Phase II Trial for Intestinal Microbiome Modulation With Antibiotics in the Neoadjuvant Treatment of Locally Advanced Rectal Cancer

NCT06793137

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FREE AND INFORMED CONSENT FORM (FICF)

RESOLUTION 466/12 CNS/MS

I - IDENTIFICATION DATA OF THE RESEARCH PARTICIPANT OR LEGAL RESPONSIBLE

1. Name of participant: .....

Date of birth: ..... /...../.....

II - DATA ON SCIENTIFIC RESEARCH

1. Title of the research protocol: PHASE II CLINICAL STUDY FOR MODULATION OF INTESTINAL MICROBIOTA WITH ORAL USE OF METRONIDAZOLE, IN THE NEOADJUVANT TREATMENT OF LOCALLY ADVANCED RECTUM ADENOCARCINOMA.

2. Responsible researcher:

- Dr. Samuel Aguiar Junior – Reference Center for Colorectal Tumors, A.C. Camargo Cancer Center, São Paulo.

3. Researchers involved:

- Dr. Renata Takahashi – Reference Center for Colorectal Tumors, A.C. Camargo Cancer Center, São Paulo.
- Dr. Bruna Elisa Catin Kupper – Reference Center for Colorectal Tumors, A.C. Camargo Cancer Center, São Paulo.
- Dr. Paulo Roberto Stevanato Filho – Reference Center for Colorectal Tumors, A.C. Camargo Cancer Center, São Paulo.
- Dr. Paula Moura Mendonça – Reference Center for Colorectal Tumors, A.C. Camargo Cancer Center, São Paulo.
- Dr. Virgílio Souza e Silva – Reference Center for Colorectal Tumors, A.C. Camargo Cancer Center, São Paulo.

4. RESEARCH DURATION: 24 months

III - INFORMATION TO THE PARTICIPANT

You are being invited to participate in the research “Phase II Clinical Study for Modulation of Intestinal Microbiota with Oral Use of Metronidazole, in the Neoadjuvant Treatment of Locally Advanced Rectal Adenocarcinoma .”

Please read this form carefully, as it tells you what you need to know about this research. When you receive this form, we will explain the purpose of the research, the procedures that will be performed, and the potential risks and benefits. Before you decide to participate in this research, take the time to ask questions of the researcher, as well as talk to your family, friends, doctor, or other health care

professional. The researcher will fully answer any questions you have before you decide about whether or not to participate in this research.
If you agree to participate in this study, you must initial all pages, sign and date this Consent Form in 2 copies. One will remain in your possession and the other will be filed by the researcher. Your signature means that you have received the necessary information and wish to participate in this research.
All research must be approved by a Research Ethics Committee before any individual may participate. The Ethics Committee helps protect the interests of participants in research studies. This study was approved by the Research Ethics Committee of the A.C. Camargo Cancer Center (São Paulo, SP), and complies with the standards that regulate research involving human subjects in Brazil.

IV – RESEARCH OBJECTIVES

You have been diagnosed with rectal adenocarcinoma and will undergo neoadjuvant treatment (before surgery) with chemotherapy and radiotherapy, according to the institutional protocol. In this study, which you are being invited to participate voluntarily, we aim to evaluate whether the use of the antimicrobial metronidazole is effective in improving the response to treatment.

V- JUSTIFICATION FOR THE RESEARCH PROPOSAL

Treatment of rectal tumors may involve radiotherapy, chemotherapy and surgery. In cases where radiotherapy and chemotherapy are indicated before surgery, the response to treatment may be so satisfactory that surgery may even be avoided, if the response to treatment is complete. This may also provide a reduced risk of future recurrence of the disease and a longer disease-free survival.
The microorganisms normally present in the intestinal environment, which are called microbiota, produce different substances that can have a positive or negative effect on human health.

VI – RESEARCH DESIGN

This is a clinical study in which all participants will receive oral metronidazole at a daily dose of 1,500 mg, in three doses of 500 mg every 8 hours, during the first seven days of neoadjuvant radiotherapy (before surgery). It is expected that 100 (one hundred) people will participate in this study, which will be developed over 2 (two) years.

VII – DESCRIPTION OF PROCEDURES

If you agree to participate in this research, it is important that you agree to participate in all stages of the study. These are: providing accurate information about your illnesses, previous and current treatments, and medications you are taking; attending visits on the scheduled dates; using metronidazole, undergoing blood and imaging tests, and using a contraceptive method if you can get pregnant. If you do not think it is feasible, it is recommended that you do not participate in this research.
After agreeing to participate and signing this informed consent form, participants will receive oral metronidazole tablets at a daily dose of 1,500 mg, in three doses of 500 mg every 8 hours, during the first seven days of neoadjuvant radiotherapy (before surgery). In addition, they will have to collect stool samples for analysis of intestinal microorganisms before and after the use of metronidazole.

The procedures that will be carried out are divided into the following periods:

Screening period: You must provide detailed information about your illnesses, treatments, medications, lifestyle habits, and eating habits; you must undergo the stool test proposed in this study before starting treatment. If any criteria are identified that do not allow your inclusion in the study, the researcher will inform you.

Treatment period: during this period you will receive metronidazole, in a daily dose of 500mg and must take 3 (three) tablets, orally, per day, for 7 days, during the first seven days of neoadjuvant radiotherapy (before surgery).

Post-treatment period: You must perform the stool test proposed in this study after using metronidazole. You must also perform the proposed standard tests and attend medical appointments to assess your response to treatment.

We will ask you to collect stool samples at two different times, before and after taking metronidazole. This collection will be done at your home and the study team will provide you with all the material necessary for the collections, at no additional cost. This sample will be stored at the A.C. Camargo Cancer Center, in a specific biorepository for the study (a specific place where biological material collected in research is stored and will be used specifically for this study).

VIII - EXPECTED DISCOMFORT AND RISKS RESULTING FROM THE PROCEDURE

You would already be doing all the tests and consultations to be carried out by the study as part of your treatment. The metronidazole ones will be delivered to you at no additional cost.

Metronidazole is a commercial medication that is already approved for use and widely used commercially, with extremely rare potential side effects. We do not expect to observe serious adverse events or events that lead to intolerance. However, if intolerance occurs, we will recommend discontinuing the use of the medication.

Adverse events associated with the use of metronidazole are uncommon. Rare adverse events or those with unknown frequency include gastrointestinal disorders (nausea, vomiting, diarrhea, changes in taste (metallic taste in the mouth), loss of appetite, mouth ulcers), immune/defense system disorders (severe allergic reaction), ear disorders (difficulty hearing), fever. There are also reports of very rare events (occurring in less than 0.01% of patients taking this medicine), and these include: nervous system disorders (changes in tactile/touch sensitivity, headache, convulsions, dizziness, confusion, changes in gait/walking, tremor, difficulty speaking), psychiatric disorders (confusion and hallucinations, depressed mood), visual disturbances (transient visual changes such as double or blurred vision, changes in color vision), blood and lymphatic system disorders (decrease in leukocytes and platelets in the blood), liver disorders (changes in liver enzymes, alkaline phosphatase, hepatitis), skin disorders (allergies, itching, blisters, redness).

Any adverse effects should be reported to the researchers and recorded in the patient diary that you will receive. All adverse effects will be carefully evaluated by the study staff.

There is also a minimal risk of loss of confidentiality (revealing your identity). Every effort will be made to maintain the privacy of information, which will be restricted to researchers directly involved in this project. In the databases, the numbers used to identify you will be different from your medical record number and at no time will information that could identify you, such as your name, initials or date of birth, be used.

IX - BENEFITS THAT CAN BE OBTAINED

This is a clinical trial and there is no guarantee that you will benefit from it. It is possible that some participants will not benefit directly from this study. The primary goal is that the information obtained through your participation in the research (scientific advances) will be valuable for decision-making and benefit future patients.

X - CONFIDENTIALITY

All data collected will be used solely for scientific research, aiming to better understand the association between intestinal bacteria and response to treatment. Every effort will be made to maintain the privacy of the information, which will be restricted to researchers directly involved in this project. In this sense, all data that may lead to your identification will be encrypted, making the risk of loss of confidentiality, which may occur, minimal. The confidentiality of your information will be maintained, and your identity will be protected, and only members of the medical team and the Research Ethics Committee will have access to the records.

In order to conduct more relevant research, it is important for researchers to share their findings. They do this by publishing their research in international scientific journals. Data is always submitted anonymously and your name and other information that could directly identify you will never be included in a scientific database.

XI - RESEARCH-RELATED DAMAGES

Any harm resulting from your participation in the study will be assessed and treated in accordance with the benefits and care to which you are entitled. By signing this consent form, you are not waiving any of your legal rights, including the right to seek compensation for any harm resulting from your participation in this study.

XII – VOLUNTARY PARTICIPATION/DISCONTINUATION OF THE STUDY

Your participation in this study is completely voluntary (you decide whether or not to participate). Even if you have already agreed to participate and provided your signature, you are free, at any time and without giving any explanation, to stop participating in the research and to withdraw from the research without this causing any harm to you or your treatment. If this happens, the doctors will no longer collect data about you, but they may publish non-personal information collected before you canceled. This decision will not affect your future medical treatment in any way.

The principal investigator of the study may also remove you from this research if he/she feels it is in your best interests, after discussing and explaining the reasons to you, or if the study is stopped earlier than planned because it is considered unsafe.

If you agree to participate, this will be a voluntary collaboration. Your participation in this research will not entail any additional costs and will in no way affect what will be charged to you.

After the end of the research, research participants will maintain their right to medical monitoring and assistance, in accordance with the best medical practices in force in the context of their case and defined by their oncologist.

If you do not accept (or are unable) to participate in this study, your doctor will maintain the standard treatment in this scenario and there will be no detriment to your treatment or care.

Initial of the Researcher Responsible/Delegated Team:	Initial of the participant:

XIII. PAYMENT TO RESEARCH PARTICIPANT

In this research study, in which you are being invited to participate voluntarily, all expenses related to your participation in the study will be paid by the study. If you agree to participate in this research, we clarify that you will not incur any additional costs. It is, however, recommended that you continue to follow up with your usual doctors and health services, for routine procedures not related to the study.
No other payment will be made to you if you agree to participate, as your participation is voluntary. You are entitled to immediate/emergency assistance at no cost in situations related to your participation in the study.

XIV. WHO SHOULD I CONTACT IN CASE OF QUESTIONS:

Colorectal Tumor Reference Center, A.C. Camargo Cancer Center, São Paulo. The researcher and the team involved in the research undertake to provide updated information throughout the study, if this is their wish.

TELEPHONE NUMBERS TO CONTACT IN CASE OF CLINICAL INTEROCCURRENCES, ADVERSE REACTIONS OR ANY QUESTIONS ABOUT THE STUDY: +55 (011) 2189-5000 – extension: 2832, contact Dr Samuel Aguiar Junior.
Address: 211, Professor Antonio Prudente Street, Liberdade, São Paulo.
Emergency telephone number: +55 (11) 2189-5000 and ask the attendant to contact the 24-hour clinical research telephone number, available 24 hours a day.

If the responsible researcher does not provide sufficient information/clarifications, please contact the Research Ethics Committee of the Antônio Prudente Foundation/ A.C. Camargo Cancer Center, by telephone +55 (11) 2189-5020 cep_accamargo@accamargo.org.br .
This Ethics Committee is located at Rua Prof. Antônio Prudente, 211, Liberdade; opening hours: Monday to Thursday from 8 am to 6 pm and Friday from 8 am to 5 pm. The Research Ethics Committee is a group formed by scientists and non-scientists who perform the initial and ongoing ethical review of the clinical study to maintain your safety and protect your rights.

At any time, even if you have already agreed to participate and provided your signature, you are free to withdraw and request the disposal of the collected sample, without this causing any harm to you or your treatment. If this happens, we must formalize your withdrawal in writing and signed, and it will be valid from the date of communication of the decision.

Initial of the Researcher Responsible/Delegated Team:	Initial of the participant:

This document will be prepared in 2 (two) copies. You will receive one of the original copies and the other will be filed by the researcher in his/her research file.

I, _____
declare that, after having been invited to participate in this study, having read, understood and discussed the content of this Consent Form, I agree to participate in this study freely and in an informed manner, authorizing the procedures listed above:

Signature of participant or legal guardian	Signature of the researcher responsible/
_____/_____/_____	Team delegated to apply the Consent Form
Date	_____/_____/_____
	Date

Initial of the Researcher Responsible/Delegated Team:	Initial of the participant: