NRG ONCOLOGY

NRG-GI003

(ClinicalTrials.gov NCT #: 03186898)

A Phase III Randomized Trial of Protons Versus Photons for Hepatocellular Carcinoma

Amendment 4: December 19, 2025

Study Title for Study Participants: "Comparing Proton Therapy to Photon Therapy for Liver Cancer"

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
NRG-GI003, **"**A Phase III Randomized Trial of Protons Versus Photons For Hepatocellular Carcinoma," (NCT #03186898) (18-OCT-2019)

What is the usual approach to my Hepatocellular Carcinoma?

You are being asked to take part in this research study because you have liver cancer. People who are not in a study are usually treated with surgery, chemotherapy, and radiation therapy. There are several FDA-approved chemotherapy drugs that are commonly used along with the radiation therapy. For patients who receive the usual approach for this cancer, about 0 out of 100 are free of cancer at five years.

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, but you may want to receive comfort care to relieve symptoms.

Why is this study being done? (19-DEC-2025)

The purpose of this study is to compare any good and bad effects of using one of two kinds of radiation: proton therapy or photon therapy.

Photon therapy, which uses high-energy x-rays to send the radiation inside the body to the tumor, is the most common radiation treatment approach for liver cancer. There are many advanced ways to give photon radiation. When radiation is given in five doses or less, it is often called "stereotactic body radiation therapy" or "SBRT". When it is given in more than 5 doses, it can be called "3-dimensional conformal radiation therapy (3D-CRT)", "intensity modulated radiation therapy (IMRT)" , or "image-guided radiation therapy (IGRT)" among many other names. Sometimes the photons are produced by a machine called a linear accelerator. Sometimes they come from a very strong radioactive source (cobalt).

The other type of radiation is proton therapy, which uses a beam of protons (rather than x-rays) to send radiation inside the body to the tumor. This is the type of radiation therapy being studied in this trial. Because protons act differently inside the body than x-rays, proton radiation may result in better survival. Both photon and proton therapy precisely deliver radiation to the tumor and use special images to help guide accurate delivery of a full dose of radiation to the tumor without damaging much of the healthy tissue around it.

Both proton and photon therapy have already been tested for safety. Both of these types of radiation could shrink your cancer, but both could also cause side effects, and doctors and scientists do not know if one is better than the other or if they work equally well. This study will allow the researchers to know if proton radiation is better, the same, or worse than the photon radiation. To be better, 40 out of 100 patients should be alive two years after starting treatment.

There will be about 118 people taking part in this study.

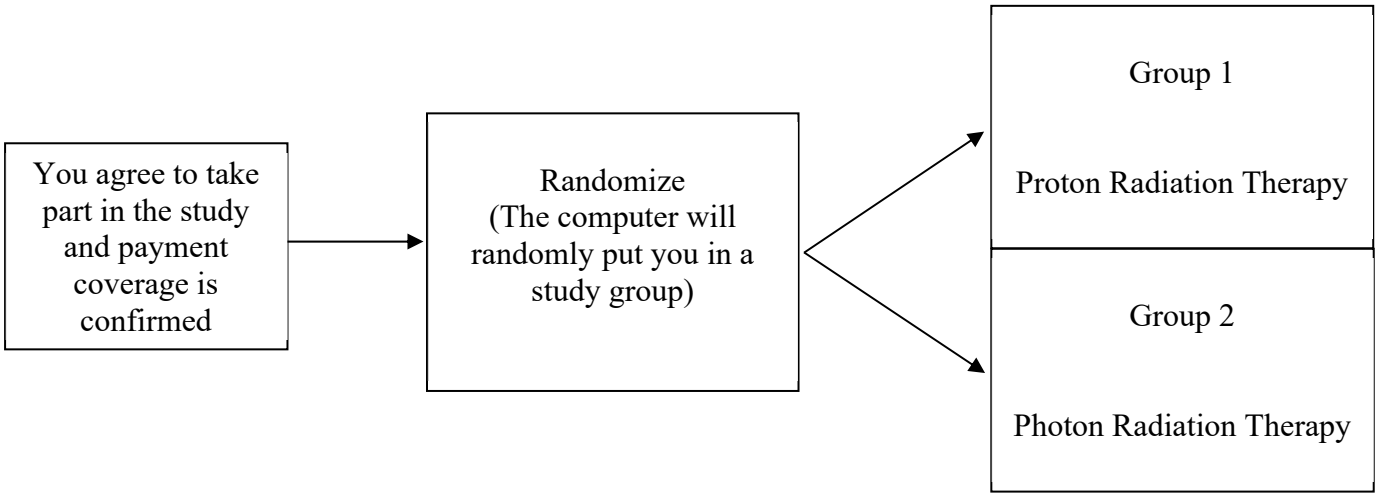
What are the study groups?

This study has two study groups.

- Group 1 will receive Proton Radiation Therapy for the usual length of time at the usual total dose for this type of cancer, as recommended by your treating physician. This may be 5 treatments over two weeks or 15 treatments over three weeks.
- Group 2 will receive Photon Radiation Therapy for the usual length of time at the usual total dose for this type of cancer, as recommended by your treating physician. This may be 5 treatments over two weeks or 15 treatments over three weeks.

Before you are assigned to a study group, your healthcare team will find out if your insurance will pay for proton radiation therapy to the liver. If it does not, you will need to decide if you want to continue participation in this study without insurance coverage if you are assigned to Group 1 (proton group).

A computer will by chance assign you to a treatment group in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other. You will have an equal chance of being placed in either group. Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



How long will I be in this study? (19-DEC-2025)

You will receive the radiation therapy for the usual length of time (either 5 or 15 treatments over over a period of 15 to 24 days) unless you are no longer benefiting from or you can no longer tolerate the treatment. Your physician will decide if you are benefiting from treatment based on

your answers to questions about how you feel during radiation, and based on physical exam. Additionally, at any time, you may choose to stop treatment. After you finish the radiation therapy, your doctor will continue to watch you for side effects and monitor your condition as follows. For the first two years, you will be seen in clinic approximately every three months. Then, you will be seen in clinic approximately twice yearly for 3 years. Thereafter, you will be seen in clinic approximately once a year for your lifetime. If visits are challenging for you (due to transportation or mobility problems, for example), you will be contacted by phone.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests and procedures that you will need to have if you take part in this study.

Quality of Life Study

You will be asked to fill out three different forms with questions about your physical and emotional well-being. Researchers will use this information to better understand how patients feel during treatments and what effects the treatments are having.

You will be asked to fill out forms at 5 times:

- Before you receive treatment on this study
- During months 1, 3, 6, and 12 after treatment

Each form will take between 5 and 15 minutes to complete. The forms will ask about things like your pain level, your energy level, and your own health concerns. You may feel uncomfortable answering some of the questions, and you can skip any you do not want to answer.

Neither you nor your health care plan/insurance carrier will be billed for your participation in this quality of life study.

If you do not speak English or a language in which the forms are available, you will not be asked to complete the forms.

What possible risks can I expect from taking part in this study? (30-July-2018)

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual.
- You may be asked sensitive or private questions which you normally do not discuss
- The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.

The radiation therapy 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 be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.

The table below shows the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Research Radiation Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 may have:
• Tiredness • Swelling, redness, and/or sores in the area of radiation • Lymphopenia

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• Nausea, vomiting • Pain • Internal bleeding • Diarrhea, passing gas, blockage of the stomach • Broken bone • Bruising, bleeding

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• Liver damage which may cause yellowing of eyes and skin, swelling

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The radiation therapy used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while receiving treatment on this study.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The 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.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for the radiation therapy, and all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge.

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. Once you register for this study, your

healthcare team will find out if your health insurance will pay for proton radiation to the liver. If it does not, you will need to decide if you want to continue participation in this study without insurance coverage if you are randomized to the proton group.

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

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information? (18-OCT-2019)

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, and/or information about your specimen, from this study will be kept in a central database for research. Your name or 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 inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. They must keep your information private, unless required by law to give it to another group. Some of these organizations are:

- The study sponsor [NRG Oncology (NRG)];
- The Department of Defense office of the Congressionally Directed Medical Research Programs (CDMRP), which is a grant-funding entity that fosters novel approaches to biomedical research in response to the needs of the American public, the military and Congress.
- Other organizations in the National Clinical Trials Network (NCTN): Alliance for Clinical Trials in Oncology (ALLIANCE), ECOG-ACRIN Cancer Research Group (ECOG-ACRIN), SWOG and Imaging and Radiation Oncology Core (IROC).
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

- The Cancer Trials Support Unit (CTSU), an organization sponsored by the NCI to provide greater access to cancer trials

Where can I get more information?(18-OCT-2019)

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).*

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

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is an optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records nor will you or your study doctor know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies (10-AUG-2022)

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

Optional Sample Collection for Laboratory Study If you choose to take part in this study, the study doctor for the main study would like to collect samples of your blood at 3 time points: before you begin treatment, at 1 month after you finish study treatment, and if your disease gets worse. These samples will be used for research on understanding changes in blood and how it relates to liver cancer treated with radiation. If you agree to the biobanking described next, any leftover samples will be saved for future studies.

Optional Sample Collections for Biobanking for Possible Future Studies If you choose to take part, a sample of tissue from your previous biopsy will be collected, and samples of blood will be collected. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by NRG Oncology and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) If you agree to both the Laboratory Study and the Biobanking, about 3-4 tablespoons of blood from a vein in your arm will be collected 3 times (before you start treatment, at 1 month after the start of treatment, and if your disease gets worse). If you agree to only the biobanking, then blood will still be collected 3 times (before you start treatment, at 3 months after you finish treatment, and if your disease gets worse). These samples will be sent to the Biobank.
2) Your samples and related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.

2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and NRG Oncology staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom NRG Oncology sends your samples and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option (*include only applicable questions)*:

SAMPLES FOR THE LABORATORY STUDIES:

I agree to have my blood collected and I agree that my specimen samples and related information may be used for the laboratory study described above.

YES NO

SAMPLES FOR FUTURE RESEARCH STUDIES:

My blood and tissue and related information may be kept in a Biobank for use in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main 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 copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____