RANDOMIZED PHASE II STUDY COMPARING CABOZANTINIB (NSC #761968 AND IND #116059) WITH COMMERCIALLY SUPPLIED SUNITINIB IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED OR METASTATIC RENAL CELL CARCINOMA

This is a clinical trial, a type of research study. Your study 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 study doctor for more explanation.

You are being asked to take part in this study because you have advanced or metastatic kidney cancer

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, two study drugs called sunitinib and cabozantinib have on you and on advanced or metastatic kidney cancer. Sunitinib has been approved by the FDA and cabozantinib is an investigational drug. Both medications target special proteins that are on the surface of the kidney cancer cell and both drugs are taken by mouth.

How many people will take part in the study?

About 150 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A medical history and physical examination, which includes questions about your health, current medications, pulse & blood pressure, weight and any allergies.
- Performance status, which evaluates how you are able to carry on with your usual activities.
- An assessment of your tumor by CT (Computerized Tomography) or MRI (Magnetic Resonance Imaging) scans of the chest, abdomen, or brain.
- Blood and urine tests.
- Pregnancy test (if you are a female of child-bearing potential)
- Bone scan (a scanning test to detect if cancer has spread to bones)

- An electrocardiogram known as EKG (to test your heart rate and rhythm)
- An echocardiogram or a MUGA scan (to test your heart function)

If the exams, tests and procedures show that you can be in the study and you choose to take part, then you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group. The two treatment groups are:

Group 1 (often called "Arm A"): cabozantinib

Group 2 (often called "Arm B"): sunitinib

During the study …
Both treatment groups will receive treatment over 6 weeks. This 6-week period is called a "cycle."

If you are in Group 1, you will take cabozantinib by mouth every day (no break). You should take cabozantinib on an empty stomach. Do not eat for two hours before through one hour after taking cabozantinib. You should avoid taking antacids while taking cabozantinib. If you need to use antacids, it is recommended that you take them at least 2 to 4 hours after taking cabozantinib but at least 14 hours before the next dose of cabozantinib.

If you are in Group 2, you will take sunitinib by mouth once every day for 28 days, and then will have a 14-day break (no drug taken). Sunitinib does not have to be taken on an empty stomach. There will be a yellowing of the skin area following direct contact with the capsules. Wash the exposed area with soap and water immediately.

You will be asked to record the day, number of pills taken, and time of each dose of sunitinib or cabozantinib on a medication calendar. You will be asked to bring the calendar with you to your clinic visits. Cabozantinib and sunitinib must be taken whole and not crushed or chewed. You should not have grapefruits, grapefruit juice, Seville orange, or St. John's wort while on this study. You should also check with your doctor or pharmacist before using any new medicines, including over-the-counter drugs because of possible drug interactions.

	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Group 1	Cabozantinib every day	Cabozantinib every day	Cabozantinib every day	Cabozantinib every day	Cabozantinib every day	Cabozantinib every day
Group 2	Sunitinib every day	Sunitinib every day	Sunitinib every day	Sunitinib every day	REST	REST

Tests and Procedures:
During the time that you are receiving study treatment, you will need the following tests and procedures. They are part of regular cancer care.

For the first 6 weeks that you are in the study, the following tests will be done every 2 weeks, then they will be done every 6 weeks:

- A medical history and physical examination, which includes questions about your health, current medications, pulse & blood pressure, weight and any allergies.
- Performance status, which evaluates how you are able to carry on with your usual activities.
- Blood and urine tests

These tests and procedures are being done more often because you are in this study.

You will also have CT or MRI scans every 12 weeks (or as necessary) to monitor your disease.

When I am finished taking the study treatment:
After you have finished receiving the study treatment, you will be asked to have physical examinations and scans with your doctor to monitor your disease for up to 5 years. These will be part of standard cancer care.

How long will I be in the study?

The study treatment will be continued for as long as your kidney cancer is responding to or is stabilized by the drug and you do not have any severe side effects from the drug.

If your cancer worsens, you will be removed from the study. Whether or not you remain on study treatment, the study doctor will continue to follow your progress for up to five years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the 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 cabozantinib and sunitinib 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 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 risk lists 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.

Precautionary drug interactions: Please review with your doctor all medications that you are currently taking--including nonprescription medications, vitamins, herbal supplements, and naturopathic preparations--to avoid possible drug interactions.

Risks and side effects for medications involved with normal supportive care will be provided by your physician or healthcare professional.

Group A (Cabozantinib)

COMMON, SOME MAY BE SERIOUS In 100 people receiving cabozantinib, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Weight loss, loss of appetite • Changes in taste

- Redness, pain or peeling of palms and soles
- High blood pressure which may cause headaches, dizziness, blurred vision

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

- Anemia which may require blood transfusion
- Pain
- Constipation, heartburn
- Dry mouth, skin
- Sores in the mouth which may cause difficulty swallowing
- Swelling of arms, legs
- Infection
- Bruising, bleeding
- Dehydration
- Dizziness, headache
- Cough, shortness of breath
- Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood or blood in urine
- Bleeding from multiple sites including the nose
- Hair loss, rash
- Change in hair color
- Blood clot which may cause swelling, pain, shortness of breath
- Muscle weakness
- Changes in voice

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

- A tear or hole in internal organs that may require surgery
- Non-healing surgical site
- Damage to the jawbone which may cause loss of teeth
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Lung collapse
- Bleeding in the brain which may cause confusion
- Stroke which may cause paralysis, weakness

Group B (Sunitinib):

COMMON, SOME MAY BE SERIOUS
In 100 people receiving sunitinib malate (SU011248 L-malate), more than 20 and up to 100 may have:

- Pain
- Constipation, diarrhea, heartburn, nausea, vomiting
- Sores in the mouth
- Tiredness
- Loss of appetite

- Changes in taste
- Sore throat
- Redness, pain or peeling of palms and soles

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving sunitinib malate (SU011248 L-malate), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Blurred vision with chance of blindness
- Bloating, passing gas
- Dry mouth, skin
- Chills, fever
- Swelling of arms, legs
- Flu-like symptoms including body aches
- Bruising, bleeding
- Weight loss
- Infection, especially when white blood cell count is low
- Dehydration
- Dizziness, headache
- Feeling of "pins and needles" in arms and legs
- Depression
- Difficulty sleeping
- Cough, shortness of breath
- Nose bleed
- Hair loss, rash, itching, skin changes
- Change in hair color
- High blood pressure which may cause headaches, dizziness, blurred vision

RARE, AND SERIOUS

In 100 people receiving sunitinib malate (SU011248 L-malate), 3 or fewer may have:

- Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis
- Blood clot which may cause confusion, paralysis, seizures or swelling, pain, shortness of breath
- Damage to organs (heart, brain, others) which may cause shortness of breath, swelling of ankles, and tiredness, changes in thinking
- Heart failure, heart attack which may cause shortness of breath, swelling of ankles, and tiredness
- Pain and swelling of thyroid
- Visual loss
- Difficulty swallowing
- A tear or hole in or between internal organs which may cause drainage and may require surgery
- Swelling of the gallbladder
- Liver damage which may cause yellowing of eyes and skin, swelling
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Flesh-eating bacteria syndrome
- Non-healing surgical site

- Change in the heart rhythm
- Kidney damage which may require dialysis
- Damage to the jawbone which may cause loss of teeth
- Damage to muscle which may cause muscle pain, dark red urine
- Cancer of bone marrow caused by chemotherapy
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- Stroke
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Sores on the skin
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Unanticipated side effects may occur which have not been reported. If you have any unusual symptoms, report them immediately to your doctor.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while receiving study treatment and for at least 4 months after completing or discontinuing study treatment. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask the study doctor. Contact information for your study doctor is listed on the consent cover page.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope cabozantinib will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about cabozantinib as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

No matter what you decide to do, and whether or not you decide to participate in this study, your decision will not harm the care that you receive or your relationship with your doctor or nurses or other healthcare providers. If you have any study-related questions, please talk to your doctor or nurse.

Contact information for your study doctor is listed on the consent cover page. For information about your rights as a research participant call our institutional review board (IRB) at (406) 238-5657.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Billings Clinic Institutional Review Board
- Montana Cancer Consortium
- The Alliance for Clinical Trials in Oncology (Alliance)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Exelixis (the makers of cabozantinib)

The Cancer Trials Support Unit (CTSU) may also view your records if you are participating in this trial through one of their institutions.

The Alliance has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services, or for purposes of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

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

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The NCI will supply cabozantinib at no charge while you take part in this study. The study does not cover the cost of filling the prescription, so you or your insurance company may have to pay for this. Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the cabozantinib to the NCI for some reason. If there is no cabozantinib available at all, no one will be able to get more and the study would close.

You or your health plan will be billed for the cost of the sunitinib.

If a problem with getting cabozantinib occurs, your study doctor will talk to you about these options.

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

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

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

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

It is important that you tell your study doctor, if you feel that you have been injured because of taking part in this study. Contact information for your study doctor is listed on the consent cover page.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

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

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact information for your study doctor is listed on the consent cover page.

IRB

For questions about your rights as a research participant, contact the Billings Clinic Institutional Review Board (IRB), which is a volunteer group that acts as a research subject advocate. The IRB has reviewed this consent form for clarity of information. If you have any questions, comments, or concerns about this study or about your rights as a research subject, you may call the IRB at (406) 238-5657.

You can also contact the Montana Cancer Consortium at 406-969-6060.
Montana Cancer Consortium
2132 Broadwater Avenue, Suite A1
Billings, MT 59102
406-969-6060
Fax: 406-969-6070

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to the following study. Please mark your choice for the study.

Research on Tissue

Please read this section of the informed consent on related research studies and ask about anything that is not clear to you. This is to inform you of the possible risks, benefits and limits of giving your samples for research.

You are being asked to give some of your samples (called specimens) and related information to be used for research. This may help researchers learn more about how to prevent, find and treat cancer and other diseases.

The choice to have your samples used for the research described in this consent and stored for future research is up to you. No matter what you decide, it will not affect your medical care and it will not affect whether you take part in other studies.

What are samples and where are they stored?

A sample is any material taken from your body such as tissue, blood, urine and other fluids. If you agree, your samples will be stored for research in a Cooperative Group bank supported by the National Cancer Institute. A Cooperative Group bank contains samples and information. Your samples are kept along with those from other people in this bank. Researchers then ask for samples from the bank to study them.

What information will be collected?

Your samples will be sent to the Alliance Bank. Any personal information sent with the samples to the bank is not given to researchers. The personal information is used only by the bank. Your privacy will be protected to the fullest extent possible. This will be discussed later in the section "How will information related to my samples be protected?"

Other information that might be stored for future research by the Alliance includes:

- Dates of medical procedures
- Any diagnosis and stage of your disease (if you have cancer)
- Your age and race
- Medical and family history
- Treatments you had
- How you responded to treatments

What will happen to my samples if I agree to give them for research?

Your samples will be stored in the Alliance Bank. The samples will be kept until they are used up or destroyed. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

You or your doctor will not be given reports or other information about the research that uses your samples. You will not be named or identified by other personal information if any results are published. Most publications contain results from many patients. Results may be used for future research.

Your samples and related information will be used only for research and will not be sold. It is possible that research may help to create new products or treatments. If this should happen, you will not be paid.

Because the information gained from the research studies performed on your samples can be very useful to the research community, several groups including the National Institute of Health (NIH) have requested that some of these data be placed in a central database. Therefore, some of the coded research information may be sent to a central database. The goal is to speed up the process of discovery of new treatments, prevention and diagnosis of disease. The information will continue to be made available for approved research. Your name or contact information will not be put in the database.

What kind of research will be done with my samples?

Many types of research use normal or diseased (**cancerous**) samples. Researchers can study proteins, RNA and DNA (genes). The study of genes (DNA) is often called **genetic research**.

Genetic research looks at whether a trait is passed down in families from one generation to the next (**inherited**). This type of research may help to explain why some cancers run in families or why some people have side effects of treatment while others do not. This is often studied through blood cells and DNA (**genes**).

Genetic research also looks at changes in the body that happen after you were born (**non-inherited**). For example, being in the sun too much can cause changes in cells that lead to skin cancer.

We would like to request your permission to study cells from your tumor. The tumor samples were previously obtained when your disease was first diagnosed or when you had surgery. No additional biopsy will be required. These tumor samples will be used in a laboratory to investigate kidney cancer. This will include looking at the cells in your tumor tissue to detect changes in genetic material that may have occurred. Your tumor cells may be used soon after this study in kidney cancer is over, and they may be kept to be studied later in the future.

Will it help me if I give my sample for research?

Using your samples for research will probably not help you. We do hope the research results will help people in the future. The best way to prevent, find or treat cancer and other diseases is by studying human samples and data.

What are the risks of giving my samples for research?

- There is a risk that your information could be misused**.** The chance of this happening is very small. We have many protections in place to lower this risk. See the next section, “How will the information related to your samples be protected?” Your privacy will be protected to the fullest extent possible.
- There can 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 research study. Even though your genes are unique, you share some of the same genes

with your blood relatives. Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Some states have laws to protect against genetic discrimination. A new federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please check the Internet or ask the study staff.

Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because research results on your samples will not be returned to you or your doctor.

How will information related to my samples be protected?

We have many ways to protect the information related to your samples:

- Your samples and information receive a unique code. Researchers only receive coded samples and information, and will not be able to link the code to you. Only approved people in the Alliance can match you to the code on your samples and related information.
- Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include, but are not limited to, restricted access to buildings, rooms and freezers housing patient samples, numeric coding of both patient data and samples, and password protected access to databases housing patient data.
- Before samples are given to researchers, studies are reviewed for the quality of the science and for patient protection. Records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies. This is to make sure the research follows the rules of the Cooperative Group and state or federal laws.
- Research results from your samples will not be returned to you or your doctor. If research results are used in a publication, your name and other personal information will not be given.
- The Alliance also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. The Certificate protects against the forced release of personal information from the Cooperative Group bank or database.

What this means is that the Alliance cannot be forced to disclose your identity to any third party. It is possible that for some legal proceedings, the Certificate of Confidentiality could be over-ridden by a court of law.

Making your choice

The choice to take part is up to you. You may choose not to let us use and store your samples. If you decide not to let us store and use your samples, you will still receive the same medical care. You may also take part in other research studies.

To learn more, ask the study staff for the booklet called "Giving Samples for Research" or visit http://www.cancer.gov. You may want to read the section "What types of research use samples?"

If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff at your hospital and let them know that you do not want your samples used for research [*406-969-6060]*. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers cannot be returned or destroyed.

Thank you for considering whether to allow your samples to be used for the research described above and/or banked for future research.

1. My coded samples and related coded information **may be used** in the research described above to learn about, prevent, find or treat **cancer**. This may also include research on inherited traits (genes passed on in families).

Yes____ No____

2. My coded samples and related coded information **may be kept for use** in future research to learn about, prevent, find or treat **cancer**. This may also include research on inherited traits (genes passed on in families).

Yes____ No____

3. My coded samples and related coded information **may be kept for use** in future research to learn about, prevent, find or treat **other health problems** (for example: diabetes, Alzheimer's disease, or heart disease). This may also include research on inherited traits (genes passed on in families).

Yes____ No____

4. Someone from my hospital or the Alliance may contact me in the future to ask me to take part in more research.

Yes____ No____

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

You can also contact the Montana Cancer Consortium at 406-969-6060.
Montana Cancer Consortium
2132 Broadwater Avenue, Suite A1
Billings, MT 59102
406-969-6060
Fax: 406-969-6070

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)