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

Rachel Riechelmann (Principal Investigator)[1], Milton Barros[1], Mauro Donadio[1], Rodrigo Taboada[1], Tiago Felismino[1], Celso Abdon[1], Virgílio Souza[1], Marcos Camandaroba[1], Victor Hugo de Jesus[1], Rubens Chojniak[2], Eduardo Nóbrega[3]
Departments: 1-Clinical Oncology A.C.Camargo Cancer Center, 2-Image Department A.C.Camargo Cancer Center, 3-Nuclear Medicine A.C.Camargo Cancer Center

A.C.Camargo Cancer Center – Brazil

Registration Number on Institutional Research Ethics Committee: 3025/20

March 2021

Abstract

Neuroendocrine tumors (NET) are rare neoplasms, which frequently present metastatic and incurable at diagnosis. In this context, few effective therapies exist. When the disease becomes refractory to standard therapies, treatments with limited efficacy (eg, surgical debulking, cytotoxic chemotherapies, interferon alpha) that could lead to important adverse events are used. Therefore, clinical studies that test new therapeutic strategies in NET patients with refractory disease are needed. Treatment with radiopharmaceuticals have been studied in NET and showed to be promisor. As an example, is the treatment with Lutetium^{177} octreotate, disponible in Brazil for decades, and one of the most active therapeutic options to NET.

The radiopharmaceutical MIBG-I^{131} (metaiodobenzylguanidine linked to Iodine^{131}) is the first treatment choice for patients with paraganglioma/ pheochromocytoma (PggF), a rare type of neuroendocrine neoplasm originated from neural ganglia. Patients with this neoplasia are submitted to scintigraphy with MIBG-I^{131}, a norepinephrine analog whose transporter protein is highly expressed in this tumor. If the uptake is positive, patients receive treatment with therapeutic doses of MIBG-I^{131}. The disease control with this intervention could last two years. Old and small studies suggested that MIBG-I^{131} could also have an activity in other NET besides PggF. Gastrointestinal (GI) or lung NET could have a positive expression on MIBG-I^{131} scan in up to 50% of the cases. With this rationale, retrospective series reported that MIBG-I^{131} could offer clinical benefit in patients with GI NET, with disease control in up to 80% of the cases. However, the literature regarding therapeutic MIBG-I^{131} to NET not PggF is scarce, heterogeneous regarding population, methods of response assessment, doses of the radiopharmaceutical, and short follow-up time. Therefore, due to the absence of effective therapeutic options for patients with metastatic well-differentiated NET refractory to standard treatments, the evidence that NET can have a positive expression on MIBG-I^{131} scan, and that small retrospective studies with a low level of evidence suggest a benefit for control disease and improvement of symptoms, the investigators proposed a phase II study of MIBG-I^{131} to well-differentiated GI or lung NET patients with positive MIBG-I^{131} scan.

Adult patients, ECOG 0-2, with good organic functions, with progressing metastatic or locally advanced NET of GI or lung origin, with refractory disease or intolerant to available standard therapies, and with positive MIBG-I^{131} scintigraphy in metastatic lesions are eligible for receive up to 4 doses of 7,400Mbq (200 mCi) each, with an interval of at least 60 days. The primary outcome will be the disease control rate (DCR) at 6 months after the end of treatment, per RECIST 1.1; secondary outcomes will be DCR at 3 months post treatment, progression-free survival, radiological and biochemical response (functional NET), toxicities and quality of life measured by the EORTC QLQ-C30 and GINET21 questionnaires. Laboratory tests and clinical evaluation will be performed every 2 weeks during the study; Imaging exams will be performed every 3 months until progression. The study sample will be 22 patients. For this calculation, we consider the H0 of DCR in 6 months of 40% (placebo arm of phase III studies in TNE), H1 as 67%. Two-tailed type I error margin of 10%, power of 80% and loss of follow-up/non-adherence of 10% were considered. We estimated a 50% screening failure (50% positivity on MIBG-I^{131}).

If the study is positive, it can be cost-effective, as we estimate that 67% of patients will obtain disease control lasting at least 12 months, which will provide time free of toxic therapies with a low level of evidence and costly to patients and paying sources. In addition, the study has the potential to change the treatment guidelines for NET, facilitating the incorporation of MIBG-I^{131} as a therapeutic strategy in the treatment protocols for NET at A.C.Camargo Cancer Center. The study, therefore, may allow the institution in the future to offer treatment with MIBG-I^{131} to patients with supplementary health, recovering the costs invested in the MIBNET study.

Introduction

Neuroendocrine tumors (NET) are rare neoplasms, but with increasing incidence and prevalence in the last decades. In more than half of the cases, they present metastatic and incurable at diagnosis. Few effective therapies are approved for these tumors (somatostatin analogues, everolimus, and sunitinib), none have demonstrated gains in overall survival, and none is approved in the Brazilian public health system (SUS).

Well-differentiated NET express, in more than 80% of the cases, somatostatin receptors. Somatostatin analogues, lanreotide or octreotide, have anti-proliferative and anti-secretory activity, and, frequently, are considered the first-line treatment in the metastatic setting.[1] Somatostatin receptors expression, through scintigraphy scan marked with radionuclide and octreotate (Octreoscan©) or positron emission tomography labelled with Ga^{68} (Ga^{68}-PET-CT), is mandatory to effectively indicate the treatment with $Lutetium^{177}$ radionuclide. The NETTER-1 study demonstrated the efficacy of $Lutetium^{177}$, a type of peptide receptor radionuclide therapy (PRRT), in combination with long-acting releasing (LAR) octreotide 30 mg in second-line, with progression-free survival of approximately 40 months versus 8.5 months for the group treated only with LAR octreotide monthly in patients with midgut NET metastatic (HR: 0.20; $p < 0.0001$).[2] The NETTER-1 study established one more therapeutic strategy to NET, the PRRT.

However, invariably, metastatic NET patients develop disease progression to standard treatment. Different chemotherapeutic regimens (FOLFOX, cisplatin/ etoposide, cisplatin/irinotecan, capecitabine/oxaliplatin, and capecitabine/ temozolomide), hepatic debulking surgery, and interferon alpha are used based on small phase 2 trials and/or retrospectives studies. In the Brazilian consensus of NET, these treatment modalities, even with low evidence level, are recommended when there are no other effective treatments available. Although some patients could benefit from these therapeutic options, the results relating to tumor response and quality of life tend to be modest and the toxicity significant (Table 1). Therefore, new treatment should be investigated in this context.

The role of other PRRT therapies for NET has been the focus of research with new radiopharmaceuticals. Scintigraphy exam with I^{123} or I^{131}-metaiodobenzylguanidine (MIBG) is the standard for the staging and therapeutic planning of patients with paraganglioma/pheochromocytoma (PggF), a rare type of NET. Metaiodo-benzylguanidine is molecularly analogous to norepinephrine and, therefore, is used in exams and treatment in these tumors of origin in sympathetic and parasympathetic neural ganglia. Patients whose tumors show positive uptake on the MIBG-I^{131} exam are treated with therapeutic doses of MIBG-I^{131}. The radiolabelled norepinephrine/ norepinephrine analogue is injected intravenously, reaching target cells and emitting Beta radiation within them. In patients with metastatic PggF, therapy with MIBG-I^{131}

demonstrates objective tumor response rates of 30% and 50% of biochemical response in PggF.[4] In 2018, at the American Society of Clinical Oncology (ASCO) congress, the first clinical study with PRRT with a noradrenaline analogue in patients with PggF, AZEDRA® (iobenguane I^{131}), was presented. In this study, 88 patients with metastatic PggF received a maximum dose of 18.5 GBq (500 mCi every 3 months twice).[5,6] The primary outcome was the proportion of participants who reduced at least 50% of antihypertensive medications for at least 6 months; secondary outcomes were response rate and survival. The study was positive (25% decreased the use of antihypertensive medications), the median overall survival was 17.5 and 48.7 months in the participants who received one or two doses of treatment, respectively.[7] Adverse events were considered manageable, the most common of which were haematological (mainly thrombocytopenia), fatigue and nausea.

Retrospective studies demonstrated that 50% to 60% of patients with gastroenteropancreatic (GEP) NET may have tumors with positive expression of MIBG-I^{123},[8,9] especially those with well-differentiated G1 and functioning tumors (producers of amines that cause clinical symptoms , such as carcinoid syndrome). Based on this information, it is intuitive to investigate the treatment with MIBG-I^{131} in other types of NET than PggF. In the largest series of cases, 211 patients with GEP or pulmonary NET treated with MIBG-I^{131} from 1994 to 2014, at the maximum dose of 18,500 MBq, had a median survival of 29 months since the start of treatment, 71% of clinical improvement with a median duration of 12 months and 20% with radiological response (80% disease control).[10] Retrospective study with 38 patients with progressive NET GEP treated with a single dose of 7,400 MBq demonstrated 75% of radiological control of disease (3% of objective response), 63% with improvement of symptoms and median overall survival of 4 years.[11] Toxicity was manageable, with 10% of transient neutropenia or thrombocytopenia and without complications. In another retrospective study of 38 patients with NET (most GEP NET [25 midgut]; one patient with lung NET and 4 with PggF), MIBG-I^{131} was administered at a dose of 5.5 GBq in three cycles at intervals of 10 to 12 weeks.[12] The median progression-free survival was 13 months, the median overall survival was 48 months and the disease control rate was 65% (3 objective responses and 22 with stable disease).[12] In terms of tolerability, only 2 patients (5%) had grade 3 myelotoxicity, which prevented the third application of MIBG-I^{131}.[12] Another

retrospective study with 25 metastatic (17 NET) patients treated with MIBG-I^{131} with a cumulative dose of 27.7 GBq (751mCi) showed improvement in symptoms in 80% of cases and 48% of radiological response by WHO criteria. The median overall survival was 17 months since the last dose of MIBG-I^{131}, with a 5-year survival rate of 59%.[13] Other studies have assessed the role of MIBG-I^{131} in controlling symptoms of refractory carcinoid syndrome. A retrospective study from the 1990s reported improvement in carcinoid symptoms in 14 out of 30 patients, with a median duration of 8 months.[9]

Despite the encouraging data, the few existing studies have important methodological limitations, such as, heterogeneous population (patients with GEP NET and PggF in the same study), varied criteria for evaluating efficacy (WHO and RECIST) and eligibility (presence or absence of disease progression in the baseline; distinct types of tumors with different prognosis), varying doses of MIBG-I^{131} and do not report data on quality of life or symptom control prospectively.

Therefore, based on the premises that: (1) there is a need for research on rare neoplasms; (2) no effective systemic treatment for patients with well differentiated metastatic NET refractory to standard therapy; (3) GEP and lung NET may show positive expression in the MIBG-I^{123}/^{131} scintigraphy exam, (4) data from retrospective studies suggest disease control and symptom improvement, but without data on quality of life and outcomes evaluated prospectively, (5) treatment of MIBG-I^{131} is available in the Brazilian public health system for the treatment of PggF, so there is no need for structural investment in the services that have this therapy, we propose a phase II study of MIBG-I^{131} for patients with GEP or pulmonary well differentiated NET with positive expression on MIBG-I^{131} scintigraphy.

Hypotheses

Well-differentiated NETs, with positive expression in the MIBG-I^{131} scintigraphy exam, will obtain significant radiological, symptomatic and biochemical control, and improved quality of life with therapeutic MIBG-I^{131}, which may be a treatment option instead of expensive, toxic and ineffective treatments, such as chemotherapy regimens, interferon alpha and/or liver debulking surgery.

Objectives

Primary:

1 - Control of radiological disease at 6 months after the end of treatment.

2- Control of clinical/biochemical (functional NET) at 6 months after the end of treatment.

Secondary:

1- Control of radiological disease at 3 months after the end of treatment.

2- Control of clinical/biochemical (functional NET) at 3 months after the end of treatment.

3- Progression-free survival.

4- Radiological response and duration of response.

5- Biochemical response in patients with functional NET.

6- Evaluate tolerability and quality of life.

Outcomes

Primary:

Disease control rate (DCR). Defined by absence of radiological progression in conventional imaging examinations by RECIST 1.1 at 6 months after the end of treatment. For patients with functioning syndrome, beside radiological DCR, patients should have improved in at least 10% of the baseline score of quality-of-life (EORTC QLQ-GINET21) and stability or decrease in tumor markers.

Secondary:

1- Disease control rate (DCR). Defined by absence of radiological progression in conventional imaging examinations by RECIST 1.1 at 3 months after the end of treatment. For patients with functioning syndrome, beside radiological DCR, patients should have improved in at least 10% of the baseline score of quality-of-life (EORTC QLQ-GINET21) and stability or decrease in tumor markers.

2- Progression-free survival. Defined by time from day 1 cycle 1 to death from any cause or radiological progression by RECIST 1.1, whichever occurs first. Patients alive and without progression at the time of study analysis will be censored for time-to-event analysis.

3- Radiological response rate. Assessed by RECIST 1.1 criteria.

4- Rate of Biochemical response. Defined by at least 30 percent drop in the tumor marker (24-hour urine 5-hydroxyindoleacetic acid (5-HIAA) and/or specific hormone), if functioning syndrome, at any time of treatment in relation to pre-treatment value.

5- Quality of life. Assessed by the EORTC QLQ-C30 and QLQ-GINET21; both available in Brazilian Portuguese. Improvement of at least 10% in the baseline score at 3 and 6 months after the end of the treatment will be considered clinically meaningful. Improvement by 10% of the baseline score at 3 and 6 months will be considered clinically meaningful.

6- Incidence of Treatment-related Adverse Events. Frequency of adverse events of grades 2 or more by Common Adverse Event Toxicity Criteria (CTCAE) version 5.0.

Methodology

Study design

This is a single-arm, unicentric, single-stage, phase 2 clinical study of therapeutic metaiodobenzylguanidine (MIBG) for patients with metastatic well-differentiated neuroendocrine tumors and radiological progression or intolerance after standard lines of treatment and with MIBG-I^{131} positive scan.

Eligible patients will receive MIBGI-^{131} in up to 4 doses of 7,400Mbq (200 mCi) each, with an interval of at least 60 days. The administration of the cycles will depend on the results of the haematological exams, therefore, each patient will be able to receive from 1 to 4 cycles; In the experience of A.C.Camargo Cancer Center, most patients receive between 3 and 4 cycles. MIBG-I^{131} is administered intravenously to an inpatient, being discharged when reaching limits of radiological exposure recommended by the National Nuclear Energy Commission (invariably, 24 hours). The dose of 200mCi

per application for up to 4 doses of MIBG-I^{131} used in this protocol is the same used in routine at the institution and is also used in other PPRT treatments. This dose is safe and practiced by the service for at least a decade.

Clinical and toxicity assessments will take place every 2 weeks with medical history, physical examination and general laboratory until resolution of toxicities (usually 30 days after treatment). Imaging exams (chest, abdomen and pelvis CT scans) and 5-HIAA dosage in 24-hour urine (functioning tumors) will be performed at the beginning of treatment, and every 3 months until progression or exit from the study. Symptom assessment will be conducted using quality of life questionnaires that will be administered before treatment and every 3 months until progression. Toxicities will be measured in all medical visits through CTCAE version 5.0. Consultations, laboratory and imaging tests are already part of the treatment routine of these patients. The extra routine interventions, that is, the study, are the MIBG-I^{131} scintigraphy exam, the treatment with MIBG-I^{131} and the quality-of-life assessments.

Clinical data will be prospectively collected in an electronic database (REDCap) and will include sex, age, primary tumor site, performance scale status, functionality, metastatic disease duration, metastasis sites, degree of liver impairment, comorbidities, previous treatments, scores of quality of life results and toxicity.

Study population

Research participants will be recruited from the Clinical Oncology outpatient clinics and must meet all the inclusion criteria and none for exclusion.

Inclusion criteria

• Age greater than or equal to 18 years.

• Well-differentiated metastatic NET from GEP, unknown primary with hepatic metastases or advanced/metastatic lung, inoperable, with no possibility of curative treatment.

• MIBG-I^{131} scintigraphy with positive expression in at least one lesion that presents significant uptake and compatible with therapeutic effectiveness.

• Disease with radiological progression (at least 10% tumor volume growth) in the last 12 months or with clinical and biochemical progression to functional NET according to clinical judgment.

• Progression or intolerance to previous standard treatments according to scenario (private [somatostatin analogue, everolimus] or public [somatostatin analogue]).

• Measurable disease.

• ECOG performance scale 0 to 2.

• Adequate organic function as defined by the following criteria:

- Aspartate serum aminotransferase (AST), alanine serum aminotransferase (ALT) ≤ 2.5 times the upper limit of normal of the local laboratory (ULN-LL);

- Total serum bilirubin ≤ 2.0 x ULN-LL;

- Absolute neutrophil count ≥ 1,500/mm^3;

- Platelet count ≥ 100,000/mm^3;

- Hemoglobin ≥ 9.0 g/dL;

- Estimated creatinine clearance using the MDRD equation ≥ 60ml/min

- Informed consent form signed by the patient or legal representative.

Exclusion Criteria

• Patients already treated with MIBG-I^{131}.

• History of serious clinical or psychiatric illness that, due to clinical judgment, may pose a risk for participation in this study.

• Patients being treated with other protocols with experimental drugs.

• Patients who have had recent major surgery less than 4 weeks ago.

• Patients who received chemotherapy or other cancer therapy less than 3 weeks ago.

• Pregnant or lactating patients.

• Another synchronic neoplasia that requires systemic treatment.

MIBG-I^{131} Treatment

MIBG scintigraphy:

Scintigraphy with MIBG-I^{131} will be performed as the method of choice for research and identification of active anatomical sites of expression of norepinephrine

receptors; for the staging of PggF and for the assessment of theranostic eligibility of patients for treatment with high doses of MIBG-I^{131}.

All patients will receive and must follow preparation prior to the exam, making use of iodized solutions to block the physiological uptake of eventual free iodine by the thyroid. Patients will be interviewed prior to the administration of doses, obtaining information about the correct preparation and the possible use of drugs that could potentially interfere with the result.

The exams will be performed 24 hours after the intravenous administration of 1.0 mCi of MIBG-I^{131}, using the GE Discovery 640 or 630 Gamma Camera equipment where images of the entire body and those associated with anatomy (Spect_CT) will be obtained, following the Nuclear Medicine protocols of the A.C.Camargo Cancer Center. The exam will be considered as presenting a positive result when the concentration observed in the 24-hour images is considered to be of moderate to severe degree and still in agreement with the target lesions to be treated. The results will be obtained through the individual reading of the exams by two or more nuclear physicians, with experience varying between 30 and 6 years, with doubts being resolved in consensus with the most experienced.

Treatment with high-dose MIBG-I^{131}

MIBG-I^{131} is a radioactive drug that emits Beta particles (0.61 MeV of energy) with a physical half-life of 8 days and a gamma-ray emitter of 364 keV of energy (which allows the performance of imaging tests), where metaiodobenzylguanidine is a norepinephrine analogue. MIBG-I^{131} is selectively concentrated in tissues enriched by adrenergic innervation (mainly tissues of neuroectodermal origin, which include neuroectodermal neoplasms such as NET. MIBG-I^{131} enters cells through diffusion passive or by neuronal uptake mechanism and is stored in neuro-secretory granules. Unlike noraepinephrine, MIBG-I131 is not metabolized, which allows its intracellular retention for many days, making its theranostic use feasible; it is excreted in its entirety via the urinary tract. The mechanism of antitumor action occurs by the emission of ionizing radiation from the decay of I131; 90% of this radiation comes from the emission of Beta radiation, which has an average penetration of 0.5 mm in the tissues.

The main adverse effect of MIBG-I^{131} is myelotoxicity, which occurs between 4 to 6 weeks after MIBG-I131, with variable frequency according to heterogeneous studies (20-70% of all grades). Acute adverse events are of low intensity and include mild nausea and fatigue, elevated blood pressure (described in patients with PggF). Late events: hypothyroidism could occur if preventive measures described below are not taken; Persistent myelosuppression is uncommon and has been described in pre-treated patients with many previous regimens and chemotherapy (this treatment is uncommon in TNE); myelodysplasia, renal dysfunction or any other organ are considered to be rare and have no proven causality. The absolute contraindications are severe renal failure that requires dialysis, pregnancy/lactation and life expectancy less than 3 months; Relative contraindications are: moderate renal failure, refractory and resistant urinary tract infection, myelosuppression (serum platelet levels less than 100,000/mm^3 and total leukocytes less than 3,000/mm^3). Given the teratogenic potential, women of childbearing potential should undergo contraceptive measures during and for at least 4 months after treatment.

MIBG-I^{131} is administered at a dose of 200mCi intravenously every 8 weeks for up to 4 cycles. Laboratory tests are performed every 15 days, with a focus on assessing myelotoxicity. Laboratory blood tests within the appropriate results (see "inclusion criteria") allow the administration of the next cycle. In the case of any toxicity with a degree equal to or greater than 3 or intolerable and persistent grade 2 toxicity, the next course of treatment will not be administered until the toxicity is grade 1 or resolves. If the toxicity does not resolve or becomes grade 1 within 8 weeks, the next cycle is not administered, and treatment is stopped.

Administration protocol with MIBG-I^{131}

The treatments will be carried out in the Radioisotope Therapy Unit of the A.C.Camargo Cancer Center, which complies with the regulatory standards of the CNEN (National Nuclear Energy Commission) for treatments with radioisotopes and is part of the institutional routine.

After admission, patients will be evaluated by anamnesis, will receive radiological safety instructions and sign the consent form for the procedure, then be

prepared with venepuncture, placement of infusion and hydration equipment with saline, medication with antiemetics (ondansetron) and the collection of control exams.

The dose of MIBG-I^{131} provided by IPEN (Energy and Nuclear Research Institute - CNEN -SP) will be unpacked and its content and radioactive activity checked by the Nuclear Physician responsible for the procedure. The verified and authorized dose will be connected to the infusion equipment properly shielded from radiation and administered slowly between 45 and 180 minutes, under constant heart rate and blood pressure monitoring. Increases in blood pressure should be followed by stopping or slowing down the administration of the dose or/and using beta-blockers until normalization. The discharge will occur after the rate of radiological exposure produced by the patient is reduced to outpatient levels, which occurs within a maximum of 24 hours.

The bone marrow is the organ that receives the highest dose of unwanted radiation originating from the procedure, and during follow-up in cases of any toxicity with a degree equal to or greater than 3 or intolerable and persistent degree 2 toxicity, the next treatment cycle will not be administered until the toxicity is grade 1 or resolves; if it does not run within 8 weeks, treatment is stopped. Women of childbearing potential should use contraception for 6 months and men should consider using a sperm bank.

Thyroid protection is recommended so that it does not absorb radioactive iodine, with the ingestion of potassium chloride syrup twice a day, which begins 72 hours before MIBG-I^{131} and continues for 72 hours after treatment. This procedure is routine in the Nuclear Medicine service.

Guidance on hospital discharge, the participant/patient and their family members/caregivers on safety and radiation protection will be done according to the institution's routine.

Security Assessments

Baseline Assessments:

After signing the informed consent form, patients will be submitted to the baseline eligibility assessment (see Table 2).

Within 6 weeks of the first treatment dose: search for noraepinephrine expression by MIBG-I^{131} scintigraphy. If positive, eligibility is confirmed, and the following procedures are:

• Within 4 days of D1C1: Medical history, including previous diagnosis and treatment, history of other diseases (active and resolved), medications in use and general demographic data. Complete physical examination, ECOG performance index (PS) and vital signs.

• Within 4 days of the first treatment dose, laboratory tests will be performed: blood count, urea, creatinine, ALT, AST, total bilirubin, sodium, potassium, and pregnancy test for women of childbearing age; these patients will be oriented to contraception.

• Baseline imaging exams performed within 8 weeks of the first treatment dose will be accepted: CT scan (or MRI, if applicable) of the abdomen, pelvis and chest.

• For patients with functioning NET, it will be accepted that baseline tumor marker exams have been performed within 8 weeks of the first treatment dose (eg 5HIAA in 24-hour urine).

With the exception of MIBG scintigraphy, which is used routinely for patients with PggF (but not TNE), all of the above tests are already part of the routine in the treatment of NET at A.C.Camargo Cancer Center.

Safety assessments during treatment:

Patients will be evaluated clinically and with laboratory tests (Table 2) every 15 days between treatment cycles and after completion until resolution of any adverse treatment effects. +/- 3 days window will be allowed.

• Complete physical examination, measurement of vital signs, weight measurement, ECOG, use of medications.

• Assessment of adverse events.

• Laboratory evaluation: blood count, urea, creatinine, ALT, AST, total bilirubin, sodium, potassium, and others, if clinically indicated.

To grade toxicities we will use the CTCAE 5.0 criteria. Patients who have intolerable grade 2 or grade 3 toxicity that the investigator deems to be related to MIBG-I131 will have their treatment cycle delayed to grade 1 or resolution. If there is no reduction in the intensity of the adverse event to grade 1 within 8 weeks, treatment is discontinued.

All adverse effects will be graded and assessed whether or not they are related to treatment. If there is no CTCAE 5.0 classification for an adverse event, the degree of severity of mild, moderate, severe and life threatening will be used.

An adverse event for the purposes of this protocol is the appearance of (or worsening of pre-existing) undesirable sign(s), symptom(s) or medical condition(s) that occurs(s) after signature. informed consent, even if the event is not considered to be related to the drug(s) under study. The occurrence of adverse events should be obtained through indirect questions asked to the patient at each visit during the study. Adverse events can also be detected when they are reported voluntarily by the patient during or between visits or through physical examination, laboratory tests or other assessments.

Whenever possible, each adverse event should be assessed to determine:

1. Severity (mild, moderate, severe and life threatening) or (CTCAE 5.0 grade)
2. Its relationship to each drug under study (suspected / not suspected)
3. Its duration (initial and final dates or if they continue in the final exam)
4. Conduct adopted (no conduct adopted; study drug dosage adjusted/ temporarily interrupted; study drug permanently discontinued due to the referred adverse event; concomitant medication administered; non-drug therapy administered; hospitalization / prolonged hospitalization).

Patients requiring hospitalization should be immediately identified by the investigators in the study who monitor all patients.

Criteria suspension of treatment:

Patients may interrupt study treatment for one or more of the following reasons:

• Disease progression (documented by images and defined by the RECIST 1.1 criteria).

Clinical progression, based on the investigator's assessment

• Death.

• Intolerable or persistent adverse event (s) of grade 2 or higher.

• Withdrawal of consent by the patient.

• Need for new cancer therapy and / or surgery.

Effectiveness and Follow-up Assessments:

For evaluation of efficacy, patients will undergo imaging tests (chest, abdomen and pelvis tomography or abdomen and pelvis resonance) at baseline (within 8 weeks of starting treatment) and every 12 weeks (+/- 5 days) until progression or withdrawal from the study. Patients will also be evaluated for signs and symptoms that may be related to disease progression. Patients who present clinical progression, according to the investigator's judgment, but without radiological progression, will be able to discontinue the treatment and continue the image evaluation until progression; however, if new treatment is instituted, the last date of receipt of MIBG-I^{131} will be the censorship date in the progression-free survival analysis.

After documenting progression or leaving the study for other reasons, patients will be followed up by the investigator or another oncologist from the Clinical Oncology team for symptom control, image monitoring and possible future therapies. The patient continues to be cared for at the A.C.Camargo Cancer Center, if desired.

Quality of Life Assessment:

The quality-of-life assessment will be conducted by two questionnaires from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire group, composed of the general questionnaire EORTC QLQ-C30 and its specific domain for TNE, the QLQ-GINET21, both available in Portuguese of Brazil by cross-cultural validation.[14]

The QLQ – C30 general quality of life questionnaire was developed for cancer patients and is one of the most used in clinical cancer research, having already been applied by more than 80,000 cancer patients. Version 3 is the one currently used.[16] It is

multidimensional, can be self-administered and consists of 30 questions that assess the patient in the last two weeks. The questionnaire addresses general questions about cancer, such as symptoms, side effects of treatment, psychological suffering, physical functioning, social interaction, sexuality, body image, global health, quality of life and satisfaction with medical care, regardless of the type of cancer. It is a generic quality of life document for cancer, composed of 30 questions that define the general quality of life, through five functional scales (physical, role/performance, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting) and six simple items (dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties).

The scale in this questionnaire constitutes the following score: 1 (no), 2 (little), 3 (moderately), and 4 (a lot), except the global health scale. This consists of 2 questions that ask the individual to rate their general health and quality of life in the last week, through a score from 1 to 7, 1 being terrible and 7 being excellent. Scores are calculated separately for each of the scales (functional, QOL and symptoms), ranging from zero - 100.[17] On the Global Health and functionality scale, the higher the score, the better the quality of life. In the symptom scales, the higher the score, the worse the score. In order to know the calculation in each scale, the average score in each of the scales is performed. After this average we make the linear transformation for the score to be 0-100, according to the formulas below:

- Gross score or Raw Score (RS): adds the score of each item and divides it by the number of items

- S score for functional scales: {1 - (RS - 1) / variation} x 100

- S score for symptom scale: {(RS - 1) / variation} x 100

- S-score for general health status / general quality of life: {(RS - 1) / variation} x 100

The variation is generally 3, since the items score from 1 to 4, except for the global health and quality scales that score a maximum of 7 and, therefore, there is a general variation of 6.

The complement of the QLQ-C30 for TNE, the QLQ-GINET21 questionnaire, is composed of 5 multi-item scales that address common symptoms in patients with NET, such as gastrointestinal and endocrine, concerns about illness, social role and symptoms of treatments; it also contains five items that assess weight loss/gain, bone/muscle pain,

sexual function. The methodology for calculating the scores is the same as that used by the questionnaire QLQ-C30.[18]

Missing data often occurs in questionnaire studies. Researchers will try to minimize missing data by providing guidance to study participants. However, if it still occurs, several imputation methods can be used, and there is no standard method. The most common is to calculate the average of the scale of the answered items and use this average to input the missing value, provided that at least 50% of the items of that scale have been answered.[19] This will be the method used in this study to treat possible missing data. When missing data occurs in single items, they should be excluded from the analysis.

The EORTC quality of life questionnaires will be applied at the baseline (within 4 days of treatment) and every 12 weeks (window of +/- 5 days) until the study leaves. The administration should preferably be on the day of the image, and always before the patient knows the result of the exam (so that the result does not influence the responses to the questionnaires) and by a trained investigator.

The total time to complete the QLG-C30 and LQL-GINET21 is approximately 20 to 30 minutes. The patient himself will complete the questionnaires; however, he may be helped by an investigator, if in doubt. In the end, it will be inserted in a closed envelope to ensure confidentiality and privacy.

Statistical plan

Descriptive statistics will be used to report population characteristics, binary outcomes and adverse events. The Kaplan-Meyer method will be used to report time-to-event variables and the reverse Kaplan-Meyer method will be used to calculate the follow-up time for patients. For the analysis of quality of life, we will report the proportion of patients who increase the sum of the total score by at least 10% at 3 and 6 months after treatment - improvement of at least 10% is considered to be clinically significant by patients.15 We will also evaluate whether the global score varies and how much varies during the study for each patient; this analysis will be carried out in percentage and descriptively. The scores will be calculated according to the instruction manual of the EORTC group.16 The quality-of-life analysis will be carried out using the

intention to treat method, where patients who do not respond will be considered “non-responders” in terms of the effectiveness of the treatment.

Missing data in the questionnaires will be dealt with as described in the section above "Quality of Life Assessment".

The study sample will be 22 patients. For this calculation, we considered the 40-month disease control rate H0 to be 40% (placebo arm of phase III studies in TNE, such as the RADIANT417 study), H1 to 67%. Two-tailed type I error margin of 10%, power of 80% and loss of follow-up / non-adherence of 10% were considered.
We estimated a 40% screening failure (40% positivity on MIBG-I131).

All analyzes will be by intention to treat. Patients who receive at least one dose of MIBGI131 will be evaluated for toxicity and efficacy.

Study time

About 35 to 40 patients with metastatic NET are treated annually at the A.C.Camargo Cancer Center. Therefore, we estimate to recruit the study population in a maximum period of 2 years and have the first assessment in 3 years.

Ethical Considerations

The study will be carried out in accordance with the protocol, the Good Clinical Practice guidelines of the International Harmonization Conference (ICH GCP) and the applicable local laws and regulatory requirements. The informed consent form (IC) must comply with ICH GCP guidelines, local regulatory regulations and legal requirements.
The investigator must ensure that each patient in the study, or their legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator will obtain written consent from each patient before any specific study activity is performed. The investigator will retain one copy of each consent form signed by the patient. It will be emphasized that participation is voluntary, and that the patient has the right to refuse participation or leave in the middle of the study whenever he wishes. This will not affect subsequent patient care. Female patients will be instructed not to become pregnant during treatment, being

instructed to use contraceptive methods if they are of childbearing age, as has been done in the routine. There is a risk of loss of confidentiality, if patient data is identified, however, all reasonable measures will be taken to prevent this from happening.

The protocol will be approved by the Local Ethics Committee. The study will be registered with the international clinical trial registration database ClinicalTrial.gov.

Study Funding and Sponsorship

The patient will not incur any costs in relation to the MIBG-I^{131} scintigraphy exam or treatment with MIBG-I^{131}, which will be paid for by the Brentani Prize and will be carried out at the Dept. Nuclear Medicine, under the supervision of Dr. Eduardo Nobrega. Everything else (laboratory tests, hormone dosages produced by TNE, conventional imaging tests, medical consultations) is not part of this protocol as it is already part of the routine treatment of patients with NET at the A.C.Camargo Cancer Center, both in the Unified Health System and in the supplementary/private health sector. For this study, insurance against risks of serious adverse events and / or requiring medical intervention (complementary exams, hospitalization or emergency at A.C.Camargo Cancer Center) will be contracted due to an adverse event related to treatment with MIBG-I^{131}.

Global innovation potential and for A.C.Camargo Cancer Center

PRRT therapies have been shown to be highly effective in NET and today they are an active area of research with the development of new radiopharmaceuticals. There is a scientific rationale to test MIBG-I^{131} prospectively and with an adequate methodology, in addition to assessing the impact on patients' quality of life for the first time. If the study is positive, it has the potential to change national and international guidelines for the treatment of NET, helping many patients and giving visibility to the institution. In addition, the incorporation of MIBG-I^{131} as a therapeutic strategy in the treatment protocols for NET in the A.C.Camargo Cancer Center will allow that, after the study, the institution will be able to offer MIBG-I^{131} to supplementary health patients, recovering the costs invested in the study MIBNET.

Potential for cost-effectiveness

Treatment with MIBG-I^{131}, in addition to being available at SUS for the treatment of patients with PggF, appears to offer significant disease control for patients with NET. If the study is positive, it can be cost-effective, as we estimate that 67% of patients will obtain disease control lasting at least 12 months, which will provide time free of toxic therapies, with a low level of evidence and costly to patients and paying sources. In addition, in the absence of a clinical study, these toxic and ineffective therapies are used sequentially, so that each patient will do, in the period of 12 months, at least two of them.

Table 1. Treatments used in midgut NET or refractory lung, respective toxicities, efficacy and levels of scientific evidence[9]

Treatment	Disease control rate (%)	Time of disease control (months)	Common toxicities	Evidence level
Folfox/Capox	0-10%	4 – 6	Peripheric neuropathy, diarrhea, nausea, vomiting, thrombocytopenia, anaemia	Retrospective, heterogeneous population*
Capecitabine/ Temozolomide	0-10%	4 – 6	Nausea/Vomiting, diarrhea	Retrospective, phase 1/2 with heterogeneous population
Interferon alpha (3 to 6 million units/week)	20 – 30% (symptoms), 50% (radiological)	10	Psychiatric disorders, immunes, fatigue, myopathy, myelosuppression	Phase III for radiological control, retrospective studies for symptomatic control
Debulking hepatic surgery (R2)	50 – 90% (only symptoms)	19 – 45	Surgical risk compared to a hepatectomy	Retrospective, heterogeneous population
MIBG-I^{131}	63 – 80%	12 – 24	Myelosuppression	Retrospective, heterogeneous population

* neuroendocrine tumors of different origin, efficacy measured with distinct criteria

TABLE 2. Complete procedural summary of the study after signing the informed consent form

Procedure	Screening *	Baseline evaluation	D1 **	S2 **	S4 **	… **	S8 **	S12 **	S16 **	… **	S24 **	Every 12 or 8 weeks
Eligibility assessment												
MIBG scan	x											
Demographics, medical history and previous treatment	x											
Therapeutic MIBG												
200mCi MIBG-I^{131} IV administration			x				x		x		x	
Clinical safety assessment												
Physical exam		x	x	x	x	x	x	x	x	x	x	X
Vital signs, body weight and ECOG		x	x	x	x	x	x	x	x	x	x	x
Signs and symptoms assessment		x	x	x	x	x	x	x	x	x	x	x
Adverse Event Assessment		x		x	x	x	x	x	x	x	x	x
Laboratory safety assessment												
Hemogram	x	x	x	x	x	x	x	x	x	x	x	
Urea/creatinine	x	x	x	x	x	x	x	x	x	x	x	
Bilirubin, AST/ALT	x	x	x	x	x	x	x	x	x	x	x	
NA, K	x	x	x	x	x	x	x	x	x	x	X	
Pregnancy test in women of childbearing age		x										
Image assessment												
CT of lung, abdomen and pelvis ***	x							x			x	x
Tumor marker **												
Specific hormone		x						x			x	x
Quality of life **												
EORTC QLQ-C30		x						x			x	x
EORTC QLQ GINET21		x						x			x	x

IV, intravenous; MIBG, metaiodobenzylguanidine
* within 6 weeks of the first dose and within 4 working days of D1;
** window of +/- 3 days
*** baseline tests within 8 weeks of D1; Resonance of the abdomen and pelvis in special cases (allergy to iodinated contrast); window +/- 5 days

References:

1- Rinke, A. et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol, 2009

2- Strosberg, J.R., et al. (2016) Netter-1 Phase III: Progression-Free Survival, Radiographic Response, and Preliminary Overall Survival Results in Patients with Midgut Neuroendocrine Tumors Treated with 177-Lu-Dotatate. N Engl J Med, 2017 3- Riechelmann R. Guidelines for the management of neuroendocrine tumours by the Brazilian gastrointestinal tumour group. EcancerMedicalScience, 2017

4- van Hulsteijn LT et al. (131)I-MIBG therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis. Clin Endocrinol, 2014

5- www.clinicaltrials.gov: NCT00874614

6- Pryma D et al. Azedra (iobenguane I 131) in patients with malignant, recurrent and/or unresectable pheochromocytoma or paraganglioma (PPGL): Updated efficacy and safety results from a multi-center, open-label, pivotal phase 2 study. ASCO 2018, abstr #4005

7- Noto RB et al. Long-term survival and safety from a multi-center, open-label, pivotal phase 2 study of iobenguane I 131 in patients (Pts) with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL. ASCO 2019, abstr #4108)

8- Ezziddin S. et al. Factors predicting tracer uptake in somatostatin receptor and MIBG scintigraphy

of metastatic gastroenteropancreatic neuroendocrine tumors. J Nucl Med, 2006 9- Riechelmann RP et al. Refractory carcinoid syndrome: a review of treatment options. Ther Advan Med Oncol, 2017

10- Kane A et al. Predictors of Survival in 211 Patients with Stage IV Pulmonary and Gastroenteropancreatic MIBG-Positive Neuroendocrine Tumors Treated with 131I-MIBG. J Nucl Med, 2018

11- Mulholland N, Long-term outcomes of (131)Iodine MIBG therapy in metastatic gastrointestinal pancreatic neuroendocrine tumours: single administration predicts non-responders. Eur J Nucl Med Mol Imaging, 2015

12- Navalkissoor S. Et al. Efficacy of using a standard activity of (131)I-MIBG therapy in patients with disseminated neuroendocrine tumours. Eur J Nucl Med Mol Imaging, 2010
13-Bomanji JB et al. Treatment of neuroendocrine tumours in adults with 131I-MIBG therapy. Clin Oncol, 2003
14- EORTC QOL website: https://qol.eortc.org/questionnaire/qlq-ginet21/
15- Yadegarfar G, Friend L, Jones L, Plum LM, Ardill J, Taal B, Larsson G, Jeziorski K, Kwekkeboom
D, Ramage JK and on behalf of the EORTC Quality of Life Group. Validation of the EORTC QLQ
GINET21 questionnaire for assessing quality of life of patients with gastrointestinal neuroendocrine
tumours. British Journal of Cancer. Jan 2013. 15- Osoba D et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol, 1998 16- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993; 85: 365-376
17. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by European Organisation for Research and Treatment of Cancer, Brussels 2001
18- Singh, S. Et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. The Lancet, 2016
19- Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by European Organisation for Research and Treatment of Cancer, Brussels 2001