Novartis Lutathera® significantly reduced risk of disease progression or death by 72% as first-line treatment for patients with advanced gastroenteropancreatic neuroendocrine tumors

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- *In the Phase III NETTER-2 trial, Lutathera plus octreotide LAR significantly extended median PFS to 22.8 months vs. 8.5 months with high-dose octreotide LAR in patients with newly diagnosed grade 2 and 3 advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs)*[1]
- *NETTER-2 is the first and only positive Phase III trial for a radioligand therapy (RLT) in the first-line setting, demonstrating the benefit of RLTs in earlier lines*
- *Novartis, a leader in radioligand therapy, is investigating a broad portfolio of RLTs in advanced cancers, in addition to GEP-NETs, including lung, prostate, breast, colon, glioblastoma and pancreatic cancers to continue reimagining medicine for patients*

East Hanover, January 19, 2024 – Novartis today presented data from the Phase III NETTER-2 trial showing that Lutathera® (lutetium Lu 177 dotatate) plus long-acting release (LAR) octreotide reduced the risk of disease progression or death by 72% as first-line therapy in patients with somatostatin receptor-positive (SSTR+) well-differentiated grade 2/3 advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs) versus high-dose octreotide LAR alone[1]. Data were presented at the 2024 American Society of Clinical Oncology (ASCO) Gastrointestinal (GI) Cancers Symposium.

“These positive results for Lutathera are practice-changing and offer new first-line treatment data for patients who have a significant unmet need. This study confirms the clinical benefit of first-line radioligand therapy for newly diagnosed patients living with these types of advanced GEP-NETs,” said Dr. Simron Singh, Associate Professor of Medicine at the University of Toronto and cofounder of the Susan Leslie Clinic for Neuroendocrine Tumours at the Odette Cancer Centre, Sunnybrook Health Sciences Centre, Ontario, Canada. “These findings should instill confidence among physicians in using Lutathera as a first-line treatment for patients with this life-threatening type of cancer.”

Efficacy endpoint[1]	**Lutathera plus octreotide LAR vs. high-dose octreotide LAR**
Progression-free survival	HR 0.28 (95% CI: 0.18, 0.42; *p*<0.0001)
Median PFS (months)	22.8 months (95% CI: 19.4 -not estimable) vs. 8.5 months (95% CI: 7.7-13.8)
Objective response rate (ORR)*	43% (95% CI: 35.0-51.3) vs. 9.3% (95% CI: 3.8-18.3), p<0.0001)

**Assessed via RECIST 1.1*

“This is the first positive Phase III trial of a radioligand therapy in the first-line setting, and the overall efficacy and safety results are amongst the most clinically relevant observed to date in this kind of advanced cancer, addressing a significant unmet need for patients with newly diagnosed advanced GEP-NETs,” said Jeff Legos, Global Head of Oncology Development at Novartis. “The positive results are a significant advancement and further reaffirm our strategy to research and develop radioligand therapies in earlier lines of treatment or stages of disease to improve outcomes for patients.”

No new or unexpected safety findings were observed in the study and data are consistent with the already well-established safety profile of Lutathera[1]. Most patients (88%) in the Lutathera arm received all four cycles of Lutathera treatment. The most common all-grade AEs (≥20%) for the Lutathera arm vs. control arm were nausea (27.2% vs 17.8%), diarrhea (25.9% vs 34.2%) and abdominal pain (17.7% vs 27.4%), and the most common grade ≥3 AE (>5%) was lymphocyte count decreased (5.4% vs 0%).

NETs are a type of cancer that originate in neuroendocrine cells throughout the body and are commonly considered slow-growing malignancies. However, some NETs are associated with rapid progression and poor prognosis and in many cases, diagnosis is delayed until patients have advanced disease[2-4]. Even though NETs are a rare (orphan) disease, their incidence has increased over the past several decades[2-5] and there is a need for continued research into treatment options for newly diagnosed patients.

The NETTER-2 trial is ongoing for further evaluation of secondary endpoints including overall survival and long-term safety.

About NETTER-2

NETTER-2 (NCT03972488) is an open-label, multi-center, randomized, comparator-controlled Phase III trial assessing whether Lutathera plus octreotide LAR when taken as a first-line treatment can prolong PFS in patients with high-proliferation rate tumors (G2 and G3), compared to treatment with high-dose (60 mg) long-acting octreotide[6]. Eligible patients were diagnosed with SSTR-positive advanced GEP-NETs within 6 months before enrollment[6].

About Lutathera®

Lutathera® (lutetium Lu 177 dotatate) is approved in the US for the treatment of adult patients with SSTR-positive GEP-NETs, including those in the foregut, midgut and hindgut, an indication which includes the NETTER-2 population. Lutathera is also approved in Europe for unresectable or metastatic, progressive, well-differentiated (G1 and G2), SSTR-positive GEP-NETs in adults[7,8], and in Japan for SSTR-positive NETs.

Novartis and Radioligand Therapy (RLT)

Novartis is reimagining cancer care with RLT for patients with advanced cancers. By harnessing the power of radioactive atoms and applying it to advanced cancers, RLT is theoretically able to deliver radiation to target cells anywhere in the body[9,10].

Novartis is investigating a broad portfolio of RLTs, exploring new isotopes, ligands and combination therapies to look beyond gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and prostate cancer and into breast, colon, lung and pancreatic cancer.

With established global expertise, and specialized supply chain and manufacturing capabilities across the Novartis network, we are supporting growing demand for our RLT medicines. Our production capabilities continue to expand and now include sites in Millburn, US, Zaragoza, Spain, Ivrea, Italy and our new state-of-the-art facility in Indianapolis, US. We recently announced plans to expand our manufacturing capabilities and build additional points of supply in Sasayama, Japan, and Haiyan, Zhejiang, China, to produce RLTs for patients in Japan and China. We are continually evaluating additional opportunities to increase capacity around the world.

What is Lutathera?

LUTATHERA is a prescription medicine used to treat adults with a type of cancer known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that are positive for the hormone receptor somatostatin, including GEP-NETs in the foregut, midgut, and hindgut.

Lutathera Important Safety Information

What are some important things to know about the safety of LUTATHERA?

LUTATHERA is associated with some serious safety considerations and, in some cases, these may require your health care provider to adjust or stop your treatment. You should always follow your health care provider's instructions. Safety considerations include:

- **Radiation exposure:** Treatment with LUTATHERA will expose you to radiation, which can contribute to your long-term radiation exposure. Overall radiation exposure is associated with an increased risk for cancer. The radiation will be detectable in your urine for up to 30 days following administration of the drug. It is important to minimize radiation exposure to household contacts consistent with good radiation safety practices as advised by your health care provider.
- **Bone marrow problems:** Treatment with LUTATHERA increases the risk of myelosuppression, a condition in which bone marrow activity is decreased, resulting in a drop in blood cell counts. You may experience blood-related side effects such as low red blood cells (anemia), low numbers of cells that are responsible for blood clotting (thrombocytopenia), and low numbers of white blood cells (neutropenia). Speak with your health care provider if you experience any signs or symptoms of infection, fever, chills, dizziness, shortness of breath, or increased bleeding or bruising. Your health care provider may need to adjust or stop your treatment accordingly.
- **Secondary bone marrow and blood cancers:** Other serious conditions that you may develop as a direct result of treatment with LUTATHERA include blood and bone marrow disorders known as secondary myelodysplastic syndrome and cancer known as acute leukemia. Your health care provider will routinely check your blood cell counts and tell you if they are too low or too high.
- **Kidney problems:** Treatment with LUTATHERA will expose your kidneys to radiation and may impair their ability to work as normal. You may be at an increased risk for kidney problems after LUTATHERA treatment if you already have kidney impairment before treatment. In some cases, patients have experienced kidney failure after treatment with LUTATHERA. Your health care provider will provide you with an amino acid solution before, during, and after LUTATHERA to help protect your kidneys. You should stay well hydrated before, on the day of, and on the day after your treatment. You should urinate frequently before, on the day of, and on the day after administration of LUTATHERA. Your doctor will monitor your kidney function and may withhold, reduce, or stop your LUTATHERA treatment accordingly.
- **Liver problems:** In clinical studies of LUTATHERA, less than 1% of patients were reported to have tumor bleeding (hemorrhage), swelling (edema), or tissue damage (necrosis) to the liver. If you have tumors in your liver, you may be more likely to experience these side effects. Tell your health care provider right away if you have any of these signs and symptoms of liver problems: yellowing of the skin or the whites of the eyes (jaundice), unusual darkening of the urine, unusual tiredness, right upper stomach area (abdomen) pain, confusion, and/or swelling of the stomach area (abdomen). Your health care provider will monitor your liver using blood tests and may need to withhold, reduce, or stop your LUTATHERA treatment accordingly.
- **Allergic reactions:** Allergic reactions have occurred in people who were treated with LUTATHERA. Notify your health care provider if you develop symptoms of an allergic reaction. Seek emergency help right away for any serious allergic reactions. Symptoms may include trouble breathing or swallowing; raised bumps (hives); rash or itching; and swelling of the face, lips, tongue, throat, or arms.
- **Hormonal gland problems (carcinoid crisis):** During your treatment you may experience certain symptoms that are related to hormones released from your cancer. These symptoms may include flushing, diarrhea, difficulty breathing (bronchospasm), and low blood pressure (hypotension), and may occur during or within the 24 hours after your first LUTATHERA treatment. Your health care provider will monitor you closely. Speak with your health care provider if you experience any of these signs or symptoms.

- **Pregnancy warning:** Tell your health care provider if you are pregnant. LUTATHERA can harm your unborn baby. Females should use an effective method of birth control during treatment and for 7 months after the last dose of LUTATHERA. Males with female partners should use an effective method of birth control during treatment with LUTATHERA and for 4 months after the last dose.
- **Breastfeeding warning:** You should not breastfeed during treatment with LUTATHERA and for 2.5 months after your last dose of LUTATHERA.
- **Fertility problems:** Treatment with LUTATHERA may cause infertility. This is because radiation absorbed by your testes or ovaries over the treatment period falls within the range of exposure in which temporary or permanent infertility may occur.

What are the most common side effects of LUTATHERA?
The most common and most serious side effects of LUTATHERA include decreased blood cell counts, increased liver enzymes, vomiting, nausea, increased blood glucose, and decreased blood potassium levels.

Talk to your doctor if you experience any of these side effects. There are other possible side effects of LUTATHERA. For more information and to learn more about LUTATHERA, talk to your doctor or health care provider.

What other medicines may interact with LUTATHERA?
Tell your health care provider if you are taking any other medications. Somatostatin analogs and glucocorticoids may affect how your LUTATHERA treatment works. You should stop taking your long-acting somatostatin analog at least 4 weeks before LUTATHERA treatment. You may continue taking short-acting somatostatin analogs up to 24 hours before your LUTATHERA treatment. Avoid repeated high doses of glucocorticoids during treatment with LUTATHERA.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full Prescribing Information for LUTATHERA at
https://www.novartis.com/us-en/sites/novartis_us/files/lutathera.pdf**.**

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pandemic diseases; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis is an innovative medicines company. Every day, we work to reimagine medicine to improve and extend people's lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach more than 250 million people worldwide.

Reimagine medicine with us: Visit us at **https://www.novartis.com** and connect with us on **LinkedIn, Facebook, X/Twitter** and **Instagram.**

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