Official Title: LCI-GU-URO-CRI-001: A Phase II Study of Crizotinib in Patients With c-MET or RON-Positive Metastatic Urothelial Cancer
NCT02612194
IRB-Approved Date: 7/6/2018

CAROLINAS HEALTHCARE SYSTEM
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Sponsor / Study Title:	**Levine Cancer Institute / "A PHASE II STUDY OF CRIZOTINIB IN PATIENTS WITH c-MET OR RON-POSITIVE METASTATIC UROTHELIAL CANCER"**
Protocol Number:	**LCI-GU-URO-CRI-001**
Principal Investigator: (Study Doctor)	**Earle Burgess, MD**
Telephone:	**[redacted] (24 Hours)** **[redacted] (24 Hours)**
Address:	**Levine Cancer Institute** **[redacted]**

INTRODUCTION

The study doctor and his associates (the investigators) are asking you to participate in a research study at Levine Cancer Institute (LCI) and Carolinas HealthCare System (CHS) of a study with crizotinib (Xalkori®) in the treatment of subjects with metastatic urothelial cancer of the bladder, upper (ureter or renal pelvis) or lower (urethra) urinary tracts. The purpose of this study is to see if this experimental drug has a potential benefit in subjects with stage 4 urothelial cancer. You are being asked to take part in this study because you have metastatic urothelial cancer, have received treatment with cisplatin or carboplatin in the past, and your tumor contains certain proteins.

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 have also been told that you have the option not to participate. 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.

This study is being carried out under the sponsorship of Levine Cancer Institute (LCI). Pfizer Inc. is the company that makes crizotinib that will be used in this study and is providing the drug for this study.

WHY IS THIS STUDY BEING DONE?

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Urothelial cancer that has spread to another part of the body and is resistant to treatment is considered very difficult to treat. The most common approved treatment includes chemotherapy containing either cisplatin or carboplatin with other medications. No currently approved standard of care exists for subjects whose cancers worsen after this initial treatment. Additional chemotherapy medications often prevent cancer growth for no more than three months.

This study tests crizotinib used alone in subjects with urothelial cancer, previously treated with chemotherapy, and whose tumors have certain proteins. Proteins are complex natural substances essential to the structure and function of all living cells. These proteins, c-MET or RON, may trigger molecular pathways that are involved in the growth and spread of bladder or upper urinary tract cancer. Crizotinib is a drug taken by mouth that blocks these pathways. Early laboratory research suggests that crizotinib may benefit patients with urothelial and other cancers with these molecular pathways. Although crizotinib is currently approved by the Food and Drug Administration (FDA) for the treatment of lung cancer that has spread, its use in subjects with urothelial cancer is experimental and the potential benefits are not yet known.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

You will be one of approximately 53 subjects participating in this study at multiple centers in the United States.

HOW THE STUDY WORKS

Before you begin the study (Baseline)

In order to participate in this study, you will need to review, sign and date this consent form. We have previously collected information from your medical record to determine your eligibility to enroll on the study. We have also collected information about your demographics (i.e. age, race, etc.), medical history, your current disease, any treatments received before, and any medications you are taking. Please let us know if any of this information has changed since your last consent.

If not already done within 30 days before starting study treatment on the study, you will have scans of the chest, abdomen, pelvis and bones. The scans performed will be either a computerized tomography (CT) of your chest, abdomen, and pelvis (x-ray machine that uses a computer to take pictures or computerized tomography) and a bone scan (produces pictures of internal body parts using small amounts of radioactive material called a radionuclide scan), or a PET/CT scan (using an imaging scanner called a Positron Emission Tomography (PET) in combination with a CT scan). The method of scan performed will be determined by your study doctor. We will also collect blood for laboratory tests. The labs will help evaluate your kidneys, liver, other organ function, and blood cell counts.

Please tell your study doctor if you have noticed new visual floaters or flashes of light in your eyes in the last three months. An eye exam performed by an ophthalmologist may be necessary prior to study entry.

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A urine pregnancy test will also be done for women who can have children. The results of the pregnancy test must be negative in order to be in the study.

You will also have an electrocardiogram (EKG) to evaluate the electrical activity of your heart.

The sample of your tumor has already been tested and we have determined that it does contain the proteins needed to qualify for study participation.

If you qualify for the study and agree to participate, you will be enrolled and we will make arrangements to supply you with the study drug. The first dose of study drug should be taken on the day of your enrollment visit on Cycle 1 Day 1.

During the study (Intervention)

During the study treatment period, each 4-week period of time is considered a "cycle." The cycles are repeated every 28 days, unless a study treatment delay is needed due to side effects. Study treatment will be given to you to take home. One 250mg crizotinib capsule should be taken twice daily with or without food. Your dose may be adjusted by your study doctor if you experience significant side effects. If side effects or complications from study treatment occur, your study doctor may tell you to temporarily stop taking the study drug or to adjust the dose.

In addition to taking crizotinib twice daily, you must also do the following:

- Swallow the capsule whole. Capsules should not be broken or crushed.
- Keep the tablets in their original bottle.
- If you miss a dose, you should take it as soon as possible unless the next dose is due within 6 hours.
- If vomiting occurs after taking a dose, an extra dose should not be taken.
- Do not eat grapefruit or drink grapefruit juice.
- Do not take any new (including herbal) medication without first speaking with your study doctor or research staff.
- Use caution when driving a car, using machinery, or doing anything that needs you to be alert if you experience changes in your vision, dizziness and tiredness.

Every two weeks for the first eight weeks, you will meet with your study doctor and/or clinical study staff. After that, you will meet with your study doctor and/or clinical study staff every four weeks for as long as you are being treated on the study. During these visits, we will take some blood to periodically check your blood counts and kidney and liver function. We will also check your vital signs and weight and ask about any side effects you may have. We may ask that you have additional office visits and/or laboratory testing if you have symptoms or side effects. An EKG will be done 28 days after your first dose of study drug (+/- 7 days) and then only repeated if your study doctor feels it is necessary.

A CT scan of your chest, abdomen, and pelvis or PET/CT scan will be planned every eight weeks, ± 7 days from cycle 1 day 1 while you are receiving the study drug. If your study doctor is following

your disease using CT scan, a bone scan will also be done at the same interval if you had evidence of bone metastases (spread) to your bones at your screening scans. Also, a bone scan may be done if you have new bone pain or other signs that the cancer may be spreading or worsening in your bones.

You will continue to receive the study drug until your cancer gets worse, until side effects become unbearable even if they are being medically treated, or until you are too ill to continue. You also have the option to voluntarily discontinue study treatment and withdraw from the study at any time.

Your study doctor may also choose to withdraw you from the study for any reason.

After you complete the intervention (Follow-up)

Within 30 days of your last dose of study drug, you will come in and meet with your study doctor and/or clinical study staff. At this visit, you will have blood drawn.

Following this visit, study staff will contact you every six months after you stop taking the study drug for follow-up.

RISKS

Crizotinib has been approved by the FDA for the treatment of certain metastatic lung cancers, so the risks of the drug have been studied extensively for these other disease types. While you are on this study, you are at risk for the side effects listed below. Most people do not experience all of the side effects listed. A side effect may get worse during the course of study treatment, or more side effects may develop as the study treatment goes on. Your study doctor will closely monitor and treat/prevent the side effects you might have through the study period. The side effects of crizotinib are:

Most Common (25% or more of patients):

- Vision problems. These problems usually happen within 1 week of starting the study drug. Vision problems can be severe and may cause partial or complete loss of vision in one or both eyes. Tell your study doctor right away if you have any change in vision, such as double vision, flashes of light, blurred vision, light hurting your eyes, new or increased floaters.
- Swelling and redness of the eyelids
- Change or loss of taste
- Decreased appetite
- Dizziness
- Nausea
- Diarrhea
- Vomiting
- Constipation
- Edema or swelling of your hands and feet
- Abnormal liver function or damage
- Low white blood cells, which can cause infection

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- Fatigue or feeling tired
- Upper Respiratory Infection
- Damage to the nerves that may interfere with walking or organ function which may cause numbness, tingling, weakness, or pain in the muscles

Less Common (less than 25% of patients):

- Slowing of heart rate or irregular heart rhythm; may cause fainting
- Acid reflux (heartburn)
- Blood clot in the lung that may cause pain or shortness of breath
- Muscle spasms
- Rash
- Fever
- Increased or decreased weight
- Headache
- Blood testosterone decreased
- Esophagitis (inflammation of the esophagus)

Some other rare but serious risks include but are not limited to:

Hepatotoxicity (Abnormal liver function or damage)
Symptoms of abnormal liver function may include yellowing of your eyes, decreased appetite, darkening or change to your urine color to orange or brown, bleeding or bruising more easily, abdominal pain, itching, nausea or severe fatigue. You must report these symptoms and inform your study doctor immediately.

Pulmonary Symptoms (Lung problems or pneumonitis)
If you experience any new or worsening pulmonary symptoms such as difficulty breathing, shortness of breath, cough with or without mucus, or fever, you must report these symptoms and inform your study doctor immediately. Crizotinib can cause scarring of the lungs.

Bradycardia (slow heart rate)
Symptoms of bradycardia include dizziness, lightheadedness, and syncope or fainting. If you experience any of these while taking the study drug, you must report these symptoms and inform your study doctor about the use of any heart or blood pressure medications.

Other Risks

Computed Tomography (CT), Positron Emission Tomography (PET) and Radionuclide Bone Scan Risks

The CT, PET/CT, and bone scans will expose you to some radiation. Radiation levels are within acceptable limits. Ask the study doctor about the risk from these scans in this study. IV contrast dye given with a CT scan may cause an allergic reaction or kidney function abnormality.

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Blood Drawing Risks

During this study, small amounts of blood will be drawn from a vein to perform tests that allow your study doctors to see how you are doing. Drawing blood may cause pain where the needle is inserted, and there is a small risk of bruising and/or infection at the place where the needle is inserted. Some people experience dizziness, upset stomach, or fainting when their blood is drawn.

Reproductive Risks

Because of risks of fetal harm, women who are pregnant cannot participate in this study and women of child-bearing potential must not become pregnant while on the study drug. Women on this study and the partners of men on this study must use adequate forms of contraception while on study treatment and for at least 90 days after last taking study drug. If you or your partner becomes pregnant during the study, you must inform your study doctor immediately.

Highly effective methods

- Male sterilization (vasectomy). For female subjects, the vasectomized male partner should be the only partner
- True abstinence, if this is your preferred and usual lifestyle

Effective methods

- Placement of intrauterine device or intrauterine system
- Condom with spermicidal foam/gel/film/cream/suppository
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ suppository
- Hormonal contraceptives

Unacceptable methods

- Abstinence at certain times of the cycle only, such as during the days of ovulation or after ovulation (based on symptoms or temperature)
- Pre-ejaculatory withdrawal

It is not known whether the study drug is secreted in breast milk. Because many drugs are secreted in breast milk, women who are breastfeeding are not eligible for this study.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study doctor or study staff right away if you have any problems.

WILL I BENEFIT FROM PARTICIPATING IN THIS STUDY?

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If you agree to take part in this study, there may or may not be direct medical benefit to you. The use of crizotinib in metastatic urothelial cancer is experimental and the potential benefits for its use are unknown. Other subjects with cancer may benefit in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

You may choose not to participate in this study. Instead of being in this study, your options include but are not limited to:

- Other investigational drugs
- Treatment with other anticancer drugs
- No therapy with comfort care only

Please talk to your study doctor about these options and their potential risks and benefits. Please ask any questions you may have and take as much time as you need to make your decision.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You and/or your health plan/insurance will need to pay for all routine care procedures. Levine Cancer Institute will provide you with the study drug, crizotinib, at no charge. There is no additional cost to you to take part in this study. Some health insurance plans may not cover certain procedures and medical treatments. You may wish to discuss coverage with your insurance company before agreeing to participate in this research study.

You will not receive payment 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.

STUDY STAFF PAYMENT/FINANCIAL DISCLOSURE

None of the doctors asking you to participate in this study has received or will receive money or other benefits for personal use from the study sponsor. However, the sponsor will give money or other benefits to a research fund, foundation, educational institution, or other organization with which the doctor or study staff is associated.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

If you become ill or are hurt while you are in the study, get the medical care that you need right away.

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In the event that you are harmed as a result of your participation in this study, inform your study doctor immediately so you can access medical treatment. You and/or your health plan will be charged for this treatment in the usual manner. The study will not pay for standard medical treatment.

By signing this form, you do not waive any of the legal rights that you may have. You still have the right to make a claim through the legal system even if you sign this form, accept medical care, or accept payment for medical expenses.

CONFIDENTIALITY

The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a patient. Your record for this study may, however, be reviewed and/or photocopied, by Levine Cancer Institute, Carolinas HealthCare System, or by representatives of the Food and Drug Administration or other government agencies. To that extent, confidentiality is not absolute.

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location.

AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

If you wish to take part in this clinical study, you will be asked to sign this consent form. It allows the study sponsor and the study investigator to collect, process and pass on to the sponsor organizations any relevant personal health information collected from you during the study. These are activities routinely carried out during all clinical studies.

You have been told that personal information about you (including sensitive personal health information, such as your medical history and your racial/ethnic origin if relevant to the study) will be reviewed, collected on a computer database, stored in electronic or manual files, audited, and/or otherwise processed by:

- the study doctor and study staff,
- the study sponsor and/or its associated companies, Levine Cancer Institute,
- regulatory or other governmental authorities of the United States and other countries,
- other persons authorized by the study sponsor,
- Carolinas HealthCare System employees,
- other persons or agencies as required by law or allowed by federal regulations.

You have been told that your personal data are being collected and processed to:

- check your suitability to take part in the study,
- monitor your treatment with the study drug,
- compare and pool study treatment results with those of other subjects in clinical studies,

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- support the development of the study drug,
- support the licensing application for regulatory approval of the study drug in the world
- support the marketing, distribution, sale and use of the study drug anywhere in the world.

You have been told that your personal information may be processed within the U.S. or elsewhere in the world or transferred to or from the U.S. for review, processing and/or storage by an associated company or a carefully selected third-party organization. By signing this document, you explicitly consent to the transfer of your personal information, including sensitive personal information, collected during this clinical study, for review, processing and/or storage. Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, the groups are committed to keeping your personal health confidential.

You may refuse this authorization to transfer your personal information. If you choose not to agree to this authorization, you might be ineligible to participate in the study. If you decide not to sign this authorization, that will not harm your relations with your doctors or with Carolinas HealthCare System.

You have the right to inspect your medical record at any time. Your research record may be unavailable until the conclusion of the study. At that point, it will be available. Please speak with the study doctor if you desire to access your record.

You have been told that whenever your personal information is processed; it will be kept confidential and secure, to the best of our ability. It will be used only for the purpose for which it was collected.

This Authorization does not have an expiration date. You have been told that according to the guidelines for good clinical practice, the study investigator and sponsor will keep your personal information for at least 6 years. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely. If you wish to revoke authorization to use your personal information, you will notify the study doctor in writing at the address and telephone number listed on the first page of this form. Some of the data obtained from your record prior to your revocation may still be used if considered necessary for the study.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

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- By mail:
  Study Subject Adviser
  [redacted]
- or call **toll free**: [redacted]
- or by **email**: [redacted]

PLEASE REFERENCE THE FOLLOWING NUMBER WHEN CONTACTING THE STUDY SUBJECT ADVISER: PRO00015549.

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.

BEING A STUDY VOLUNTEER AND WITHDRAWING FROM THE STUDY

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not to be in the study, that will not in any way harm your relations with your doctors or with Carolinas HealthCare System. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Carolinas HealthCare System.

- You may always say no. You do not have to take part in the study.
- If you start a study, you may stop at any time. You do not need to give a reason.
- If you do not want to be in a study or you stop the study at a later time, you will not be penalized or lose any benefits.
- If you stop, you should tell the study staff and follow the instructions they may give you.

Your part in the research may stop at any time for any reason, such as:

- The sponsor or the study doctor decides to stop the study.
- The sponsor or the study doctor decides to stop your part in the study for your safety.
- You need additional medicine.
- You do not follow the study rules.
- You have a new injury or illness.
- You decide to stop.

You may be asked to stop the study even if you do not want to stop.

NEW INFORMATION ABOUT THE STUDY

You will be told about any new information found during the study that may affect whether you want to continue to take part.

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STATEMENT OF CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____ ____/____/____ _____

Signature of Research Subject Date Time

_____

Printed Name of Research Subject

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject the nature and purpose of the above study. There has been an opportunity for the subject to ask questions about this research study. I have been available to answer any questions that the subject has about this study.

_____ ____/____/____ _____

Signature of Person Explaining Consent Date Time

_____

Printed Name of Person Explaining Consent

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