Title for Study Participants: Testing the addition of the antibody nivolumab to the combination of two approved chemotherapy drugs in advanced small cell lung cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: EA5161: Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) Alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

What is the usual approach to the treatment of my small cell lung cancer?

You are being asked to take part in this research study because you have advanced small cell lung cancer. People who are not in a research study are usually treated with FDA-approved chemotherapy treatment. Radiation may also be used after chemotherapy.

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 your care. For example:

- 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
- or you may choose not to be treated for cancer with chemotherapy and choose to receive comfort care to relieve symptoms.

Why is This Study Being Done?

The purpose of this research study is to compare any good and bad effects of using nivolumab (OPDIVO®) along with the usual chemotherapy regimen of cisplatin/carboplatin and etoposide to using the usual chemotherapy approach alone. Nivolumab is a drug that may turn on the body's immune system to attack cancer cells. The addition of nivolumab to the usual chemotherapy could shrink your cancer and could delay it from returning but it could also cause side effects. This research study will allow the researchers to determine whether this different approach is better, the same, or worse than the usual chemotherapy approach. In order to be better, the study drug/study approach would have to improve how long you are able to live with your cancer under control by approximately 3 or more months compared to the usual approach. This study drug, nivolumab, is already FDA-approved for use in a different type of lung cancer

called nonsmall cell lung cancer. It is also used for melanoma, head & neck cancer, kidney cancer, bladder cancer and a certain type of lymphoma but is not approved for the treatment of small cell lung cancer. There will be about 150 people taking part in this research study.

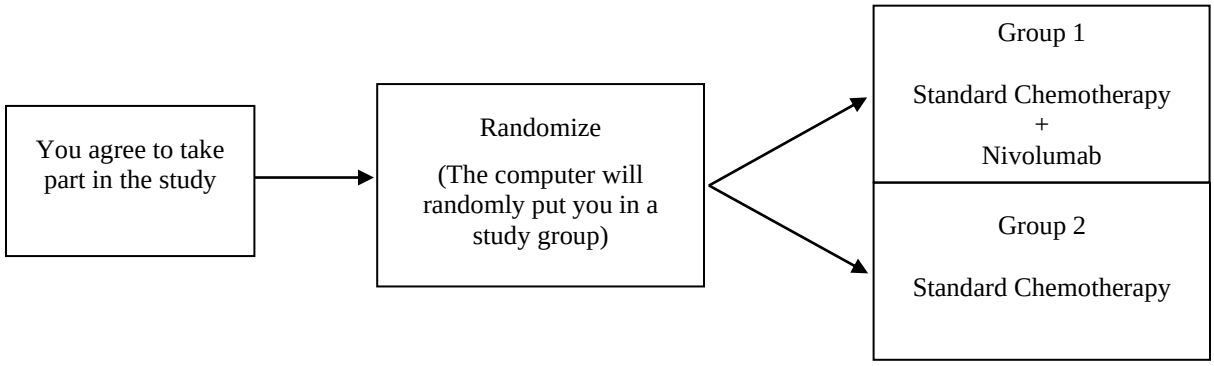
What are the Study Groups?

This research study has two study groups.

- Group 1 will receive the study drug nivolumab in combination with the usual chemotherapy regimen of platinum (cisplatin or carboplatin) and etoposide administered by an intravenous (IV) infusion
- Group 2 will receive the usual chemotherapy alone administered by an intravenous (IV) infusion.

A computer will by chance assign you to treatment groups in the research 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.

Another way to find out what will happen to you during this research 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?

In Group 1, you will receive the study drug, nivolumab, along with platinum and etoposide chemotherapy for 4 cycles. A cycle is 3 weeks. After 4 cycles, your doctor may have you continue treatment with nivolumab until your disease becomes worse or your study doctor believes it is no longer working for you. In Group 2, you will receive platinum and etoposide for 4 cycles. After you finish taking the study drugs, your doctor will continue to watch you for side effects and follow your condition for up to 5 years by telephone or doctor's office visits.

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 care for your cancer. However, there are some extra blood draws and exams that you may need to have if you take part in this study.

Before you begin the study:

You will need to have some or all of the following extra exams, tests, and/or procedures *(if you have not had them done recently within the usual approach to your cancer)* to find out if you can be in the study:

- Blood tests, urine sample, EKG
- Pregnancy test (if woman of child-bearing potential)

Before the study begins, we will also ask you for permission to obtain archival tumor tissue (obtained from a prior biopsy or surgery for your cancer) and additional blood draws. This is an optional part of the study and is discussed in the ADDITIONAL STUDIES SECTION.

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

If you choose to take part in this research 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 drugs/study approach may not be better, and could possibly be worse, than the usual approach for your cancer.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back 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. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

The drugs used in this study (nivolumab, cisplatin/carboplatin, etoposide) 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. These risks are described in more detail below.

There is also a risk that you could have other side effects from the study drugs/study approach. There is increased risk of side effects with the combiniation of nivolumab, cisplatin/carboplatin, etoposide comepared to cisplatin/carboplatin, etoposide.

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 study doctor may adjust the study drugs to try to reduce side effects.

The tables below show 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.

Study Group 1 & 2– Possible Side Effects of Cisplatin, Carboplatin and Etoposide

Possible Side Effects of Cisplatin (Table Version Date: April 20, 2015)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• Nausea, vomiting, • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require blood transfusions • Bruising, bleeding • Kidney damage which may cause swelling, may require dialysis • Hearing loss including ringing in ears

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Hair loss • Change in taste

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Diarrhea • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Confusion • Difficulty with balance • Numbness and tingling of the arms and legs • Blurred vision or changes in ability to see colors (especially blue or yellow)

RARE, AND SERIOUS In 100 people receiving Cisplatin, 3 or fewer may have:
• Cancer of bone marrow caused by chemotherapy later in life • Seizure

Possible Side Effects of Carboplatin (Table Version Date: March 24, 2015)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, more than 20 and up to 100 may have:
• Hair loss • Vomiting, nausea • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require blood transfusions • Bruising, bleeding • Belly pain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, from 4 to 20 may have:
• Diarrhea, Constipation • Numbness and tingling in fingers and toes • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Changes in taste • Changes in vision

RARE, AND SERIOUS In 100 people receiving Carboplatin, 3 or fewer may have:
• Damage to organs which may cause hearing and balance problems

Possible Side Effects of Etoposide (Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Etoposide, more than 20 and up to 100 may have:
• Hair loss • Chills • Sores in mouth which may cause difficulty swallowing • Diarrhea, loss of appetite, nausea, vomiting • Infection, especially when white blood cell count is low • Anemia which may require transfusion • Bruising, bleeding • Tiredness • Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Etoposide, from 4 to 20 may have:
• Heart failure or heart attack which may cause chest pain, shortness of breath, swelling of ankles, and tiredness • Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body • Liver damage which may cause yellowing of eyes and skin, swelling

RARE, AND SERIOUS In 100 people receiving Etoposide, 3 or fewer may have:
• Cancer of bone marrow caused by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Study Group 1 – In addition to side effects outlined above, people who are in Group 1 may also experience the possible side effects of Nivolumab listed below (Table Version Date: December 2, 2020).

Special precautions

Side effects of Nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when Nivolumab is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Nivolumab, more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Nivolumab, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Swelling and redness of the eye
- Pain
- Diarrhea, nausea
- Dry mouth
- Fever
- Swelling and redness at the site of the medication injection
- Bruising, bleeding
- Pain or swelling of the joints
- Loss of appetite
- Reaction during or following a drug infusion which may cause fever, chills, rash

Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Nivolumab, from 4 to 20 may have:

vomiting; drowsiness; pain in the right upper belly

- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urination; dizziness or fainting.

RARE, AND SERIOUS
In 100 people receiving Nivolumab, 3 or fewer may have:

- Dry eyes
- Sores in the mouth which may cause difficulty swallowing
- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause blurred vision, ringing in the ears, changes in hair or hair loss
- Swelling of the bowels

Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host

RARE, AND SERIOUS In 100 people receiving Nivolumab, 3 or fewer may have:
organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

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 become pregnant or father a baby while on this research study because the drugs in this study can affect a fetus. Also, women should not breastfeed a baby while on this research study.

If you are female and become pregnant while on this research study or within 28 days after the last dose of study drug, you will be asked information concerning the outcome of your pregnancy. If you are male and your female partner becomes pregnant while you are on the study or within 28 days after the last dose of study drug, you must notify the investigator. The pregnant female partner should be advised to call her healthcare provider immediately.

It is important that you understand that you need to either practice "abstinence" (that is avoiding sexual activity) or use birth control while on this research study. Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must agree to use an accepted and effective method(s) of birth control. Check with your doctor about what kind of birth control methods to use. Birth control must be used for at least one week prior to the start of the treatment and continue for 5 months after the last dose of study drug for women and 7 months after the last dose of study drug for males. If you choose to be sexually active during the study, you must accept that pregnancy could still result, exposing you or your sexual partner to potential loss of pregnancy as well as other unknown effects on the developing fetus.

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

It is not possible to know at this time if the study drugs/study approach is better than the usual care for this cancer so this research study may or may not help you. But, this research 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 research 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, you may contact the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

What are the costs of taking part in this study?

Nivolumab will be supplied at no charge while you take part in this research study. The cost of getting nivolumab ready and giving it to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that nivolumab may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options. Carboplatin, cisplatin, and etoposide are commercially available and you and/or your insurance company are/will be responsible for the costs associated with these standard treatments.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this research study, including the cost of study drug preparation and administration, tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are being done at no charge. Examples include blood tests such as blood count, kidney and liver evaluation and CT scans. Before you decide to be in the research 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 research 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 research study and need medical treatment, please tell your study doctor. Contact information for your study doctor is listed on the consent cover page. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for research 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 research study.

No funds have been set aside to compensate you in the event of injury.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. 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.

The ECOG-ACRIN Cancer Research Group is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, ECOG-ACRIN cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

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. Some of these organizations are:

- Montana Cancer Consortium
- The study sponsor and the drug company supporting the study
- 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

Additional Studies Section:

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

This part of the consent form is about 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 and you or your study doctor will not 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.

Optional Sample Collections for Laboratory Studies and Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples of 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.

If you choose to take part , we are requesting that you allow the collection and submission of blood for research to determine how well your cancer is responding to treatment.

If you choose to take part, we are also requesting that you allow the storage of your tumor tissue from your diagnostic biopsy as well as blood leftover after the laboratory research studies for future research projects. The research that may be done is unknown at this time. Storing samples for future studies is called "Bio-banking." The Biobanks are run by ECOG-ACRIN staff and researchers and are financially supported by the National Cancer Institute.

What is involved if you provide your samples for research?

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

1. About four (4) teaspoons of blood will be collected from a vein in your arm before you start therapy and on cycle two, day one. The blood will usually be collected at the same time as the blood collected for your clinical tests to monitor your health.
2. Tumor tissue that was collected at the time of your biopsy or surgery as well as blood left over after the laboratory research studies will be sent to the Biobank for research.
3. Your samples and some related health information will be sent to researchers for use in the studies described above and remaining samples stored in the Biobank, along with samples and information from people who took part in this or other research studies. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
4. Only qualified researchers can submit a request to use the materials stored in the Biobanks. A committee of experts at ECOG-ACRIN, and/or the National Cancer Institute, will review each request to use the samples for research. All research projects using these samples will also be reviewed by an ethics or institutional review board 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.

5. 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.
6. Results from the research may be placed in centralized storage systems called databases. It is possible that some of your genetic information and your health information may be placed in these databases. It is also possible that some of these databases may be public, however, information that could directly identify you will not be included.

What are the possible risks in providing your samples for research?

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.

When my samples are used for research, 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 samples and health information. Any Biobank and ECOG/ACRIN staff with access to the list must sign an agreement to keep your identity confidential.
3. Researchers to whom ECOG/ACRIN 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 of allowing my samples to be used for research?

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 associated with providing my samples for research?

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 about allowing my samples to be used for research?

If you decide you no longer want your samples to be used, you can call the study doctor, who will let the researchers know. Contact information for your study doctor is listed on the consent cover page. Then, any samples that remain 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. Contact information for your study doctor is listed on the consent cover page.

Please circle your answer to show whether or not you would like to take part in each option

SAMPLES FOR THE LABORATORY STUDIES:

May we have samples of your blood for laboratory research studies?

- **I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies described above.**

YES **NO**

SAMPLES FOR FUTURE RESEARCH STUDIES:

May we have samples of your tissue for future research?

- **I agree to provide additional samples for research.**

YES **NO**

May we keep any blood leftover after the laboratory research studies for future research?

- **My samples and related information may be kept in a Biobank for use in future health research.**

YES **NO**

This is the end of the section about optional studies.

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 https://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.

Who can answer my questions about this study?

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 information for your study doctor is listed on the consent cover page.

Signature:

This study has been explained to me, and I have been told what my enrollment in the study involves. I have read all pages of this consent and have had my questions answered to my satisfaction at this time. I consent to participate in this study and any additional studies where I circled 'yes'. I understand that by signing this form I have not given up any of my legal rights. I will be given a copy of this consent form. I may also request a copy of the protocol (full study plan).

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)