

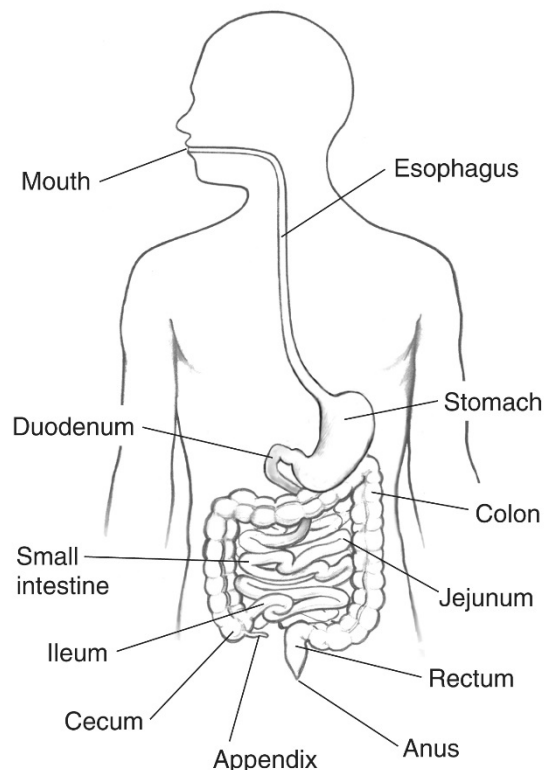
Lu 177-Dotatate (Lutathera) Therapy Information

Information for Lu 177-dotatate therapy also known as Lutathera, for the treatment of metastatic midgut neuroendocrine tumor and other metastatic neuroendocrine malignancies.

What are neuroendocrine tumors (NET)s?

You have been diagnosed with a neuroendocrine tumor (NET) that has spread (metastasized) in the body. NETs begin in the hormone-producing cells of the body's neuroendocrine system, which is made up of cells that are a combination of nerve cells and cells that produce hormones. Among other problems, NETs can release large amounts of hormones into the blood, causing numerous problems such as diarrhea and flushing—a condition known as carcinoid syndrome.

The most common type of NET is a **midgut tumor**. The midgut is defined as the area from the middle portion of the small intestine (jejunum) to the initial portion of the colon (ascending colon) These are called “carcinoid” tumors. Midgut NETs are rare tumors among all cancers. It is estimated that only 5 in 10,000 are midgut NET tumors. Other types of NETs are Gastroenteropancreatic (GEP)-NETs. These can occur anywhere along the gastrointestinal tract.



Midgut NETs can be viewed with Positron Emission Tomography (PET) and Computed Tomography (CT) scanning. A PET/CT scan is a way to create pictures of organs and tissues inside the body. Having both scans at once shows the structure of cells and tissues and how well they are functioning.

How does Lu 177-Dotatate work?

Lu 177-Dotatate is a type of Radioisotope therapy, also called **Peptide Receptor Radionuclide Therapy or PRRT**. Radioisotope therapy delivers radiation directly into the cancer cells by adding radioactive material to proteins that bind with specific cancer cells. These special drugs are called **radionuclides**. The patient takes the drug as a capsule, drink or injection into a vein. As the proteins enter the body they bind into the cancerous cells and deliver the radioactive material directly to the tumor.

Researchers discovered that that cells in most NETs cells bind to a specific hormone called somatostatin. Octreotide is a laboratory-made version of somatostatin and Lu 177-Dotatate is the combination of Octreotide with a small amount of radioactive material. This creates a radionuclide drug that delivers a high dose of radiation directly to the NET tumor.

Studies have shown that PRRT is effective in treating midgut “carcinoid” tumor and (GEP)-NETs that have spread (metastasized). This treatment has been approved by the FDA, Jan 26th, 2018.

How will I take Lu 177-Dotatate?

Lu 177-Dotatate is injected directly into the vein through an IV. An IV is a needle or a thin tube that is inserted into a vein. You will receive Lu 177-Dotatate 4 times, with a 2 months break in between. The dose is injected over 30 minutes. To reduce the radiation exposure to the kidneys, patients receive kidney-protecting amino acid infusion before Lu 177-Dotatate. This infusion

lasts 4 hours starting 30 minutes before Lu 177-Dotatate. This strategy can cut down radiation exposure to the kidneys by a half. Patients also receive medication to stop nausea and vomiting which may occur mainly due to the amino acid infusion.

Am I a suitable candidate to receive Lu 177-Dotatate treatment?

Candidates for Lu 177-Dotatate treatment are people with an NET tumor that has spread and has following features:

- PET/CT scan shows high uptake of gallium 68-Dotatate.
- Tumor is inoperable (cannot be treated with surgery)
- Tumor is described as “differentiated” (not appropriate for patients with a “poorly differentiated” tumor).

Patients with poor kidney function and low reserves of bone marrow are not good candidates for Lu 177-Dotatate.

Is there any special preparation for this treatment?

- Tell your doctor if you are on a somatostatin analogues (SSA) drugs such as lanreotide or octreotide LAR, used to treat patients with NET tumors that cannot be treated with surgery.
- It is recommended that your kidney function will be measured before your first treatment with Lu 177-Dotatate (baseline measurement) and at end of treatment (6 months from our first dose). This is needed in order to monitor any changes in your kidney function and Glomerular Filtration Rate (GFR).

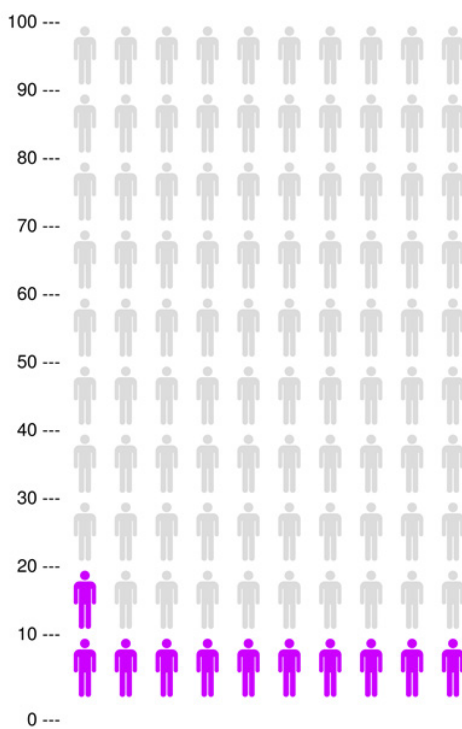
What are the benefits and efficacy of Lu 177-Dotatate treatment?

Research has shown that treatment with Lu 177-Dotatate is more effective than treatment with Octreotide LAR. That means that patients who took Lu 177-Dotatate lived longer without the disease getting worse (progression-free

survival, or PFS), and had better response to treatment than those who took Octreotide LAR.

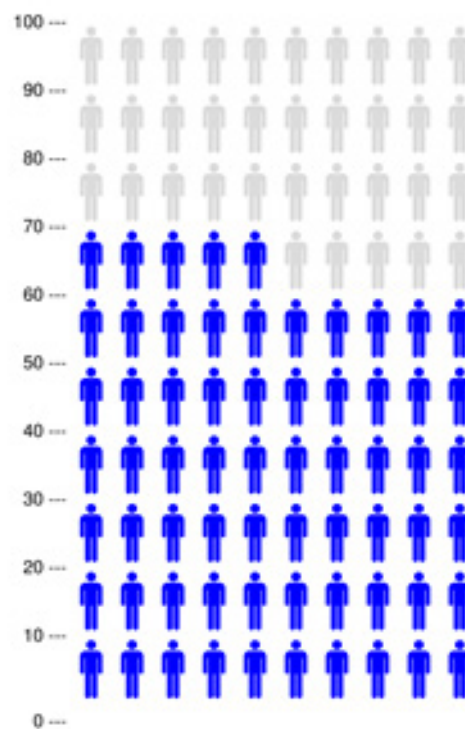
One study compared 2 groups of patients with inoperable midgut carcinoid tumors to see if their disease progressed after 20 months. In those who took Lu 177-Dotatate, the disease did not progress in 65 out of 100 patients. In patients who took Octreotide LAR., the disease did not progress in 11 out of 100 patients.

Treatment with Octreotide LAR



11 out of 100 patients survived with disease not getting worse after 20 month

Treatment with Lu 177-Dotatate



65 out of 100 patients survived with disease not getting worse after 20 month

What are the risks and side effects of Lu 177-Dotatate treatment?

The safety profile of Lu 177-Dotatate was also good.

Short-term side effects include:

- Acute mild to moderate nausea occurred in around 50 out of 100 people. Vomiting occurred less often in 10 out of 100 people. Nausea and vomiting are the result of the amino acids administration.
- Low blood counts. 9 out of 100 patients had serious (grade 3 or 4) medical problems such as low white blood cells or platelet count.
- A hormonal crisis occurred in about 1 out of 100 people. Symptoms of hormonal crisis include:
 - severe red and hot skin (flushing)
 - abnormally low blood pressure (hypotension)
 - blood pressure fluctuation
 - constriction of the airways and difficulty breathing (bronchoconstriction)
 - irregular heartbeat (arrhythmia)

The causes of the hormonal crisis are not clear but researchers believe that the effects of radiation on the tumor can result in a sudden release of large amounts of active hormones.

Long-term moderate and severe side effects

The major potential long-term side effects are kidney failure and blood cancer. They are very rare.

- Rates of kidney failure after PRRT are low, especially with amino acid administration and appropriate measurement of radiation to kidneys. One study followed 504 patients receiving Lu 177-Dotatate and none of them had kidney failure.
- Rates of blood cancers occurring after treatment with radioisotope therapy are also low. In one study that followed 807 patients, between 1-3 people developed a blood cancer.

In summary, Lu 177-Dotatate treatment is generally safe and well tolerated for the great majority of patients. long-term serious side effects are rare.

Do I have to follow specific instruction to manage radiation exposure to family, friends or the general public?

Yes, this medicine is most effective in treating your tumor because it is radioactive. This is also the reason why it is necessary to follow certain precautions in order to limit the exposure of the people around you. Your clinic nurse will explain the precautions and give you a handout describing them.

The estimated health risks to your family members and the general public are low. However, you must follow the precautions in order to maximize the safety of other persons. These precautions are the result of many years of experience in the use of radioactivity in medicine, and they include recommendations issued by international organizations.

The general rule is that you must avoid close contact with people who live with you, and should try to keep a distance of at least 3 feet from other people for 2 to 3 days after you receive Lu 177-Dotatate.

What happens after I finish treatment with Lu 177-Dotatate?

After your treatment you will continue follow-up with your referring doctor.

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