/your partner to an obstetrician/gynecologist for follow-up.

Should you/your partner become pregnant, whether or not you/your partner have the baby, the people funding and overseeing the research may ask for information on the pregnancy, even if you are no longer part of the study. You/your partner will be asked for additional written consent to share this information if that happens.

Semen/Sperm:

Drugs can be found in semen and alter sperm. Since you are taking part in a study using drugs or experimental treatments, it is recommended that 1) you use a condom, 2) you do not get a partner pregnant or expose them to semen, and 3) you do not donate semen. These recommendations apply both while you are taking the study drug, and for 3 months after you stop taking the chemotherapy. This is because levels of the chemotherapy may be present in the sperm and/or semen even after you stop taking the chemotherapy. You are encouraged to tell your female partner(s) and/or their doctor(s) that you are participating in this clinical trial.

Future Contact:

The researchers may wish to use your personal contact information to contact you in the future. Do you give the researchers permission to **contact you** in the future to request the collection of additional information about you, discuss how your private information, study data and/or samples might be used, or discuss possible participation in another research study?

Please initial your choice: Yes_____ No_____

If “Yes”, please indicate your preferred method of contact: (initial all that apply)

[ ] Email [ ] Phone [ ] Letter [ ] Text

USE OF YOUR DATA AND/OR SAMPLES:

The researchers would like your permission to keep your personal information (such as, name, address, date of birth, social security number), study data and/or samples (blood, tissue, urine, saliva, or any other body matter) to use or share in future studies. You can still be part of the study if you do not allow us to use or share them. Please select Yes or No to each of the questions below. To decline all future uses/sharing please select ‘No’ each time.

(1) Will you allow the researchers to store your data and/or samples to use in future research studies?

Please initial your choice: Yes_____ No_____

If you select No, please stop here and move to the next section, '**Your Responsibilities If You Take Part in This Research**' section below."

If yes, please continue to the next question and tell us how your personal information, study data and/or samples may be used in future research studies.

(2) The researchers can store your data and/or samples in one of two ways:

a) Anonymously (no one will know who the data and/or samples came from). If you choose this option, you can't change your mind. So, if you wanted to have your data and/or samples destroyed in the future, the team could not do it as they would not know which data and/or samples were yours.
b) Linked to your identity (using a code that can show the information came from you personally). In this case you could ask for your data and/or samples to be destroyed in the future if you want that to happen.

How would you like your data and/or samples stored? Please initial **ONE** choice below:

I would like my data and/or samples stored anonymously _____

I would like my data and/or samples stored with a link to my identity through the use of a code_____

(3) Do you give the researchers permission to keep the data and/or samples, so they could use them in future studies that are **directly related** to the purpose of the current study?

Please initial your choice: Yes_____ No_____

(4) Do you give the researchers permission to keep the data and/or samples indefinitely, so they could use them for future studies that are **not related** to the purpose of the current study (for example a different area of research)?

Please initial your choice: Yes_____ No_____

a. If the future research in a different area can be done without having to know that the data and/or samples came from you personally, that will be done.
b. If the future research in a different area requires that it is known specifically who the data and/or samples came from, then one of the following will be done:
   I. If you allowed the researchers to contact you in the future, they may be able to contact you to explain why your data and/or samples is needed and what will be done with it. Your permission will be asked to use your data and/or samples in that research project.

II. If you do not give permission to be contacted in the future, or if it is found that contacting you is not practical (for example, because you have moved), your data and/or samples may still be used. The Institutional Review Board (IRB) will be asked for permission to use the data and/or samples linked to your identity. The IRB can give permission for researchers to use and share identifiable health information without contacting you, but only if it determines that sharing the data and/or samples will not be more than minimal risk to you or your privacy. The IRB is a committee of doctors and scientists and nonscientists, including people not associated with this hospital or medical school, whose job it is to protect people who participate in research.

(5) Do you give permission to have your data and/or samples given **to other researchers,** including those at Mount Sinai, other medical or scientific institutions and for-profit companies, for use in research within the limits you have chosen above?

Please initial your choice: Yes_____ No_____

YOUR RESPONSIBILITIES IF YOU TAKE PART IN THIS RESEARCH:

If you decide to take part in this research study, you will be responsible for the following things: taking prescribed medications, and attendance at study visits. At each visit, you will be asked about any symptoms you have experienced since the previous visit. And, you will be asked to provide the names of any medication you took since the last visit– whether prescribed or bought. If you are unsure about taking a particular drug, please check with your doctor first. The research team recommend you keep a list of drugs you are taking and bring it with you to each visit. At each visit you should also let your doctor know of any changes in your health/condition including possible drug side effects. You must agree to use the type of contraception and duration of precautions approved by your study doctor for the entire time that you are taking part in the study, including for 8 weeks after you have finished taking the medication. You must inform your study doctor immediately if you think that you or your partner may be pregnant at any time while on this study. If you are nursing a baby, you should not breast feed the baby while on this study.

You must also let your doctor know immediately if there are any major changes in your health/condition between visits because your doctor may need to adjust the dosage of your medication. If you think you are having a severe allergic reaction, please seek medical attention immediately**.** If you have any concerns regarding the study, you should also contact your doctor. If you see another doctor/nurse/health care person you are encouraged to tell them you are taking part in this study and that they can contact the research team for information. If you are admitted to a hospital between study visits you must inform your study doctor as soon as possible.

COSTS OR PAYMENTS THAT MAY RESULT FROM PARTICIPATION:

There may be costs to you for taking part in this study.

You or your insurance company will be responsible for the costs of all items and services during the research study which you would have received for your condition if you were not enrolled in this research study. You or your insurance company will also be responsible for the costs of all services that occur during the research study that your physician believes are medically necessary to treat you. You or your insurance company will not be responsible for the costs of the items and services associated with this research study which are provided to you only for research purposes and not to treat your condition.

All treatments and all clinical tests including HPV testing are standard care and will be billed to your insurance or you. You will be responsible for all co-payments. Some research blood tests and any research done on your samples will not be billed to you or your insurance. All study visits are part of standard of care.

It is possible that products may someday be developed with the help of your data and/or samples, and there are no plans to share any profits from such products with you.

POSSIBLE BENEFITS:

There is a chance this study may benefit you, but this is not guaranteed. Others may benefit from what researchers learn from the study. Possible benefits to you include: fewer long term side effects of the reduced dose of radiation therapy compared to standard dose.

POSSIBLE RISKS AND DISCOMFORTS:

If you have hearing impairment, the study drug may increase the risk of further hearing loss. This risk would exist regardless of your participation in this study, since the study drug is used as part of standard treatment for your condition at Mount Sinai.

Risk Associated with Reduced Radiation Therapy:

This study substitutes the standard radiotherapy dose of 7000 cGy with a reduced dose of 5600 cGy. The lower dose of radiotherapy may have an increased risk of local or regional relapse of the cancer. This is the basic question we are asking in this study.

Risk Associated with Radiation Therapy:

Radiation therapy procedure is in itself painless. However the side effects with radiation therapy can vary depending on type, dose and organs receiving radiation. These complications occur with both proton and photon based radiation therapy.

The oral complications of head and neck radiation can be divided into two groups on the basis of the usual time of their occurrence:

- Acute complications occurring during therapy
- Late complications occurring after radiation therapy has ended

Acute complications include the following:

- Inflammation and sores in the mouth and throat
- Inflammation of the saliva glands, or dry mouth
- Infections (yeast infection in the mouth)
- Taste dysfunction (loss or change of taste)
- Redness, darkness or peeling of the skin of the neck or face
- Occasionally, tissue necrosis (severe breakdown of tissue) can be seen late during therapy, but this is relatively rare.

Chronic complications include the following:

- Stiffening or thinning of the lining of the mouth and throat
- Dry mouth
- Accelerated dental cavities related to decreased saliva
- Infections (primarily yeast infection)
- Death of the soft tissue or bones
- Loss or change of taste
- Muscle or skin thickening
- Difficulty swallowing

Risks Associated with Radiological Scans and X-Rays:

You will be exposed to radiation from the CT scans and PET scans that are done in the study. In the first year of the study you will have 3 CTs of the neck (or MRIs instead if possible) and 3 or 4 PET scans. The following information will help you understand how much radiation, and the risks from the radiation.

You will have radiation-based procedures or examinations that are part of the regular care for your condition and you would have them whether or not you participate in this research. You will not be exposed to any additional radiation because you are participating in this research.

The study team will always try to use tests that involve the lowest amount of radiation exposure possible. The radiation from the tests and treatments in this study would be in addition to any radiation you might receive from other medical tests or treatments. If you are going to have any other tests or treatments that involve radiation, please inform the study team. A possible health problem seen with radiation exposure is the development of a second cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research may range from about one in 700 to about one in 300. At such

low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

We can compare this possible extra cancer risk to other risks (over a lifetime) that everyone is participant to in everyday life. For example, the chances of a person dying of cancer with no extra radiation exposure are about one in 4. The chances of dying in a car crash are about one in 82, and the chances of being killed by a car while crossing the street are about one in 730.

In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

There is a small risk with using the contrast agent that is injected into a vein during the scan. It may worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Electrocardiogram There is no pain or discomfort during an ECG; however, removing the pads may cause some irritation to your skin.

Blood draw The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw.

Pregnancy risks If you are pregnant or become pregnant, this research may hurt your baby or your pregnancy in ways that are unknown. The unknown risks could be minor or major (death) for the pregnancy. You should not become pregnant or get someone pregnant while you take part in this study. Please read the acceptable methods of birth control found under the Description of What Is Involved section of this document.

Unknown risks In addition to these risks, this research study may hurt you in ways that are not known. The unknown risks could be minor or major (death).

Group Risks - Although your name will not be given to researchers, basic information such as your race, ethnic group, and sex may be shared. This information helps researchers learn whether the factors that lead to health problems are the same in different groups of people. It is possible that such findings could one day help people of the same race, ethnic group, or sex as you. However, they could also be used to support harmful stereotypes or discrimination.

Privacy Risks - Your name and other information that could directly identify you (such as an address, date of birth, or social security number) will never be placed into a database. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you. The risk of this happening is very small, but may grow in the future. Since the database contains genetic information, a break in security may also pose a potential risk to blood relatives as well as yourself. For example, it could be used to make it harder for you (or a relative) to get or keep a job or insurance. If your private information was misused, it is possible you would experience other harms, such as stress, anxiety, stigmatization, or embarrassment from revealing information about your family relationships, ethnic heritage, or health conditions.

Insurance Risks - There is a Federal law called the Genetic Information Nondiscrimination Act (GINA). This law makes it illegal for health insurance companies, group health plans, and most employers of over 15 people to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Risk of loss of private information; this risk always exists, but there are procedures in place to minimize the risk.

OTHER OPTIONS TO CONSIDER:

You may decide not to take part in this research study. If you decide not to take part, this will not affect the clinical care you receive at Mount Sinai. The choice is totally up to you.

Instead of being in this research study, your choices may include:

- Having treatment or care for your cancer without being in a research study. Receiving high dose radiation therapy with or without chemotherapy. Radiation therapy is standard of care available for this study. Side effects are described earlier in risk section. Chances of recurrence are increased if receiving radiation therapy alone.
- Cisplatin and Fluorouracil are the standard of care chemotherapy drugs. You may receive them with or without radiation therapy. You can discuss with your doctor what is good for you. The risks of those therapies might include nausea, vomiting, decrease in cells providing immunity increasing risk of infection, bleeding.
- Taking part in a different study with another research drug. Your study doctor for that study will discuss the benefits and risks of the drug that is being offered.

- Having no treatment. This may or may not worsen your existing condition. You may decide not to take part in this research study without any penalty. The choice is totally up to you

IN CASE OF INJURY DURING THIS RESEARCH STUDY

If you are injured or made sick from taking part in this research study, you will get medical care. Generally, it will be billed to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, copayments, and coinsurance. This does not prevent you from seeking payment for injury related to malpractice or negligence. You can contact the Lead Researcher for more information.

ENDING PARTICIPATION IN THE RESEARCH STUDY:

You may stop taking part in this study at any time. No matter what you choose, your care and benefits through Mount Sinai will not be negatively impacted.

If you decide to stop being in the study, please contact the Lead Researcher or the research staff.

You may also withdraw your permission for the researchers to use and share any of your protected information for research, but you must do so in writing to the Lead Researcher at the address on the first page. Even if you withdraw your permission, the Lead Researcher may still use the information that was already collected if that information is necessary to complete the research study. Your health information may still be used or shared after you withdraw your authorization if you have an adverse event (a bad effect) from taking part in the research study.:

If you decide you don't want your data and/or samples to be used for research anymore, you can contact the researcher and ask to have your data and/or samples withdrawn or labeled so that they will not to be used in additional projects or shared. If your data and/or samples have already been shared with researchers, those researchers will be asked to stop using them. However, if any data and/or samples have already been shared without your identity or a linking code, it won't be possible to retrieve them. Data and/or samples that have already been used will not be affected by your decision. If your data and/or samples have already been deposited in an external repository, the study team will request that your data and/or samples be removed.

Withdrawal without your consent: The Lead Researcher, the funder or Mount Sinai may stop your involvement in this research study at any time without your consent. This may be because the research study is being stopped, the instructions of the research team have not been followed, the Lead Researcher believes it is in your best interest, or for any other reason. If data and/or samples have been stored as part of the research study, they too can be destroyed without your consent.

CONTACT INFORMATION:

If you have any questions, concerns or complaints at any time about this research, or you think the research has harmed you, please contact the office of the research team and/or the Lead Researcher at phone number 212-659-5461.

If there is an emergency, please call 911 or go to the emergency room. Let the emergency room staff know you are in a research study so they can contact the Lead Researcher if needed.

DISCLOSURE OF FINANCIAL INTERESTS:

Researchers sometimes get paid for consulting or doing work for companies that produce drugs, biologics or medical devices. If you have questions regarding industry relationships, you are encouraged to talk to the Lead Researcher or visit our website at http://icahn.mssm.edu/ where Mount Sinai publicly discloses the industry relationships of our faculty.

The costs of doing this research are paid based on the number of participants enrolled.

MAINTAINING CONFIDENTIALITY – HIPAA AUTHORIZATION:

As part of this study, some of your private and/or protected health information will be obtained, used, and shared with your permission. There is a Federal Health Insurance Portability and Accountability Act (HIPAA) that makes sure this is done correctly and safely.

What is protected health information (PHI)?
PHI is the combination of two things:

1. PHI contains information that identifies you. It will be used to contact you and link you to your health information, like name, date of birth, medical record number, and address.
2. PHI also contains health information, including information about your mental and physical health from your visits to doctors or hospitals, or from study visits.

Every time you visit a hospital or your doctor, PHI is created and recorded in your medical record by your healthcare providers. In the same way, the PHI created as part of this study will be linked to who you are and your medical information.

What PHI is collected and used in this research study, and might also be shared with others?
As part of this study, the research team at the hospital(s) involved in the research will collect name, address, telephone/fax numbers, dates directly related to the individual (birth, admission, discharge, date of death, etc.), e-mail addresses, social security number and medical records number.

During the study, the researchers will gather information by:

- Reviewing and/or taking your medical history (includes current and past medications or therapies, illnesses, conditions or symptoms, family medical history, allergies, etc.)
- Doing a physical examination that generally also includes blood pressure reading, heart rate, breathing rate, and temperature.
- Completing the tests, procedures, questionnaires and interviews explained in the description section of this consent.

Why is your PHI being used?

Researchers need the information that identifies you so they can contact you during the study. They need your health information and the results of any tests and procedures being collected as part of this study to answer the questions posed in the study. The purpose of the study is discussed earlier in this consent form. Before researchers analyze the data, they remove any information that would let others know who you are or that you took part in the study. If researchers publish or present study results at scientific meetings, lectures, or other events, their presentations would not include any information that would let others know who you are, unless you give separate permission to do so.

The Lead Researcher may also use and share the results of these tests and procedures with other healthcare providers at Mount Sinai who are involved in your care or treatment. The research team and other authorized members of The Mount Sinai Health System ("Mount Sinai") workforce may use and share your information to ensure that the research meets legal, institutional or accreditation requirements. For example:

- The Mount Sinai Program for the Protection of Human Subjects is responsible for overseeing research on human participants and may need to see your information.
- If you receive any payments for taking part in this study, the Mount Sinai Finance Department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- I*f the research team uncovers abuse, neglect, or reportable diseases, this information may be disclosed to appropriate authorities.*

Who, outside Mount Sinai, might receive your PHI?

As part of the study, the Lead Researcher, research team and others in the Mount Sinai workforce may disclose your PHI, including the results of the research study tests and procedures, to the following people or organizations: (It is possible that there may be changes to the list during this research study; you may request an up-to-date list at any time by contacting the Lead Researcher.)

- The United States Department of Health and Human Services (DHHS) and the Office of Human Research Protection (OHRP) (the government organization that is responsible for protecting human research participants).
- Outside laboratory who will be performing laboratory analysis for all the research centers involved in this project: Arizona University (Dr. Anderson)

- A Data Safety Monitoring Board or other committee that will monitor the study on an ongoing basis for safety.
- The United States Food and Drug Administration.

.In all disclosures outside of Mount Sinai, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. Some records and information disclosed may be identified with a unique code number. The Lead Researcher will ensure that the key to the code will be kept in a locked file, or will be securely stored electronically. The code will not be used to link the information back to you without your permission, unless the law requires it, or rarely if the Institutional Review Board (IRB) allows it after determining that there would be minimal risk to your privacy. It is possible that a sponsor or their representatives, a data coordinating office, a contract research organization, may come to inspect your records. Even if those records are identifiable when inspected, the information leaving the institution will be stripped of direct identifiers. Additionally, when applicable, the monitors, auditors, the IRB, *OHRP, as well as the Food and Drug Administration (FDA) will be granted direct access to your medical records for verification of the research procedures and data. OHRP and FDA are authorized to remove information with identifiers if necessary to complete their task. By signing this document you are authorizing this access.* The results of this research may be published. However, your name and other identifying information will be kept confidential.

For how long will Mount Sinai be able to use or disclose your PHI?
Your authorization for use of your PHI for this specific study does not expire.

Will you be able to access your records?
During your participation in this study, you will have access to your medical record and any study information that is part of that record. The research team is not required to release research information to you that is not part of your medical record.

Do you need to give the researchers permission to obtain, use or share your PHI?
NO! If you decide not to let the research team obtain, use or share your PHI, you should not sign this form, and you will not be allowed to volunteer in the research study. If you do not sign, it will not affect your treatment, payment, or enrollment in any health plans or affect your eligibility for benefits.

Can you change your mind?
If you decide to stop being in the study, please contact the Lead Researcher or the research staff.
The research team may ask you whether they can continue to collect information from your medical record. You will also have to decide if you wish to limit the continued use of the information collected during the study. Under US privacy laws you may also withdraw your permission for the researchers to use and share any of your protected information for research, but you must do so in writing to the Lead Researcher at the address on the first page.

Even if you withdraw your permission, the Lead Researcher may still use the information that was already collected, but only to complete this research study. Your health information may still be used or shared after you withdraw your authorization if you have an adverse event (a bad effect) from taking part in the research study.

If you have not already received it, you will also be given The Hospital's Notice of Privacy Practices that contains more information about how The Hospital uses and discloses your PHI.

It is important for you to understand that once information is disclosed to others outside Mount Sinai, the information may be re-disclosed and will no longer be covered by the federal privacy protection regulations. However, where possible, Mount Sinai has entered into agreements with those who will receive your information to continue to protect your confidentiality.

If researchers are reviewing your medical records or asking questions about your medical history or conditions, it is possible that they may learn information related to your HIV status. If that is the case, the following information concerns you. If researchers are not reviewing your medical records or asking questions about your medical history or conditions, then you may ignore the following section.

Notice Concerning HIV-Related Information

If you are authorizing the release of HIV-related information, you should be aware that the recipient(s) is (are) prohibited from re-disclosing any HIV-related information without your authorization unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (888) 392-3644 or the New York City Commission on Human Rights at (212) 306-5070. These agencies are responsible for protecting your rights.

How the Institutional Review Board (IRB) can help you:

This research has been reviewed and approved by an Institutional Review Board (IRB). You may reach a representative of the Mount Sinai Program for Protection of Human Subjects at telephone number (212) 824-8200 during regular work hours (Monday-Friday, 9am-5pm, excluding holidays) for any of the reasons listed below. This office will direct your call to the right person within the Mount Sinai Health System:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You are not comfortable talking to the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

ADULT PARTICIPANT:

Your signature below documents your permission to take part in this research study and to the use and disclosure of your protected health information. A signed and dated copy will be given to you.

Signature of Participant	Printed Name of Participant	Date	Time

PERSON EXPLAINING STUDY AND OBTAINING CONSENT:

Signature of Consent Delegate	Printed Name of Consent Delegate	Date	Time

WITNESS SECTION:

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant, and that consent was freely given by the participant.

Signature of Witness	Printed Name of Witness	Date	Time