NOW

Emily

- Referred for LUTATHERA® (lutetium Lu 177 dotatate) injection immediately after progressing on first-line somatostatin analog therapy

OR

Maggie

- Referred for LUTATHERA after progressing on multiple therapies but deemed ineligible for LUTATHERA due to laboratory values associated with disease progression

NEVER?

For your patients who progress on first-line somatostatin analog therapy…

TAKE ACTION NOW WITH LUTATHERA, BEFORE IT'S NO LONGER AN OPTION[1]

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.

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

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

More than 200 patients evaluated in a phase 3 midgut NET clinical trial[2-4]

NETTER-1 Study Design

Randomized (1:1), multicenter, open-label, active-controlled phase 3 study

LUTATHERA + Octreotide Arm (n = 116)

7.4 GBq (200 mCi) LUTATHERA® (lutetium Lu 177 dotatate) injection every 8 weeks (for a total of 4 IV doses, maximum cumulative dose of 29.6 GBq) plus long-acting octreotide 30 mg IM 4 to 24 hours after each LUTATHERA dose and every 4 weeks after completion of LUTATHERA treatment until disease progression or until Week 76 of the study

Octreotide Arm (n = 113)

Active control: high-dose, long-acting octreotide (60 mg IM every 4 weeks)

Inclusion 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

Exclusion Criteria

- 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

End Points Evaluated

- Primary end point: 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 end points: overall response rate (ORR), overall survival (OS), and safety and side effect profile

CrCl, creatinine clearance; IM, intramuscular; IV, intravenous; LAR, long-acting release; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

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.

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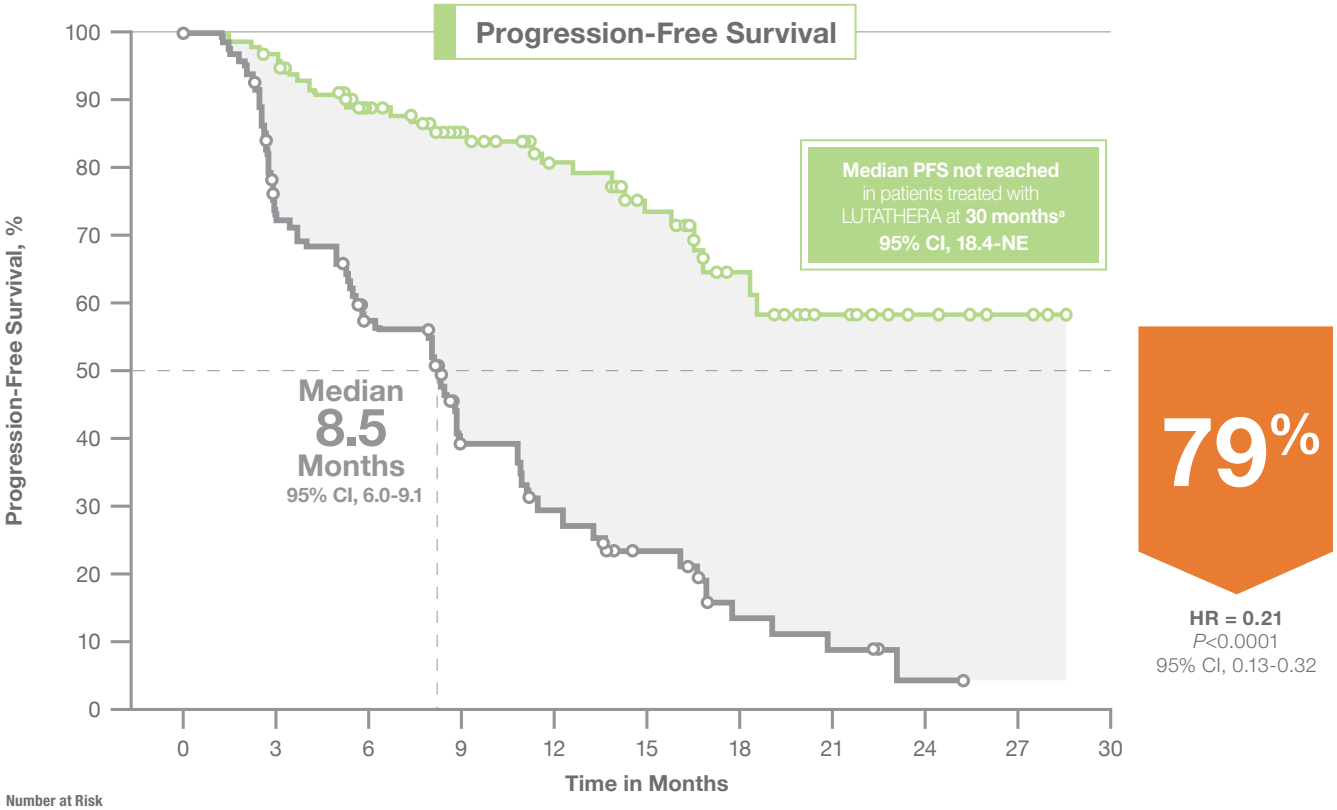
Power against progression with LUTATHERA[2,3]

79% reduction in the risk of disease progression or death with LUTATHERA[2,3]



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%)

HR, hazard ratio; NE, not evaluable.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

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.

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LUTATHERA®
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In a post hoc analysis of NETTER-1

LUTATHERA improved PFS for patients with lesions of all sizes[4]

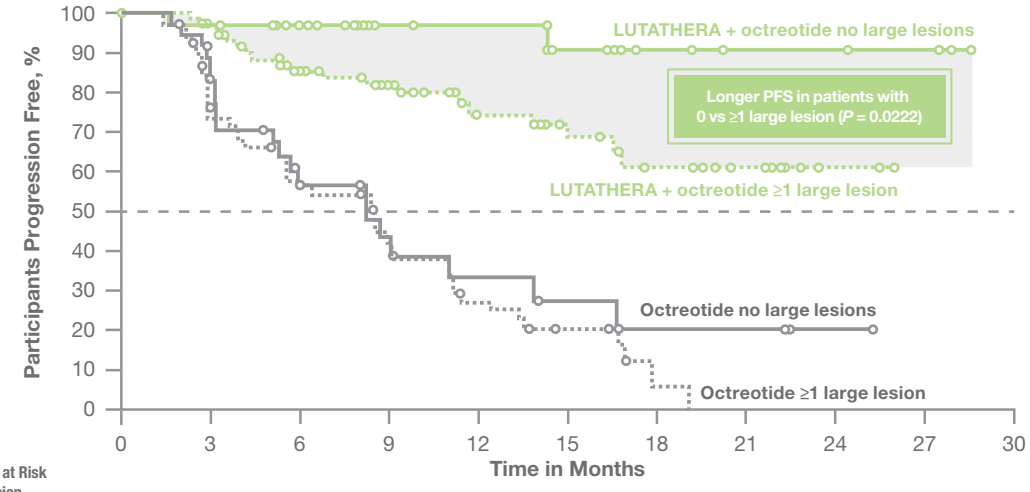
More improvement in PFS seen with LUTATHERA® (lutetium Lu 177 dotatate) injection in those with smaller lesions

Post Hoc Study Design

Patients were stratified into 2 subgroups based on the presence or absence of at least 1 target lesion >30 mm in diameter at any body site on CT or MRI at baseline. The log-rank test was used for within-treatment arm comparisons of PFS. HRs with corresponding 95% CIs and *P* values were estimated using a Cox regression model with randomized treatment, presence/absence of large target lesion, and presence/absence of large target lesion times randomized treatment interaction term as covariates.[4]

Post Hoc Study Limitations

- Data on the impact of tumor burden are from a post hoc, subgroup analysis of the NETTER-1 study[4]
- Concerns exist regarding the safety of LUTATHERA in patients with high tumor burden owing to the potential for radiation hepatitis. Data from NETTER-1 did not validate this hypothesis. Liver function test elevations were rare and did not appear to correlate with baseline tumor burden. It is important to note, however, that safety findings in patients with tumor burden >50% do not necessarily imply that treatment is equally safe in patients with extreme tumor burden (eg, >90%). A limitation of this study is that central readers did not specify the patients with extreme tumor burden (>90%) and, therefore, no specific safety analysis in that subgroup was possible[4]
- Another limitation is that the sample sizes were fractions of the 2 treatment arms, which were particularly small in the "no large lesions" group: 37 of 116 for the LUTATHERA arm and 39 of 113 for the for octreotide LAR arm[4]



Participants at Risk											
No large lesion											
LUTATHERA + octreotide LAR 30 mg	37	32	28	17	16	12	6	4	4	3	0
Octreotide LAR 60 mg	39	30	16	9	6	4	3	3	1	0	0
≥1 large lesion											
LUTATHERA + octreotide LAR 30 mg	79	68	52	44	27	22	14	9	2	0	0
Octreotide LAR 60 mg	74	51	34	21	12	7	1	0	0	0	0

Baseline Large Lesions	Treatment Arm	n	Events, n (%)	Median PFS, Months	HR (95% CI)	*P*
No large lesions	LUTATHERA + octreotide LAR 30 mg	37	2 (5.4)	NR	0.063 (0.015-0.273)	0.0002
	Octreotide LAR 60 mg	39	21 (53.8)	8.31		
≥1 large lesion	LUTATHERA + octreotide LAR 30 mg	79	19 (24.1)	NR	0.213 (0.124-0.366)	<0.0001
	Octreotide LAR 60 mg	74	49 (66.2)	8.54		

CT, computed tomography; MRI, magnetic resonance imaging; NR, not reached.

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

Expert panel recommends LUTATHERA after progression on first-line somatostatin analog[1]

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

LUTATHERA® (lutetium Lu 177 dotatate) injection is a category 1* recommended option for use after progression on a somatostatin analog in somatostatin receptor–positive, progressive midgut NETs.

LUTATHERA 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).

The National Comprehensive Cancer Network 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.

NCCN, National Comprehensive Cancer Network.
*Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
†Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

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.

LUTATHERA safety and tolerability based on the NETTER-1 trial[2]

Adverse reactions occurring at higher incidence in LUTATHERA® (lutetium Lu 177 dotatate) injection arm (between-arm difference of ≥5% all grades or ≥2% grades 3-4)[2]

	LUTATHERA and Long-Acting Octreotide (30 mg) (n = 111)		Long-Acting Octreotide (60 mg) (n = 112)	
Adverse Reaction[a]	**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[b]	13	**3**	4	**1**
Radiation-related urinary tract toxicity[c]	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**

[a]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]).

[b]Includes the terms: glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotemia, renal disorder, renal failure, renal impairment.

[c]Includes the terms: dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain, and urinary incontinence.

- Adverse events considered related to the trial occurred in 95 patients (86%) in the LUTATHERA group and 34 patients (31%) in the octreotide group[3]
  - –Premature withdrawal due to adverse reactions was more common in patients treated with octreotide alone vs LUTATHERA and octreotide (10 patients or 9% vs 7 patients or 6%, respectively)[3]

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

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

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[a,b]	**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**

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

[a]Values are worst grade observed after randomization.

[b]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]).

- 6% of patients required a dose reduction, and 13% of patients discontinued LUTATHERA[2]
  - –5 patients discontinued due to renal-related events
  - –4 patients discontinued due to hematological toxicities

Long-term safety evaluated in ERASMUS trial[2,5]

Retrospective safety analysis of long-term (median >4 years) follow-up after LUTATHERA® (lutetium Lu 177 dotatate) injection treatment (n = 811)

Serious adverse reactions:

2% of patients developed:
myelodysplastic syndrome, renal failure, cardiac failure.

1% of patients developed:
acute leukemia, hypotension, myocardial infarction, neuroendocrine hormonal crisis.

- Retrospective safety data are available from 1214 patients in ERASMUS, an international, single-institution, single-arm, open-label trial of patients with somatostatin receptor–positive tumors (neuroendocrine and other primaries)
- Retrospective medical record review was conducted on a subset of 811 patients to document serious adverse reactions
- LUTATHERA 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for at least 100 mCi (3.7 GBq) with or without octreotide and with the recommended amino acid solution and antiemetic
- 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)

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.

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References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine and Adrenal Tumors V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed February 8, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. **2.** Lutathera [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA, Inc.; 2020. **3.** 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. **4.** Strosberg J, Kunz PL, Hendifar A, et al; NETTER-1 study group. Impact of liver tumour burden, alkaline phosphatase elevation, and target lesion size on treatment outcomes with ^{177}Lu-dotatate: an analysis of the NETTER-1 study. *Eur J Nucl Med Mol Imaging.* 2020;47(10):2372-2382. **5.** Brabander T, van der Zwan WA, Teunissen JJM, 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.

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.

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

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For your patients who progress on first-line somatostatin analog therapy...

TAKE ACTION NOW WITH LUTATHERA, BEFORE IT'S NO LONGER AN OPTION[1]

- **More than 200 patients** evaluated in a **phase 3 midgut NET clinical trial**[2]
- **Power against progression with LUTATHERA® (lutetium Lu 177 dotatate) injection**[2,3]
  —79% reduction in the risk of disease progression or death vs long-acting octreotide alone as seen in NETTER-1
- LUTATHERA **improved PFS for patients with lesions of all sizes—more improvement in PFS** seen with LUTATHERA **in those with smaller lesions**[4]
- **NCCN expert panel recommends LUTATHERA** after progression on first-line somatostatin analog therapy[1]
- Long-term safety and tolerability evaluated in ERASMUS trial[2]

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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