NCI Community Oncology Research Program – Kansas City (NCORP-KC)

Study Title for Study Participants: Testing if one chemotherapy combination is better than another for high grade neuroendocrine cancers

Official Study Title for Internet Search on https://ClinicalTrials.gov:

Randomized Phase II Study of Platinum and Etoposide versus Temozolomide and Capecitabine in Patients with Advanced G3 Non-Small Cell Gastroenteropancreatic Neuroendocrine Carcinomas

Version Date: December 6, 2016

This is a clinical trial, a type of study. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more explanation.

You are being asked to take part in this study because you have an aggressive, fast-growing neuroendocrine tumor.

What is the usual approach to my cancer?

You are being asked to take part in this study because you have a particular type of neuroendocrine cancer. People who are not in a study are usually treated with the chemotherapy drug combination of etoposide and cisplatin or carboplatin. For patients who receive the usual approach for this cancer, less than 5 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 your care. 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

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- 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?

The purpose of this study is to compare the effects, both good and bad, of the study drugs temozolomide and capecitabine to the usual chemotherapy treatment for this disease of cisplatin or carboplatin (referred to as "platinum therapy") and etoposide. Usually the first treatment given for this cancer is platinum therapy and etoposide. The chemotherapy drugs temozolomide and capecitabine are also used to treat this disease but usually not until the first treatment, platinum therapy and etoposide, stops working. It is not known if this is the best approach or if the temozolomide and capecitabine should be given first instead. The use of temozolomide and capecitabine could shrink your cancer but it could also cause side effects. For patients who receive the usual treatment for this cancer, it is usually about 6 months before the usual treatment stops working and a different treatment is needed. To be better, the study drugs should increase how long you are able to live with your cancer before you need to switch to different treatment, by 4 months or more compared to the usual approach. There will be about 126 people taking part in this study.

What are the study groups?

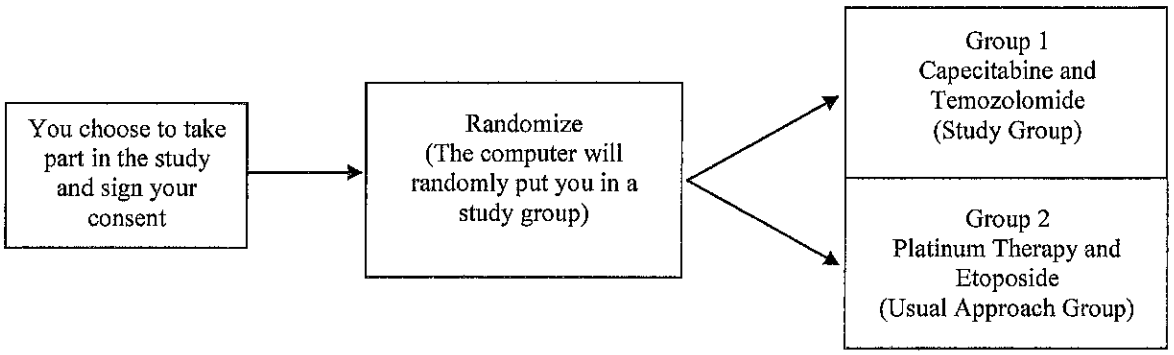
This study has two study groups, which are referred to as Group 1 and Group 2. Group 1 will receive the study drugs temozolomide and capecitabine. Group 2 will receive the usual care treatment of platinum therapy and etoposide.

If you are in Group 1, you will be taking your treatment orally. You will use a pill diary, which you must bring to each clinic visit. If you are in this group, you will take one medicine (the capecitabine) twice a day for 14 days. During the last 5 days of the capecitabine treatment, you will take temozolomide once a day as well. After the 14 days of treatment, you will have 14 days off from treatment before you start any further treatment. This 28 day period is called a cycle.

If you are in Group 2, you will receive platinum therapy and etoposide through a vein. You will receive your treatment at a clinic visit once a day for three days in a row, and then you will have 18 days off before you receive any further treatment. This 21 day period is called a cycle.

A computer will by chance assign you to treatment groups 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, or 50/50, chance of being 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?

You will receive the assigned chemotherapy treatment for as long as it seems to be working for you or until the side effects become too severe for you. After you finish your chemotherapy, your doctor will continue to watch you for side effects 30 days following your last treatment. Your doctor will follow your condition for the study for up to 5 years from when you first started the study.

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

Before you begin the study:

You will need to have the following extra exams and testing to find out if you can be in the study.

- Your doctor may decide that you should also have an octreotide scan or an FDG-PET scan. These are both nuclear imaging tests that can be helpful in locating neuroendocrine tumors in your body. Having these studies done will be a decision made between you and your doctor.
- Images obtained during your CT and MRI scans will be sent to the ECOG-ACRIN Cancer Research Group for research. Researchers will study the scans to learn more about how to use the images to monitor your disease.

During the study:

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra testing. They are not part of the usual approach for your type of cancer.

- Images obtained during your CT and MRI or other scans will be sent to the ECOG-ACRIN Cancer Research Group for research. Researchers will study the scans to learn more about how to use the images to monitor your disease. If you and your doctor have decided that you need some other types of imaging tests, including octreotide scans or FDG-PET scans, the images from these will also be sent in.
- If you participate in this study, samples of your tumor tissue from a previous biopsy or surgery will be sent to a central reviewer who will look at the characteristics of your tumor tissue. Tissue from all patients in this trial will be studied by the central reviewer. The results of the central review will not be sent to you or your doctor, will not be placed in your medical records, and will not affect your care.
- If you receive aprepitant (a medication to prevent nausea and vomiting), it may decrease the effectiveness of your oral contraceptive. Check with your study doctor.

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

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 drug(s)/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. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- The study drugs you receive may have interactions with other drugs you are taking. Some interactions can be serious and may harm you. You will need to tell your study team about all medications you are taking, including OTC products, tea, herbal medications, or other prescribed drugs as these could interfere with your cancer treatment.

The chemotherapy drugs 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. These risks are described in more detail below.

There is also a risk that you could have other side effects from the study drug(s)/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 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 – Possible side effects of Capecitabine, which is part of the chemotherapy combination being tested:

Possible Side Effects of Capecitabine

COMMON, SOME MAY BE SERIOUS In 100 people receiving Capecitabine, more than 20 and up to 100 may have:
• Swelling of the body
• Blisters on the skin
• Redness, pain or peeling of palms and soles
• Pain
• Diarrhea, loss of appetite, nausea, vomiting
• Sores in mouth which may cause difficulty swallowing
• Anemia which may require blood transfusions
• Infection, especially when white blood cell count is low
• Bruising, bleeding
• Feeling of "pins and needles" in arms and legs
• Tiredness
• Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Capecitabine, from 4 to 20 may have:
• Blurred vision, dry or itchy eyes • Muscle spasms, body aches • Abnormal heartbeat • Restlessness, irritability • Swelling of face, fingers and lower legs • Constipation • Confusion • Difficulty with balancing

RARE, AND SERIOUS In 100 people receiving Capecitabine, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Difficulty speaking, walking or seeing • Internal bleeding which may cause blood in vomit or black tarry stools • Damage to the heart

Study Group 1- In addition to side effects outlined above for Capecitabine, people in Study Group 1 may also experience the possible side effects of Temozolomide, with is part of the chemotherapy combination being tested:

Possible Side Effects of Temozolomide

COMMON, SOME MAY BE SERIOUS In 100 people receiving Temozolomide, more than 20 and up to 100 may have:
• Constipation, nausea, vomiting, diarrhea • Dizziness • Muscle weakness, paralysis, difficulty walking • Trouble with memory • Tiredness • Difficulty sleeping • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Temozolomide, from 4 to 20 may have:
• Headache, seizure • Infection, especially when white blood cell count is low • Anemia which may cause tiredness • Bruising, bleeding • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require blood transfusions

RARE, AND SERIOUS In 100 people receiving Temozolomide, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Cancer of bone marrow caused by chemotherapy • Rash • Severe skin rash with blisters and can involve inside of mouth and other parts of the body • Liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure

Study Group 2 – Possible side effects of Cisplatin, which is part of the usual approach for this type of cancer:

Possible Side Effects of Cisplatin

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 • Tingling or numbness in the hands and feet

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Confusion • Difficulty with balance

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

Study Group 2 – Possible side effects of Carboplatin, which is part of the usual approach for this type of cancer:

Possible Side Effects of Carboplatin

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

Study Group 2 – In addition to the side effects outlined above for Cisplatin and Carboplatin, people in Study Group 2 may also experience the possible side effects of Etoposide, which is part of the usual approach for this type of cancer:

Possible Side Effects of Etoposide

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

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

ask your 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 study drugs 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 in 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 drug(s)/study approach is better than the usual care for this cancer so this study may or may not help you. But, 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 NCI Community Oncology Research Program-Kansas City Institutional Review Board at 913-948-5588.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for all of the costs associated with treatment of your cancer while in this study, including the cost of study drug

preparation and administration, tests, procedures, co-pays, or medicines to manage any side effects, unless you are told that certain tests are being done 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.

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?

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:

- 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.

- Other regulatory agencies and/or their designated representatives.
- Central laboratories who receive your samples for testing or research.
- Cancer Trials Support Unit (CTSU). The CTSU is a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- The ECOG-ACRIN Cancer Research Group, which is coordinating the study.

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 the study doctor _____ (insert name of study doctor[s]) 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 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.

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

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 participate in the main part of this study, samples of your tumor tissue from your biopsy will be sent for central review. At this time, we are requesting that you allow submission of this tissue and a blood sample to be kept for future studies to learn more about cancer and other health problems. Some research may include looking at your DNA, to learn more about your disease. If you allow your samples to be stored for future research, the tissue will be stored in a "biobank". The Biobanks are run by ECOG-ACRIN staff and researchers and they 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. If you agree to allow your tumor tissue and a blood sample to be used for the research, samples of your tumor collected previously and about one tablespoon of blood will be collected from a vein in your arm. These samples will be sent to the biobank.
2. Your samples and some related health information will be stored in the Biobank, along with samples and information from people who took part in this or other studies. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.

3. 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.
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. Results from the research may be placed in centralized storage systems call 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.

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

1. 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.
2. 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.
3. 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.
4. It is possible that not enough archival tumor tissue from your diagnostic biopsy will be left for other testing that may need to be done in the future. Please speak to your study doctor to discuss this possibility.

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 sample(s) is 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 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 sample 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, _____, *(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

SAMPLES FOR FUTURE STUDIES:

May we have some of your tissue, including any tissue left over after the central review, and a sample of your blood for future research?

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

YES **NO**

Approval Date _____ to _____

Assurance#: FWA00003582

This is the end of the section about optional studies.

Release

By signing this form you authorize NCORP-KC to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

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

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 _____

Participant's signature _____

Date of signature _____

Person obtaining consent _____

Person obtaining consent signature _____

Date of signature _____