

Cost-Effectiveness of [¹⁷⁷Lu]Lu-DOTATATE for the Treatment of Newly Diagnosed Advanced Gastroenteropancreatic Neuroendocrine Tumors: An Analysis Based on Results of the NETTER-2 Trial

Adrien Holzgreve^{1,2}, Lena M. Unterrainer¹⁻³, Maximilian Tiling¹, Nabeel Mansour⁴, Christine Spitzweg⁵, Matthias Brendel^{1,6-8}, Jens Ricke⁴, Marcus Unterrainer^{1,9}, Wolfgang G. Kunz⁴, and Dirk Mehrens⁴

¹Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Munich, Germany; ²Ahmanson Translational Theranostics Division, David Geffen School of Medicine at UCLA, Los Angeles, California; ³Bavarian Cancer Research Center, Partner Site Munich, Munich, Germany; ⁴Department of Radiology, LMU University Hospital, LMU Munich, Munich, Germany; ⁵Department of Internal Medicine IV, LMU University Hospital, LMU Munich, Munich, Germany; ⁶DZNE–German Center for Neurodegenerative Diseases, Munich, Germany; ⁷Munich Cluster for Systems Neurology (SyNergy), University of Munich, Munich, Germany; ⁸German Cancer Consortium, Partner Site Munich, a partnership between DKFZ and LMU, Munich, Germany; and ⁹Die Radiologie, Munich, Germany

The recently published results of the NETTER-2 trial suggest the use of [¹⁷⁷Lu]Lu-DOTATATE as a new standard of care in first-line therapy of patients with grade 2 or 3, well-differentiated, advanced gastroenteropancreatic neuroendocrine tumors. The NETTER-2 trial found superior median progression-free survival (22.8 mo vs. 8.5 mo) and similar adverse events and quality-of-life measures in patients treated with [¹⁷⁷Lu]Lu-DOTATATE compared with octreotide long-acting release (LAR) alone. As [¹⁷⁷Lu]Lu-DOTATATE therapy is associated with higher costs, we compared the cost-effectiveness of [¹⁷⁷Lu]Lu-DOTATATE with that of octreotide LAR in this setting. **Methods:** A partitioned survival model was established for the trial duration of 36 mo as well as a lifetime horizon of 20 y. Progression-free survival and treatment regimens for each patient group were derived from the NETTER-2 trial. Information on overall survival as well as utilities for health states and utilities and costs of adverse events were obtained from the literature. Information on treatment costs was obtained from the Centers for Medicare and Medicaid Services. The willingness-to-pay threshold was set to \$100,000 per quality-adjusted life-year (QALY). **Results:** [¹⁷⁷Lu]Lu-DOTATATE was cost-effective during the trial duration, with an incremental QALY of 0.13 at a slightly higher cost (\$8,931), leading to an incremental cost-effectiveness ratio of \$66,761/QALY. For the lifetime analysis, [¹⁷⁷Lu]Lu-DOTATATE dominated treatment with octreotide LAR. However, deterministic sensitivity analysis revealed that the incremental cost-effectiveness ratio was strongly influenced by the percentage of patients treated with [¹⁷⁷Lu]Lu-DOTATATE after disease progression as well as number of cycles of [¹⁷⁷Lu]Lu-DOTATATE they received after progression. In the probabilistic sensitivity analysis using Monte Carlo simulation with 10,000 iterations, [¹⁷⁷Lu]Lu-DOTATATE proved to be the most cost-effective strategy for 64% of Monte Carlo iterations over the trial duration. **Conclusion:** [¹⁷⁷Lu]Lu-DOTATATE is cost-effective as a first-line treatment for patients with grade 2 or 3, well-differentiated, advanced gastroenteropancreatic neuroendocrine tumors.

Key Words: neuroendocrine; oncology; radionuclide therapy; cost-effectiveness analysis; GEPNET; NETTER-2

J Nucl Med 2025; 66:1075–1081

DOI: 10.2967/jnumed.124.269416

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rising in both incidence and prevalence (1,2). In 2017, grade 3, well-differentiated GEP-NETs were classified as an independent tumor entity (3). The combination of [¹⁷⁷Lu]Lu-DOTATATE and low-dose octreotide long-acting release (LAR) was shown to be superior to high-dose octreotide LAR alone for lower-grade, mid-gut NETs in the NETTER-1 trial (4). The open-label, randomized, parallel-group, superiority, phase 3 NETTER-2 trial compared the effect of [¹⁷⁷Lu]Lu-DOTATATE and low-dose octreotide LAR with high-dose octreotide LAR in well-differentiated, grade 2 or 3, advanced GEP-NETs (5). Results of the NETTER-2 trial found superior median progression-free survival (PFS) (22.8 vs. 8.5 mo) and similar adverse events and quality-of-life measures in patients treated with [¹⁷⁷Lu]Lu-DOTATATE compared with octreotide LAR alone. [¹⁷⁷Lu]Lu-DOTATATE has already been included in guidelines as a second-line systemic option for suitable patients with higher grade GEP-NETs (6). However, the NETTER-2 trial suggests the use of [¹⁷⁷Lu]Lu-DOTATATE as a first-line treatment option for this specific patient group.

As [¹⁷⁷Lu]Lu-DOTATATE therapy is associated with higher costs, the aim of this study was to evaluate the cost-effectiveness of [¹⁷⁷Lu]Lu-DOTATATE for patients with higher-grade, well-differentiated GEP-NETs based on data from the NETTER-2 trial.

MATERIALS AND METHODS

Study Population

The study population of the NETTER-2 trial (NCT03972488) consisted of 226 individuals (Table 1) with newly diagnosed (within the past 6 mo), advanced, somatostatin receptor-positive, well-differentiated, grade 2 or 3 GEP-NETs with a Ki-67

Received Jan. 9, 2025; revision accepted Apr. 22, 2025.
For correspondence or reprints, contact Adrien Holzgreve (Adrien.Holzgreve@med.lmu.de).

Published online Jun. 5, 2025.

Immediate Open Access: Creative Commons Attribution 4.0 International License (CC BY) allows users to share and adapt with attribution, excluding materials credited to previous publications. License: <https://creativecommons.org/licenses/by/4.0/>. Details: <https://jnm.snmjournals.org/page/permissions>.

COPYRIGHT © 2025 by the Society of Nuclear Medicine and Molecular Imaging.

TABLE 1
Patient Characteristics per Study Group in the
NETTER-2 Trial

Characteristic	[¹⁷⁷ Lu]Lu-DOTATATE group	Octreotide LAR group
Age (y)	61	60
Women (%)	46	47
Grade 2 GEP-NET (%)	66	64
Metastases (%)	>99	99

Age expressed as median.

proliferation index of 10%–55%. Patients were also ineligible if they had received any previous peptide receptor radionuclide therapy (PRRT), hepatic artery embolization, or radiofrequency ablation for GEP-NETs. Previous systemic therapy for GEP-NETs was not allowed unless it was administered for less than 1 mo and not within 12 weeks before randomization.

Patients were randomized in a 2:1 ratio to receive [¹⁷⁷Lu]Lu-DOTATATE (7.4 GBq) and 30 mg of octreotide LAR every 8 wk for a maximum of 4 cycles (88% completed 4 cycles, and 93% completed 3 cycles) and monthly treatment with 30 mg of octreotide thereafter (PRRT group) or 60 mg of octreotide LAR every 4 wk (control group). After disease progression, 19% of patients in the PRRT group underwent retreatment with [¹⁷⁷Lu]Lu-DOTATATE (7.4 GBq) for 2–4 cycles every 8 wk. Retreatment with octreotide LAR in this group was based on the discretion of the investigator. Of the patients in the control group whose disease progressed, 67% chose to receive [¹⁷⁷Lu]Lu-DOTATATE (7.4 GBq) combined with 30 mg of octreotide LAR every 8 wk for 4 cycles and monthly treatment with 30 mg of octreotide LAR thereafter.

Model Structure

A partitioned survival analysis model was developed using decision-analytic software (TreeAge Pro Health Care, version 2024; TreeAge Software). Patients were assigned to the PRRT group or control group. Cycle length was set to 1 mo to depict slight changes in survival and their effect on the analysis. All patients started in the progression-free state. During each cycle, patients were classified as staying in a progression-free state, having transitioned to a postprogression state, or having transitioned to a terminal state (death) (Fig. 1).

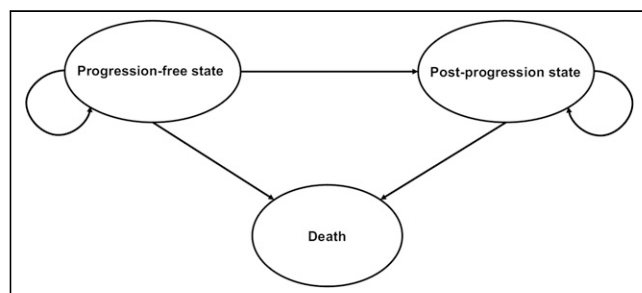


FIGURE 1. Decision model. Health state transition diagram for modeling costs and effectiveness. All patients started in progression-free state. During each cycle, patients were classified as staying in progression-free state, having transitioned to postprogression state, or having transitioned to terminal state (death).

The analysis was performed according to the Consolidated Health Economic Evaluation Reporting Standards (Supplemental Table 1) (7).

Model Input Parameters

Survival. PFS for both study groups was derived from the Kaplan–Meier data provided by the NETTER-2 trial for the study duration. For the lifetime horizon analysis, PFS data were extracted from the Kaplan–Meier survival curves by reconstruction of individual patient data (8). Subsequently, parametric distributions were fitted to individual patient data using statistical programming language R (version 4.2.1; R Core Team). Best-fit analysis was conducted using the Akaike information criterion, log-likelihood test, and visual control (Supplemental Fig. 1; supplemental materials are available at <http://jnm.snmjournals.org>).

As no long-term data for survival were available for the NETTER-2 trial at the time of our analysis, we used data from the literature to simulate overall survival (OS) for the lifetime horizon analysis of 20 y (98.1% of patients deceased in our model), according to a previous cost-effectiveness study of the NETTER-1 trial results (4,9). As no difference in OS was noted between the PRRT and octreotide group in the NETTER-2 trial, the assumption was made that long-term survival was also comparable between groups. This assumption was supported by the results of the NETTER-1 trial. Similar to the NETTER-2 trial, NETTER-1 included patients with locally advanced or metastatic, well-differentiated, somatostatin receptor–positive midgut neuroendocrine tumors. However, NETTER-1 specified a Ki-67 proliferation index of 20% or less as an inclusion criterion, whereas NETTER-2 enrolled patients using a specified Ki-67 proliferation index of 10%–55%.

The heterogeneity of both study groups was accounted for in terms of proportion of grade 2 and 3 NETs in the NETTER-2 trial (Table 1). Data extraction and fitting of parametric distributions were performed in the same manner as mentioned above. Detailed information regarding the computed parameters for each distribution is shown in Table 2.

Costs. This analysis was performed from a U.S. health care perspective. Standard treatment costs for PFS and postprogression survival (PPS) were derived from Medicare reimbursement data (10,11). Costs for end-of-life care and grade 3 and 4 adverse events were derived from the literature (12,13). An annual discount of 3% for costs was applied in the analysis. All costs were adjusted to 2024 prices using the U.S. Consumer Price Index (14).

Utilities. Treatment effectiveness was measured by quality-adjusted life-years (QALYs), calculated by multiplying years spent in progression-free and postprogression states by assigned utility weights. Utility weights for survival in the progression-free and postprogression states were derived from the literature (15). As utility data for the NETTER-2 trial were not yet available, we used the utility weights established for the NETTER-1 trial, as both study populations overlapped and study design was congruent. Frequencies for disutilities of grade 3 and 4 adverse events were derived from the NETTER-2 trial. Adverse events that occurred in more than 5% of patients were included. Values for disutilities were derived from the literature and accounted for during the treatment duration (16). Table 2 provides an overview of the input parameters. An annual discount of 3% for utilities was applied in the analysis.

Outcomes

Cost-Effectiveness Analysis. The costs, effectiveness (measured in QALYs), incremental cost-effectiveness ratios (ICERs), and net monetary benefits of [¹⁷⁷Lu]Lu-DOTATATE and high-dose

TABLE 2
Detailed Input Parameters

Input parameter	Base case value	Range for sensitivity analysis*	Distribution
Initial probability (5)			
Progression-free disease	1		
Progressive disease	0		
Death	0		
Survival probability			
PPS GEP-NET (9)			
Grade 2, stage 4	Shape, 0.9628; scale, 64.1457	Shape, 0.8182–1.1328; scale 51.6802–79.6178	Weibull
Grade 3, stage 4 [†]	2.0057 ± 1.1133	1.7875–2.2239 ± 0.9692–1.2788	Lognormal
PFS			
[¹⁷⁷ Lu]Lu-DOTATATE [†] (5)	3.2597 ± 0.9401	3.057–3.4624 ± 0.7794–1.134	Lognormal
PFS octreotide [†] (5)	2.2833 ± 1.074	2.0671–2.4994 ± 0.9134–1.2628	Lognormal
Health care cost			
[¹⁷⁷ Lu]Lu-DOTATATE (\$/cycle) (10)	57,617	54,736–60,498	γ
Patient retreatment with [¹⁷⁷ Lu]Lu-DOTATATE after progression (%) [†] (5)			
[¹⁷⁷ Lu]Lu-DOTATATE	0.19	0.18–0.20	β
Octreotide LAR	0.67	0.64–0.70	β
Standard care (\$/mo)			
Octreotide LAR 30 mg (HCPCS)	6,549	6,222–6,876	γ
Octreotide LAR 60 mg (11)	13,098	12,443–13,753	γ
End of life (12)	18,025	17,124–18,926	γ
Utilities			
PFS (15)	0.771	0.731–0.810	β
PPS (15)	0.612	0.564–0.659	β
Adverse events (grade 3 or 4)			
Disutility per mo (5,16)			
[¹⁷⁷ Lu]Lu-DOTATATE	0.01	0.008–0.012	β
Octreotide LAR	0.00287	0.0025–0.003	β
Treatment cost (\$/mo) (13)			
[¹⁷⁷ Lu]Lu-DOTATATE	3,341	3,174–3,508	γ
Octreotide LAR	2,515	2,389–2,641	γ

*Determined by 95% CI of initial probabilities and costs.

[†]Median ± SD.

HCPCS = Healthcare Common Procedure Coding System.

octreotide LAR were compared over the trial duration and lifetime horizon. Incremental costs, utilities, and ICERs were calculated for each patient subgroup separately. The willingness-to-pay (WTP) threshold was set to \$100,000/QALY (17). This threshold value classifies medical services in terms of their eligibility for reimbursement (18). As no data were available concerning the number of treatment cycles of PRRT administered in the [¹⁷⁷Lu]Lu-DOTATATE group after disease progression, 4 cycles were chosen for analysis purposes.

Sensitivity Analyses. Comprehensive deterministic and probabilistic sensitivity analyses were used to evaluate the robustness of the model. Deterministic 1-way sensitivity analysis was performed to identify variables that significantly influenced model outcomes. The ranges for deterministic sensitivity analysis were determined

by the 95% CI of the initial probabilities and costs. A range of 0–8 (with 8 equating to double treatment) were assumed for [¹⁷⁷Lu]Lu-DOTATATE treatment. Moreover, probabilistic sensitivity analyses allow simultaneous alteration of multiple input parameters using distributions according to probability density functions for second-order Monte Carlo simulation runs ($n = 10,000$) (19). Furthermore, a cost-effectiveness acceptability curve was generated from the Monte Carlo iterations at varying WTP thresholds.

The input parameters were assigned appropriate distributions (Table 2). Utilities were varied with a β-distribution. Treatment costs were modeled with a γ-distribution. β-distributions were used for disutilities as well as utilities for survival in the progression-free and postprogression states.

To further account for uncertainty in our long-term analysis of 20 y, additional analyses were performed for OS by calculating a range of hazard ratios (0.10, 0.25, 0.50, 0.75, 1.25, 1.50, 1.75, and 2.00) for both parametric distributions used for grade 2 and 3 tumors in the analysis. No difference in survival between groups was assumed. Base case analyses were performed over the trial duration and lifetime horizon (Supplemental Table 2; Supplemental Fig. 2).

RESULTS

Base Case Analyses

In the base case analyses, [¹⁷⁷Lu]Lu-DOTATATE was associated with an average of 1.5 QALYs over the trial duration, compared with 1.4 QALYs for octreotide LAR. The average treatment cost was \$469,578 for the [¹⁷⁷Lu]Lu-DOTATATE group, \$8,931 higher than those for the octreotide LAR group (\$460,647), resulting in an ICER of \$66,761 at a net monetary benefit of \$160,991. When analyzing costs and effectiveness over a lifetime horizon of 20 y, [¹⁷⁷Lu]Lu-DOTATATE dominated treatment with octreotide LAR, with higher effectiveness (2.69 QALYs vs. 2.43 QALYs) and a slightly lower cost (\$618,827 vs. \$621,142).

Results for base case analyses are summarized in Table 3. For additional base case analysis of hazard ratios for OS of 0.1–2.0, the ICER stayed below the WTP threshold of \$100,000/QALY over the trial duration (range, \$66,830/QALY to \$61,431/QALY) and lifetime horizon, with PRRT remaining the dominant strategy throughout (Supplemental Table 2).

Deterministic Sensitivity Analysis

Deterministic sensitivity analysis revealed that the number of cycles of [¹⁷⁷Lu]Lu-DOTATATE after disease progression had the strongest cumulative effect on the ICER, followed by PFS of the control group, cost of octreotide LAR, and proportion of patients in the control group receiving PRRT after disease progression exceeding the WTP threshold of \$100,000/QALY. PFS in the [¹⁷⁷Lu]Lu-DOTATATE group, costs of [¹⁷⁷Lu]Lu-DOTATATE, and costs of octreotide LAR concomitant to [¹⁷⁷Lu]Lu-DOTATATE treatment affected the ICER under the chosen range, surpassing the WTP threshold. Parameters for parametric survival in the octreotide group for PFS partially led to an increase of the ICER above the WTP threshold. All other parameters in the given ranges had no significant effect on the ICER (Fig. 2).

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis was performed for the base case scenario over 36 mo, resulting in 64.47% of the calculations to be cost-effective when applying a WTP threshold of \$100,000/QALY (Fig. 3). The distribution of calculations in each quadrant was as follows: lower right (dominant), 22.8%; upper right, 76.9%; lower left, 2.0%; and upper right (dominated), 1.0%.

In the cost-effectiveness acceptability curve, octreotide LAR remained the cost-effective option until a WTP of \$51,000/QALY was reached. At WTP thresholds above this value, [¹⁷⁷Lu]Lu-DOTATATE became the more likely cost-effective treatment (Supplemental Fig. 3).

DISCUSSION

The NETTER-2 trial was the first phase 3 trial to investigate [¹⁷⁷Lu]Lu-DOTATATE treatment in newly diagnosed patients with advanced, grade 2 or 3 GEP-NETs and the first phase 3 trial of PRRT in any metastatic first-line treatment setting. This is particularly important, as no first-line treatment has been established for this specific tumor entity.

Apart from neuroendocrine tumors, radiopharmaceutical therapy has shown promising results for advanced prostate-specific membrane antigen-positive metastatic prostate cancer, with increasing evidence to support its use as an earlier line of therapy and in earlier disease stages (20–23). This shows the increasing importance of radiopharmaceutical therapy as a treatment option in a metastatic oncologic setting, highlighting the utility of cost-effectiveness analyses to determine the economic burden for the health care system and for the inclusion of such therapies in treatment guidelines.

This study found that, for our input parameters, [¹⁷⁷Lu]Lu-DOTATATE was cost-efficient for the study duration at a WTP threshold of \$100,000/QALY and dominant over a lifetime horizon of 20 y for retreatment with [¹⁷⁷Lu]Lu-DOTATATE. When looking at the probabilistic sensitivity analyses, [¹⁷⁷Lu]Lu-DOTATATE was cost-effective in 64% of Monte Carlo iterations over the trial duration. However, in total, 22.8% of iterations were dominant over the octreotide treatment. Of the deterministic sensitivity analysis variables associated with administration of [¹⁷⁷Lu]Lu-DOTATATE, the number of treatment cycles and proportion of patients receiving treatment after disease progression had a strong influence on costs under the given assumptions. This was also reflected in the additional survival analysis with hazard ratios, as costs increase with

TABLE 3
Base Case Analysis

Patient group	Cost (\$)	IC (\$)	Effect (QALY)	IE (QALY)	NMB (\$)	ICER (\$/QALY)	Acceptability at WTP/\$100,000 (%)
Trial duration*							
[¹⁷⁷ Lu]Lu-DOTATATE	469,578	8,931	1.54	0.13	–160,991	66,761	64
Octreotide LAR	460,647		1.41		–178,812		36
Lifetime horizon†							
[¹⁷⁷ Lu]Lu-DOTATATE	618,827		2.69		–80,347		
Octreotide LAR	621,142	2,315	2.43	–0.26	–135,502	dominated	

*36 mo.

†20 y.

IC = incremental cost; IE = incremental effectiveness; NMB = net monetary benefit.

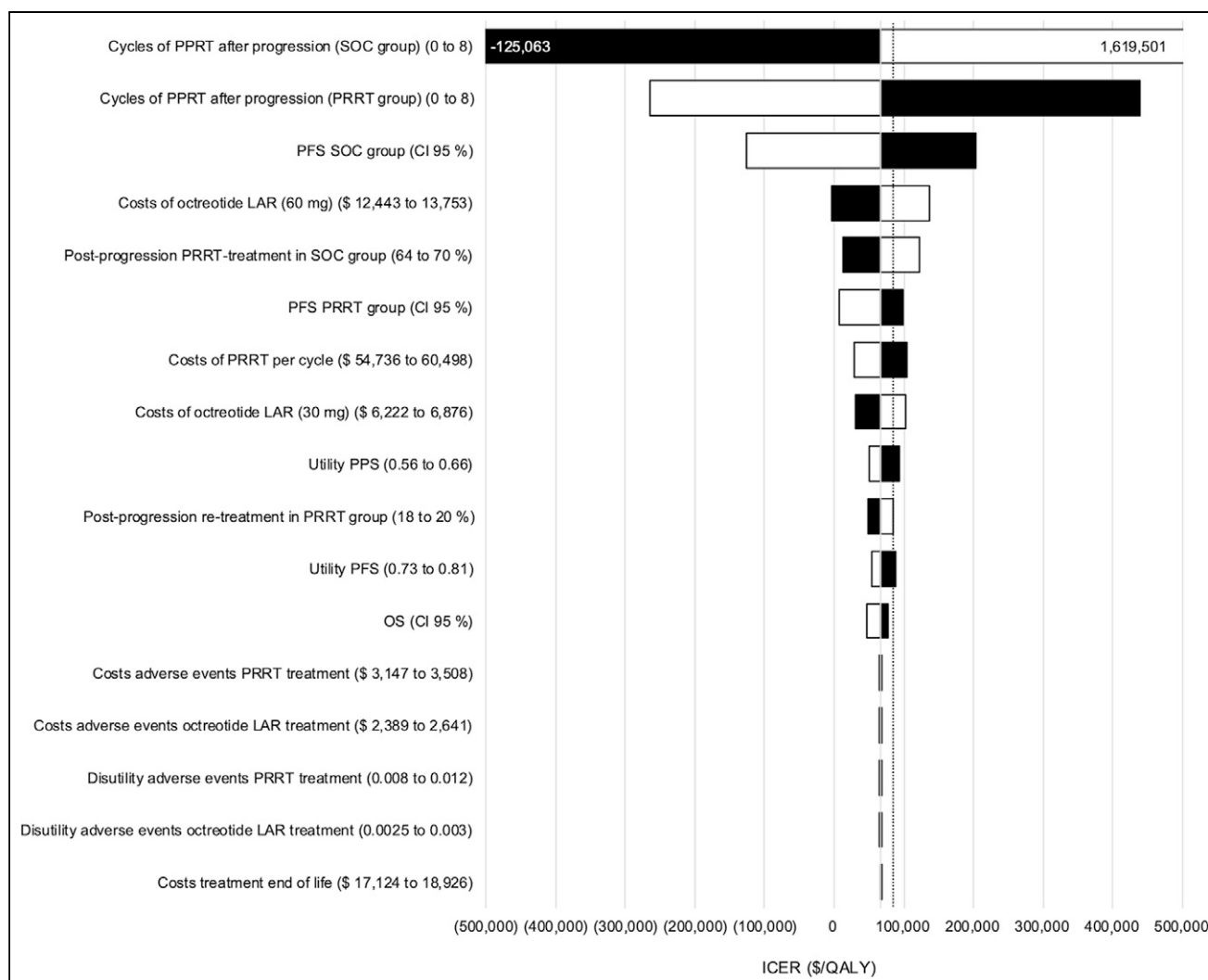


FIGURE 2. Tornado diagram for deterministic sensitivity analysis. Number of cycles of [^{177}Lu]Lu-DOTATATE after progression had strongest cumulative impact on ICER followed by PFS of control (standard of care [SOC]) group, costs for octreotide LAR, and proportion of patients in control group receiving [^{177}Lu]Lu-DOTATATE after progression. Black bars indicate changes based on lower bound of parameter variation. White bars indicate upper bound of respective parameter. Dotted line represents WTP threshold of \$100,000/QALY.

higher survival times in relation to cost-efficiency; therefore, no additional change in the ICER can be recognized. Nevertheless, these changes did not result in a significant change in the ICER, specifically over the lifetime horizon, as assumptions had to be made because data were not yet available.

With regard to the significance of our analysis, the limitations mentioned below must be considered, as the PFS of both groups and the costs for octreotide and [^{177}Lu]Lu-DOTATATE each had a borderline influence on the analysis, although the costs for both therapies were specified by the Centers for Medicare and Medicaid Services. Therefore, [^{177}Lu]Lu-DOTATATE was a cost-effective option for patients with advanced, well-differentiated, grade 2 or 3 GEP-NETs under given conditions, but long-term data from the NETTER-2 trial are needed to confirm this assessment.

Certain limitations remain. As observed from our sensitivity analysis, the number of [^{177}Lu]Lu-DOTATATE cycles for retreatment as well as the PFS of the octreotide group had a strong effect on the ICER. Furthermore, uncertainty arises from the unavailability of specific information. First, because long-term data for OS in the

NETTER-2 trial are not yet available, survival data from different sources not specifically connected to radiopharmaceutical therapy were used. However, during the trial duration, no significant difference in OS was noted between treatment groups, and the NETTER-1 trial showed no significant difference in long-term OS between groups (24). Further, base case analyses with different hazard ratios for OS showed no significant change in the analysis results. However, as OS increased in both groups, the ICER for PRRT increased because of proportionally higher postprogression costs for the PRRT group compared with the octreotide group. Second, utilities for PFS and PPS were adopted from the NETTER-1 trial, which does not reflect the study population in total, again leading to uncertainty. Third, information on postprogression therapy was not documented in the published NETTER-2 trial data. Information on costs of end-of-life care and adverse events were obtained from the literature and not connected to data from the Centers for Medicare and Medicaid Services. However, when consulting the tornado diagram (Fig. 2), both parameters had little influence on the ICER. An additional comparison with studies using Centers for Medicare and Medicaid

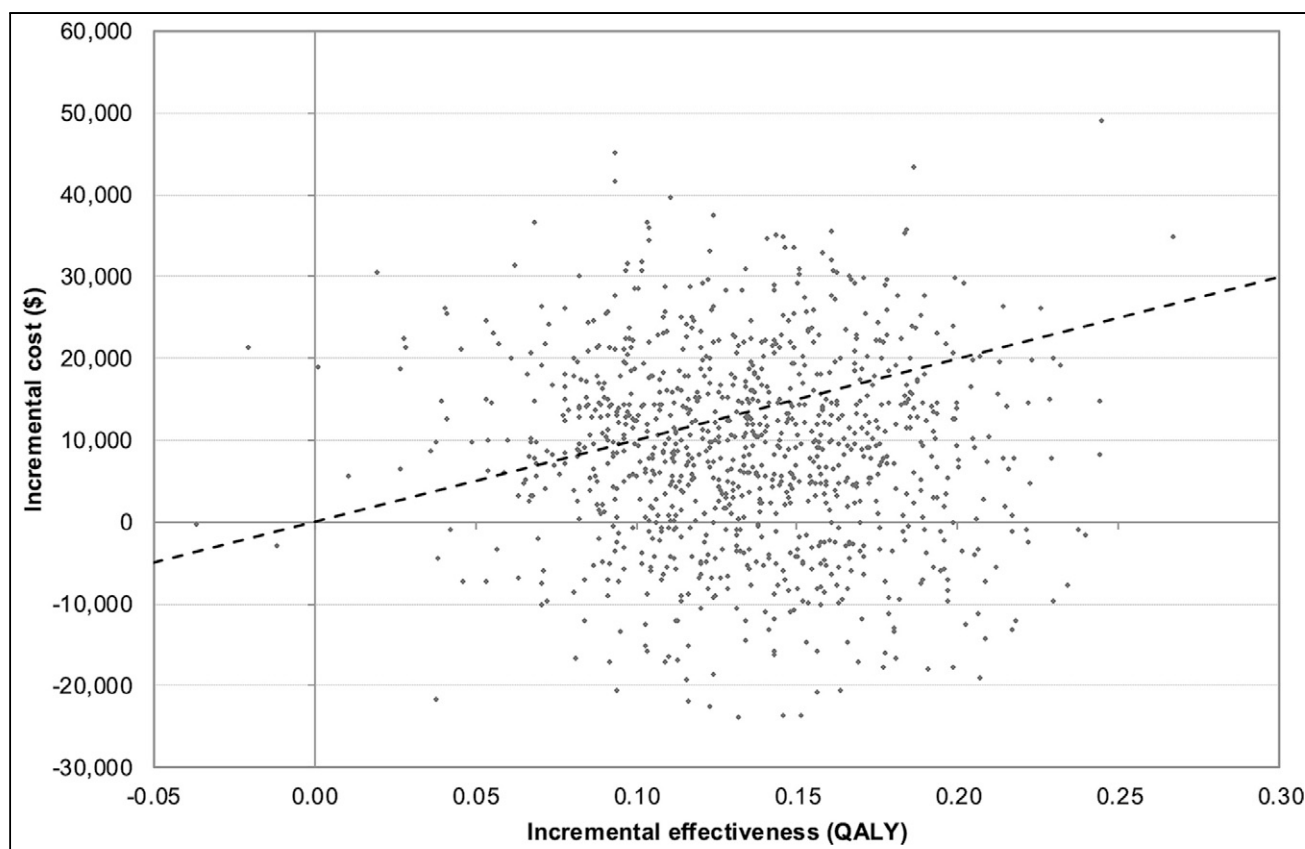


FIGURE 3. Cost-effectiveness planes of incremental costs and incremental effectiveness of [^{177}Lu]Lu-DOTATATE vs. octreotide LAR are shown for probabilistic sensitivity analysis. Each dot represents one simulation run. Dashed line indicates WTP threshold of \$100,000/QALY. Dots below this line are considered cost-effective simulation runs.

Services data found that costs were comparable for both parameters (25,26). For reasons of simplicity and to avoid further uncertainty, we assumed therapy regimens in the postprogression groups with the abovementioned therapy. We relied on data from the NETTER-2 trial, in which the control group consisted of high-dose octreotide LAR 60 mg per month. Internationally, this regimen is not a clinical routine standard for the treatment of grade 2 or 3 GEP-NETs and therefore limits generalization of our cost-effectiveness results. On the other hand, maintenance of somatostatin analog treatment after prior administration of [^{177}Lu]Lu-DOTATATE, as performed in the NETTER-2 trial, corresponds to common clinical practice, and there is evidence to support this approach after first-line treatment (27). However, data are conflicting on whether somatostatin analog maintenance is beneficial for tumor control after [^{177}Lu]Lu-DOTATATE instead of chemotherapy (28,29). The ongoing STOPNET (NCT06345079) and SAUNA (NCT05701241) trials are expected to answer these questions with high-quality data. If they show no benefit of somatostatin analog maintenance on tumor control after [^{177}Lu]Lu-DOTATATE therapy, the latter would be unrivaled in terms of cost-effectiveness, as costs for maintenance somatostatin analogs after [^{177}Lu]Lu-DOTATATE treatment could be avoided entirely.

Clinical decision-making regarding [^{177}Lu]Lu-DOTATATE must also consider the primary NET location, as different therapy options with varying toxicities exist, depending on tumor origin. Whereas few alternatives to [^{177}Lu]Lu-DOTATATE exist for extrapancreatic NETs, such as everolimus or cabozantinib (off-label), chemotherapy is an established alternative treatment to [^{177}Lu]Lu-DOTATATE for

pancreatic NETs. The latter harbors a low but severe risk for treatment-related myeloid neoplasms, reminding clinicians that clinical treatment algorithms and individual treatment decisions need to be well-balanced—beyond matters of cost-effectiveness—when transferring [^{177}Lu]Lu-DOTATATE to the first-line setting.

CONCLUSION

[^{177}Lu]Lu-DOTATATE is cost-effective as a first-line treatment for patients with grade 2 or 3, well-differentiated, advanced gastroenteropancreatic neuroendocrine tumors. [^{177}Lu]Lu-DOTATATE was cost-effective during the trial duration, with an incremental QALY of 0.13 at a slightly higher cost. In the probabilistic sensitivity analysis, [^{177}Lu]Lu-DOTATATE was the cost-effective strategy in 64% of Monte Carlo iterations over the trial duration. Our results facilitate the assessment of its economic burden for the health care system in view of potential future inclusion in treatment guidelines. Long-term data from the NETTER-2 trial are needed to confirm this assessment.

DISCLOSURE

Adrien Holzgreve received funding from the German Research Foundation (545058105). Lena Unterrainer received funding from the Bavarian Cancer Research Center and the Munich Clinician Scientist Program. Matthias Brendel received funding from the German Research Foundation under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology

(EXC 2145 SyNergy, ID 390857198). Adrien Holzgreve received compensation for scientific consulting from ABX advanced biochemical compounds. Lena Unterrainer received speaker fees from Novartis and Astellas Pharma and consultant fees from Telix Pharmaceuticals. Matthias Brendel received consulting and speaker honoraria from Life Molecular Imaging, GE HealthCare, and Roche and reader honoraria from Life Molecular Imaging. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENT

We thank Prof. Christoph Auernhammer for constructive discussions and for sharing his expertise regarding the management of patients with GEP-NETs, independent of the economic analysis reported in this manuscript.

KEY POINTS

QUESTION: Is [¹⁷⁷Lu]Lu-DOTATATE cost-effective in the first-line setting compared with octreotide LAR for the treatment of patients with newly diagnosed, advanced GEP-NETs?

PERTINENT FINDINGS: We performed a cost-effectiveness analysis based on results of the phase 3 randomized NETTER-2 trial. [¹⁷⁷Lu]Lu-DOTATATE was cost-effective during the trial duration, with an incremental QALY of 0.13 at a slightly higher cost. In the probabilistic sensitivity analysis, [¹⁷⁷Lu]Lu-DOTATATE was the cost-effective strategy in 64% of Monte Carlo iterations over the trial duration.

IMPLICATIONS FOR PATIENT CARE: [¹⁷⁷Lu]Lu-DOTATATE may be considered as a new standard of care in first-line therapy of patients with grade 2 or 3, well-differentiated, advanced GEP-NETs. Our results facilitate the assessment of its economic burden for the health care system in view of potential future inclusion in treatment guidelines.

REFERENCES

- Sonbol MB, Mazza GL, Mi L, et al. Survival and incidence patterns of pancreatic neuroendocrine tumors over the last 2 decades: a SEER database analysis. *Oncologist*. 2022;27:573–578.
- White BE, Rous B, Chandrakumaran K, et al. Incidence and survival of neuroendocrine neoplasia in England 1995–2018: a retrospective, population-based study. *Lancet Reg Health Eur*. 2022;23:100510.
- Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018;31:1770–1786.
- Strosberg J, El-Haddad G, Wolin E, et al.; NETTER-1 Trial Investigators. Phase 3 trial of ¹⁷⁷Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125–135.
- Singh S, Halperin D, Myrehaug S, et al.; NETTER-2 Trial Investigators. [¹⁷⁷Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. 2024;403:2807–2817.
- Del Rivero J, Perez K, Kennedy EB, et al. Systemic therapy for tumor control in metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: ASCO guideline. *J Clin Oncol*. 2023;41:5049–5067.
- Husereau D, Drummond M, Augustovski F, et al.; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMC Med*. 2022;20:23.
- Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2021;21:111.
- Poleé IN, Hermans BCM, van der Zwan JM, et al. Long-term survival in patients with gastroenteropancreatic neuroendocrine neoplasms: a population-based study. *Eur J Cancer*. 2022;172:252–263.
- Hospital outpatient PPS. Addendum A. Centers for Medicare and Medicaid Services website. <https://www.cms.gov/medicare/medicare-fee-service-payment/hospitaloutpatientpps/addendum-and-addendum-b-updates/april-2024>. Updated April 23, 2024. Accessed May 1, 2024.
- Medicare Part B spending by drug. Centers for Medicare and Medicaid Services website. <https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicare-spending-by-drug/medicare-part-b-spending-by-drug/data>. Accessed May 1, 2024.
- Hoverman JR, Mann BB, Phu S, et al. Hospice or hospital: the costs of dying of cancer in the oncology care model. *Palliat Med Rep*. 2020;1:92–96.
- Wong W, Yim YM, Kim A, et al. Assessment of costs associated with adverse events in patients with cancer. *PLoS One*. 2018;13:e0196007.
- CPI inflation calculator. U.S. Bureau of Labor Statistics website. <https://data.bls.gov/cgi-bin/cpi/calc.pl?cost1=0.3&year1=202206&year2=202403>. Accessed May 1, 2024.
- Swinburn P, Wang J, Chandiwana D, Mansoor W, Lloyd A. Elicitation of health state utilities in neuroendocrine tumours. *J Med Econ*. 2012;15:681–687.
- Leeuwenkamp O, Smith-Palmer J, Ortiz R, et al. Cost-effectiveness of lutetium [¹⁷⁷Lu] oxodotretotide versus best supportive care with octreotide in patients with midgut neuroendocrine tumors in France. *J Med Econ*. 2020;23:1534–1541.
- Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Glob Health Action*. 2018;11:1447828.
- 2020-2023 Value assessment framework. Institute for Clinical and Economic Review website. https://icer.org/wp-content/uploads/2020/10/ICER_2020_2023_VAF_102220.pdf. Updated October 23, 2020. Accessed May 13, 2025.
- Sheppard CW. Computer simulation of stochastic processes through model-sampling (Monte Carlo) techniques. *FEBS Lett*. 1969;2(suppl 1):S14–S21.
- Sartor O, de Bono J, Chi KN, et al.; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385:1091–1103.
- Morris MJ, Castellano D, Herrmann K, et al.; PSMAfore Investigators. ¹⁷⁷Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naïve patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. *Lancet*. 2024;404:1227–1239.
- Chi KN, Metser U, Czernin J, et al. Study evaluating metastatic castrate resistant prostate cancer (mCRPC) treatment using ¹⁷⁷Lu-PNT2002 PSMA therapy after second-line hormonal treatment (SPLASH). *J Clin Oncol*. 2021;39:TP55087.
- Tagawa ST, Sartor AO, Saad F, et al. PSMAddition: a phase 3 trial to compare treatment with ¹⁷⁷Lu-PSMA-617 plus standard of care (SoC) and SoC alone in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2023;41(suppl):TP55116.
- Strosberg JR, Caplin ME, Kunz PL, et al.; NETTER-1 Investigators. ¹⁷⁷Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22:1752–1763.
- Duncan I, Ahmed T, Dove H, Maxwell TL. Medicare cost at end of life. *Am J Hosp Palliat Care*. 2019;36:705–710.
- George S, Bell EJ, Zheng Y, et al. The impact of adverse events on health care resource utilization, costs, and mortality among patients treated with immune checkpoint inhibitors. *Oncologist*. 2021;26:e1205–e1215.
- Lepage C, Phelip JM, Lievre A, et al. Lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours: an international double-blind, placebo-controlled randomised phase II trial—Prodige 31 REMINET: an FFCD study. *Eur J Cancer*. 2022;175:31–40.
- Syguła A, Ledwon A, Hasse-Lazar K, et al. In patients with well-differentiated neuroendocrine tumours, there is no apparent benefit of somatostatin analogues after disease control by peptide receptor radionuclide therapy. *Eur J Nucl Med Mol Imaging*. 2022;49:3841–3851.
- Yordanova A, Wicharz MM, Mayer K, et al. The role of adding somatostatin analogues to peptide receptor radionuclide therapy as a combination and maintenance therapy. *Clin Cancer Res*. 2018;24:4672–4679.