Research Study Informed Consent Document

Study Title for Participants: Testing the addition of M3814 (peposertib) to standard radiation therapy for patients with advanced head and neck cancer (HNSCC) who are not able to receive cisplatin

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol NRG-HN008, "Phase I Trial with Expansion Cohort of DNA-PK Inhibition and IMRT in Cisplatin-Ineligible Patients with Stage 3-4 Local-Regionally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)"
(NCT: 04533750)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have advanced head and neck cancer and are not able to receive the chemotherapy drug cisplatin.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following questions:

Is it safe and tolerable to give M3814 (peposertib) in combination with radiation in patients with advanced head and neck cancer who cannot receive cisplatin? What is the safe dose of M3814 (peposertib), if any, that can be given in combination with radiation?

The combination of the experimental drug M3814 (peposertib) and radiation therapy (IMRT) is not approved by the Food and Drug Administration (FDA) for your cancer or any cancer.

What is the usual approach to my head and neck cancer? (09-NOV-2020)

The usual approach for patients who are not in a study is treatment with radiation therapy and the chemotherapy drug, cisplatin; or radiation therapy and cetuximab for patients who are unable to receive cisplatin. For patients who get the usual approach for this cancer and cannot receive cisplatin, about 50 out of 100 are free of cancer after 5 years.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will get the study drug M3814 (peposertib) with radiation therapy for up to 7 weeks as long as your disease does not become worse, your doctor believes it is still safe for you, or you desire to discontinue the study drug and radiation. M3814 (peposertib) is an experimental drug and is not FDA approved.

After you finish radiation, your doctor and study team will check your disease every 3 months for 2 years. Your doctor and study team will also watch you for side effects after you finish radiation therapy. This means you will keep seeing your doctor for 2 years after radiation therapy.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study drug may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the study drug. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Tiredness
- Sores in the mouth
- Nausea
- Vomiting
- Skin rash

Combining M3814 (peposertib) with radiation can result in some greater side effects experienced by the drug alone such as tiredness.

There may be some risks that the study doctors do not yet know about.

Benefits

There is some evidence in animals that the study drug in combination with radiation therapy can stabilize cancer. However, we do not know if this will happen in people. This study may help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. This may mean slowly stopping the study drug so that there is not a sudden unsafe change, risk to your health, etc. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the) Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor the National Cancer Institute. The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to determine the safety and tolerability (side effects you experience) of M3814 (peposertib) at different doses in combination with radiation. We want to find out what effects the drug has on people, if any.

There will be about 42 people taking part in this study, 30 people in the first part of the study (dose escalation) and 12 people in the second part (dose expansion) to further assess the safety and tolerability of the recommended dose finding part (dose escalation).

Another purpose of the study is to check the level of the study drug in your blood called pharmacokinetics or PK.

What are the study groups? (14-DEC-2023)

There are two parts to the study, the dose escalation (or dose finding) and the dose expansion (where the established dose is further tested). The first part tests increasing doses of M3814 (pepo**s**ertib) to find the highest dose that can be safely and tolerably given with radiation. "Dose" is defined as the amount of drug you get, such as 100 mg.

The second part tests the highest safe dose of M3814 (pepo**s**ertib) on additional participants. Your doctor will tell you which part you are in.

In the first part of this study, different people will get different doses of the study drug M3814 (pepo**s**ertib) with radiation.

The first 6 people taking part in this study will get the starting dose of M3814 (pepo**s**ertib). If the drug does not cause serious side effects, the next group of people in the study will get a higher dose. The study doctors will watch each group carefully as they increase the dose. The doses will continue to increase for every new group until people have serious side effects that require the dose to be lowered. Once this dose is found, the first part of the study is stopped.

In the second part of this study, the highest dose with manageable side effects will be given to 12 more people. This will help study doctors better understand the side effects that may happen with this drug.

<u>Dosing schedule (the same for both parts of the study)</u>:

You will receive M3814 (pepo**s**ertib) and radiation Monday through Friday (5 days a week) for 7 weeks. About 60 to 90 minutes before each radiation treatment, you will take the assigned dose of M3814 (peposertib) as a tablet by mouth in the clinic. The M3814 (peposertib) tablets must be taken at least 1 hour before or 1 hour after a meal and with a cup (8 ounces) of water. The tablets must be swallowed whole and cannot be chewed or crushed.

You will not be able to get additional doses of the drug.

What exams, tests, and procedures are involved in this study? (09-NOV-2020)

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

- If you are a woman who is able to become pregnant, you will have to take a pregnancy test before you start treatment and monthly during treatment because the study drug could be harmful to an unborn baby.
- Before you enroll in the study, you will have an electrocardiogram (EKG) to screen for heart rhythm problems that might increase the side effects of treatment.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

- Blood draws to measure the amount of M3814 (peposertib) in your blood stream. This is called a pharmacokinetics (PK) study. A total of six blood draws will be needed on Day 1 of the first 2 cycles (Weeks 1 and 2): [redacted]. You will have these blood draws taken from a needle in your arm. If you stop taking M3814 (peposertib) for any reason, the PK blood draws will no longer be required.

What risks can I expect from taking part in this study? (05-AUG-2024)

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good, and could possibly be worse, than as the usual approach for your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The drug and radiation used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 12 weeks after the last dose of M3814 (peposertib).

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Risks of Blood Draws

The most common risks related to drawing blood from your arm are brief pain and possibly a bruise. The frequent and long durations of clinic visits on Day 1 of Weeks 1 and 2 caused by the need for multiple blood draws may be burdensome. In addition, the frequent blood sticks done on those days for the PK sampling may cause some discomfort. Rarely, an infection can occur.

Side Effect Risks

The drug used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.
There is also a risk that you could have other side effects from the study drug.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drug to try to reduce side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects for M3814 (peposertib) (MSC2490484A) (CAEPR Version 1.2, June 12, 2024)

POSSIBLE, SOME MAY BE SERIOUS
[redacted]

Additional Drug Risks

The study drug M3814 (peposertib) could increase or decrease the effect of other drugs. You may have to stop a drug you are currently taking if it interacts with the study drug. Your study doctor will review your medications and discuss this with you. Please talk with your study doctor before taking any over-the-counter medicines and do not take herbal products or new prescription medications provided by another physician while you are participating in this study. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

It is possible that the use of the study drug with radiation therapy will cause short- or long-term side effects expected with radiation therapy to be more severe or more long-lasting that would be the case with radiation alone or radiation therapy with standard-of-care drugs. Examples might include soreness of the throat or difficulty swallowing, or redness of the skin, or scarring or even breakdown of soft tissues or wounds of the skin, airway or swallowing tube (e.g. esophagus) that do not heal. Other side effects might include damage to the skin, soft tissues, or other parts of the head and neck that may require a major operation to correct and, rarely, can be life threatening.

Possible Side Effects of Radiation Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving head and neck radiation, more than 20 and up to 100 may have:
• Sores in the mouth and throat which may be painful especially with swallowing • Dry mouth, changes in taste, reduced sense of smell—may be permanent • Thick saliva • Hoarseness • Skin changes that may be permanent, swelling and redness of the skin in the area of radiation • Pain or pressure in the ear • Tiredness • Weight loss • Permanent hair loss in the area of radiation (face, chin, neck) • Cavities, tooth decay; loss of teeth; tooth sensitivity

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving head and neck radiation, from 4 to 20 may have:
• Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine • Damage to the nerves of the shoulder and arm which may cause decreased movement and feeling • Ear infection • Hearing loss • Difficulty swallowing which may require a long term or permanent feeding tube

RARE, AND SERIOUS In 100 people receiving head and neck radiation, 3 or fewer may have::
• Breathing and swallowing problems that may require a surgical procedure to create an opening through the neck into the windpipe • Damage to the nerves in the head and neck that control sensation, expression, or other motor functions • Damage to the jawbone which may cause jaw pain and loosening of teeth • Damage to the voice box or nerves to the voice box which may cause hoarseness, shortness of breath, inability to speak • Damage to the skin, soft tissues, or other parts of the head and neck that may require a major operation to correct and, rarely, can be life threatening • Damage to the spinal cord which may cause permanent weakness

What are my responsibilities in this study? (14-DEC-2023)

If you choose to take part in this study, you will need to:

- Keep your study appointments.
- Follow all directions provided by your study doctor for taking M3814 (peposertib).
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while taking part in this study and for 12 weeks after the last dose of M3814 (pepo**s**ertib). **For men:** Do not father a baby while taking part in this study and for 12 weeks after the last dose of M3814 (peposertib). **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 3 months after your last dose of study drug.

What are the costs of taking part in this study? (24-JUN-2021)

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your condition. This includes:

- the costs of tests (including the extra pregnancy tests), exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the radiation therapy.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- EKG test.
- Blood draw for the PK studies.

You or your insurance provider will not have to pay for the M3814 (peposertib) while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- NRG Oncology and any company supporting the study now or in the future. This would include any organization helping the company with the study.

- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research, including the Cancer Trials Support Unit (CTSU).
- The NCI's National Clinical Trials Network and the groups it works with to conduct research, including the Imaging and Radiation Oncology Core (IROC).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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 talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ (*insert name of study doctor[s]*) at _____ (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the _____ (*insert name of organization or center*) Institutional Review Board at _____ (*insert telephone number*).

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to be contacted where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

APPENDIX I: PATIENT STUDY CALENDAR

	Procedure or Patient Activity
Before the study	
Baseline tests	Following your voluntary **consent** to take part: • Pregnancy test for women who are able to become pregnant.
During the study	
Week 1 during Radiation Therapy	• M3814 (peposertib) pill by mouth before receiving radiation Monday-Friday • Research PK blood tests on the first day only: [redacted]
Week 2 during Radiation Therapy	• M3814 (peposertib) pill by mouth before receiving radiation Monday-Friday • Research PK blood tests on the first day only: [redacted]
Week 3 during Radiation Therapy	• M3814 (peposertib) pill by mouth before receiving radiation Monday-Friday
Week 4 during Radiation Therapy	• M3814 (peposertib) pill by mouth before receiving radiation Monday-Friday • Pregnancy test for women who are able to become pregnant.
Week 5 during Radiation Therapy	• M3814 (peposertib) pill by mouth before receiving radiation Monday-Friday
Week 6 during Radiation Therapy	• M3814 (peposertib) pill by mouth before receiving radiation Monday-Friday

Week 7 during Radiation Therapy	• M3814 (peposertib) pill by mouth before receiving radiation Monday-Friday