CONSENT FOR CANCER RESEARCH

Project Title: A Phase II Study of the Addition of Pembrolizumab to Postoperative Radiotherapy in Resected High Risk Cutaneous (Skin) Squamous Cell Cancer of the Head and Neck

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Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (CaseCCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC), Hillcrest Hospital, Fairview Hospital Moll Pavilion and University Hospitals (UH)

What is the usual approach to my skin cancer?
The usual post-operative treatment for high risk cutaneous (skin) squamous cell cancer of the head and neck is six weeks of radiation treatments without any chemotherapy or immune therapy.

What are my other choices if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer. For example: comfort/palliative care

One or more of the Investigators conducting this study serve as consultants for the company that makes products used in this study. These financial interests are within permissible limits established by the local institutional Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask you study doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924 or University Hospitals Institutional Review Board at (216) 844-1529.

Why is this study being done?
You are being asked to take part in this study because you have skin cancer that was removed and demonstrated high-risk features. This means the chances of this cancer coming back are higher than most other skin cancers. Your doctor has recommended external beam radiotherapy. Usual treatment for you is six weeks of radiation treatments. If you participate in this study, you will also receive an immune therapy drug called Pembrolizumab given along with the radiation.

Immune therapy drugs have shown activity in this cancer, and this study is testing whether doing both treatments together results in a higher cure rate than we would otherwise expect.

A maximum of thirty-seven people will take part in this study.

What are the study groups?
All study participants will get the same study intervention. It will include the usual radiation therapy and the study drug pembrolizumab.

How long will I be in the study?
You will be treated on the study for four months. You will still be in the study for a full year where you will have follow up visits. Afterwards, you will have regular cancer follow up appointments by your doctors as per the usual care and no longer be in the research study.

What extra tests and procedures will I have if I take part in this study?
If you agree to participate in this study the only extra tests you will have are some extra blood tests, generally obtained at the same time standard blood work is drawn. This is to make sure it is safe to give you the Pembrolizumab and to monitor for side effects. There will also be blood drawn for research purposes to better understand how Pemrbolizumab impacts your immune profile.

What will happen if I take part in this research study?
You will have all of the routine visits and tests that you would regularly have as part of your cancer care.

Study Plan
Everyone in this study receives external beam radiation using advanced radiation technology called intensity modulated radiation therapy (IMRT) as well as Pembrolizumab. The Pembrolizumab is an intravenous infusion given over 30 minutes once every three weeks for over 4 months (6 infusions total). The radiation is delivered for six weeks, Monday through Friday starting the week after the first infusion of Pembrolizumab. Radiation treatments are about 30 minutes per day.

Below is a chart which shows when you will receive your treatments according to this study.

Treatments	**Weeks**									
	1	2	3	4	5	6	7	10	13	16
Radiation		X	X	X	X	X	X			
Pembrolizumab	X			X			X	X	X	X

Before you begin the study:

Screening assessments (days -28 to -1)

If after discussing this study with your doctor, you agree to participate you will sign the Informed Consent Form, You will need to undergo the following tests or procedures to find out if you are eligible to participate in the study. Some of these tests or procedures may be part of your regular medical care and may be done even if you do not take part in this study. If you have had some of them recently, they may not have to be repeated:

- Physical exam
- Vital signs (temperature, pulse, respiratory rate, blood pressure) with height and weight
- Immune status history
- Review of your medical and surgical history, previous cancer treatments
- Review any medications (including vitamins, herbal supplements, over the counter products) you are taking or have taken within the last 28 days.
- ECOG PS (an evaluation of your ability to carry out daily activities)
- CT of the neck and chest with contrast (if possible)
- PET/CT and or MRI (optional)
- Dental evaluation
- Approximately 3-4 tablespoons of blood will be drawn for the following:
    - Routine laboratory tests (including blood cell counts, serum chemistry, tests to assess thyroid function)
    - Research blood draw
- If you are a female of childbearing potential, a blood test for pregnancy will be performed
- Archived tumor tissue (obtained at your prior biopsy or surgery). This will be tested for expression of certain genes and proteins that may be associated with the tumor behavior and response to Pembrolizumab.

After completing the screening process, your study doctor will determine whether you are eligible to participate in the study.

On Treatment Assessments

Weeks 1-16 and Weeks 20, 32 and 52

- Physical exam including, vital signs (temperature, pulse, respiratory rate, blood pressure) with weight
- ECOG PS (an evaluation of your ability to carry out daily activities)

Weeks 1,4,7,10,13,16,20,32 and 52

- Laboratory tests (Blood cell counts, serum chemistry and thyroid function)
- Research blood draws (weeks 7, 20 and 52)
- Review medications
- Report side effects (except weeks 32 and 52)

Weeks 20, 32 and 52

- CT neck and chest imaging (CT Chest preferred, CXR acceptable)

Can I stop being in the study?
Yes. You can decide to stop at any time without any penalty. Tell the study doctor if you are thinking about stopping or decided to stop. He or she will tell you how to stop safely.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; or if the study is stopped by the sponsor.

What is known about this study drug?
Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer. Pembrolizumab works by helping your immune system to fight your cancer.

However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab.

These side effects can affect more than one of your normal organs and tissues at the same time.

What are the Risks of Being in the Study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects are temporary (occur for a short period)

and go away soon after you stop treatment. In some cases, side effects can be serious, long lasting, or may never go away. Some of the side effects may be life threatening and, in rare instances, may cause death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

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
- Sunburn on the skin
- 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

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

What side effects could the study drug(s) cause?

VERY COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, 20 or more people may have the following:
• Cough • Itching of the skin

VERY COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, 20 or more people may have the following:
• Loose or watery stools

COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, at least 5 but less than 20 people may have the following:
• Joint pain • Fever • Back pain • Rash • Pain in your belly • Loss of skin color • Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools • Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

UNCOMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, at least 1 but less than 5 people may have the following:
• Inflammation of the lungs so you may feel short of breath and cough. • Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, weak, tremble, sweat, feel tired, have loose or watery stools • Inflammation of the bowels/gut that may cause pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus • Inflammation of the skin so you may have peeling of the skin, itching, skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. • Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure, at the time of receiving your infusion (IV) or just after, or pain at the site of infusion

RARE, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, less than 1 person may have the following:
• Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis • Inflammation of the muscles so you may feel weak or have pain in your muscles

RARE, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, less than 1 person may have the following:
• Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and/or have vomiting that gets worse when you eat • Inflammation of the eye so you may have eye redness, blurred vision, sensitive sensitivity to light, have eye pain, and/or see floaters or have headaches • Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feeling tired, have a mild fever, have a pain in the right side of your belly muscle or joint aches, sick to your stomach and vomiting, pain in your belly, yellow eyes and skin, and dark urine • Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, sick to your stomach, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting • Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause causing tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan • Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots. • Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain ▪ Inflammation of the middle layer of your heart wall (myocarditis) that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. ▪ Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. ▪ A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing ▪ The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs ▪ Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

Additionally, since pembrolizumab was approved in September 2014, the following side effects, have been reported by people receiving pembrolizumab.

These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling

- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma.

In addition to the above, if you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

Potential Risk or Discomfort from Research Procedures

Blood Draws

The insertion of the needle to draw blood is painful; however, the discomfort is usually brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

CT Scans

If you take part in this research study, you will have one or more medical imaging studies which use radiation. The CT scan that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. This type of radiation is called "background radiation." No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer. The amount of radiation that scientists think can cause harmful side effects equals more than 15 times the amount of extra radiation you would receive from being in this study. Also, scientists believe the number of people who would be at risk for developing a second cancer from being exposed to large amounts of radiation to be about 1 out of every 1,000.

X-ray

We are all exposed to radiation on a daily basis both from natural (sun and earth) and man-made sources that we call background radiation. The amount of radiation from an x-ray is lower than what you are exposed to through natural sources of radiation in the environment.

The x-ray technologists and radiologists use the smallest possible dose of radiation and provide a protective lead apron when multiple x-rays are necessary.

Magnetic Resonance Imaging (MRI)
If you take part in this research, you may have an MRI (magnetic resonance imaging and/or magnetic resonance spectroscopy). MRI uses a magnet and radio waves to make images (pictures) of the inside of the head and/or body. There have been no ill effects reported from exposure to the magnetism or radio waves used for these studies; however, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal that may cause injury to you. We will ask you about metal within your body (this includes certain dyes used in tattoos and body piercings). If there is any question about potentially hazardous metal within your body, you will not be able to participate in this research study. We will also keep the MRI room locked so that no one carrying metal objects enters the room while you are having this scan performed. In addition, the MRI scanner makes a loud buzzing noise that could affect hearing ability. You will be provided with earplugs and assistance in their use in order to protect your hearing. You will be able to communicate with the scanner technologist using an intercom and/or signaling device. The technologist will try to help you feel as comfortable as possible in the scanner. You can ask to stop the scan and be removed from the scanner at any time by using the intercom or signaling device.

There is a very slight risk of an allergic reaction if contrast material is injected. Such reactions usually are mild and easily controlled by medication. If you experience allergic symptoms, a radiologist or other physician will be available for immediate assistance.

Gadolinium-based contrast agents (dyes) may increase the risk of a rare but serious disease called nephrogenic systemic fibrosis in people with poor kidney function. Nephrogenic systemic fibrosis triggers thickening of the skin, organs and other tissues. There is no effective treatment for this debilitating disease.

Are there reproductive risks to being in this study?
You should not get pregnant or father a child or donate sperm while on this study or during the first 6 months after completion of therapy because the treatment can affect an unborn baby. It is important you understand that you and/or your partner need to use birth control while on this study. You must be willing to use 2 methods of birth control or are considered highly unlikely to become pregnant. Unlikely to become pregnant is defined as surgically sterilized or postmenopausal. The 2 methods of birth control can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. For more information about risks and side effects, ask your study doctor.

Genetic Studies
A Federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Are there benefits to being in this study?
Taking part in this study may or may not make your health better. It is not known whether adding Pembrolizumab to radiation will result in higher cure rates than what we are used to with radiation on its own. The information from this study will help researchers learn more about the use of immune therapy with radiation for skin cancer. This information could help future patients with skin cancers.

What are the costs and compensation for this study?
You and/or your health plan/insurance company will need to pay for all of the usual costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects. You will not need to pay for the Pembrolizumab. This will be paid for by the study sponsor, Merck. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Research-Related Injury
If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals, Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924 or University Hospitals Cleveland Medical Center's Research Subject Rights phone line at (216) 983-4979.

Privacy and Confidentiality

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Shlomo Koyfman, MD and Min Yao, MD their research staff at Cleveland Clinic and University Hospitals for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition..

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, The University Hospitals Institutional Review Board, and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- The Food and Drug Administration;
- Merck
- Case Comprehensive Cancer Center members and collaborators
- The National Cancer Institute (NCI);
- Case Comprehensive Cancer Center Data Safety and Monitoring Board;
- The Department of Health and Human Services;
- Other Institutional Review Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Min Yao, MD
Case Comprehensive Cancer Center
University Hospitals Cleveland Medical Center
11100 Euclid Ave.
Cleveland, OH 44106

or

Shlomo Koyfman, MD
Case Comprehensive Cancer Center
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic and/or University Hospitals cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic and/or University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) and/or University Hospitals Institutional Review Board assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Termination of Participation
Your participation in this study may be discontinued by the investigator without your consent for any of the following reasons:

- Termination of the study
- Non-compliance with testing and procedures
- As clinically indicated (determined by the treating physician)

Questions About the Research

If you have any questions, you can ask the Principal Investigator and/or research staff. Shlomo Koyfman, MD (Cleveland Clinic) via phone: 216-444-7552 or Min Yao, MD (University Hospitals) via phone at 216-844-3951.

Emergency and After-hours Contact Information
If you are a University Hospitals patient, and you need to contact study staff outside normal business hours, you may contact 216-844-3951 and you will be transferred to the answering service, which can put you in contact with Min Yao, MD or the oncologist (cancer doctor) on call.

If you are a Cleveland Clinic patient, you should contact the page operator at (216) 444-2200 or toll free at (800) 223-2273, and ask for the oncologist (cancer doctor) that is on call.

If you are a Cleveland Clinic-Fairview participant, you may contact Dr. Timothy Spiro at 216-476-7606. This number can be used 24 hours a day 7 days a week.

If you are a Cleveland Clinic Hillcrest Hospital participant, you may contact Dr. Vinit Makkar at 440-312-4569. This number can be used 24 hours a day 7 days a week.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-2924 or the University Hospitals Cleveland Medical Center's Research Subjects Rights Phone line at 216-983-4979.

You may call the National Cancer Institute's Cancer Information Services at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI website at http://cancer.gov

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database
A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

Signature
Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. You also acknowledge that your blood and tissue samples will be used for research purposes. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____	_____	_____
Signature of Participant	**Date**	**Printed Name of Participant**

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____	_____
Signature of Person Obtaining Consent	**Date**

_____

Printed Name of Person Obtaining Consent