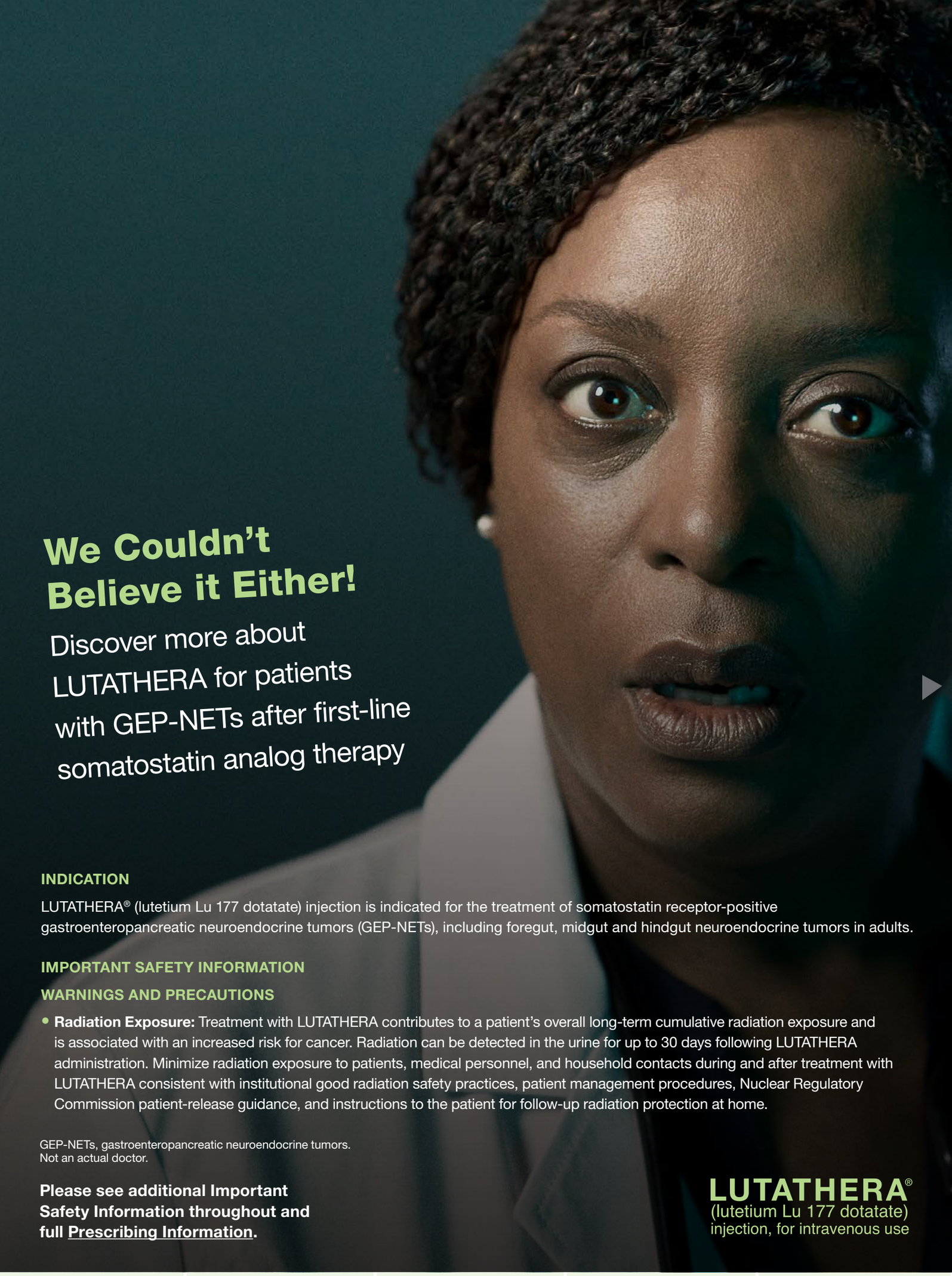


We Couldn't Believe it Either!

Discover more about LUTATHERA for patients with GEP-NETs after first-line somatostatin analog therapy

INDICATION

LUTATHERA® (lutetium Lu 177 dotatate) injection is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Radiation Exposure:** Treatment with LUTATHERA contributes to a patient's overall long-term cumulative radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices, patient management procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home.

GEP-NETs, gastroenteropancreatic neuroendocrine tumors.
Not an actual doctor.

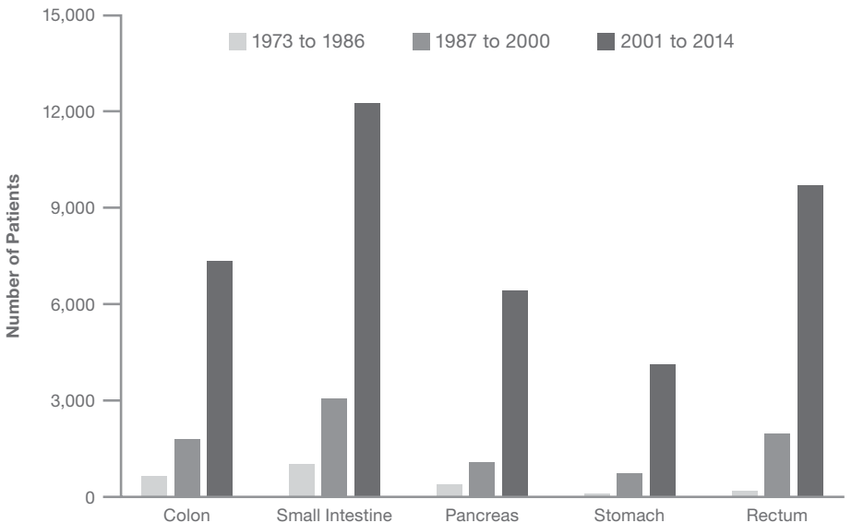
Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

GEP-NETs are diagnosed with increasing frequency and may result in death[2]

The number of patients diagnosed with GEP-NETs has steadily increased over the last 4 decades[2]

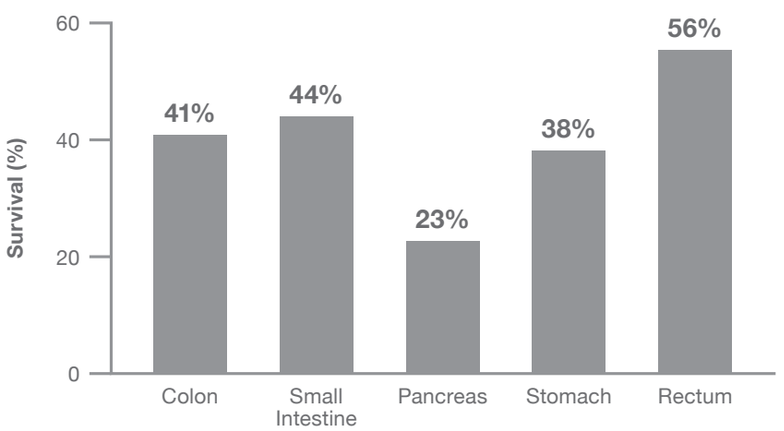
Number of Patients Diagnosed by Primary Site in Each Time Period[2]



Diagnosis trends from the SEER cancer registry. Excludes patients with NETs from other primary sites.[2]

Overall survival in patients with GEP-NETs varies by site of origin[2]

5-Year OS of Patients Diagnosed from 1973 to 2014[2]



OS data from the SEER cancer registry. Excludes patients without available disease stage data.[2]

GEP-NETs, gastroenteropancreatic neuroendocrine tumors; SEER, Surveillance, Epidemiology, and End Results.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

- **Myelosuppression:** In NETTER-1 clinical trial, myelosuppression occurred more frequently in patients receiving LUTATHERA with long acting octreotide at the following rates (all grades/grade 3 or 4): anemia (81%/0), thrombocytopenia (53%/1%), and neutropenia (26%/3%). Blood cell counts must be monitored prior to, during, and after treatment. Withhold, reduce dose, or permanently discontinue based on severity of myelosuppression.

Please see additional Important Safety Information throughout and full Prescribing Information.

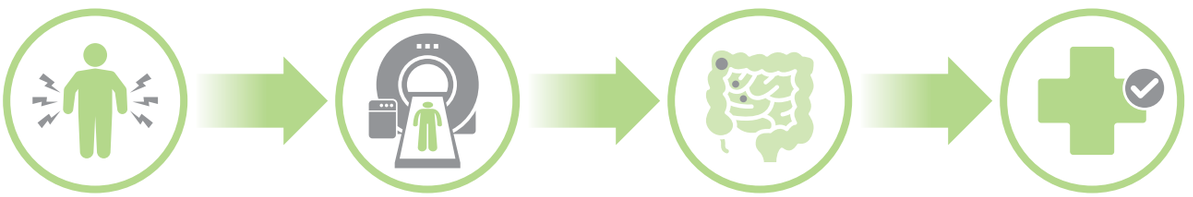
LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

How to identify patients who may benefit from treatment with LUTATHERA

Close monitoring is essential to identify patients progressing on first-line somatostatin analogs[3,4]

- Disease progression in GEP-NETs is associated with shorter OS[5]
  - Based on a retrospective landmark analysis of 440 patients with metastatic NET treated with somatostatin analogs at a single center between 1995 and 2013 who were evaluable for tumor progression[5]

An Approach to Identifying and Managing Progression in Patients With GEP-NETs



Somatostatin receptor imaging helps stage the disease and may guide therapy selection[1,6,8-10]

- Somatostatin receptor imaging for patients with GEP-NETs:
  - Helps identify patients for whom LUTATHERA may be an appropriate option[1,8]
  - Is useful in identifying primary sites as well as sensitively determining the site and extent of certain metastases[9-11]
  - May complement CT and MRI[6]

CT, computed tomography; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; MRI, magnetic resonance imaging; OS, overall survival.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

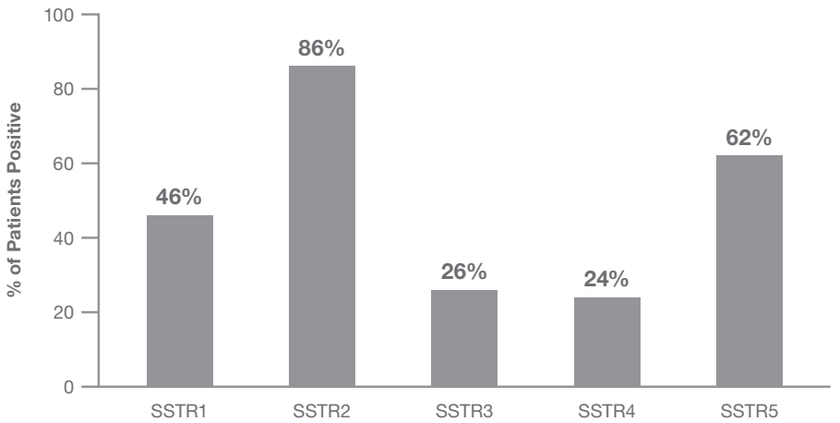
- **Secondary Myelodysplastic Syndrome and Leukemia:** In NETTER-1, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide. In ERASMUS, a Phase II clinical study, 16 patients (2%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) and 55 months (32 to 155 months) for acute leukemia.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

LUTATHERA is a radionuclide linked to a peptide that binds somatostatin receptors on the surface of GEP-NET cells[1]

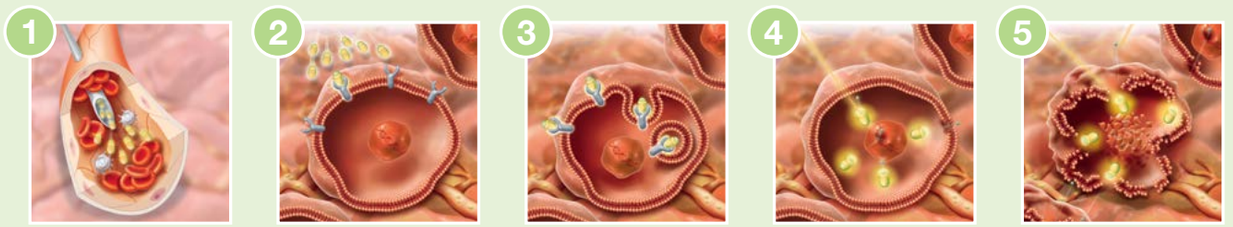
Percentage of GEP-NETs Expressing Somatostatin Receptors (N=100)[12]



Study included 67 gastrointestinal NETs, 25 pancreatic NETs, and 8 liver metastases of unknown origin. Receptor expression was determined by immunohistochemistry.[12]
Reprinted from *Dig Liver Dis.* 42(3):220-225. Zamora V, et al. © 2010, with permission from Elsevier.

- The density of SSTR expression is higher on GEP-NETs than on nontumor tissues[13]
- LUTATHERA binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSTR2)[1]

Mechanism of action of LUTATHERA



1. LUTATHERA is infused into the bloodstream.
2. LUTATHERA binds to cells expressing somatostatin receptors, including GEP-NET cells.
3. LUTATHERA is internalized into somatostatin receptor-bearing cells…
4. …where it delivers beta radiation.
5. The radiation causes damage in somatostatin receptor-positive cells and neighboring cells.

GEP-NETs, gastroenteropancreatic neuroendocrine tumors.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

- **Renal Toxicity:** Treatment with LUTATHERA will expose kidneys to radiation, which may impair renal function. In ERASMUS <1% of patients developed renal failure 3 to 36 months following LUTATHERA. Monitor serum creatinine and creatinine clearance to assess changes in renal function. Advise patients to urinate frequently during and after administration of LUTATHERA. A concomitant intravenous infusion of amino acids before, during, and after LUTATHERA administration is mandatory for renal protection. Patients with baseline renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild or moderate impairment. Withhold, reduce dose, or permanently discontinue based on severity of renal toxicity. Do not decrease the dose of amino acid solution if the dose of LUTATHERA is reduced. LUTATHERA has not been studied in patients with severe renal impairment (CrCL < 30 mL/min).

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Guidelines and clinical evidence support the use of lutetium Lu 177 dotatate after a first-line SSA

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommended option for the management of GEP-NETs[14]

- Lutetium Lu 177 dotatate is a category 1* recommended option for use after progression on a somatostatin analog in somatostatin-receptor positive, progressive midgut NETs
- Lutetium Lu 177 dotatate is a category 2A† recommended option for use after progression on a somatostatin analog in somatostatin-receptor positive, progressive GEP-NETs other than midgut NETs, including pancreatic NETs (pNETs)

NANETS/SNMMI consensus statement on patient selection and appropriate use of lutetium Lu 177 dotatate peptide receptor radionuclide therapy[15]

- In patients with midgut NET, lutetium Lu 177 dotatate should be considered in SSTR-positive patients at time of progression after treatment with first-line somatostatin analog therapy (appropriateness score 9/9‡)
- Based on registry data, the FDA included pNET within the indication for lutetium Lu 177 dotatate, and PRRT should be considered for treatment of patients with progressive pNET (appropriateness score 8/9)

*Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[14]

†Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[14]

‡Members of the guidelines workgroup scored each scenario for LUTATHERA use as ''rarely appropriate,'' ''may be appropriate,'' or ''appropriate'' on a scale from 1 to 9. Scores 7 to 9 indicate that the use of the procedure is appropriate for the specific scenario and is generally considered acceptable.[15]

FDA, Food and Drug Administration; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; MOA, mechanism of action; NANETS, North American Neuroendocrine Tumor Society; NCCN, National Comprehensive Cancer Network; PRRT, peptide receptor radionuclide therapy; SNMMI; Society of Nuclear Medicine and Molecular Imaging; SSA, somatostatin analog; SSTR, somatostatin receptor.

IMPORTANT SAFETY INFORMATION (CONTINUED)

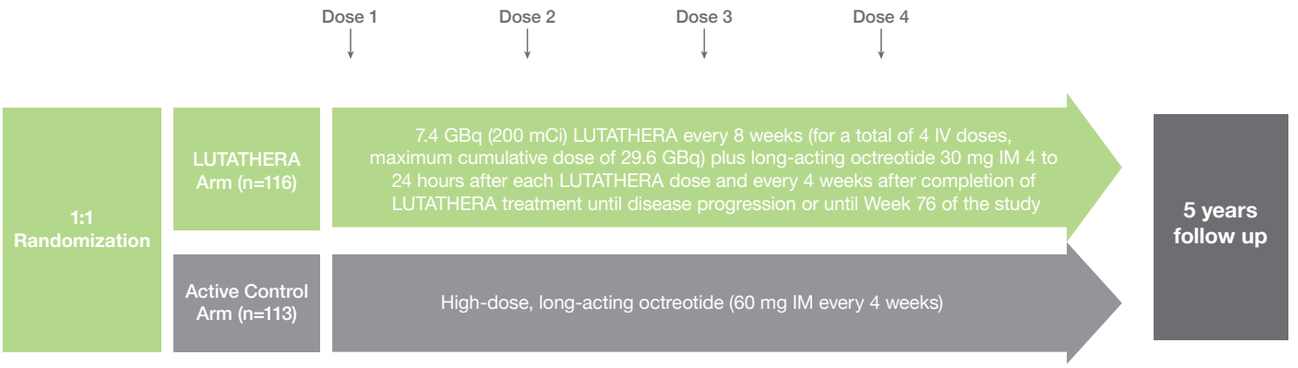
WARNINGS AND PRECAUTIONS (CONTINUED)

- **Hepatotoxicity:** In ERASMUS, <1% of patients were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure. Monitor transaminases, bilirubin, and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue based on severity of hepatic impairment.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Design of the NETTER-1 trial, a randomized, multicenter, open-label, active-controlled Phase 3 study[1,8]



Patients in both arms could receive short-acting octreotide for acute symptom management, which was withheld for at least 24 hours before each LUTATHERA dose. Concomitant amino acids and antiemetics were administered to patients in the LUTATHERA arm.

Inclusion Criteria	Exclusion Criteria
• Patients with midgut NETs that had metastasized or were locally advanced, that were inoperable, and that had progressed during treatment with long-acting octreotide • Karnofsky performance score ≥60 (median score: 90)[2] • Tumor with well-differentiated histologic features (Ki-67 index ≤20%) • Confirmed presence of somatostatin receptors on all target lesions (somatostatin receptor scintigraphy uptake greater than or equal to normal liver) • Patients must have progressive disease based on RECIST criteria, version 1.1 while receiving an uninterrupted fixed dose of octreotide LAR (20-30 mg/3-4 weeks) • CrCl ≥50 mL/min • No prior treatment with PRRT • No prior external radiation therapy to >25% of the bone marrow	• Serum creatinine level >150 µmol/L or CrCl <50 mL/min • Hemoglobin level <8.0 g/dL • White blood cell count <2000/mm^3 • Platelet count <75,000/mm^3 • Total bilirubin level >3 times upper limit of normal • Serum albumin <3.0 g/dL unless prothrombin time is within the normal range • Treatment with >30 mg long-acting octreotide within 12 weeks before randomization • PRRT at any time before randomization • Any surgery, liver-directed transarterial therapy, or chemotherapy within 12 weeks before randomization

- The primary endpoint was progression-free survival (PFS), defined as the time from randomization to documented disease progression (as evaluated per RECIST v1.1 by independent central review by radiologists who were unaware of the treatment) or death from any cause
- Secondary endpoints were overall response rate (ORR), overall survival (OS), and safety

CrCl, creatine clearance; IM, intramuscular; IV, intravenous; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

- **Neuroendocrine hormonal crisis:** Manifesting with flushing, diarrhea, bronchospasm and hypotension, neuroendocrine hormonal crisis occurred in <1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial LUTATHERA dose. Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms of tumor-related hormonal release. Administer intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes as indicated.

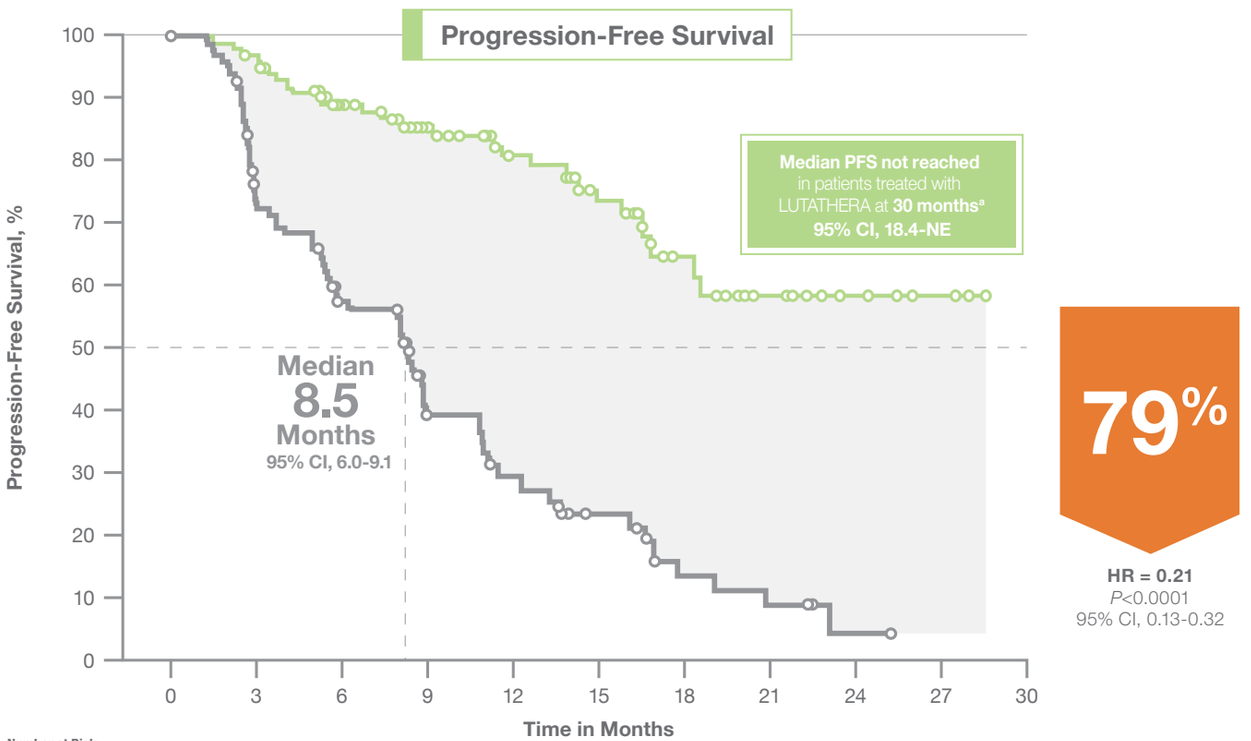
Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

79% reduction in the risk of disease progression or death vs control[1,8]

POWER AGAINST PROGRESSION

Median PFS was not yet reached in the LUTATHERA arm vs 8.5 months in the control arm*



Number at Risk

LUTATHERA plus long-acting octreotide 30 mg	116	102	84	66	48	38	22	13	6	3	0
Long-acting octreotide 60 mg	113	84	57	35	21	14	6	4	1	0	0

LUTATHERA plus long-acting octreotide 30 mg — Long-acting octreotide 60 mg

[a]At time of analysis that produced values included in Prescribing Information.

PFS in NETTER-1		
Progression-Free Survival	**LUTATHERA Plus Long-Acting Octreotide (30 mg) (n = 116)**	**Long-Acting Octreotide (60 mg) (n = 113)**
Events, n (%)	27 (23%)	78 (69%)
Progressive disease, n (%)	15 (13%)	61 (54%)
Deaths, n (%)	12 (10%)	17 (15%)

CrCl, creatinine clearance; HR, hazard ratio; IM, intramuscular; IV, intravenous; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

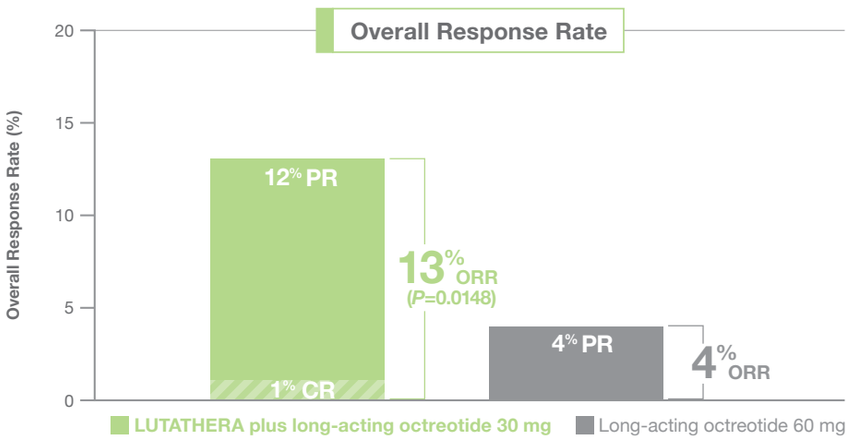
- **Embryo-Fetal Toxicity:** LUTATHERA can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose. Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

More than 3X greater ORR vs control[1,8]

13% ORR (secondary endpoint) in the LUTATHERA arm vs 4% ORR for high-dose, long-acting octreotide 60 mg



Overall Response Rates in NETTER-1		
ORR by IRC	**LUTATHERA Plus Long-Acting Octreotide (30 mg) (n=116)**	**Long-Acting Octreotide (60 mg) (n=113)**
ORR, % (95% CI)	13% (7%, 19%)	4% (0.1%, 7%)
Complete response rate, n (%)	1 (1%)	0 (0%)
Partial response rate, n (%)	14 (12%)	4 (4%)

- Response criteria were defined according to RECIST 1.1
  - **Complete response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
  - **Partial response (PR):** ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters

IRC, independent review committee; ORR, overall response rate.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

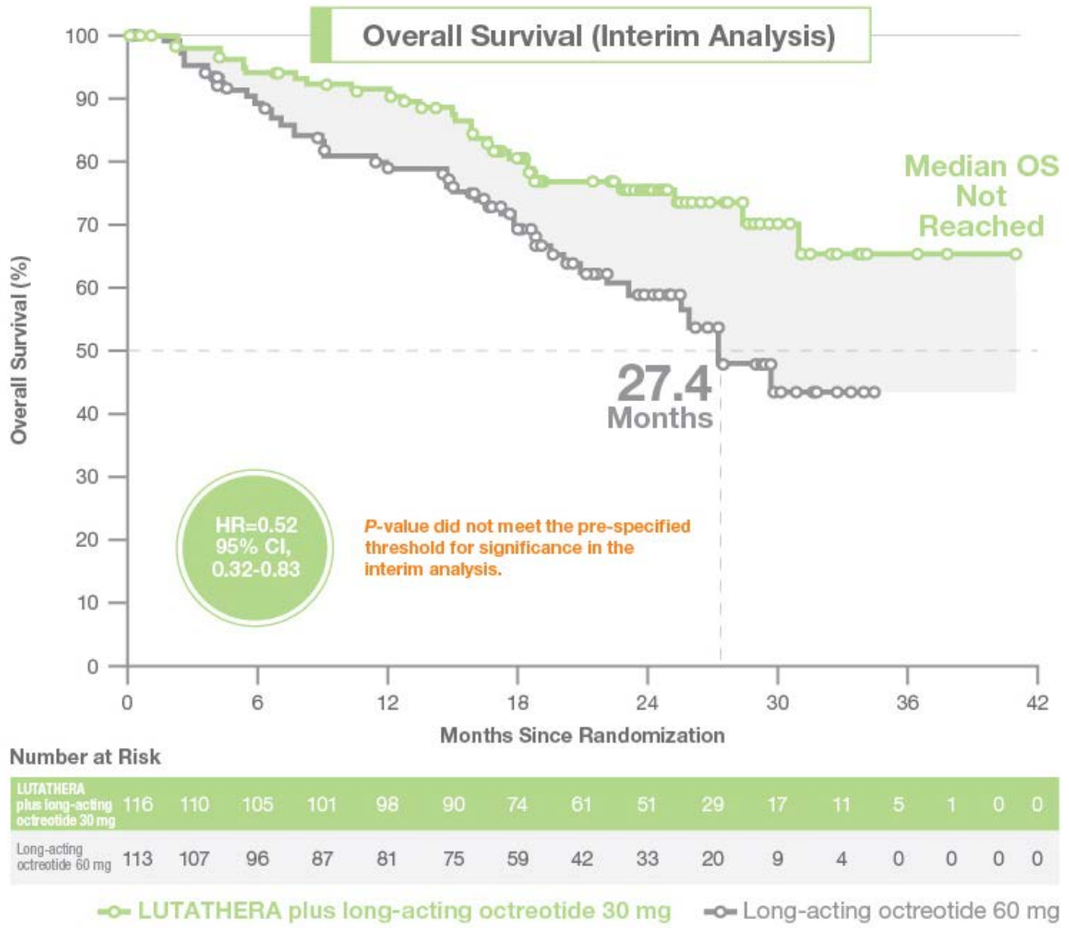
- **Risk of Infertility:** LUTATHERA may cause infertility in males and females. Radiation absorbed by testes and ovaries from the recommended cumulative LUTATHERA dose falls within the range in which temporary or permanent infertility can be expected following external beam radiotherapy.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Interim analysis of OS[1,8]

Median OS (secondary endpoint) was not yet reached in the LUTATHERA arm vs 27.4 months in the control arm



Overall Survival in NETTER-1		
Overall Survival (OS)	**LUTATHERA Plus Long-Acting Octreotide (30 mg) (n=116)**	**Long-Acting Octreotide (60 mg) (n=113)**
Deaths (%)	27 (23%)	43 (38%)

- The final analysis of OS is planned after 158 cumulative deaths or 5 years from last patient randomization, whichever comes first

IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS

The most common Grade 3-4 adverse reactions (≥ 4% with a higher incidence in LUTATHERA arm) observed in NETTER-1 were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), elevated AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%).

In ERASMUS, the following serious adverse reactions have been observed with a median follow-up time of more than 4 years after treatment with LUTATHERA: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%). Patients should be counseled and monitored in accordance with the LUTATHERA Prescribing Information.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Safety and tolerability in NETTER-1[1]

Adverse reactions occurring at higher incidence in LUTATHERA arm (between arm difference of ≥5% all grades or ≥2% grades 3-4)

	LUTATHERA and Long-Acting Octreotide (30 mg) (N=111)		Long-Acting Octreotide (60 mg) (N=112)	
Adverse Reaction*	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Gastrointestinal disorders				
Nausea	65	5	12	2
Vomiting	53	7	10	0
Abdominal pain	26	3	19	3
Diarrhea	26	3	18	1
Constipation	10	0	5	0
General disorders				
Fatigue	38	1	26	2
Peripheral edema	16	0	9	1
Pyrexia	8	0	3	0
Metabolism and nutrition disorders				
Decreased appetite	21	0	11	3
Nervous system disorders				
Headache	17	0	5	0
Dizziness	17	0	8	0
Dysgeusia	8	0	2	0
Vascular disorders				
Flushing	14	1	9	0
Hypertension	12	2	7	2
Musculoskeletal and connective tissue disorders				
Back pain	13	2	10	0
Pain in extremity	11	0	5	0
Myalgia	5	0	0	0
Neck pain	5	0	0	0
Renal and urinary disorders				
Renal failure†	13	3	4	1
Radiation-related urinary tract toxicity‡	8	0	3	0
Psychiatric disorders				
Anxiety	12	1	5	0
Skin and subcutaneous tissue disorders				
Alopecia	12	0	2	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	1	6	0
Cardiac disorders				
Atrial fibrillation	5	1	0	0

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays adverse reactions occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2% (grades 3-4)].

†Includes the terms: Glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotemia, renal disorder, renal failure, renal impairment.

‡Includes the terms: Dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain, and urinary incontinence.

- 6% of patients required a dose reduction, and 13% of patients discontinued LUTATHERA
  - 5 patients discontinued due to renal-related events
  - 4 patients discontinued due to hematological toxicities

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Safety and tolerability in NETTER-1[1] (cont.)

Laboratory abnormalities occurring at higher incidence in LUTATHERA arm (between arm difference of ≥5% all grades or ≥2% grades 3-4)

	LUTATHERA and Long-Acting Octreotide (30 mg) (N=111)		Long-Acting Octreotide (60 mg) (N=112)	
Laboratory Abnormality*†	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Hematology				
Lymphopenia	90	44	39	5
Anemia	81	0	55	1
Leukopenia	55	2	20	0
Thrombocytopenia	53	1	17	0
Neutropenia	26	3	11	0
Renal/Metabolic				
Creatinine increased	85	1	73	0
Hyperglycemia	82	4	67	2
Hyperuricemia	34	6	30	6
Hypocalcemia	32	0	14	0
Hypokalemia	26	4	21	2
Hyperkalemia	19	0	11	0
Hypernatremia	17	0	7	0
Hypoglycemia	15	0	8	0
Hepatic				
GGT increased	66	20	67	16
Alkaline phosphatase increased	65	5	55	9
AST increased	50	5	35	0
ALT increased	43	4	34	0
Blood bilirubin increased	30	2	28	0

*Values are worst grade observed after randomization.

†National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays laboratory abnormalities occurring at a higher incidence in LUTATHERA-treated patients (between arm difference of ≥5% [all grades] or ≥2% [grades 3-4]).

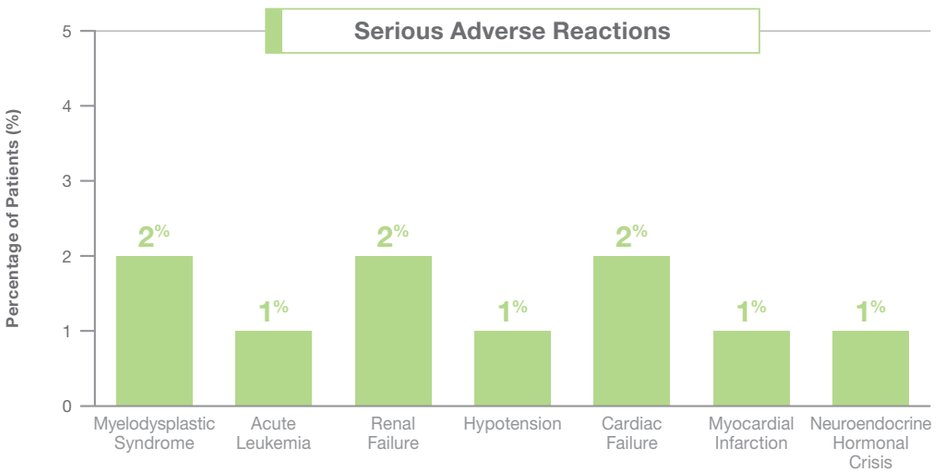
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Long-term safety in ERASMUS[1,16]

Retrospective safety analysis of long-term (median >4 years) follow-up after LUTATHERA treatment (n=811)



- Retrospective safety data are available from 1,214 patients in ERASMUS, an international, single-institution, single-arm, open-label trial of patients with somatostatin receptor-positive tumors (neuroendocrine and other primaries)
- LUTATHERA 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses with or without octreotide and with the recommended amino acid solution and antiemetic
- Retrospective medical record review was conducted on a subset of 811 patients to document serious adverse reactions
- 81% of patients in the subset received a cumulative dose ≥22.2 GBq (≥600 mCi)

Please see warnings and precautions for myelosuppression and secondary myelodysplastic syndrome and leukemia. Monitor blood cell counts. Withhold, reduce dose, or permanently discontinue based on severity of adverse reactions.

IMPORTANT SAFETY INFORMATION (CONTINUED)

DRUG INTERACTIONS

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of LUTATHERA. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. Administer short- and long-acting octreotide during LUTATHERA treatment as recommended.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Radiation safety

Important safety instructions[1]

- Radiopharmaceuticals, including LUTATHERA, should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals
- Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices and patient management procedures

Radiation characteristics[1]

- LUTATHERA is a beta emitter that decays with a half-life of 6.647 days
- The maximum radiation penetration in tissue is 2.2 mm, and the mean penetration is 0.67 mm

Radiation associated with LUTATHERA treatment is within recommended limits

Results of a Study Performed to Evaluate the Safety of Outpatient Treatment With Lutetium Lu 177 Dotatate by Measurement of Radiation Exposures of Hospital Personnel and Caregivers[17]

Methods	Results
• 76 patients with progressive, metastatic NETs received 4 cycles of 7.8 GBq lutetium Lu 177 dotatate at 8-week intervals in an outpatient setting • 4 patients were treated in 1 room, with each patient remaining until radiation exposure was below the release limit • Radiation exposures to healthcare providers and caregivers were monitored by personal dosimeter	• Mean whole-body exposures per therapy day for HCPs administering LUTATHERA ranged from 6.8 µSv (nuclear medicine technologist) to 33.2 µSv (nurse) • Mean total exposure to 25 caregivers during the day of therapy and at home for a period of up to 5 days was 90 µSv, with a median exposure of 40 µSv and range of 10 µSv to 470 µSv • Exposures to healthcare providers, caregivers, and family members were within the limits recommended by the International Commission on Radiological Protection

- Radiation exposure is common from other sources, for example:
  - Approximately 3,000 µSv annually from natural background radiation[18]
  - 14.5 µSv on a 5.2-hour flight from Los Angeles to Honolulu[19]

HCPs, health care professionals; NETs, neuroendocrine tumors.

IMPORTANT SAFETY INFORMATION (CONTINUED)

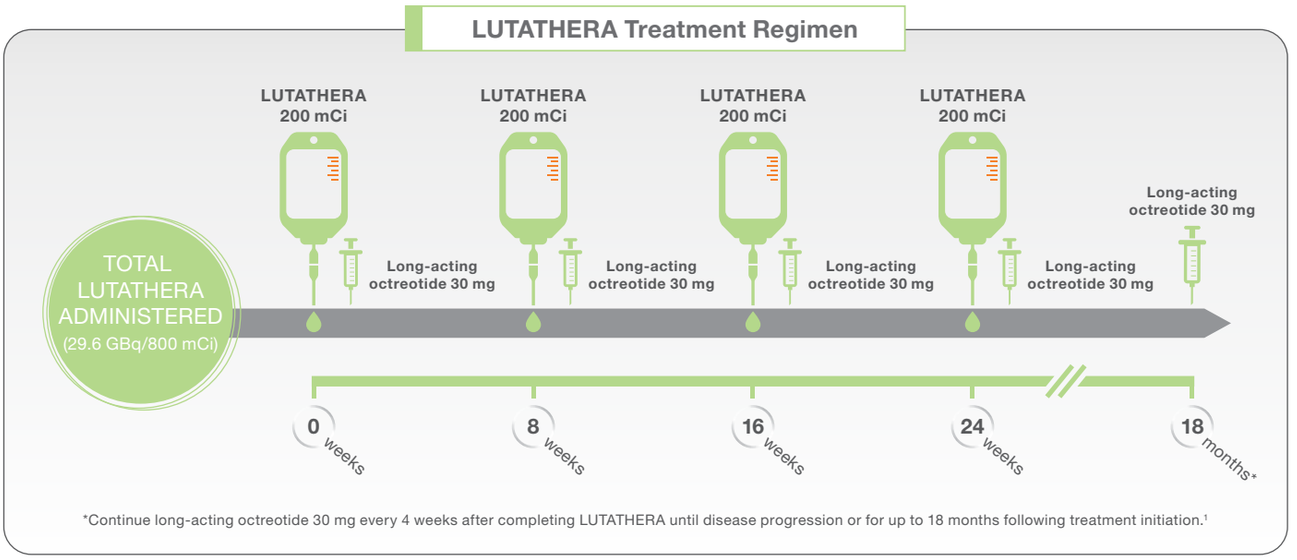
DRUG INTERACTIONS (CONTINUED)

Corticosteroids can induce down-regulation of subtype 2 somatostatin receptors (SSTR2). Avoid repeated administration of high doses of glucocorticosteroids during treatment with LUTATHERA.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Defined, 4-dose treatment regimen[1]



- The recommended LUTATHERA dosage is 7.4 GBq (200 mCi) IV, every 8 weeks, for a total of 4 doses
- The 4-dose LUTATHERA regimen may be completed in 24 weeks from treatment initiation
- LUTATHERA dosage should be modified based on hematologic, renal, hepatic, or other adverse reactions (see full Prescribing Information)
  - For reduced dose administration instructions, refer to section 2.5 (Preparation and Administration) of the full Prescribing Information
- Discontinue long-acting somatostatin analogs for at least 4 weeks prior to initiating LUTATHERA
- Administer short-acting octreotide as needed for acute symptom management; discontinue at least 24 hours prior to initiating LUTATHERA

IV, intravenous.

IMPORTANT SAFETY INFORMATION (CONTINUED)

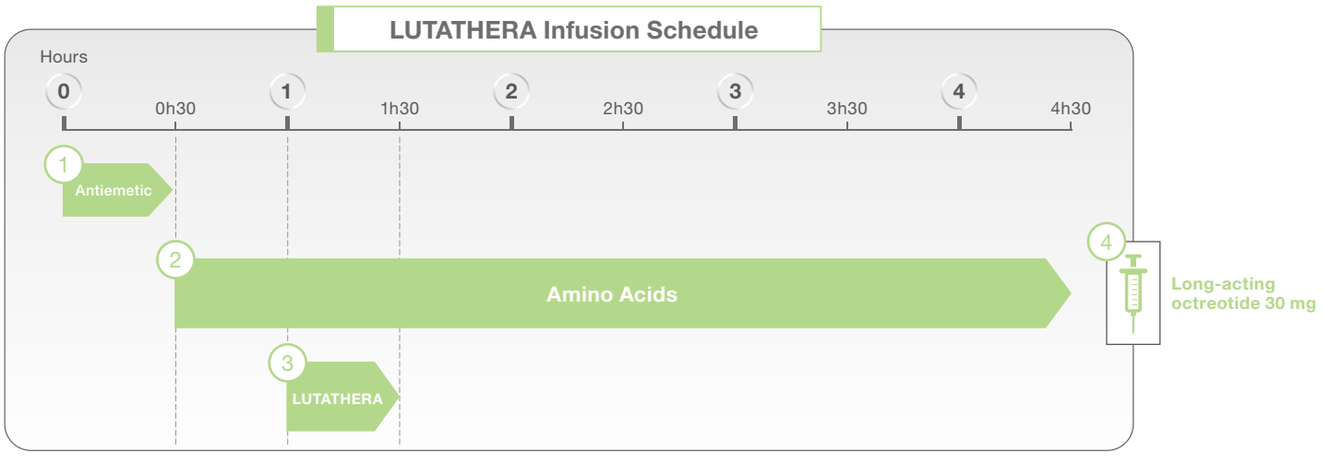
SPECIFIC POPULATIONS

- **Lactation:** Because of the potential risk for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Timing of LUTATHERA and concomitant medications[1]



1 Pretreatment antiemetic

Administer an antiemetic to help avoid treatment-related nausea and vomiting before the start of the amino acid solution infusion

2 Concomitant amino acid infusion

For renal protection, initiate an IV amino acids infusion containing L-lysine and L-arginine 30 minutes before administration of LUTATHERA. Continue amino acids during and for at least 3 hours after the LUTATHERA administration

Do not decrease the dose of the amino acid solution if the LUTATHERA dose is reduced

3 LUTATHERA infusion

LUTATHERA must be administered as an IV infusion over 30 to 40 minutes

- 50 mL/hour to 100 mL/hour for 5 to 10 minutes
- 200 mL/hour to 300 mL/hour for the following 25 to 30 minutes

4 Long-acting octreotide 30 mg

Administer long-acting octreotide 30 mg intramuscularly between 4 to 24 hours after each LUTATHERA dose

IV, intravenous.

IMPORTANT SAFETY INFORMATION (CONTINUED)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or www.report.novartis.com/, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Distributed by: Advanced Accelerator Applications USA, Inc., NJ 07041

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Patient management before and during LUTATHERA treatment

NANETS/SNMMI Recommended Laboratory Thresholds for LUTATHERA treatment	
Laboratory	**Acceptable value before first treatment**
Hemoglobin	>8 g/dL
WBC count	>2,000/mm^3
Platelet count	>70,000/mm^3
eGFR	>50 mL/min
Total bilirubin	≤3 x ULN
Serum albumin	>3.0 g/dL

These values should be considered general guidelines only.
This research was originally published in JNM. Hope TA, et al. *J Nucl Med.* 2019;60(7):937-943. © SNMMI.

- Laboratory values should be checked shortly before the treatment is ordered (typically 2 weeks before each cycle)[20]
- These should include BUN, creatinine, albumin, ALP, AST, ALT, total bilirubin, WBC count with differential, hemoglobin, and platelet counts[20]
- Pregnancy status must be verified in women of childbearing potential[1]
- The threshold values provided above may be taken as general eligibility guidelines for therapy[20]

Preparing the patient for LUTATHERA treatment

- Detailed information regarding what to expect on the day of treatment will be provided by the treating center
- The treating center will also provide direction on how to avoid or minimize radiation exposure to household contacts
- Patient education materials can be downloaded from hcp.lutathera.com

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; ULN, upper limit of normal; WBC, white blood cell.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Radiation Exposure:** Treatment with LUTATHERA contributes to a patient's overall long-term cumulative radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices, patient management procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Long-term follow-up and monitoring

NANETS/SNMMI Recommendations for Long-Term Monitoring After Completion of LUTATHERA Therapy[20]				
Time after treatment*	**Clinical evaluation**	**Laboratory tests†**	**Markers‡**	**Diagnostic imaging**
2 to 4 weeks	X	X		X§
2 months		X		
3 months	X	X	Per team	
6 months	X	X	Per team	X
12 months	X	X	Per team	X
Long term	Per team	Per team	Per team	Per team

*Increase monitoring based on clinical presentation, symptoms, concern for progressive disease, or posttreatment sequelae.
†Complete blood count with differential, AST, ALT, ALP, total bilirubin, albumin, and serum creatinine/GFR.
‡Monitoring of markers should be based on clinical indication/presentation.
§Imaging is recommended once between 1 and 3 months after therapy.

This research was originally published in *JNM.* Hope TA, et al. *J Nucl Med.* 2019;60(7):937-943. © SNMMI.

Patient monitoring considerations[20]

- If there are no laboratory abnormalities or clinical symptoms concerning for posttreatment sequelae, patients can resume clinical follow-up per the primary team
- Clinical symptoms and presentations that could reflect possible progression, increased symptoms from carcinoid syndrome, or posttreatment sequelae warrant closer monitoring

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GFR, glomerular filtration rate; NANETS, North American Neuroendocrine Tumor Society; SNMMI, Society of Nuclear Medicine and Molecular Imaging; ULN, upper limit of normal; WBC, white blood cell.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

- **Myelosuppression:** In NETTER-1 clinical trial, myelosuppression occurred more frequently in patients receiving LUTATHERA with long acting octreotide at the following rates (all grades/grade 3 or 4): anemia (81%/0), thrombocytopenia (53%/1%), and neutropenia (26%/3%). Blood cell counts must be monitored prior to, during, and after treatment. Withhold, reduce dose, or permanently discontinue based on severity of myelosuppression.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

INDICATION

LUTATHERA® (lutetium Lu 177 dotatate) injection is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrinetumors in adults.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Radiation Exposure:** Treatment with LUTATHERA contributes to a patient's overall long-term cumulative radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices, patient management procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home.

- **Myelosuppression:** In NETTER-1 clinical trial, myelosuppression occurred more frequently in patients receiving LUTATHERA with long acting octreotide at the following rates (all grades/grade 3 or 4): anemia (81%/0), thrombocytopenia (53%/1%), and neutropenia (26%/3%). Blood cell counts must be monitored prior to, during, and after treatment. Withhold, reduce dose, or permanently discontinue based on severity of myelosuppression.

- **Secondary Myelodysplastic Syndrome and Leukemia:** In NETTER-1, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving LUTATHERA with long-acting octreotide. In ERASMUS, a Phase II clinical study, 16 patients (2%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) and 55 months (32 to 155 months) for acute leukemia.

- **Renal Toxicity:** Treatment with LUTATHERA will expose kidneys to radiation, which may impair renal function. In ERASMUS <1% of patients developed renal failure 3 to 36 months following LUTATHERA. Monitor serum creatinine and creatinine clearance to assess changes in renal function. Advise patients to urinate frequently during and after administration of LUTATHERA. A concomitant intravenous infusion of amino acids before, during, and after LUTATHERA administration is mandatory for renal protection. Patients with baseline renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild or moderate impairment. Withhold, reduce dose, or permanently discontinue based on severity of renal toxicity. Do not decrease the dose of amino acid solution if the dose of LUTATHERA is reduced. LUTATHERA has not been studied in patients with severe renal impairment (CrCL < 30 mL/min).

- **Hepatotoxicity:** In ERASMUS, <1% of patients were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure. Monitor transaminases, bilirubin, and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue based on severity of hepatic impairment.

- **Neuroendocrine hormonal crisis:** Manifesting with flushing, diarrhea, bronchospasm and hypotension, neuroendocrine hormonal crisis occurred in <1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial LUTATHERA dose. Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms of tumor-related hormonal release. Administer intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes as indicated.

- **Embryo-Fetal Toxicity:** LUTATHERA can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose. Verify pregnancy status of females of reproductive potential prior to initiating LUTATHERA.

- **Risk of Infertility:** LUTATHERA may cause infertility in males and females. Radiation absorbed by testes and ovaries from the recommended cumulative LUTATHERA dose falls within the range in which temporary or permanent infertility can be expected following external beam radiotherapy.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

IMPORTANT SAFETY INFORMATION (Continued)

ADVERSE REACTIONS

The most common Grade 3-4 adverse reactions (≥ 4% with a higher incidence in LUTATHERA arm) observed in NETTER-1 were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), elevated AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%).

In ERASMUS, the following serious adverse reactions have been observed with a median follow-up time of more than 4 years after treatment with LUTATHERA: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%). Patients should be counseled and monitored in accordance with the LUTATHERA Prescribing Information.

DRUG INTERACTIONS

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of LUTATHERA. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each LUTATHERA dose. Administer short- and long-acting octreotide during LUTATHERA treatment as recommended.

Corticosteroids can induce down-regulation of subtype 2 somatostatin receptors (SSTR2). Avoid repeated administration of high doses of glucocorticosteroids during treatment with LUTATHERA.

SPECIFIC POPULATIONS

- **Lactation:** Because of the potential risk for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose.

To report SUSPECTED ADVERSE REACTIONS, contact Advanced Accelerator Applications USA, Inc. at 1-844-863-1930, or us-pharmacovigilance@adacap.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information.

Distributed by: Advanced Accelerator Applications USA, Inc., NJ 07041

Reference: 1. LUTATHERA® [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA, Inc.; May 2020.

Please see additional Important Safety Information throughout and full Prescribing Information.

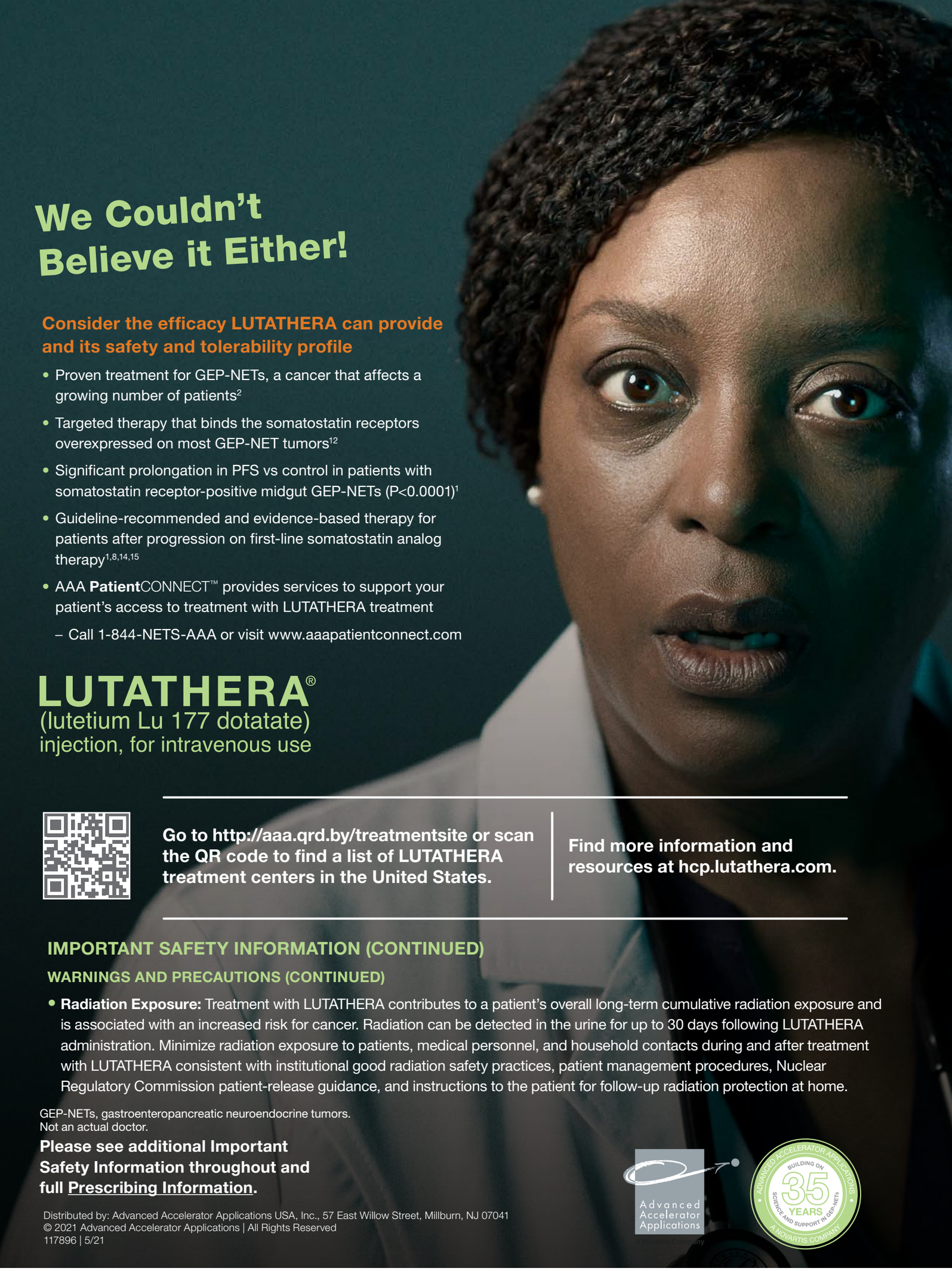
LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

References

1. LUTATHERA® [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA, Inc.; May 2020.
2. Man D, Wu J, Shen Z, Zhu X. Prognosis of patients with neuroendocrine tumor: a SEER database analysis. *Cancer Manag Res.* 2018;10:5629-5638.
3. Oxnard GR, Morris MJ, Hodi FS, et al. When progressive disease does not mean treatment failure: reconsidering the criteria for progression. *J Natl Cancer Inst.* 2012;104(20):1534-1541.
4. Merino-Casabiel X, Aller J, Arbizu J, et al. Consensus document on the progression and treatment response criteria in gastroenteropancreatic neuroendocrine tumors. *Clin Transl Oncol.* 2018;20(12):1522-1528.
5. Ter-Minassian M, Zhang S, Brooks NV, et al. Association between tumor progression endpoints and overall survival in patients with advanced neuroendocrine tumors. *Oncologist.* 2017;22(2):165-172.
6. de Mestier L, Dromain C, d'Assignies G, et al. Evaluating digestive neuroendocrine tumor progression and therapeutic responses in the era of targeted therapies: state of the art. *Endocr Relat Cancer.* 2014;21(3):R105-R120.
7. Maxwell JE, Howe JR. Imaging in neuroendocrine tumors: an update for the clinician. *Int J Endocr Oncol.* 2015;2(2):159-168.
8. Strosberg J, El-Haddad G, Wolin E, et al, for the NETTER-1 trial investigators. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376(2):125-135.
9. Society of Nuclear Medicine and Molecular Imaging. About Nuclear Medicine and Molecular Imaging. www.snmmi.org/Patients/About/content.aspx?ItemNumber=13294&navItemNumber=13295. Accessed March 24, 2020.
10. Buchmann I, Henze M, Engelbrecht S, et al. Comparison of ^{68}Ga-DOTATOC PET and ^{111}In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2007;34(10):1617-1626.
11. Gabriel M, Decristoforo C, Kendler D, et al. ^{68}Ga-DOTA-Tyr^{3}-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med.* 2007;48(4):508-518.
12. Zamora V, Cabanne A, Salanova R, et al. Immunohistochemical expression of somatostatin receptors in digestive endocrine tumours. *Dig Liver Dis.* 2010;42(3):220-225.
13. Thundimadathil J. Cancer treatment using peptides: current therapies and future prospects. *J Amino Acids.* 2012;967347:1-13.
14. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine and Adrenal Tumors V.1.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed February 8, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
15. Hope TA, Bodei L, Chan JA, et al. NANETS/SNMMI consensus statement on patient selection and appropriate use of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy. *J Nucl Med.* 2020;61(2):222-227.
16. Brabander T, van der Zwan WA, Teunissen J, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res.* 2017;23(16):4617-4624.
17. Calais PJ, Turner JH. Radiation safety of outpatient ^{177}Lu-octreotate radiopeptide therapy of neuroendocrine tumors. *Ann Nucl Med.* 2014;28(6):531-539.
18. American Cancer Society. Natural background radiation. www.cancer.org/cancer/cancer-causes/radiation-exposure/x-rays-gamma-rays/natural-background-radiation.html. Accessed January 12, 2019.
19. Friedberg W, Copeland K, Duke FE, O'Brien K III, Darden EB Jr. Radiation exposure during air travel: guidance provided by the Federal Aviation Administration for air carrier crews. *Health Phys.* 2000;79(5):591-595.
20. Hope TA, Abbott A, Colucci K, et al. NANETS/SNMMI procedure standard for somatostatin receptor-based peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE. *J Nucl Med.* 2019;60(7):937-943.

Please see additional Important Safety Information throughout and full Prescribing Information.

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use



We Couldn't Believe it Either!

Consider the efficacy LUTATHERA can provide and its safety and tolerability profile

- Proven treatment for GEP-NETs, a cancer that affects a growing number of patients[2]
- Targeted therapy that binds the somatostatin receptors overexpressed on most GEP-NET tumors[12]
- Significant prolongation in PFS vs control in patients with somatostatin receptor-positive midgut GEP-NETs ($P<0.0001$)[1]
- Guideline-recommended and evidence-based therapy for patients after progression on first-line somatostatin analog therapy[1,8,14,15]
- AAA **Patient**CONNECT™ provides services to support your patient's access to treatment with LUTATHERA treatment
  - Call 1-844-NETS-AAA or visit www.aaapatientconnect.com

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

Go to http://aaa.qrd.by/treatmentsite or scan the QR code to find a list of LUTATHERA treatment centers in the United States.

Find more information and resources at hcp.lutathera.com.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

- **Radiation Exposure:** Treatment with LUTATHERA contributes to a patient's overall long-term cumulative radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following LUTATHERA administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with LUTATHERA consistent with institutional good radiation safety practices, patient management procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home.

GEP-NETs, gastroenteropancreatic neuroendocrine tumors.
Not an actual doctor.

Please see additional Important Safety Information throughout and full Prescribing Information.

Distributed by: Advanced Accelerator Applications USA, Inc., 57 East Willow Street, Millburn, NJ 07041

117896 | 5/21

Advanced Accelerator Applications
A Novartis Company

ADVANCED ACCELERATOR APPLICATIONS · BUILDING ON 35 YEARS OF SCIENCE AND SUPPORT IN GEP-NETs · A NOVARTIS COMPANY