INFORMED CONSENT FORM (ICF)

Phase II Study of MIBG-I^{131} in Patients With Well-Differentiated Neuroendocrine Tumors and MIBG Positive Scan (MIBNET)

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A.C.Camargo Cancer Center – Brazil

Registration Number on Institutional Research Ethics Committee: 3025/20

March 2021

I. RESEARCH PARTICIPANT OR LEGAL RESPONSIBLE IDENTIFICATION DATA

1.NAME:.....
IDENTITY DOCUMENT NUMBER: ..... SEX: M F
BIRTH DATE: ...../...../.....
ADRESS: ..... Nº..... APT: .....
DISTRICT:.....CITY:.....
ZIP:.....PHONE:(.....).....

2.LEGAL RESPONSIBLE:.....
NATURE (kinship, guardian, healer, etc.): .....
IDENTITY DOCUMENT NUMBER: ..... SEX: M F
BIRTH DATE: ...../...../.....
ADRESS: ..... Nº..... APT: .....
DISTRICT:.....CITY:.....
ZIP:.....PHONE:(.....).....

INTRODUCTION

You are being invited to participate in a clinical study. This Consent Form contains information that will help you decide on your participation. Feel free to consult your family members or others who can help you make the decision. Don't be in a hurry to make that decision, carefully read this Consent Form, and if you have any questions, ask the study doctor or someone of your trust. You must sign this agreement consent only when you understand all the information presented on the following pages and when all your questions about the study are answered satisfactorily. Your participation is voluntary, which means that you will participate in the study only if you want to. You may refuse to participate or withdraw from participating in this study at any time without be harmed or lose any benefit to which you are entitled. You will continue to be accompanied and treated for your condition in the same way.

All research studies must be approved by a research ethics committee before any individual can participate. The ethics committee helps protect the interests of participating in research studies. This study was approved by the Research Ethics Committee of A.C.Camargo Cancer Center for Research and Treatment and complies with the standards regulate research involving human beings in Brazil.

Please read this term carefully as it tells you what you need to know about the objectives of this study. If you agree to take part in this study, you must sign and date this term. Your subscription means you have received the necessary information and wish to participate in this study.

TITLE OF THE RESEARCH PROTOCOL

Phase II Study of MIBG-I131 in Patients With Well-Differentiated Neuroendocrine Tumors and MIBG Positive Scan (MIBNET)

RESPONSIBLE RESEARCHER

Dr. Rachel Riechelmann - Director, Medical Oncology Department, A.C.Camargo Cancer Center - Brazil.

STUDY DESIGN AND OBJECTIVE

You are diagnosed with advanced/ metastatic neuroendocrine tumor. Neuroendocrine tumors they are rare neoplasms, where there are few effective treatments against the tumor. Even after the patient receiving standard treatments (eg, lanreotide or octreotide), the tumor may grow. When this happens, often there are no effective treatments or if there are, they can offer a lot of side effects (example: intravenous chemotherapy). For this reason, research /clinical studies that testing new therapies against refractory neuroendocrine tumors are needed to treat these patients.

One of the possible therapies for certain types of neuroendocrine tumors and that has been promising is the use of radiopharmaceuticals. The principle of these forms of treatment are that neuroendocrine tumors can express receptors (proteins on the cell surface of the neuroendocrine tumor) that work as targets for treatment. The injected therapeutic agent is able to bind to these receptors (targets) and along with it is associated a radioactive particle with the ability to kill cells. This therapy for being target-specific has limited and known adverse effects profile.

In certain subtypes of neuroendocrine tumors, radiopharmaceutical therapy plays a role established. Examples are therapy with the radiopharmaceutical Lutetium^{177} associated with octreotate and MIBG (metaiodobenzylguanidine) associated with iodine (MIBG-I^{131}) for the treatment of paragangliomas and pheochromocytomas. Therapy with MIBG-I^{131} requires that the patient be previously submitted to a scintigraphy exam with lower doses of MIBG to confirm that the neuroendocrine tumor of the patient presents the specific and necessary targets so that the treatment can be effective. The therapy with MIBG-I^{131} has been used, demonstrating antitumor effect in small and with patients with neuroendocrine lung or gastrointestinal tumors. However, until now, we do not have more precise information about its effectiveness in this context.

RESEARCH OBJECTIVES

The objective of the research is to evaluate whether therapy with MIBG-I^{131} is able to control the disease and for how long in patients with neuroendocrine lung or gastrointestinal tumors. Secondly, we will assess the MIBG-I^{131}'s ability to reduce the volume of control symptoms of functioning syndromes (diarrhea, facial flushing, among others), if exist, tolerability to treatment and quality of life of the participant.

PROCEDURES TO BE CARRIED OUT AND THEIR PURPOSES

If you agree to participate in this clinical study, which aims to assess in an integrated manner all mentioned components, it is important that you agree to participate in all stages of the study. Your participation should be discussed with your doctor and depends on when you have been contacted and their eligibility criteria.

All participants who accept to participate in the study must:

● Perform MIBG-I 131 scintigraphy exam to confirm positive expression of markers (targets) of treatment. Purpose: to determine which patients are most likely to benefit with treatment.

● If eligible, they will receive treatment with MIBG-I 131 in up to 4 doses of 7,400 Mbq (200 mCi) each, at least 60 days apart. The administration of the cycles will depend on the result blood tests carried out previously, therefore, each patient will be able to receive from 1 to 4 cycles. In this study for which you are being invited to participate on a voluntary basis, the treatment will continue as long as the tumor is controlled and you feel well, up to the limit of 4 cycles. MIBG-I 131 is administered intravenously with the hospitalized patient, being discharged when reaching limits of radiological exposure recommended by the National Nuclear Energy Commission (invariably, 24 hours). The dose of 7,400 Mbq (200 mCi) per application for up to 4 doses of MIBG-I 131 used in this protocol is the same used in routine at the institution, being also used in other radiopharmaceutical treatments. This dose is safe and practiced by the service for at least a decade in patients with tumors of the paraganglioma type or pheochromocytoma.

● Attend clinical visits that will take place every 2 weeks, which will include blood tests, until resolution of toxicities (usually 30 days post-treatment). Purpose: evaluate, monitor and treating symptoms related to the disease and possible toxicities. These consultations are already part of evaluation routine and would occur independently of the research.

● Perform imaging tests (chest, abdomen and pelvis CT scans) and urine test at the beginning of the treatment, and every 3 months until progression or withdrawal from the study. Purpose: to assess whether the treatment is being effective in controlling the disease. These exams are already part of your routine evaluation and would occur independently of the research.

● Answer the quality of life questionnaires that will be carried out before treatment and the every 3 months as long as the tumor is controlled. You may not be able to answer any question from the questionnaire if you are not comfortable or embarrassed to do so. The estimated time for answering the questionnaire is 20 minutes. Purpose: to assess patients' quality of life.

● Authorize researchers to use their clinical data from medical records. These information will only be used by researchers at the A.C.Camargo Cancer Center. These information will be evaluated anonymously and do not interfere with anything in its treatment. Purpose: we seek to understand what factors can influence your treatment.

● Sign this Free and Informed Consent Form, or your legal representative, in two routes. One will remain in your possession and the other will be filed by the researcher. Initial all pages. Purpose: to confirm that you have received the necessary information, understood it and wish to voluntarily participate in this clinical study. Consultations, blood tests and imaging are already part of your treatment routine. At extra routine interventions, that is, of the study, are the MIBG scintigraphy exam, the treatment with MIBG-I^{131} and quality of life assessments. We clarify that you are completely free to participate or not in the study, and your decision, be it whatever, it will not affect your treatment in any way. If you agree, this will be a voluntary collaboration, with no form of remuneration for this. In the same way, this decision in no way affects what will be charged to you or your health insurer during treatment. At any time, even if you have already agreed to participate and provided with your subscription, you are free to withdraw and request the interruption of your participation in the clinical study, without causing any harm to you or your treatment.

DESCRIPTION OF EXPECTED DISCOMFORTS AND RISKS

If you agree to participate in this study, we clarify that there will be no extra costs beyond necessary to cover the tests requested by your doctor for the evaluation of your case.

● Scintigraphic exams: radioactive materials administered intravenously are used.
These materials emit radiation that is detected by Nuclear Medicine devices, forming functional images of the organs.

o The materials used are not contrasts like those used in radiological examinations, are radiopharmaceuticals. It is rare for a radiopharmaceutical to cause an allergic reaction. When this occurs is easy to treat.

o Radioactive activities administered for examinations are low. Are used materials and dosages according to national and international safety standards.

o The patient continues to emit radiation for an average period of 48 hours after radiopharmaceutical MIBG-I^{131}. During this period, you should not have contact with pregnant women and children under the age of ten.

o The radiation doses used in Nuclear Medicine exams are considered low and safe for the patient. However, theoretically, there is the possibility of damage that can cause damage to embryos and fetuses or cancer. So it is not recommended getting pregnant during and up to 6 months after treatment.

BENEFITS FOR THE PARTICIPANT

The hypothesis of the study is that therapy with MIBG-I 131 is able to control the neuroendocrine tumor, controlling the disease for longer than the available alternatives and improving quality of life.

However, only at the end of the study can we conclude about the presence of any benefit. If this proves, it is possible that, in the future, larger studies will need to be carried out before the proposed scheme can be used on a larger scale. It is possible that some participants are not directly benefit from this study. The primary objective is to contribute to scientific and technological advances information obtained from this study may benefit patients in the future.

ALTERNATIVE TREATMENTS

If you do not accept (or cannot) participate in this study, your oncologist will discuss available therapies (example: intravenous chemotherapy) in your case and there will be no any damage to your treatment or care.

PAYMENT TO THE RESEARCH PARTICIPANT

Participating in this study will not incur any additional costs for you and any type of payment will be made if you agree to participate in this study. You are entitled to compensation if you incur damages associated with the study. Any damage resulting from your participation in the study will be assessed and treated according to the benefits and care

provided you have the right. By signing this consent form you are not giving up on any of your legal rights. The participant and his/her companion(s) may have reimbursement of all expenses related to transportation / food during the tests and procedures that were considered experimental in this study.

VOLUNTARY PARTICIPATION AND STUDY DISCONTINUATION

Participation in this study is completely voluntary (you decide whether you want to be part of it or not). Even if you decide to participate in the study, you can leave it at any time, without give explanations for this, and may even refuse to publish collected data to your respect. If this happens, doctors will no longer collect data about you, but may publish non-personal information collected prior to cancellation. That decision it will not affect your future medical treatment in any way. The study doctor may also withdraw you from this study if you think this is best for you or if the study is interrupted earlier than planned because it is considered not safe.

CONFIDENTIALITY INFORMATION

If you choose to participate in this study, your health information and health record your participation will be kept confidential and confidential. All data collected will be used only for scientific research, aiming at a better understanding of tumors neuroendocrine and current and future therapeutic possibilities. All efforts will be made to maintain the privacy of information, which will be restricted to doctors, researchers and nurses directly involved in this project. In this sense, all and any data that could lead to your identification will be encrypted, making the risk of loss of confidentiality is minimal. Your name will not be used. One way of this Informed Consent will be filed in your A.C.Camargo Cancer Center medical record. However, there is a risk of loss of confidentiality; we will take all possible measures to this does not happen.

GUARANTEED ACCESS

Questions about the procedures should be directed directly to the listed researchers at the end of this consent form.

POST-INFORMED CONSENT

I declare that, after being invited to participate and adequately informed of the risks and benefits of this study, as defined above, I agree to participate in the MIBNET project.

Through my signature, I agree to participate in this study as a volunteer. I have received a copy of this Informed Consent.

Participant Name (Capital) Date ____/____/_____

Participant Signature

Investigator's name (capital) Date ____/____/_____

Investigator Signature

In case a witness or legal representative is required:

Name of witness / legal representative (capital) Date ____/____/_____

Signature of Witness / Legal Representative

São Paulo, 202_____

Project MIBNET TCLE version 2.0 February / 2021

In case of doubt about this clinical study, contact your doctor and/or Dra. Rachel Riechelmann, in the Department of Medical Oncology at A.C.Camargo Cancer Center, at e-mail: rachel.riechelmann@accamargo.org.br or by phone: (11) 2189-5000 (extension 2779 - Medical Oncology), (extension 5188 - Clinical Research) or (11) 98565-9911 (Clinical Research). If the responsible researcher does not provide sufficient information/clarification, please contact with the Research Ethics Committee of Fundação Antônio Prudente/A.C.Camargo Cancer Center by calling (11) 2189-5020. This Ethics Committee is located at Rua Prof. Antônio Prudente, 211, Liberdade; office 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 conduct the initial and ongoing ethical review of the clinical trial to maintain their security and protect your rights.