PRINCIPAL INVESTIGATOR: Ravi A. Madan, M.D.

STUDY TITLE: A Single Arm Phase II Study Combining CRLX101, a Nanoparticle Camptothecin, with Enzalutamide in Patients with Progressive Metastatic Castration Resistant Prostate Cancer Following Prior Enzalutamide Treatment

STUDY SITE: NIH Clinical Center

Cohort: *Standard*

Consent Version: 03/02/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Ravi Madan, M.D.
Tel: 301-480-7168
Email: madanr@mail.nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

You have been diagnosed with metastatic, castration-resistant prostate cancer. There are several therapies available to treat your disease. One of them is enzalutamide, a modern hormonal therapy, that is FDA approved to treat metastatic prostate cancer. Unfortunately, enzalutamide only works for a period of time before the cancer becomes resistant to enzalutamide. This study will evaluate if combination with a second treatment could make enzalutamide effective again in people who have already had enzalutamide.

In this manner, this study will test a new way of potentially treating prostate cancer using an investigational drug called CRLX101 in combination with enzalutamide in people with progressive metastatic, castration-resistant prostate cancer following prior enzalutamide treatment.

CRLX101 is a sugar molecule called cyclodextrin that is linked to a chemotherapy drug called camptothecin. Linked together, the combined molecule or "nanoparticle drug conjugate" travels through the bloodstream. Once inside the cancer cells, the chemotherapy drug is released from the combined carrier molecule. The study will test how safe it is to receive CRLX101 and how well it works in prostate cancer in combination with enzalutamide.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

Because you have been diagnosed with metastatic castration-resistant prostate cancer and have prior history of enzalutamide treatment, you are invited to take part in this clinical research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 30 subjects will be enrolled in this study.

DESCRIPTION OF RESEARCH STUDY

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

Before you begin the study

Before beginning the study, you will need to have tests and/or procedures to help your doctor decide whether you can take part in the study. This is called screening. Most of the exams, tests, and procedures you will have are part of regular cancer care. However, there are some extra tests that you will need to have if you take part in this study. If you have had some of them recently, they may not need to be repeated.

These tests include:

- Review of your previously collected tissue or a laboratory report to confirm your diagnosis
- History and physical evaluation including vital signs
- Routine blood tests
- Urine tests
- CT scan of chest/abdomen/pelvis or MRI
- Bone scan
- Testosterone and prostate-specific antigen (PSA) levels
- Electrocardiogram (EKG)

During the study

Participants meeting eligibility criteria will be enrolled to receive standard dose of enzalutamide in combination with CRLX101. The duration of each cycle will be 28 days. Enzalutamide will be administered orally and will be taken once daily. CRLX101 will be administered as IV infusion.

The participants will be evaluated by a provider, with history, physical exams and standard blood tests and panels on day 1 and day 15 of each cycle. Serum PSA will be drawn on day 1 and day 15 of each cycle, and testosterone levels will also be evaluated on day 1 of each cycle. Bone scans and CT scans will be done on the first day of every 3rd cycle (Cycle 3 Day 1, Cycle 6 Day 1, etc.) until evidence of disease progression present. Participants will have an EKG at baseline. If the baseline EKG is abnormal, it will be repeated again on C1D1, C1D15 and C2D1 1-3 hours after CRLX101 infusion is completed.

Additionally, throughout the study, participants will be encouraged to drink fluids before and after CRLX101 treatment during the cycle, with the administration of IV fluids. As part of a research test, we will collect your urine on day 1 of cycle 1 and day 15 of cycle 2. Participants will be asked to take sodium bicarbonate tablets starting from 48 hours before and through one day after the CRLX101 infusion on C2D15. This is being done to determine whether adding bicarbonate can reduce bladder inflammation that is sometimes caused by camptothecin. Urine collection is not required if you have incontinence or other conditions preventing urine collection by standard techniques. If you have incontinence and you are willing to participate, a sterile catheter inserted into your bladder will be placed on C1D1 and C2D15 to allow urine collection. Participants will need to stay in hospital up to 24-26 hours after end of infusion for research sample collection and urine collection, at the discretion of the Principal Investigator.

We will first enroll 3 to 6 subjects to receive enzalutamide with a lower dose of CRLX101. This is called lead-in period. If no subjects develop intolerable side effects in the first two cycles, these same participants will continue with a higher dose of CRLX101. For these participants, CRLX101 will be administered every 2 weeks for each subsequent cycle.

All other subjects enrolled after the lead-in period will receive enzalutamide with a higher dose of CRLX101. CRLX101 will be administered every 2 weeks for each cycle.

You will continue to receive the study drugs (in repeated 28-day cycles) until you cancer worsens, you have unacceptable side effects, you decide to no longer take part in the study or your study doctor decides it is no longer suitable for you to continue. The study doctor will continue to follow-up with you indefinitely.

Research Samples:

Research tests will be done on blood taken at various times during your participation in this study: prior to treatment dose on Cycle 1 Day 1, Cycle 2 Day 15 and Cycle 6 Day 1, and at the time that your disease gets worse. The NIH has set a limit on the maximum amount of blood that can be taken for research. This limit is based on your age. For adults, no more than 37 tablespoons can be taken over an 8-week period.

Research tests will also be done on urine samples taken on Cycle 1 Day 1 and Cycle 2 Day 15.

When you are finished taking the drugs

We would like to see you again within 30 days after you have stopped taking the study drug in order to perform the following tests:

- History and physical evaluation including vital signs

- Standard blood tests including a complete blood count
- CT scan of chest/abdomen/pelvis or MRI
- Bone scan
- EKG

Additionally, you will be asked to come back 30 days after you have stopped taking the study drug for an end of treatment visit. These 2 visits can happen simultaneously or at 2 different times. After the end of treatment visit you will be contacted every 6 months via telephone to enquire about your disease status.

If you are unable to return to clinic for either of these visits you will be contacted by phone to assess toxicities.

BIRTH CONTROL

Your study doctor will discuss the risks to unborn children for the drugs used in this study. The effects of the study drugs, if any, on unborn children are unknown. If your partner is capable of becoming pregnant and you wish to participate in this study, you must agree to use a condom during the study treatment period and for 120 days following the last dose of study drug. You must also agree not to donate sperm during the study and through 120 days following your last dose of study medication.

If your partner becomes pregnant or suspect she is pregnant while you are participating in this study, she should inform her treating physician immediately and you should inform your study doctor immediately.

RISKS OR DISCOMFORTS OF PARTICIPATION

What side effects or risks can I expect from being in this study?

As with all treatments, there are several side effects or risks from the treatments provided in this study. However, doctors don't know all the side effects that may happen with this combination of drugs, so it is important to report any changes that you notice, even if your study team does not ask specifically about them. Side effects may be mild or severe. Your study team will give you medicines to help lessen side effects. Many side effects go away with those medicines and others may go away soon after you stop treatment. In some cases, side effects can be serious, long-lasting, or may never go away. In very rare instances, they could cause death.

Possible side effects of CRLX101

The following risks and discomforts have been reported from previous and ongoing studies of CRLX101.

Very common (>10% of people reported):

- Low number of red blood cells that can cause tiredness and shortness of breath (anemia) If this becomes severe, you may need to come into the clinic or hospital to have a transfusion of red blood cells.
- Feeling tired or lacking energy (fatigue)

- Nausea
- Inflammation of the bladder (cystitis)
- Blood in the urine (hematuria)

Common (3-10% of people reported):

- A decrease in white blood cells (specific type called neutrophils), which can lead to infection requiring antibiotic treatment and possibly hospitalization (neutropenia)
- Diarrhea
- Vomiting
- Dysuria (painful or uncomfortable urination, typically a sharp, burning sensation)
- Difficulty passing stool (constipation)
- Fever or chills
- A decrease in white blood cells (not specified by type) in blood (leukopenia)
- A reduction in platelets (blood cells that help the blood to clot), which can lead to bleeding requiring one or more platelet transfusions (thrombocytopenia)
- Numbness, tingling or weakness in hands or feet (peripheral neuropathy)
- Loss of hair (alopecia)
- Decreased appetite
- Presence of white blood cells in the urine (leukocyturia)
- Presence of protein in the urine, which may cause fluid retention (proteinuria)

Uncommon (1-2% of people reported):

- Swelling or build-up of fluids in the extremities (peripheral edema)
- Muscle discomfort or pain (myalgia), joint pain (arthralgia)
- Altered taste
- Bladder spasm
- Blood in the urine and painful voiding (hemorrhagic cystitis)
- Increased need to urinate at night (nocturia)
- Decreased urine flow or incomplete emptying of bladder (urinary retention)
- Infusion related reaction (symptoms, such as skin rash or red areas on the skin (hives) that are intensely itchy (urticarial), fast heart rate, low blood pressure, coughing or

breathing difficulties, are related to the drug administration and may range from symptomatic discomfort to fatal events)

- Shortness of breath (dyspnoea)
- Urinary tract infection
- Increased ALT (a liver enzyme) in the blood
- Dehydration
- Haemoglobin Decreased
- Pain in the extremities (arms and legs)
- Abdominal pain
- Increased AST (a liver enzyme) in the blood
- Weakness (asthenia)
- Blood creatinine increased
- Chills
- Dizziness
- Increased need to urinate (micturition urgency)
- Abdominal distension
- Increased blood alkaline phosphate
- Bone pain
- Cough
- Indigestion (Dyspepsia)
- Flatulence
- High levels of sugar in the blood, if sugar in the blood is too high, it may require hospitalization or treatment (hyperglycemia)
- Abnormally susceptible or sensitive physiologically to a specific agent (as a drug or antigen) (hypersensitivity)
- Low potassium level in the blood (hypokalaemia)
- Difficulty sleeping or falling asleep (insomnia)
- Lymphocyte count decreased
- Muscle discomfort or pain (myalgia)
- Urinary frequency (pollakiuria)

- Rash
- Puncture or hole in the last part of the small bowel (ileal perforation)
- Pinpoint, round spots that appear on the skin as a result of bleeding (petechiae)
- Infection in one or both of the lungs, symptoms vary from mild to severe, such as high fever, shaking chills, a cough with phlegm that does not improve or get worse, shortness of breath, chest pain when breathing or coughing (pneumonia)

Possible side effects of enzalutamide

Likely:

- Ankle swelling.
- Fatigue
- Headache
- Hot flashes
- Diarrhea
- Low blood counts
- Back pain
- Upper respiratory tract infection

Less Likely:

- High blood pressure
- Dizziness, anxiety
- Dry skin
- Blood in urine
- Jaundice
- Weakness of muscles

Rare but Serious:

- Seizures
- *Posterior reversible encephalopathy syndrome (PRES)

*There have been rare reports of posterior reversible encephalopathy syndrome (PRES), a rare, reversible condition involving the brain, in people treated with enzalutamide. If you have a seizure, worsening headache, confusion, blindness or other vision problems, please contact your doctor right away. Your doctor will stop enzalutamide if you develop PRES.

Other Risks

Blood draws: There may be some side effects associated with the procedures for drawing blood in this study, but the person drawing your blood will attempt to minimize this discomfort. Side effects include pain and bruising in the area where the needle is inserted, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) is a risk.

CT scan and PET contrast: Although rare, the intravenous (IV) contrast material involved in some CT and PET scans causes medical problems or allergic reactions in some people. Most reactions are mild and result in hives or itchiness. In rare instances, an allergic reaction can be serious and potentially life threatening. Make sure to tell your study doctor if you've ever had a prior reaction to contrast material during medical tests.

WHAT ARE THE RISKS OF RADIATION?

During your participation in this research study, you will be exposed to radiation from CT scans and bone scans. The amount of radiation exposure you will receive from these procedures is equal to approximately 6.0 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scan and bone scan that you get in this study will expose you to the roughly the same amount of radiation as 20 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.6 out of 100 (0.6%) and of getting a fatal cancer is 0.3 out of 100 (0.3%).

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

We do not know if you will receive personal, medical benefit from taking part in this study. The knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS.

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

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study

- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. You must notify your study doctor and your regular doctor of your decision as soon as possible..

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Ellipses Pharma or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using drugs developed by Ellipses Pharma through a joint study with your researchers and the company. The companies also provide financial support for this study.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the

information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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

1) The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
2) National Institutes of Health Intramural Institutional Review Board
3) The study Sponsor (Center for Cancer Research) or their agent(s)
4) Qualified representatives from Ellipses Pharma, the pharmaceutical company who produces CRLX101.

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or

2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Ravi Madan, M.D., Email: madanr@mail.nih.gov, Telephone: 301-480-7168. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.