

Phase II study of hormone therapy with tamoxifen in patients with well differentiated neuroendocrine tumors and hormone receptor positive expression (HORMONET)

Time of researchers and respective Departments:

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Registration Number on Institutional Research Ethics Committee: 2626/18

March,06,2019

Introduction

Neuroendocrine tumors (NET) are rare neoplasms, but with increasing incidence and prevalence in the last decades. Although they may manifest in the most diverse tissues, the vast majority of cases will affect organs of the digestive tract and lung. At diagnosis, more than half of the cases present metastatic disease, and among patients with localized disease, up to one-third will have recurrence of the disease. Unfortunately, the minority of patients with metastatic disease are eligible for curative intent.¹

Although there are many types of NET, they are often studied together as a group because their cells share common histological findings, have special secretory granules, and the ability to secrete bioactive amines and polypeptide hormones. Approximately 25 percent of the tumors present functional hormonal syndromes (situation of great morbidity for these patients), being the carcinoid syndrome, the most common one. From the molecular point of view, these neoplasias are largely dependent on the activation of the mTOR pathway and neoangiogenesis.²

Another striking feature of neuroendocrine cells is the expression of cell surface hormone receptors whose activation or blockade may exert an important regulatory function. The discovery of somatostatin, and consequently its receptors, is one of the major advances in the treatment of this neoplasm. Due to the increased ability of somatostatin to inhibit the secretion of several hormones, its antitumor property has long been studied. However, only after the development of synthetic long-life formulations can their use be used in clinical practice. Well-differentiated neuroendocrine tumors (G1 and G2 according to WHO classification) present in more than 80 percent of somatostatin receptor cases. In this population, the use of somatostatin analogues promotes symptomatic improvement of functioning syndromes in the order of 70 to 77 percent and biochemical improvement around 50 percent.³ Regarding antiproliferative activity, two phase III studies evaluated the role of octreotide LAR and of lanreotide autogel, both somatostatin analogs, in the population of well differentiated tumors and, almost entirely, somatostatin receptor hyperexpressors when evaluated by octreoscan. In these studies, the use of

somatostatin analogue was associated with reduced risk of progression or death from 53 percent to 66 percent when compared to placebo. Currently, this class of drugs is often considered as the first treatment option for patients with progressing metastatic disease, when the strategy of watchful waiting is not opted for (because they are tumors of sometimes indolent behavior, some cases are selected for observation only) .4.5

In general, there are few options for systemic therapies that are approved for these tumors in addition to somatostatin analogs (mTOR and antiangiogenic inhibitors), none of which clearly demonstrate overall survival gain, are costly and none are available for use in the public health system (SUS). Therefore, it is very important to develop studies with new therapies for patients with NET, especially, molecularly defined therapies with greater access to patients. In this context, other anti-hormonal therapies could be explored in patients with NET, such as the role of the sex hormones estrogen and progesterone, as well as their receptors.

A few studies have evaluated the expression of estrogen and progesterone receptors in NET and suggest interesting results. One of the largest series was conducted at the AC Camargo Cancer Center where the immunohistochemical expression of these receptors was evaluated in 96 patients with NET from various sites. About 35 percent of the cases presented positivity for some hormonal receptor (HR) in the tumor tissue. 6 Among the HR positive cases, there was no difference between sex, more frequent in thin, pancreatic and lung tumors and in well differentiated tumors (G1 and G2 by the WHO). 6 Viale et al. Evaluated the expression of progesterone receptors (PR) in 96 patients with pancreatic neuroendocrine tumors. Nuclear immunoreactivity for PR was observed in 58 percent of cases, with no difference in PR expression according to gender, age, or functioning syndromes.7 About 163 primary tumors of the gastroenteropancreatic site and 115 metastases were evaluated by Zimmermann and colleagues for expression of female hormone receptors. Progesterone receptor was more frequently found in pancreatic tumors and rarely in non-pancreatic ($p < 0.001$), estrogen receptor was more frequently expressed in non-pancreatic tumors (< 0.001) and in women ($p: 0.019$). 8 There was no difference between primary site and presence of metastases.8

Apparently, HR positive tumors may present a more favorable evolution. Estella et al. Evaluated 160 patients with pancreatic neuroendocrine tumors operated for expression by PTEN immunohistochemistry (negative regulator of the mTOR pathway) and PR. Approximately 69 percent of the cases were positive for PR and PTEN, 28 percent were positive for one of the two markers and only 3 percent were negative for both. Combined positivity for PTEN and PR was associated with metastasis-free survival in stages I and II ($p < 0.001$) and overall survival in all patients ($p < 0.001$), even after adjustment for other prognostic variables. Patients with negative PR and PTEN tumors had the shorter survival times when compared to those who had only one or both markers ($p < 0.001$).⁹ Similarly, Kim et al. Demonstrated a retrospective analysis of 277 patients with neuroendocrine tumors (95 percent vs. 76 percent, $p < 0.05$), and a higher survival rate ($p < 0.05$) than in the control group ($p < 0.05$).¹⁰

Even rarer in the literature is the role of antiestrogen therapies as a form of control of this neoplasia. Case reports point to antiproliferative activity of tamoxifen in patients with NET and, in some cases, patients presenting more than 12 months of disease control.¹¹ Reports of control of carcinoid syndrome and even regression of associated retroperitoneal fibrosis have also been described.^{12,13,14} However, the only study to assess the activity of tamoxifen in neuroendocrine tumors dates back to 1984. Sixteen patients were evaluated clinical benefit in only 19 percent of cases and no radiological response. However, in this study, no patient was previously selected for HR tumor expression or degree of differentiation, which we believe limited benefit in disease control.¹⁵

Therefore, based on the premise that there is a need for research and treatment strategies for this rare neoplasm; there is clear therapeutic embezzlement in the SUS due to the high cost of the treatments approved in the country for this neoplasia; NET are tumors that may present positivity to estrogen and / or progesterone receptors; evidence points to the possibility of antiproliferative effect using hormonal therapy, we propose a phase II study of tamoxifen for patients with well differentiated NET and positive for HR, estrogen and / or progesterone expression.

Hypotheses:

Primary: Tamoxifen, an estrogen receptor agonist, exerts antitumor action in patients with well differentiated NET and positive for the expression of HR, estrogen and / or progesterone.

Secondary:

(1) Tamoxifen will promote reduced levels of chromogranin A and / or specific hormones in biochemically active tumors;

(2) The toxicity profile of tamoxifen will be compatible with the toxicity profile described in the literature.

Purposes:

Primary: To evaluate the efficacy of tamoxifen in patients with well-differentiated NETs, with HR, estrogen and / or progesterone expression, and progression.

Secondary: (1) Evaluate progression-free survival; (2) Evaluate biochemical response; (3) objective response rate; (4) disease control rate according to HR expression intensity and primary site; (5) toxicities

Exploratory:

(1) To evaluate variation of intensity and number of sites capturing PET-CT gallium-68 with tamoxifen;

(2) Document the presence of circulating tumor cells (CTC) and possible diagnostic role, such as liquid biopsy.

Outcomes:

Primary: Disease control rate at 24 weeks after initiation of tamoxifen (since day 1 cycle 1), defined by absence of radiological progression in conventional imaging

examinations by RECIST 1.1 (Appendix I). Isolated increase of biomarker (chromogranin A) or specific hormone will not be considered progression.

Secondary:

(1) Progression-free survival, defined by time from tamoxifen 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.

(2) Biochemical response will be defined by at least 30 percent drop in the marker (chromogranin and / or specific hormone) at any time of treatment in relation to pre-treatment value (s).

(3) Radiological response rate by RECIST criteria 1.1 during the study period.

(4) Disease control rate, defined by absence of radiological progression by RECIST 1.1 criteria, according to the intensity of expression by immunohistochemistry (IHC) of HR and also according to primary site (pancreas, gastrointestinal or lung) during the study period.

(5) Toxicities frequency: Adverse events of grades 2 or more by Common Adverse Event Toxicity Criteria (CTCAE) version 5.0 during the study period.

Exploratory:

(1) Evaluate possible variations in intensity and number of sites between PET-CT gallium-68 pre-treatment and 12 weeks after initiation of tamoxifen as a continuous variable for each capture lesion. Although this examination is part of the evaluation routine of NET, in this study we will evaluate differences in the intensity of uptake with tamoxifen.

(2) Evaluate the percentage of CTC positivity in NET, as well as average number of cells in case of positivity. To evaluate the presence of estrogen and progesterone receptors in CTC.

Methodology:

Study design:

A single-arm, unicentric, single-stage clinical study of tamoxifen for patients with well differentiated neuroendocrine tumors and radiological progression with positive (> 1 percent) HR (estrogen and / or progesterone) expression by IHC.

Patients eligible for the clinical and radiological criteria and signing the Informed Consent Form (ICF) will have the biopsy material (tumor stored in paraffin) evaluated for IHC of HR. If the expression is positive, eligibility will be complete and patients will receive tamoxifen continuously until radiological progression by RECIST 1.1, unacceptable toxicity or withdrawal of consent. If the expression for HR is negative, the patient will be informed of their ineligibility for this study and will continue to be treated by the Clinical Oncology team without any detriment to their care.

Patients will be followed up by the study team for assessments of:

(1) Safety: first in 3 weeks after tamoxifen day 1 cycle 1, and then every 6 weeks from tamoxifen day 1 cycle 1 for anamnesis with active questioning of disease symptoms and possible adverse events, physical examination and routine laboratory routine (hemogram, biochemistry, liver and renal function);

(2) Efficacy: patients will perform imaging (chest, abdomen and pelvic tomography or abdominal and pelvic resonance imaging) at baseline or pre-treatment and every 12 weeks until progression or intolerance / exit from the study. The image response evaluations will be through RECIST 1.1. For evaluation of the biochemical response, patients will undergo hormonal dosing with serum chromogranin A and specific hormones in cases of functioning NET (eg 5-HIAA dosing in 24-hour urine) at the baseline and every 12 weeks until progression (increased chromogranin and / or the functioning hormone will not be characterized as disease progression if imaging shows progression).

(3) Exploratory assessment: Patients will be assessed for somatostatin receptor expressiveness by the functional examination of PET-CT Gallium-68, which will be performed before treatment and at week 12. This evaluation, because it is exploratory, does not will be part of the definition of disease progression.

Also as an exploratory analysis, a blood sample will be collected to search for circulating tumor cells at the baseline visit (a collection only).

After a period of one year, the consultations laboratory and imaging examinations will be performed every 12 weeks until the disease progresses. Collection and evaluation times are summarized in the Table of Procedures (TABLE 1).

The following clinical data will be collected prospectively and structured in an electronic database: gender, age, primary tumor site, NET type (G1 or G2 or NET G3), Eastern Cooperative Oncology Group (ECOG) status, metastasis sites, degree of hepatic impairment (greater than or equal to less than 50 percent in conventional imaging), previous treatments, comorbidities (defined as any clinical condition requiring pharmacological therapy), concomitant medications of chronic use, body mass index, IHC expression intensity of HR, NET-related symptoms, time from the diagnosis of advanced disease to day 1 cycle 1 of tamoxifen, efficacy, adherence and toxicity results.

TABLE 1. Complete procedural summary of the study after signing the ICF

Procedure	Screening *	baseline evaluation n	w S 3 **	S 6 **	w 12 **	w 18 **	w 24 **	w 30 **	w 36 **	w 42 **	w 48 **	Short visit [#]
Eligibility assessment												
Fulfills eligibility criteria	x											
Demographics data, medical history, and prior treatment		x										
IHC Request for Hormone Receptors (ER and / or RP)> 1 percent	x											
Provision of tamoxifen		x	x	x	x	x	x	x	x	x	x	x
Clinical safety assessment												
physical examination		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

Assessment of signs and symptoms		x	x	x	x	x	x	x	x	x	x	x
Review of concomitant medications		x	x	x	x	x	x	x	x	x	x	x
Evaluation of adverse events			x	x	x	x	x	x	x	x	x	x
Laboratory safety assessment												
Blod count	x			x	x	x	x	x	x	x	x	x
Creatinine / urea	x			x	x	x	x	x	x	x	x	x
AST / ALT / bilirubin levels	x			x	x	x	x	x	x	x	x	x
Serum sodium / potassium	x			x	x	x	x	x	x	x	x	x
Pregnancy test in women of childbearing age	x											
INR, albumin	x											
Adherence assessment												
Adherence for days taken / month			x	x	x	x	x	x	x	x	x	x
Image evaluation												
CT scan of the chest, abdomen and pelvis ***	x				x		x		x		x	x
Tumor marker												
Specific hormone		x			x		x		x		x	x
Dosage of serum chromogranin A		x			x		x		x		x	x
Exploratory analysis												
PET-CT-Gallium 68 Somatostatin Receptors		x			x							
Collection of circulating tumor cells		x										

* within 21 calendar days of the first dose;

** window of - / + 3 days

***baseline examinations within 8 weeks of day 1; Resonance of abdomen and pelvis in special cases (allergy to iodinated contrast)

#After 1 year of treatment the frequency of exams and visits will be every 12 weeks (+/- 3 days)

Methodology for research on the expression of Hormone Receptors (HR)

For the immunohistochemical study, the original blades of each case, stained by the hematoxylin-eosin method, will be re-evaluated by the study pathologist to select

the most representative and most preserved paraffin block of the tumor. From the chosen paraffin block, slides containing sequential sections (5-micrometer thickness) of the sample will be obtained and subjected to immunohistochemistry for estrogen receptor (ER) and progesterone receptor (PR). The entire immunohistochemical reaction will be performed in an automated platform using the Ventana Autostainer machine, following the BenchMark ULTRA® system (Ventana Medical Systems, Tucson, AZ, USA) and the Ultraview Universal DAB Detection Kit).

The protocol will follow the following steps:

1. The slides will be deparaffinized in EZ PREP solution (Ventana Medical Systems, Tucson, AZ, USA);
2. Antigen reactivation will be performed by heating in solution CC1 (Ventana Medical Systems Ultra Cell Conditioning Solution) at pH 9.0 to 96°C for 64 minutes;
3. Blocking endogenous peroxidase for 5 minutes using peroxidase blocking reagent (Ultraview Universal DAB Inhibitor, 3 percent H₂O₂);
4. Passages in Wash Buffer;
5. Incubation with the primary antibodies to ER and PR for 30 minutes;
6. Passages in Wash Buffer;
7. Incubation with HRP polymer (HRP Multimer) with subsequent washes in buffer;
8. Incubation with chromogen Diaminobenzidine (DAB), passage in wash buffer and counter-staining with Hematoxylin II;
9. Wash in water with detergent and then in distilled water;
10. Passage in xilol, alcohol and assembly of the blades.

Primary antibodies, dilutions, manufacturers, antigen retrieval methods and cutoff values used in the immunohistochemical study for evaluation of HR expression are presented in TABLE 2.

For the evaluation of the expression of estrogen and progesterone receptors, we will use previously published criteria in the literature. In this way, the cases in which more than 1 percent of the neoplastic cells show nuclear marking for these markers will be considered positive. In the absence of nuclear labeling or if it is present in less than 1 percent of the neoplastic cells, the research will be considered negative.^{16,17,18}

TABLE 2 - Primary Antibodies, Diluents, Manufacturers and Antigen Recovery Methods Used in the Immunohistochemical Study

Antibody	Clone	Dilution	Maker	Antigen Recovery	Cut Values
ER	SP1	Ready to use	Ventana Medical Systems, Tucson, AZ, EUA	CC1 solution with pH 9.0 at 96 ° C	≥1 percent (positive)
PR	1E2	Ready to use	Ventana Medical Systems, Tucson, AZ, EUA	CC1 solution with pH 9.0 at 96 ° C	≥1 percent (positive)

Methodology for Research of Circulating Tumor Cells (CTC)

As part of this project, we will collect a 10 ml sample of peripheral blood pre-study intended for the research of circulating tumor cells (CTC) as well as characterize protein expression through immunocytochemistry. The purpose of this evaluation is to

explore whether the net biopsy, through CTC, could serve as a diagnostic method for NET, without the need for invasive tumor biopsy, often difficult to perform in these patients. In case of results that indicate good accuracy of CTC in this neoplasia, these results can be applied as a diagnostic tool for patients with tissue biopsy contraindication.

- Isolation and Purification of CTC (blood samples):

Blood samples collected in EDTA tubes (10 mL) will be processed within 4 hours, diluted 1:10 in erythrocyte lysis buffer and filtered in the ISET system. After filtration, the membranes will be washed with PBS, dried at ambient temperature, protected from light and stored at -20 ° C until analysis.

- Immunocytochemistry in ISET Membranes:

For immunocytochemistry and for protein expression analysis, the spots of the membranes will be cut and placed in 24-well plates. Each spot will be hydrated with Tris Buffered Saline (TBS) for 10 minutes. Cells will be permeabilized with 0.2 percent Triton X-100 TBS for 5 min at room temperature. After a further TBS wash, the membranes will be incubated for 15 minutes in the dark and at room temperature with a 3 percent solution of hydrogen peroxide, and washed again with TBS. Then the antibodies to be screened will be applied to the spots and incubated for one hour. For the negative control, the primary antibody will be omitted. The development will be done with Dual long HRP system (Dako™) and Diaminobenzidine chromium 3,3 '(DAB) (Dako™). For reading, the spots will be stained with hematoxylin for 1 minute and adhered to the slides with aqueous mount medium. The CTC will be characterized according to the following criteria: nuclear size equal to or greater than 16µm, nuclear contour irregularity, presence of visible cytoplasm, high nucleus-cytoplasm ratio (> 0.8), as described by KREBS et al .19 When any of the criteria described are missing, the cells will be classified as atypical. The results will be given in CTC number per mL of blood.

Methodology for the PET-CT scan with Gallium-68 for the detection of somatostatin receptors

The PET-CT scan with gallium 68 to investigate somatostatin receptors will be performed using the Gemini PET-CT equipment (PET-CT-Dedicated) after administration of 0.1mCi of ⁶⁸Ga-DOTATATE, as already performed in the routine of AC Camargo as a staging method for NET. The images will be started in the minimum interval of 30 minutes and maximum of 60 minutes after the dose. CT - Helicoidal: contiguous anatomical tomographic sections 2.5 mm thick (without intravenous contrast) throughout the body (cranial, thoracic, abdominal, pelvic and lower limb segments). The Standard Uptake Value (SUV) calculation or standard capture value performed for clinically significant areas.

Study population:

Elegibility:

Research participants will be recruited from Clinical Oncology outpatient clinics and must meet all criteria below Inclusion and none of Exclusion:

Inclusion criteria

- Age greater than or equal to 18 years
- Histological diagnosis of well differentiated NET (typical and atypical lung carcinoids, NET G1, NET G2 of all gastroenteropancreatic sites and pancreatic NET G3 according to WHO 2017 classification) 20 advanced / metastatic, inoperable, with no possibility of curative treatment
- Immunohistochemical expression ≥ 1 percent for estrogen and / or progesterone receptor
- Disease with radiological progression (at least 10 percent tumor volume growth) in the last 12 months before day 1 cycle 1.
- No possibility of established treatments due to lack of access, risk of toxicities or without clinical indication. Patients who meet criteria for watchful waiting (low-dose disease and non-functioning NET) may be included.

- Measurable disease
- ECOG performance scale 0 to 2.
- Adequate organ function as defined by the following criteria:
 - serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) \leq 2.5 times the upper limit of local laboratory normality (LSN-LL);
 - Total serum bilirubin \leq 2.0 x ULN-LL;
 - Absolute neutrophil count \geq 1,500 / mm³;
 - Platelet count \geq 80,000 / mm³;
 - Hemoglobin \geq 9.0 g / dL;
 - Estimated creatinine clearance by the MDRD equation \geq 30ml / min
 - Albumin \geq 3.5 g / dL;
 - INR \leq 1.5
 - Term of free and informed consent signed by the patient or legal representative.

Exclusion criteria

- Patients already on tamoxifen.
- Patients with aggressive disease requiring cytotoxic therapy or locoregional therapies (eg hepatic embolization)
- A history of serious clinical or psychiatric illness that, by clinical judgment, may involve participation risk in this study
- Patients participating in other protocols with experimental drugs.
- Patients with oral food difficulties.
- Patients who underwent major recent surgery less than 4 weeks previously.
- Patients receiving chemotherapy or other oncologic therapy for less than 3 weeks.

- Patients who use oral anticoagulation
- Previous history of deep vein thrombosis or pulmonary embolism in the last 12 months.
- Pregnant or lactating patients.
- Patients with postmenopausal vaginal bleeding with no defined etiology.
- Patients with breast cancer who need to use tamoxifen for this neoplasm
- Another synchronous neoplasm that requires systemic treatment

Treatment:

Tamoxifen:

Tamoxifen Citrate was the first selective modulator of the developed estrogen receptor. It is a prodrug that has, in itself, little affinity for its target protein, the estrogen receptor. Tamoxifen is metabolised in the liver by the CYP2D6 and CYP3A4 isoforms of cytochrome P450 in its active metabolites afimoxifene and endoxifen, which present 30-100 times more affinity for the estrogen receptor. These active metabolites compete with estrogen for the body binding to the estrogen receptor, possessing 178 percent and 338 percent more affinity for estrogen and alpha receptors, respectively, than estradiol. They have different activities depending on the target tissue. In mammary tissue, they act as receptor antagonists. In other tissues, such as the endometrium, it is agonist. Because of this variable activity, tamoxifen is considered a selective modulator of the estrogen receptor. In hormone receptor-positive breast cancer tumor cells, active metabolites bind to the receptor producing a nuclear complex that decreases DNA synthesis by modulating gene expression, inhibiting estrogenic proliferative effects. The antitumor effect occurs by maintaining the cells in the G0 and G1 phases of the cell cycle, therefore, being a cytostatic rather than cytotoxic agent. Since the demonstration of antineoplastic activity in breast cancer in clinical studies in 1971, tamoxifen has become the prototype drug for

hormone treatment of breast cancer patients positive for hormone receptors at all stages of the disease, both pre- and post- menopause.²¹

The metabolism of tamoxifen is complex (about 10 major metabolites have been identified) and is mediated in the liver by cytochrome P450. Metabolites are excreted mainly by bile. The initial plasma half-life of tamoxifen ranges from 4 to 14 hours, with a secondary half-life of approximately 7 days. The concentration stability of tamoxifen is reached after 4 to 16 weeks of treatment. This prolonged half-life reflects levels of plasma protein binding and enterohepatic recirculation. There is no need for adjustment for renal function and has not been studied in patients with severe hepatic dysfunction.

The main adverse effects of tamoxifen are hot flushes, dry skin, nausea, vaginal discharge, fatigue and changes in the menstrual cycle. Rarely, but importantly may be associated with retinal changes, hepatotoxicity, hematological changes, thromboembolic phenomena and endometrial neoplasia. Given the teratogenic potential, women of childbearing potential should undertake contraceptive measures. Such medication should be contraindicated in cases of hypersensitivity to tamoxifen or any component of the formulation, concomitant use of coumarins and history of deep vein thrombosis or pulmonary embolism.

Administration

The treatment to be used will be tamoxifen 20mg VO once daily with a glass of water. In cases of vomiting occurring after 1 hour of taking or when a dose is missed, the patient will be instructed to skip this dose and not compensate for the next dose. Each cycle will be defined for 42 days (6 weeks).

Aderence:

The dispensation of tamoxifen will be made by the research pharmacy of the institution. Approximately 20 mg tamoxifen tablets will be given to each patient until the next return to the oncologist (see TABLE 1).

To assess adherence to treatment we will require patients to bring the blisters at each visit and at the time of discontinuation of treatment.

Dose reduction:

Dose interruption or reduction will be allowed in case of any toxicity of degree equal to or greater than 3 or intolerable grade 2 toxicity, as shown in the table below.

TABLE 3 - Dose adjustment according to toxicity

Study drug and dose	Tamoxifen 20mg orally once daily
Haematological or non-haematological toxicity grade ≥ 3 or grade 2 intolerable.	<p>Suspend therapy until recovery of the condition (with weekly evaluation by the investigator until the end of the recovery).</p> <p>When improvement of the picture (grade 1 toxicity), restart with tamoxifen 10mg tablet orally daily</p> <p>If there is no improvement in clinical status within 3 weeks (persisting with grade 3 or grade 2 intolerable toxicity) or patient does not tolerate the 10 mg / day dose, the patient will be excluded from the study for unacceptable toxicity.</p>
Haematological or non-haematological toxicity <grade 2	No dose reduction will be performed for tolerable grade 1/2 toxicities.

Security Assessment

Baseline Assessment:

After signing the informed consent form, patients will be submitted to baseline evaluation to assess the patient's eligibility (see TABLE 1):

- Within 21 days of the first dose of treatment: investigation of the immunohistochemical expression of RH in the paraffin-shaped tumor material. If expression ≥ 1 percent, eligibility is confirmed and the following procedures are:

- Within 3 days of day 1 cycle 1: Medical history, including diagnosis and previous treatments, history of other diseases (active and resolved), medications in use and general demographic data. Complete physical examination, ECOG (PS) performance index, body weight and height, and vital signs.
- Laboratory tests: blood count, urea, creatinine, ALT, AST, total bilirubin, sodium, potassium, INR and albumin and pregnancy test for women of childbearing age will be performed within 3 days of the first dose of treatment; these patients will be directed to contraception.
- It will be accepted that baseline imaging has been performed within 8 weeks of the first dose of treatment: Computed tomography (or nuclear magnetic resonance, if applicable) of the abdomen, pelvis and chest.
- All of these above exams are already part of the routine in treating NET at the AC Camargo Cancer Center.

Security Assessment at Week 3:

Adherence and presence of adverse events will be assessed at this time (see Safety Assessment). Will be allowed window of +/- 5 days

Safety evaluation on other weeks:

At each medical appointment, the adverse effects and toxicity related to the treatment will be evaluated by means of anamnesis, physical examination and laboratory evaluation, as follows:

- Complete physical examination, measurement of vital signs, measurement of weight and height, ECOG, use of concomitant medications.
- Evaluation of adherence to treatment.
- Evaluation 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 CTCAE 5.0 criteria. Patients who present intolerable grade 2 toxicity or grade 3 that the investigator judges to be related to tamoxifen will have the reduced dose of treatment (see TABLE 3) and will be conducted as previously discussed. All adverse effects will be graded and evaluated whether or not they are related to treatment.

If there is no CTCAE 5.0 classification for an adverse event, the severity degree of mild, moderate, severe and life threatening will be used. Adverse event monitoring will be performed at Week 3 after initiation of treatment (window - / + 3 days) and at each return with the oncologist every 6 weeks (window - / + 3 days). Monitoring of adverse events should be continued for at least 4 weeks after the last dose of study treatment.

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

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

1. Severity (mild, moderate, severe and life threatening) or (CTCAE grade 5.0)
2. Their relationship to each study drug (suspected / suspected)
3. Their duration (starting dates and final or continuing in the final exam)
4. Conduct adopted (no dosage adopted, dosage of study drug adjusted / temporarily discontinued, study drug permanently discontinued as a result of said adverse event, concomitant medication given, non-medicated therapy, prolonged hospitalization / hospitalization).

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

Treatment suspension criteria:

Patients can discontinue study treatment for one or more of the following reasons:

- Progression of the disease (documented by images and defined by RECIST 1.1 criteria)

Clinical progression, based on the evaluation of the investigator

- Death.
- Adverse event
- Withdrawal of consent by the patient.
- Need for new cancer therapy and / or surgery.

Efficacy and Follow-Up Assessment

For evaluation of efficacy, patients will perform imaging (chest tomography, abdomen and pelvis or abdominal and pelvic resonance) at baseline and every 12 weeks until progression or intolerance. Patients will also be evaluated for signs and symptoms that may be related to disease progression. Patients who present clinical progression at the investigator's judgment, but without radiological progression, may discontinue treatment with tamoxifen and continue imaging until progression; however, if new treatment is instituted, the last date of receipt of tamoxifen will be the date of censor in the analysis of progression-free survival.

Patients will also be evaluated for somatostatin receptor expressiveness through the functional examination of PET-CT Gallium-68, which will be performed before treatment and at week 12, in addition to biochemical response through the dosage of chromogranin A and / or specific hormone every 12 weeks, in conjunction with imaging (tomography and / or resonance). An interval of +/- 5 days will be

allowed for imaging and PET-CT Gallium-68 exams. Patients with suspected progression (eg worsening of symptoms) may perform images within less than 12 weeks to assess progression of disease, at the discretion of the investigator.

After documentation of progression or exit from the study for other reasons, patients will be followed up by the investigator or other oncologist from the Clinical Oncology team for symptom control, imaging monitoring and possible future therapies. The patient continues to be cared for at the AC Camargo Cancer Center, if desired.

Other concomitant medications

In general, concomitant medications and therapies deemed necessary for the intensive treatment and safety of the patient are permitted provided that their use is documented in the patient's records and in the appropriate clinical record. Tamoxifen may have drug interaction with coumarin anticoagulants (Marcoumar, Marevan, Coumadin) and those with some of the new anticoagulants (Pradaxa, Xarelto). These drugs should be avoided during the study (moderate contraindication). Concomitant administration of investigational medicinal products is not permitted. Administration of any other anticancer agents including chemotherapy, target therapy and biological agents is not permitted.

Statistical Considerations

Statistical plan

Descriptive statistics will be used to report the results of categorical and continuous variables. The time-to-event variables will be reported in medians and Kaplan Meyer curves. The degrees of toxicity will be tabulated. The number of patients discontinuing treatment due to toxicity will be presented.

Efficacy and toxicity analyzes will be performed by intention to treat. Patients receiving at least one dose of tamoxifen will be evaluated for toxicity and efficacy.

Inferential analyzes of the primary outcome according to primary site and IHC HR expression intensity will be conducted to depend on the number of cases per subgroup; if possible, these analyzes will be performed with the chi-square test. The analyzes of intensity of uptake intensity to PET-CT gallium-68 will be with paired T-test. The CTC analysis will be presented in a descriptive way.

Sample Size Calculation

To calculate the sample size, we considered the disease control rate H0 at 6 months of 50 percent (placebo arm result of the phase III studies) 5,23 and H1 as a 6 months disease control rate of 70 percent. A 10 percent bitailed type I error was considered, 80 percent power loss and 30 percent follow up loss. With these calculations, the sample number will be 22 patients.

Recruitment and Study Duration

At the AC Camargo Cancer Center, 30 patients with advanced NET are treated annually. Therefore, considering the patients already under treatment and the possible candidates without previous treatment and that out of every 10 patients, N = 4 will meet eligibility criteria (NETs with positive HR), we estimate to recruit the study population in a maximum period of 3 years and have the first full evaluation in 3 ½ years.

Ethical Considerations

The study will be conducted in accordance with the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization (ICH GCP) and applicable local laws and regulatory requirements. The Free and Informed Consent Term (ICF) must be in accordance with ICH GCP guidelines, local regulatory regulations, and legal requirements. See Appendix 2 for ICF.

The investigator should ensure that each study patient, or his / her legal representative, is fully informed about the nature and objectives of the study and

possible risks associated with participation. The investigator will obtain the written consent of each patient before any specific study activity is performed. The investigator will retain one path 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 to leave in the middle of the study whenever he wishes. This will not impair subsequent care to the patient. Female patients will be instructed not to become pregnant during treatment, being advised to use contraception methods if they are of childbearing age, as already done in routine. There is a risk of loss of confidentiality if patient data are identified, however, all appropriate measures will be taken to prevent this from happening.

The protocol was approved by the Local Ethics Committee (Registration Number: 2626/18). The study will be enrolled in the ClinicalTrial.gov international clinical trial bank.

Funding and Sponsorship of the Study

The patient will not incur any costs in relation to the immunohistochemical test for HR or use of tamoxifen to be funded by development. All the rest (laboratory tests, hormonal dosages, conventional imaging tests, gallium-68 PET-CT, medical consultations) is not part of this protocol because it is already part of the routine treatment of NET patients in the AC Camargo Cancer Center and therefore, paid by the paying source. For this study, insurance will be contracted against risks of adverse events requiring medical intervention (complementary examinations, hospitalization or emergency passage of AC Camargo due to adverse events related to tamoxifen)

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Appendix

APPENDIX 1- RECIST 1.1

Subgroups that designated a response category (complete response [CR], partial response [PR], stable disease [SD] and progressive disease [PD], see definitions below) are all patients receiving at least one cycle of tamoxifen. All patients with an objective CR or PR response should have the response confirmed at least 4 weeks after the initial response documentation.

Radiological Response Rate

RECIST

The response and progression will be evaluated in this study using the new international criteria proposed by the RECIST (Response Criteria in Solid Tumors) committee.¹⁹ Changes only in the largest diameter (one-dimensional measurement) of tumor lesions are used in the RECIST criteria.

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longer diameter to be recorded) as > 20 mm with conventional techniques (physical examination, CT, MRI) or as > 10 mm with spiral CT. All tumor measurements should be recorded in millimeters (or decimal fractions of centimeters).

The same evaluation method and the same technique should be used to characterize each lesion identified and reported in the baseline examination and during follow-up.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (for example, cutaneous nodules, palpable lymph nodes). For the case of cutaneous lesions, the documentation is recommended by means of color photography, including a ruler to estimate the size of the lesion.

CT / MRI: Tomography and resonance are the best reproducible and currently available methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in cross-section, contiguously. Spiral CT should be performed using a contiguous reconstruction algorithm of 5 mm. This applies to the chest and abdomen.

Unmeasurable disease. All other lesions (or disease sites), including small lesions (diameter greater than <20 mm with conventional techniques or <10 mm with spiral CT) are considered to be non-measurable diseases. Bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusions, lymph nodes and cystic lesions are all non-measurable.

Target Injuries. All lesions measurable up to 5 lesions per organ and 10 lesions in the total representation of all involved organs should be identified as target lesions and be recorded and measured at the baseline examinations. Target lesions should be selected based on their size (lesions with the longest diameters) and their suitability for accurate repeated measurements (by techniques per image or clinically). The sum of the largest diameters (LD) of all target lesions will be calculated and reported on the baseline examinations. This will be used as a reference for the characterization of the objective tumor response. If there are > 10 measurable lesions, those not selected as target lesions will be considered, along with non-measurable diseases, as non-target lesions.

Non-target lesions. All non-measurable lesions (or disease sites) in addition to any measurable lesions and above 10 listed as target lesions. Measurements are not

required, but these lesions should be specified on the baseline examination and followed up as "absent" or "present".

All patients will have their BEST RESPONSE in the classified study as summarized below:

Complete Response (CR): disappearance of all clinical and radiological evidence of tumor (target or non-target), and subsequent confirmation at ≥ 4 weeks.

Partial Response (PR): a reduction of at least 30 percent in the sum of LD of target lesions, based on the baseline examination, and subsequent confirmation at ≥ 4 weeks.

Stable Disease (SD): state of equilibrium of the disease. Neither reduction sufficient to qualify as PR nor sufficient increase to qualify as PD, documented at least once > 4 weeks from the baseline examination.

Progression disease (PD): an increase of at least 20 percent in the LD sum of the lesions measured with reference to the smallest sum of LD registered since the beginning of the treatment. The appearance of new lesions will also constitute progressive disease. In exceptional circumstances, evident progression of non-target lesions may be accepted as evidence of disease progression.

TABELA 4 – Classificação de resposta conforme RECIST 1.1

Target lesions	Non Target lesions	New lesions	Overall response	The best answer to this category also requires
CR	CR	No	CR	Confirmation of > 4 weeks
CR	Non CR / Non PD	No	PR	Confirmation of > 4 weeks
PR	Non PD	No	PR	
SD	No PD	No	SD	Documented at least once > 4 weeks from baseline
PD	Any	Yes or No	PD	Not before SD, PR or CR

Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	
<p>* In exceptional circumstances, evident progression of non-target lesions may be accepted as evidence of disease progression.</p> <p><u>Note:</u></p> <p>Patients with significant clinical deterioration requiring discontinuation of treatment without objective evidence of disease progression should be described as "symptomatic deterioration - clinical progression". All efforts should be made to document objective progression even after discontinuation of treatment.</p>				

APENDIX 2- Term of Free and Informed Consent (ICF)

TERM OF FREE AND INFORMED CONSENT

IDENTIFICATION DATA FOR THE SUBJECT OF THE RESEARCH OR LEGAL ENTITY

1.NAME: :REGISTRATION NUMBER.....

IDENTITY DOCUMENT N° : SEX : M ☐ F ☐

BIRTH DATE:/...../.....

ADRESS N°

APT:

DISTRICT.....CITY.....

ZIP:.....PHONE: (.....)

2.LEGAL ENTITY

NATURE (degree of kinship, tutor, healer etc.

IDENTITY DOCUMENT N° :SEX: M ☐ F ☐

BIRTH DATE:/...../.....

ADRESS: N°

APT:

DISTRICT:

CITY:

ZIP:

PHONE: (.....).....

—

You are being invited to participate in a survey.

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

RESEARCH DATA

RESEARCH PROTOCOL TITLE: PHASE II HORMONOTHERAPY STUDY WITH TAMOXIFEN IN PATIENTS WITH DIFFERENTIATED NEUROENDOCRIN TUMORS WITH POSITIVE EXPRESSION FOR HORMONE RECEPTORS (HORMONET).

RESPONSIBLE RESEARCHERS:

POSITION / FUNCTION:

DR. RACHEL RIECHELMANN - HEAD OF THE CLINICAL ONCOLOGY
DEPARTMENT OF THE HOSPITAL AC CAMARGO CANCER CENTER

DR. MILTON BARROS - CLINICAL ONCOLOGIST AT AC CAMARGO CANCER
CENTER HOSPITAL.

RESEARCH DURATION: 3 YEARS

STUDY DESIGN AND OBJECTIVE

You are being invited to participate in this clinical study to be performed at the Hospital AC Camargo Cancer Center.

You have the diagnosis of a well differentiated advanced / metastatic, inoperable Neuroendocrine Tumor (NET). At this time, there was progression of the disease (i.e., the tumor grew) and. there are no proven effective treatments or treatments available or offer many side effects or there is no clinical indication for your case right now.

In this study for which you are being invited to participate voluntarily, we aim to assess whether hormone therapy with the tamoxifen drug is able to control the growth of NET; for this, the NET must contain in its cells proteins called hormonal receptors (HR), which are the target of the tamoxifen remedy; that is, tamoxifen exerts its possible antitumor action when binding to these receptors. The treatment continues as long as the tumor gets controlled and you feel good. If the NET does not contain the hormone receptors, there is no place for tamoxifen and therefore the treatment could not be effective. Therefore, if NET does not contain the hormone receptors, you will not be able to participate in this study because it would not be good for you; you will continue to be treated by the Clinical Oncology team, with other treatments, without any detriment to your care.

PROCEDURES TO BE CARRIED OUT AND ITS PURPOSES

All patients who agree to participate in the study will receive oral treatment continuously with tamoxifen (20 milligram tablets / day) for as long as there is a benefit, according to the oncologist's evaluation. The dose may be decreased if there are significant side effects.

You will be accompanied by the study team by consultation at 3 weeks after the start of tamoxifen and thereafter every 6 weeks, where we will evaluate symptoms related to the disease and possible side effects, physical examination and routine laboratory (blood count, biochemistry, hepatic and renal); every 12 weeks (or 3 months) you will perform imaging tests (chest tomography, abdomen and pelvis or abdominal and pelvis resonance), according to the other treatments you may have already done, as well as dosages of some hormones that can be produced by NET. The goal of imaging and hormone testing is to evaluate whether tamoxifen is controlling NET.

The PET-CT Gallium-68 test is already an exam used to evaluate NET. However, in this study, we will evaluate how PET-CT gallium-68 changes with the use of tamoxifen; for this, you will do this test before starting tamoxifen and at 12 weeks, in order to evaluate its effect on NET. As an exploratory analysis, a single sample of 10 ml (or 2 tablespoons) of blood will be collected for research of circulating tumor cells, that is, if

we can detect the NET in the blood; if this is proven, this may be a diagnostic examination that in the future prevents the patient from undergoing tumor biopsy.

After a period of one year in the study, the laboratory and imaging appointments will be performed every 12 weeks, for as long as you feel good and the NET is not growing in the imaging tests.

Except for the test of circulating tumor cells, blood tests, PET-CT gallium-68 and CT scans are already part of the AC Camargo Cancer Center treatment routine and you will not do more tests than you would already be doing if not participate in this research.

DESCRIPTION OF THE DISCUSSIONS AND RISKS EXPECTED IN THE STUDY PROCEDURES

Tamoxifen:

Tamoxifen is a medicine used to treat breast cancer since the 1970s. It is considered a safe remedy since it has been used by thousands of people. Below are the expected side effects:

- Common (> 10 percent):
 - Dermatologic: menopause flushing (41-80 percent).
 - Reproductive: irregular menstruation (9 to 25 percent); vaginal discharge (13 to 30 percent).
- Uncommon or rare (<10 percent):
 - Hematologic: Deep venous thrombosis (DVT) (0.8 percent); thromboembolic disease (1.7 percent).
 - Ophthalmic: cataract (7 to 8.7 percent).
 - Reproductive: Endometrial cancer in women (<1 percent).

BLOOD COLLETS FOR CIRCULATING TUMOR CELL RESEARCH:

The risks to which you will be subject are the risks inherent in any venipuncture such as: local pain at the time of puncture, some bleeding at the site, hematoma and rarely phlebitis (punctured vein infection), but this will be avoided by proper cleaning of the site puncture and performance of the procedure by a trained professional. Although rare, ecchymosis may occur (when blood leaves the skin, resulting in a blue or purple patch, not raised or irregular) after collection of blood. If this happens to you, there is nothing to be done except wait for it to disappear (disappears in up to 7 days).

RISKS RELATED TO PREGNANCY

Tamoxifen can affect the fetus (unborn baby). The effects of the study drug on pregnancy are not completely known and can be harmful. Therefore, to participate in this study women of childbearing age should agree to use effective methods to avoid pregnancy.

Female patients of childbearing age will be advised not to become pregnant during the study. For them, a pregnancy test will be done before the start of treatment. If you become pregnant during your study participation, you should notify the study doctor immediately.

BENEFITS FOR THE PARTICIPANT

The hypothesis of the study is that tamoxifen exerts antitumor action in patients with TNE that contain hormone receptors in their cells and that is a safe treatment, without the addition of serious adverse effects. Therefore, we hope that tamoxifen treats your illness and preserves your quality of life.

But only at the end of the study can we conclude on the presence of some benefit. If this proves to be true, it is possible that in future larger studies need to be done before the proposed scheme can be used on a larger scale. Other patients in the future may benefit from the information obtained from this study.

ALTERNATIVE TREATMENTS

If you do not accept (or can not) participate in this study, your oncologist will discuss other therapies that may range from loco-regional therapies (hepatic embolization) to chemotherapy, depending on the case.

PAYMENT TO THE RESEARCH PARTICIPANT

Participation in this study will not incur any additional cost to you and no payment will be made if you agree to participate in this study. You are entitled to damages if you incur damages associated with the study.

VOLUNTARY PARTICIPATION / DISCONTINUATION OF THE STUDY

Participation in this study is entirely voluntary (you decide whether you want to be a part or not). Even if you decide to participate in the study, you can leave it at any time,

without giving explanations for it, and may even refuse to publish data collected about you. If this occurs the doctors no longer have collected the data about you, but may publish non-personal information collected before the cancellation. This decision will not affect your future medical treatment in any way.

The study doctor may also remove you from this study if you feel that this is in your best interest, or if the study is interrupted earlier than planned because it is considered unsafe.

CONFIDENTIALITY

If you choose to participate in this study, your health information and registration of your participation will be kept confidential and confidential. Researchers will identify you through a unique number and through the initials of your name (not using your full name). A copy of this informed consent will be filed in your AC Camargo Cancer Center medical record. However, there is a risk of loss of confidentiality; we will take all possible steps to prevent this from happening.

ACCESS GUARANTEE

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

Signatures

I, who confirm the Term of Free and Clarified Consent and offer a chance to clarify my needs related to this study. The chance to have another additional vocabulary is not the future related to the study or my participation in it, I can contact the phone 11-2189-2779.

Through my signature, I agree in favor of this study as a volunteer. I received a free and informed consent form.

Name of Participant (letter of form)

Date / /

Signature of Participant (letter of form)

Name of Investigator (letter of form) Date / /

Signature of Investigator

If witness or legal representative is required:

Name of witness / legal representative Date / /

Signature of witness / legal representative

Contact with research team:

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Brazil; Phone: (11) 2189-2779

