This form is intended to provide you with the fullest possible information on the medical, technical and administrative procedures related to PRRT therapy. A thorough understanding of all aspects of this therapy is in fact a necessary basis for a proper course of the treatment. If you still have questions after reading this text, please contact someone from the medical or paramedical staff of the Department of Nuclear Medicine or Medical Oncology of the Bordet Institute (via the secretary 02/541 32 40).
We recommend that you read this form prior to presenting yourself for the PRRT consultation at the Jules Bordet Institute (possibly in consultation with your treating physicians or family doctor). This is to ensure optimal communication between you and the doctors, as you will be discussing a lot of information in a short time.

Background information

You have been diagnosed with a neuroendocrine tumour, which cannot be completely surgically removed. You have already undergone one or more standard treatments (such as injections with somatostatin analogues, chemotherapy or a treatment with one of the new generation of "biological" molecules such as Sutent or Afinitor). These previous treatments were insufficiently effective in your case, however, or you have had to stop the treatment prematurely due to significant side effects.
In this case, you may be eligible for a new form of targeted radiotherapy called PRRT (Peptide Receptor Radio Therapy) using Lutetium-177 octreotate. After having received a favorable advice from the Superior Health Council of Belgium, this therapy is now available in Belgium for some years (July 2013).
This therapy (PRRT) makes use of a particular characteristic of neuroendocrine tumours, namely the presence of somatostatin receptors at the level of the cell membranes. PRRT uses small molecules (peptides; in our case: octreotate) which exhibit a very strong attraction to these receptors. A radioactive isotope is attached to these molecules (in our case: Lutetium-177, a mixed beta and gamma emitter) which are then administered intravenously to the patient. As a result, the octreotate (the vector molecule) takes the radioactivity very close to the cancer cells, which consequently receive a lethal radiation dose. This is done with as little as possible collateral irradiation of the other sensitive organs that contain fewer receptors or none at all. The main advantage of Lutetium-177 in comparison with the previous generation of isotopes (such as Yttrium-90) is that significantly less renal and bone marrow toxicity occurs. In addition, repeated imaging immediately following the administration of PRRT allows for improved monitoring of the distribution of the Lutetium-177 in the body. This makes it possible to measure the amount of radiation reaching the tumour and the sensitive organs after each treatment.

Effectiveness PRRT

In more than half of the patients, the irradiation of the tumour will bring about a pause or long-term stabilisation of the malignant growth. Furthermore, the majority of patients will very quickly cease to experience the disturbing characteristic symptoms related to the tumour (for example: diarrhea and flushing), resulting in a rapid, remarkably favorable effect on their overall quality of life. In the meantime, the effectiveness of PRRT for patients with metastatic neuroendocrine tumours has been proven without any doubt in a randomized clinical trial (publication in 2017 in the 'New England Journal of Medicine'). Compared to the control arm (high doses of somatostatin analogues), the PRRT treatment results in a very significant prolongation of overall and disease free survival.
In order to acquire more knowledge related to PRRT, all data and results of all PRRT treatments performed in our country must be carefully recorded in databases. This gathering of information is done in a completely anonymous manner, in accordance with the law on the protection of privacy. In order to do so, you do have to give us your formal consent by signing a form (this form will be given to you during your first consultation).

Possible side effects PRRT

Although the list of possible side effects is long, the incidence of severe side effects is very low. In the Erasmus Medical Centre in Rotterdam, over 500 people have already been treated with Lu177 octreotate. Serious, long-term side effects were only found in approximately 1% of these cases. Possible side effects are listed below (Source: website Erasmus Medical Centre Rotterdam/PRRT).
Short-term side effects that occur during or shortly after therapy and are of a temporary nature:

- Fatigue
- Nausea (25% of treatments)
- Vomiting (10% of treatments)
- Pain (10% of patients)
- Hair loss (65%). This is usually mild and the hair returns once the therapy has been stopped. Total baldness, as is often the case with chemotherapy, does not occur.
- In case of some patients with tumours that produced many hormones before the treatment, the symptoms of hormone production increased substantially soon after treatment. This may lead to an extended hospital stay. Generally, full normalisation occurs in a short period, if appropriate treatment is given.
- Temporary, usually slight decrease in blood cell counts. A more significant decrease in blood cell counts, which may be the reason to temporarily postpone a planned course of therapy, occurs after approximately 5% of the treatments.

More serious side effects (as seen in 1% of patients), which were found in the long term, are:

Renal function: Serious deterioration of the renal function may occur, especially in patients who already suffered from an impaired renal function prior to the treatment, or who have conditions, which may affect the renal function (hypertension, diabetes).
Hepatic function: Severe deterioration of the hepatic function may be found in patients with pre-existing extensive liver damage caused by the tumour or by liver disease (liver cirrhosis).
Bone marrow: Myelodysplastic syndrome of the bone marrow. This serious disease is usually a precursor to leukaemia (cancer of the blood). The risk is only relevant for patients with a pre-existing impairment of the bone marrow function (following several courses of chemotherapy, for example) or with very extensive, generalised tumoural invasion of the bone marrow.

PRRT in practice

In general, four administrations (called cycles) are performed with an interval of 10 - 12 weeks between them. One or more cycles may be added, however, if you respond well to the therapy and if the measurements of radiation doses and toxicity in the kidneys and bone marrow allow for it. If, on the other hand, you are already experiencing significant side effects during the first cycles, the decision may be made to administer fewer cycles or to administer only half the dose.
You will understand that the accurate calculation of the radiation doses administered to the tumour, but also to the vital organs at risk of radiation damage (particularly the kidneys and bone marrow), is an important aspect of this therapy, as it will determine the number of cycles that may be administered. Therefore, it is necessary for us to perform a series of tests before, during and following the administration of the medication. These tests involve blood tests and all kinds of imaging (SPECT and PET), which we will discuss more in detail below.

Which tests are required before you present yourself for the PRRT consultation?

- Report of the last consultation with your medical oncologist (including a copy of a relevant summary of your medical history). It is important that your oncologist objectively establishes a progression of the disease, either clinically (increase of typical symptoms), biologically (increase of tumour markers), or through imaging (tumour growth visible on CT scan or MRI). A stable disease is normally not treated with PRRT.
- General blood sampling: In particular, bone marrow, hepatic and renal function. A renal function of more than 50 ml/min (GFR) is required for a full-dose therapy.
- Certificate of Multidisciplinary Oncological Consultation (performed in the hospital with which your treating physician is affiliated), explicitly stating that you are eligible for PRRT. This Multidisciplinary Oncological Consultation may also take place at the Bordet Institute, but it is certainly advisable to already have a certificate prior to presenting yourself for the PRRT consultation in order to ensure a quick start of the administrative process (including, for example: obtaining an agreement for reimbursement by the insurance company involved).
- OctreoScan SPECT-CT or (preferably) Gallium-68 octreotate PET-CT: this must demonstrate that the tumour carries the somatostatin receptor to a significantly increased extent (this is also called an increased receptor expression). In principle, the intensity of expression must be higher than the activity measured in the normal liver tissue.

PRRT consultation at the Bordet Institute

This consultation concerns a combined consultation Digestive Oncology / Nuclear Medicine, in the presence of both specialist physicians and takes place on Tuesday or Thursday morning at the first floor (boxes 6/7). Please make an appointment for this consultation via the secretary of the Nuclear Medicine Department (02/541 32 40). In order to ensure the proper carrying out of this consultation, all elements of the dossier as listed above must be available.

This consultation is also attended by a PRRT coordinator (specialised nurse or technologist) and by a specialist physician. They will ensure that everything will run smoothly, both practically and administratively. Generally, they can always be reached during office hours (telephone number: 02/541 37 71) and will be your primary contact person in case of questions, scheduling of tests, and all sorts of administrative problems.

Additional tests (these are generally conducted at the Jules Bordet Institute and requested during the PRRT consultation):

- Cr51-EDTA determination of renal function, possibly in combination with dynamic renal scintigraphy (MAG3)
- Ga68-octreoPET (if not performed previously)
- FDG PET-CT (to determine the tumour aggressiveness and prognosis of the disease)
- Targeted CT or MRI scan of the main tumour foci to precisely determine the size of the tumour for the purpose of subsequent follow-up and response determination. These tests involve the use of intravenous iodine-containing contrast products. If you are allergic or intolerant to these products, please make sure to inform us of this.

Supplemented with the results of these tests, your file is resubmitted to a Multidisciplinary Oncological Meeting by the Digestive Oncology department of the Jules Bordet Institute (which meets every Friday afternoon and at which all relevant specialist physicians and paramedics are present). At that time, the final approval for PRRT is given and the first cycle scheduled.

PRRT practical information

The administration of the therapy takes place in a specialised isolation room specifically designed to avoid radioactive contamination and to protect personnel, the public and the environment. You will normally stay in this room for a period of 24 hours. During treatment, three people will be present in the room: the Nuclear Physician whom you met during the consultation, the responsible radiation physicist and the ward nurse (Floor B1).

Two peripheral IVs will be inserted, one in each of the elbow folds (if you already have a PAC system, this may be used as well). In one arm, a mixture of amino acids will be administered which makes sure that the irradiation of the kidneys is largely reduced. This administration is started 30 minutes before the start of the administration of the Lutetium-177 octreotate and will continue for a period of 4 to 6 hours. As this infusion is sometimes accompanied by discomfort and vomiting, appropriate preventive medication is administered by perfusion.

The injection of the Lutetium-177 octreotate takes place by perfusion in the other arm. This takes about 20 minutes (usually at around 12 o'clock). Afterwards, the perfusion is removed. Shortly after the injection of the Lu177 octreotate, of which you will generally notice little to nothing, a blood test is performed.

At the end of the afternoon (around 4 pm - 5 pm), you will be transferred to the Department of Nuclear Medicine for a first imaging session. Specifically, the Lutetium-177 sends out gamma rays as well captured using gamma cameras. The SPECT-CT images take about an hour to produce, after which you will be returned to your room. At that time, a second blood test will be carried out through the existing infusion in the right arm.
The following morning, the same imaging (without any additional injections) is performed once more, again linked to a blood sample (via the perfusion). You will be seen, and briefly examined, by the specialist physician.
If no problems occur, you may then leave the hospital (after the radiation physicist has measured the residual radioactivity). S/he will also give you the guidelines you need to protect your loved ones during the 2 weeks following the treatment.

Subsequent follow-up

- After one week (on day 7 or 8), you must present yourself again at the Institute at the Department of Nuclear Medicine. The same imaging (SPECT-CT) will then be performed. Subsequently, you are seen and examined during a Nuclear Medicine consultation.
- Blood sampling for monitoring purposes (particularly renal and bone marrow functions) after one month. Further blood sampling depends on results and specific risk.
- Assessment of the tumour response to PRRT. This is done by means of CT or MRI, approximately two weeks before the start of the next cycle. If the FDG PET-CT was positive prior to the start of the treatment, this is also repeated.

Your referring oncologist and family doctor will receive a detailed report after each cycle.

Questions related to reimbursement of PRRT

At this time, the RIZIV (the National Institute for Health and Disability Insurance) does not offer complete reimbursement for PRRT (Lutetium177 octreotate). As long as this situation does not change, patients can have a partial reimbursement through the Solidarity Fund of the RIZIV. The PRRT coordinator of the Department of Nuclear Medicine will assist you in this process in order that all administrative procedures run as smoothly as possible. Anyhow, the patient will have to pay an advance to enable the ordering of the product. Inclusion in a clinical trial (Lumen) is also possible; then the product is for free only if the patient meets certain conditions (inclusion criteria).

Taking into account that the reimbursement if not included in the LUMEN trial is only partially, it is very important to submit a request for additional financial intervention to the medical adviser of your health insurance provider. Obtaining their approval may sometimes take several weeks.

Based upon the favorable results of recent randomized studies (2017), which did clearly prove the
efficiency of PRRT (see above), further steps have been undertaken to obtain the complete reimbursement from the national health insurance.

Chief physician: Prof. Dr Patrick Flamen, Head of Nuclear Medicine.

Mrs. Marie-Noëlle Gheeraert
Technologist
02/541 37 71
E-mail: marienoelle.gheeraert@bordet.be

Mr. Pauwel Thijs
Technologist
02/541 37 71
E-mail: pauwel.thijs@bordet.be

Prof. Patrick Flamen
Dr Ioannis Karfis
Nuclear Medicine
E-mail: patrick.flamen@bordet.be
E-mail: ioannis.karfis@bordet.be

Dr Leila Shaza (Leila.shaza@bordet.be)
Dr Lieve Machiels (lieve.machiels@bordet.be)
Dr Alain Hendlisz (alain.hendlisz@bordet.be)
Digestive Oncology

Emergency service of the Jules Bordet Institute: 02/541 33 62