compete

Efficacy and Safety of n.c.a. Lutetium-177-Edotreotide PRRT in GEP-NET Patients vs. Everolimus.

Patient Organizations:
For national and international registered NET patient organizations or cancer groups please see:

International Neuroendocrine Cancer Alliance (INCA)
www.incalliance.org

Further Information:
www.clinical-trials.gov
www.compete-clinical-trial.com

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Phase III Clinical Trial

Patient Information

A clinical trial investigating Targeted Radionuclide Therapy in Neuroendocrine Tumors

Introduction

Dear patient,

This brochure will give you an overview of neuroendocrine tumors (NETs) and introduce a new treatment option that is being investigated in the COMPETE clinical trial.

This Phase III clinical trial is aimed at evaluating the efficacy and safety of Targeted Radionuclide Therapy with n.c.a. Lutetium-177-Edotreotide* in patients with neuroendocrine tumors of gastroenteric** or pancreatic origin (GEP-NET). It is intended specifically for patients who have progressive NETs which have spread to other parts of the body (metastatic) or that cannot be removed with surgery.

If you are interested in taking part in the study, please ask your attending physician whether you comply with the inclusion criteria.

You will find further information on this form of treatment, including a list of trial centers, in the following chapters.

Your COMPETE Team

* n.c.a (no-carrier-added). Lutetium-177-Edotreotide: N.c.a. Lutetium-177 is a synthetically produced low-energy Lutetium isotope emitting beta radiation. The radiopharmaceutical releases radioactivity in a maximum radius of 1.7 mm to the tumor tissue, which is then destroyed. A highly precise localization of the radioactivity ensures that healthy tissue in the surroundings of the targeted tumor is minimally affected. The special characteristic of no-carrier-added Lutetium-177 is its high purity.

** The gastroenteric tract includes stomach and bowel

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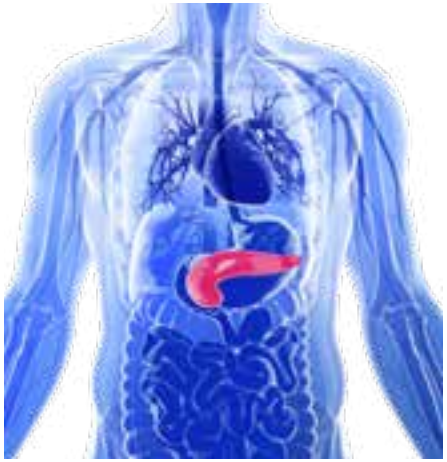
1. Neuroendocrine Tumors (NETs)

Neuroendocrine tumors (NETs) are a rare form of cancer that originates in neuroendocrine cells and often develop slowly over several years. Neuroendocrine cells are part of both the endocrine and the nervous system. These cells release neurotransmitters, cell messengers or hormones, which control how our body works.

75 % of all neuroendocrine tumors derive from gastroenteric or pancreatic origins. They are called gastroenteric pancreatic neuroendocrine tumors (GEP-NET) and are found throughout the digestive system or related parts of the body.

Surgery is the main treatment for NETs. This is often the only treatment you need. Sometimes, though, NETs can spread to other parts of the body, or your doctor may not be able to completely remove the cancer during surgery. There are other treatments available if this happens, such as chemotherapy or targeted drugs.



One targeted therapy that has been developed for the treatment of NETs in the pancreas and small bowel is Everolimus, which is currently defined as the standard of care. Various other treatment options for neuroendocrine tumors such as Targeted Radionuclide Therapy are being investigated.

75 % of all neuroendocrine tumors derive from gastroenteric or pancreatic origins.

2. What are Clinical Trials?

Clinical trials play an important role in the development of new treatment opportunities. Patients can decide voluntarily to take part in them. The studies are subject to a strict quality control plan in order to guarantee the safety of the participants.

To obtain approval for a clinical trial of the European Medicines Agency (EMA) or the Food and Drug Administration (FDA), the results from the preclinical phase have to be known. Therefore, the scrutinizing substance is tested for possible dangerous effects in labs. After the drug is considered to be safe, it receives the permission for clinical trials. These are divided into three phases, where efficacy and safety of the investigating substance is evaluated in a large number of patients (more than 100 or 1.000).

Phase	Typical number of participants	Primary goal
I	20 – 100 normal healthy volunteers (or for cancer drugs, cancer patients)	• Testing of drug on heallhy volunteers for dose-ranging • determines whether drug is safe to check for efficacy
II	100 – 300 patients with specific diseases	• Testing of drug on patients to assess efficacy and side effects • determines whether drug can have any efficacy; at this point, lhe drug is not presumed to have any lherapeutic effect whatsoever
III	200 – 3.000 patients with specific diseases	• Testing of drug on patients to assess efficacy, effectiveness and safety • determines a therapeutic effect; at this point, the drug is presumed to have some effect
IV	anyone seeking treatment from their physician	• Postmarketing surveillance – watching drug use in public • watch drug's long-term effects

The drug-development process will normally proceed through four phases over many years. If the drug successfully passes through the phases I, II and III it will usually be approved by the national regulatory authority for use in the general population.

A new treatment option for neuroendocrine tumors is being investigated in the COMPETE clinical trial. COMPETE is a phase III study, which means that the Targeted Radionuclide Therapy option being investigated has already proven itself in prior phases.

> The main objective of the phase III clinical trial COMPETE is now to find out whether Targeted Radionuclide Therapy has a greater efficacy for people with NETs than the standard therapy with Everolimus.

Please find further information about ongoing studies on www.clinical-trials.gov, ask your attending doctor or a patient organization in your country/nearby.

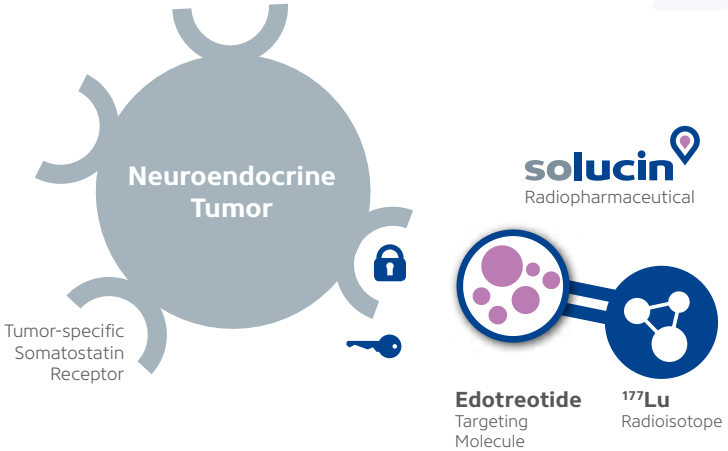
3. Targeted Radionuclide Therapy in this Clinical Trial

COMPETE is led as an international, prospective, randomized, controlled, open-label, multicenter phase III study. This means, that during the study new data will be collected (prospective), that results in patients receiving the new treatment are compared to a control group receiving the standard therapy (controlled) and that patients are randomly allocated to receive either n.c.a. Lutetium-177-Edotreotide or the current standard of care (randomized). Additionally, patients and physicians know what drug is being administered (open-label) and the study is conducted at multiple sites in multiple countries simultaneously (multicenter).

The trial will evaluate the efficacy and safety of the targeted radiopharmaceutical n.c.a. Lutetium-177-Edotreotide compared with the standard therapy Everolimus in patients with NETs. Targeted Radionuclide Therapy (TRT) or Peptide Receptor Radionuclide Therapy (PRRT) is the treatment option for NETs being investigated in this trial. It is not to be confused with traditional radiation therapy, which irradiates tumors from outside of the body.

Targeted Radionuclide Therapy uses a very small amount of a medical radioactive substance combined with a targeting biomolecule (radiopharmaceutical). In this study the radiopharmaceutical is called n.c.a. Lutetium-177-Edotreotide. It consists of two parts: the medical radioisotope n.c.a. Lutetium-177 which is responsible for destroying the tumor cells, and the biomolecule Edotreotide, a synthetic form of somatostatin, a peptide hormone.

Healthy neuroendocrine cells have so called somatostatin receptors on their surface. Somatostatin regulates the endocrine system by binding to these receptors according to a lock and key principle. This mechanism is used in treating neuroendocrine tumors by Targeted Radionuclide Therapy. This therapy utilizes the fact that neuroendocrine tumor cells overexpress somatostatin receptors on their surface. Just like the real hormone somatostatin, n.c.a. Lutetium-177-Edotreotide binds to these receptors allowing the medical radioactivity to be delivered directly into the unhealthy neuroendocrine cells thus destroying the tumor. The highly precise localization ensures that healthy tissue surrounding the targeted tumor is minimally affected.



4. Key Facts about the COMPETE Clinical Trial

COMPETE is led as an international, prospective, randomized, controlled, open-label, multicenter phase III clinical trial.

Investigational Medicinal Product
Targeted Radionuclide Therapy with n.c.a. Lutetium-177-Edotreotide

Reference Product
Standard therapy: targeted therapy with Everolimus

Primary Objective
Prolong progression-free survival

Indication
Neuroendocrine tumors of gastroenteric or pancreatic origin (GEP-NETs)

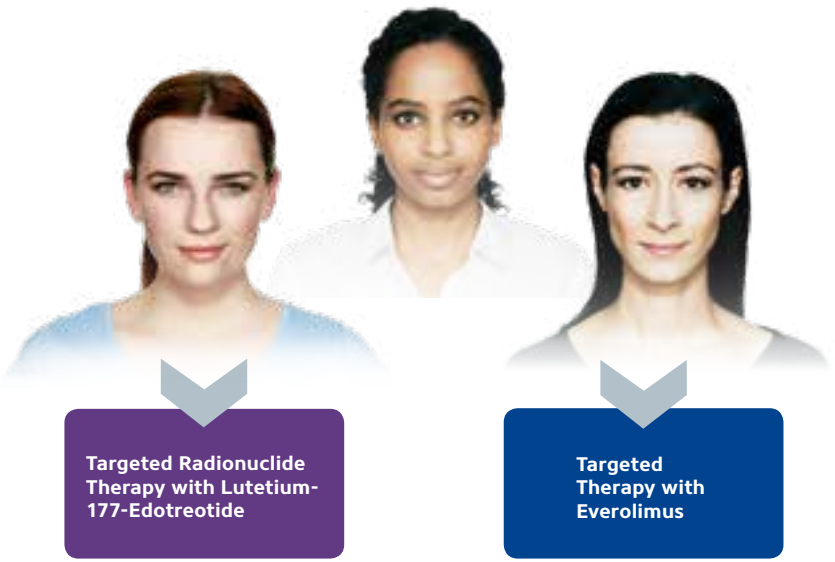
Study Entirety
300 GEP-NET patients will be randomized 2:1. Neither you nor your doctor will be able to decide which group you are in. You are two times more likely to receive a Targeted Radionuclide Therapy with n.c.a. Lutetium-177-Edotreotide than the standard therapy with Everolimus.

- 200 Patients: Targeted Radionuclide Therapy with Lutetium-177-Edotreotide with a maximum of 4 cycles, administered as an infusion at 3-month intervals

- 100 Patients: Everolimus, 10 mg daily, administered orally as a tablet

Study Duration
24 months / patient

Study Conduction
Europe, North America, South Africa and Australia,
min.12 countries and 43 sites



5. Key Benefits of Participating in the COMPETE Clinical Trial

- Maximum therapeutic properties meet minimum possible side effects through special kidney protection
- All treatment costs will be fully covered
- Travel expenses will be covered*
- Patients randomized for standard therapy with Everolimus will be offered fully covered n.c.a. Lutetium-177-Edotreotide treatment after the 24 month study-period is completed

*based on travel distance & country and according to sponsorship regulations

6. Who can take part in the COMPETE Clinical Trial?

The following list shows the entry conditions for this trial. Talk to your doctor or the trial team if you are unsure about any of these. They will be able to advise you.

6.1 Inclusion Criteria

You may be able to join this trial if all of the following apply:

- your NET started in the small bowel, stomach or pancreas
- your NET is growing slowly
- your cancer has spread to other parts of the body (metastatic) or doctors think they cannot remove the tumor completely with surgery
- you are willing to have a sample of tissue taken (biopsy) if there isn't a suitable sample available
- you have at least two areas of NETs that can be seen and measured on a CT scan or an MRI scan
- you have had a scan in the last three months
- your tumor has somatostatin receptors on its surface (somatostatin receptor positive)
- your NET has progressed in the past three years
- you are able to care for yourself but not able to carry on with all your activities or do active work (Karnofsky performance status of 70 or more)
- your kidneys are working well
- you have satisfactory blood test results
- you are at least 18 years old
- you are willing to use reliable contraception during treatment and for around two months afterwards if there is any possibility that you or your partner could become pregnant

6.2 Exclusion Criteria

You cannot join this trial if any of these apply:

Cancer related conditions

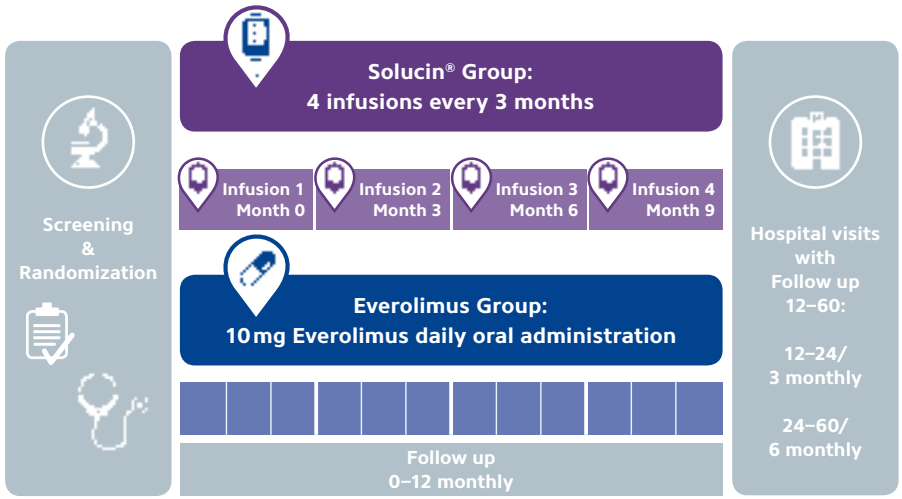
- your NET has spread to the brain
- you have a large amount of NET in the liver (more than 70 %)
- your NET makes hormones that go into the bloodstream (functioning NET). You can take part if you have a functioning NET that started in the pancreas
- your doctors don't know where your NET started (unknown primary)
- you have had another form of cancer in the last five years apart from basal cell skin cancer
- you have had treatments for your NET in the past month
- you are going to have other treatments for your NET such as chemotherapy, radiotherapy, chemoembolization or immunotherapy
- your doctors think you can have surgery to cure the NET
- you still have moderate or serious side effects from previous NET treatments
- you have had treatment with Everolimus or any other similar drug
- you have had Targeted Radionuclide Therapy

Medical conditions

- you have had an investigational treatment in the past month
- you have other serious medical conditions or mental health problems that the trial team think could affect you taking part
- you have had a live vaccine in the last month
- you are sensitive to any of the treatments used in this trial or anything they contain

7. COMPETE Treatment & Assessments

The following graphic shows how and at what intervals Lutetium-177-Edotreotide and the reference product Everolimus are given. Furthermore, you will receive a chronological overview of the accompanying examinations.



COMPETE treatment and assessment plan

On the following pages we will explain exactly:

- which examinations are performed before and during the COMPETE Clinical Trial
- how treatment with Lutetium-177-Edotreotide Targeted Radionuclide Therapy works
- how standard therapy works with the reference product Everolimus
- how often hospital visits are required during the COMPETE Clinical Trial
- how Lutetium-177-Edotreotide affects you on a day-to-day basis

7.1 Pre-Treatment & Follow-up Tests

You will be closely monitored during the study. Therefore, it is very important that your trial team knows everything about your current health status. This should include all symptoms you have and all medications you are taking, especially if you are taking a somatostatin analogue.

Your trial team will conduct some tests to make sure you are ready for the treatment.

The tests might include:

- a physical examination
- blood tests and an urine test
- a pregnancy test
- a heart trace (ECG)
- a CT scan or a MRI scan
- a radioactive scan
- a kidney scan called renal scintigraphy

The trial team will ask to use a sample of your tumor taken at the time of your diagnosis, because doctors need to look at the proteins (receptors) on the surface of the tumor cells. You only need to have a biopsy if there isn't a suitable sample available.

You will need to complete a quality of life (QoL) questionnaire before the start of treatment and at set times during the trial. The questionnaire asks about how you have been feeling and what side effects, if any, you have been experiencing.

7.2 Treatment Cycles with n.c.a. Lutetium-177-Edotreotide

You will be given Targeted Radionuclide Therapy with n.c.a. Lutetium-177-Edotreotide once every three months. This continues for nine months (up to four doses of treatment). For the treatment a short stay in hospital is mandatory. Initially at the hospital, your trial team will do the pretreatment tests. After that, under closely supervised conditions you will receive Targeted Radionuclide Therapy.

YOUR INFUSION

Your trial team will conduct some tests to track the treatment progress. Before every infusion, you will be given an amino acid solution as an infusion to protect your kidneys. The amino acid infusion will continue during and after you receive n.c.a. Lutetium-177-Edotreotide and will last 4–6 hours. During this time, n.c.a. Lutetium-177-Edotreotide will be administered for 10–20 minutes

AFTER YOUR TREATMENT

After each treatment you will need to stay in hospital for about three days or in accordance with local regulations. Your trial team will explain how n.c.a. Lutetium-177-Edotreotide will affect you on a day to day basis, the precautions you need to take at home and for how long

AFTER YOUR INFUSION

Directly after your infusion more tests will be conducted including the monitoring of the progress of n.c.a. Lutetium-177-Edotreotide through your body

7.3 Standard Therapy with Everolimus

The reference treatment Everolimus, used in this study, is the current standard of care according to the current guidelines for the treatment of NETs. You will take Everolimus in tablet form that is swallowed whole every day. This continues for as long as it is helping you and the side effects are not severe. It can be taken for up to two years.

The trial team will ask you to keep a diary recording each time you take Everolimus. This helps your doctor know how many doses of treatment you have had.

After the 24-month study-period is completed or if your NET progresses during treatment with Everolimus standard therapy with, you may be able to receive Targeted Radionuclide Therapy. Your doctor can tell you more about this.

7.4 Hospital Visits during COMPETE Clinical Trial

During treatment, you will be closely monitored and will see the trial team every month for blood tests and a physical examination. This continues for one year, after that you will see them every three months.

You will have a CT scan or MRI scan every three months and six months into the treatment you will receive a kidney scan.

After completing the treatment, you will see the trial team every six months, for five years.

7.5 How does n.c.a. Lutetium-177-Edotreotide Therapy affect You on a Day-to-Day Basis?

- You should shower daily for at least the first week after receiving n.c.a. Lutetium-177-Edotreotide
- For the first week after you receive n.c.a. Lutetium-177-Edotreotide make sure to flush twice and wash your hands every time you use the toilet
- If a caregiver helps you in the bathroom, they should wear disposable gloves for the first week after you are given n.c.a. Lutetium-177-Edotreotide
- It is important to drink plenty of fluids on the days before, during, and after you receive n.c.a. Lutetium-177-Edotreotide and to urinate often. This helps the radionuclides leave your body faster
- For the following weeks after receiving n.c.a. Lutetium-177-Edotreotide, dependent on local regulations, you will be advised on the close physical contact you can have with others, especially children and pregnant women
- You should use effective contraception during n.c.a. Lutetium-177-Edotreotide treatment and for seven months post-treatment
- Your doctor or nurse will inform you about all the precautions you need to take before you go home. Most of the radiation will be gone within two weeks

8. Potential Side Effects

The trial team will be monitoring you during treatment and afterwards. You will be given a phone number to call them if you are worried about anything. The team will tell you about possible side effects before you start the trial.

Potential risks caused by n.c.a. Lutetium-177-Edotreotide may arise from radiation exposure and somatostatin-related side effects. Most side effects generally subside within two months of treatment completion. However, some side effects may continue after treatment is over, as it takes time for healthy cells to recover from the effects of radiation therapy. Please consult your doctor should you feel sick or are in pain.

The most common side effects of Targeted Radionuclide Therapy with n.c.a. Lutetium-177-Edotreotide are:

- drop in the number of blood cells increasing your risk of infection and anemia, which may make you feel tired, lacking in energy with reduced exercise tolerance
- Feeling or being sick during and after treatment, tummy (abdominal) pain, loss of appetite, change in bowel habit, dizziness

The most common side effects of Everolimus are:

- Lung and breathing problems
- infections
- mouth sores
- kidney and liver problems
- change in bowel habit
- loss of appetite
- headache
- pain in arms and legs
- temporary hair loss

9. Participating Sites

AUSTRALIA

Austin Hospital
Olivia Newton-John Cancer & Wellness Centre
145 Studley Road, Heidelberg VIC 3084, Australia

Peter MacCallum Cancer Centre
Department of Medical Oncology
305 Grattan Street, Melbourne VIC 3000, Australia

Fiona Stanley Hospital
Locked Bag 100, Palmyra DC WA 6961, Australia

Royal North Shore Hospital
Department of Medical Oncology
Reserve Road, St Leonards NSW 2065, Australia

AUSTRIA

Allgemeines Krankenhaus Wien
Universitätsklinik für Radiologie und Nuklearmedizin,
Klinische Abteilung für Nuklearmedizin
Währinger Gürtel 18-20, 1090 Wien, Austria

FRANCE

Hospices civils de Lyon,
Groupement Hospitalier Est
Service de Médicine Nucléaire,
Fédération d'endocrinologie
59 Boulevard Pinel, 69500 Bron, France

Hôpital Beaujon
Hôpitaux universitaires Paris Nord Val-de-Seine
(HUPNVS), Assistance Publique des Hôpitaux
de Paris (APHP)
Consultation de Pancréato-gastro-entérologie
100 Boulevard du Général Leclerc, 92110 Clichy
Cedex, France

Hôtel Dieu – CHU de Nantes
Service de Médecine Nucléaire
1 Place Alexis Ricordeau, 44093 Nantes
Cedex 1, France

ICM, Cancer Institute of Montpellier
Aul Lamarque Val d´Aurelle, Parc Euromédecine
208 rue des Apothicaires, 34298 Montpellier, France

GERMANY

Zentralklinik Bad Berka GmbH
Klinik für Molekulare Radiotherapie/Zentrum für
Molekulare Bildgebung (PET/CT)
Robert-Koch-Allee 9, 99437 Bad Berka, Germany

Charité, Universitätsmedizin Berlin
Campus Virchow
Augustenburger Platz 1, 13353 Berlin, Germany

LMU – Klinikum der Universität München
Campus Großhadern, Klinik und Poliklinik
für Nuklearmedizin
Marchioninistraße 15, 81377 München, Germany

Universitätsklinikum Würzburg
Klinik und Poliklinik für Nuklearmedizin, Zentrum für
Innere Medizin
Oberdürrbacher Straße 6, 97080 Würzburg, Germany

Universitätsklinikum Bonn
Klinik und Poliklinik für Nuklearmedizin
Sigmund-Freud-Straße 25, 53105 Bonn, Germany

Universitätsklinikum Gießen und Marburg GmbH
Klinik für Gastroenterologie und Endokrinologie
Baldingerstraße, 35043 Marburg, Germany

Universitätsklinikum des Saarlandes
Klinik für Nuklearmedizin
Kirrberger Straße 100, 66421 Homburg, Germany

Universitätsklinikum Erlangen
Medizinische Klinik 1, Endokrinologie
Ulmenweg 18, 91054 Erlangen, Germany

Universitätsklinikum Ulm
Klinik für Nuklearmedizin
Albert-Einstein-Allee 23, 89081 Ulm, Germany

Universitätsklinikum Magdeburg A.ö.R.
Otto-von-Guericke Universität, Klinik für Radiologie
und Nuklearmedizin
Leipziger Straße 44, 39120 Magdeburg, Germany

ITALY

Istituto Scientifico Romagnolo per lo Studio e la
Cura dei Tumori (IRST) Srl
Unità Operativa Medicina Nucleare
Via Piero Maroncelli 40, 47014 Meldola (FC), Italy

Istituto Europeo di Oncologia
Unità di Brachiterapia e Imaging Molecolare IEO 1
Via Giuseppe Ripamonti 435, 20141 Milan, Italy

POLAND

MSC Memorial Cancer Centre
Centrum Onkologii – Instytut im.
M. Skłodowskiej-Curie Oddział w Gliwicach
Institute of Oncology
Wybruch AK 15, 44100 Gliwice, Poland

University Hospital Krakow
Nuclear Medicine Department
Ul. Kopernika 17, 31-501 Krakow, Poland

SOUTH AFRICA

Steve Biko Academic Hospital
Department of Nuclear Medicine
Cnr Steve Biko Road & Malan Street, 0001 Pretoria,
South Africa

University Cape Town (UCT),
Groote Schuur Hospital
LE34 Department Radiation Oncology
Anzio Road, Observatory, 7925 Cape Town,
South Africa

SPAIN

Vall d'Hebron University Hospital
Medical Oncology Department, Gastrointestinal and
Endocrine Tumor Unit
Pg Vall d'Hebron 119-129, 08035 Barcelona, Spain

Hospital MD Anderson Cancer Center Madrid
C/ Arturo Soria 270, 28033 Madrid, Spain

SWITZERLAND

Universitätsspital Basel
Klinik für Onkologie
Petersgraben 4, 4031 Basel, Switzerland

Inselspital, Universitätsspital Bern
Universitätsklinik für Medizinische Onkologie
Freiburgstraße 10, 3010 Bern, Switzerland

Universitätsspital Zürich
Klinik für Onkologie
Raemistraße 100, 8091 Zürich, Switzerland

Kantonsspital St. Gallen
Klinik für Radiologie und Nuklearmedizin
Rorschacher Straße 95, 9007 St. Gallen, Switzerland

THE NETHERLANDS

Academic Medical Center
Oncology department F4-224
Meibergdreef 9, 1105 AZ Amsterdam,
The Netherlands

UK

Royal Free NHS Foundation Trust
Department of Nuclear Medicine
Pond Street, London NW32QG, UK

Kings College Hospital NHS Foundation Trust
Centre for Gastroenterology
Denmark Hill, London SE5 9RS, UK

Queen Elizabeth Hospital
Mindelsohn Way, B15 2TH Birmingham, UK

Gartnavel General Hospital
Beatson Oncology Centre
1089 Great Western Road, G12 0YN Glasgow, UK

USA

Excel Diagnostics & Nuclear Oncology Center
9701 Richmond Avenue, Houston, TX 77042, USA

Moffitt Cancer Center & Research Institute
Department of Gastrointestinal Oncology
12902 Magnolia Drive, Tampa, FL 33612, USA

Virginia Mason Hospital and Seattle Medical
Center
1100 Ninth Avenue D4-CRP, Seattle, WA 98101, USA

University of Michigan Comprehensive Cancer
Center
2800 Plymouth Road, Ann Arbor, MI 48109, USA

Stanford University
Stanford Nuclear Medicine and Molecular Imaging
Division of Nuclear Medicine and Molecular Imaging
300 Pasteur Drive, Stanford, CA 94305, USA

MD Anderson Cancer Center
Banner Health d.b.a.
2946 East Banner Gateway Drive,
Gilbert AZ 85234, USA