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RAPID COMMUNICATION

Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With ^{177}Lu-Dotatate in the Phase III NETTER-1 Trial

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ABSTRACT

Purpose
Neuroendocrine tumor (NET) progression is associated with deterioration in quality of life (QoL). We assessed the impact of ^{177}Lu-Dotatate treatment on time to deterioration in health-related QoL.

Methods
The NETTER-1 trial is an international phase III study in patients with midgut NETs. Patients were randomly assigned to treatment with ^{177}Lu-Dotatate versus high-dose octreotide. European Organisation for Research and Treatment of Cancer quality-of-life questionnaires QLQ C-30 and G.I. NET-21 were assessed during the trial to determine the impact of treatment on health-related QoL. Patients completed the questionnaires at baseline and every 12 weeks until tumor progression. QoL scores were converted to a 100-point scale according to European Organisation for Research and Treatment of Cancer instructions, and individual changes from baseline scores were assessed. Time to QoL deterioration (TTD) was defined as the time from random assignment to the first QoL deterioration ≥ 10 points for each patient in the corresponding domain scale. All analyses were conducted on the intention-to-treat population. Patients with no deterioration were censored at the last QoL assessment date.

Results
TTD was significantly longer in the ^{177}Lu-Dotatate arm (n = 117) versus the control arm (n = 114) for the following domains: global health status (hazard ratio [HR], 0.406), physical functioning (HR, 0.518), role functioning (HR, 0.580), fatigue (HR, 0.621), pain (HR, 0.566), diarrhea (HR, 0.473), disease-related worries (HR, 0.572), and body image (HR, 0.425). Differences in median TTD were clinically significant in several domains: 28.8 months versus 6.1 months for global health status, and 25.2 months versus 11.5 months for physical functioning.

Conclusion
This analysis from the NETTER-1 phase III study demonstrates that, in addition to improving progression-free survival, ^{177}Lu-Dotatate provides a significant QoL benefit for patients with progressive midgut NETs compared with high-dose octreotide.

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BACKGROUND

Neuroendocrine tumors (NETs) are biologically diverse neoplasms, often characterized by a propensity to secrete active hormones such as serotonin. Carcinoid syndrome, the most prominent hormonal disorder, is characterized by flushing, diarrhea, and bronchospasm. Somatostatin analogs are typically used in the front-line setting for control of tumor growth and palliation of hormonal symptoms.[1] However, disease progression eventually occurs in most patients with metastatic disease.[2,3] Quality of life (QoL) may be significantly affected by symptoms related to tumor growth as well as hormone production.[4,5] Therapeutic options for control of progressive disease are limited, and toxicities of treatment can outweigh benefits. Thus, health-related QoL (HRQoL) is a vitally important criterion to assess when evaluating the overall benefit of new treatments.

The European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ) is a commonly used and

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Appendix
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validated metric for analysis of HRQoL in patients with cancer.[6] In addition to a nonspecific 30-question survey (QLQ C-30) that can be applied to any patient with cancer, a 21-question module (G.I. NET-21) has been designed to address specific NET-related symptoms.[7] Results of the 24 individual questions or multiple-question domains are converted into a 100-point score. Longitudinal changes can be compared with individual baseline scores. A 10-point change in score is frequently considered a minimal clinically important difference.[8,9] Using Kaplan-Meier methodology, time to deterioration (TTD) can be measured using a 10-point decline as analogous to a progressive event.[10]

Multiple studies have demonstrated that patients with NETs have a lower HRQoL compared with the general population. In a study conducted in Sweden using the EORTC QLQ C-30, patients with NETs reported a significantly worse QoL compared with the general population in several domains, including role function, social function, fatigue, diarrhea, and global QoL.[11] Similarly, in a survey of patients with NETs in the United States, patients with advanced NETs demonstrated worse HRQoL scores compared with the general population.[4] Physical functioning and role functioning (including physical, general health, and vitality scores) were all worse among patients with advanced NETs compared with the general US population by at least one half of a standard deviation or more. HRQoL was more significantly impaired in patients with carcinoid syndrome compared with patients with nonfunctional tumors.

Consequently, there is a need for new therapies that not only improve survival but also have a positive impact on HRQoL. ^{177}Lu-Dotatate is a novel systemic therapy belonging to a category of treatment known as peptide receptor radiotherapy.[12,13] This therapy has demonstrated promising effects on HRQoL in single-arm studies. In one analysis of 265 patients with NETs treated with ^{177}Lu-Dotatate, significant improvements on the EORTC QLQ C-30 scale were noted in global health status, emotional functioning, social functioning, insomnia, loss of appetite, and diarrhea.[12] The phase III NETTER-1 trial was the first prospective, randomized study, to our knowledge, to evaluate the effects of a radiolabeled somatostatin analog with a high level of evidence. Patients with advanced progressive midgut NETs were randomly assigned to receive ^{177}Lu-Dotatate versus high-dose octreotide.[14] The primary end point of the trial was met with improvement in the hazard ratio (HR) for progression-free survival by 79%. HRQoL was a major secondary end point and was measured using the EORTC QLQ C-30 and G.I.NET-21 questionnaires. Trial patients completed these questionnaires at baseline and every 12 weeks until central radiologic confirmation of disease progression. Herein, we report the longitudinal change in HRQoL on the NETTER-1 study comparing TTD in both arms of the study to determine the overall impact of treatment on HRQoL.

METHODS

Study Design and Patients

NETTER-1 was a multicenter, international, randomized phase III study investigating the effects of ^{177}Lu-Dotatate on patients with advanced, progressive midgut NETs. Adult patients (≥ 18 years) were eligible for the study if they had pathologically confirmed low- or intermediate-grade midgut NETs with baseline radiographic progression and evidence of somatostatin receptor expression on all target lesions using ^{111}In-pentetreotide scan (OctreoScan, Mallinckrodt, St. Louis).

Random Assignment and Treatment

Patients were randomly assigned 1:1 to receive ^{177}Lu-Dotatate (200 mCi every 8 weeks × four treatments, followed by octreotide long-acting repeatable [LAR] 30 mg) or high-dose octreotide (60 mg every 4 weeks). Random assignment was performed with the use of a centralized permuted block (block size of 4) scheme, with stratification according to the highest tumor uptake score on somatostatin receptor scintigraphy (grade 2, 3, or 4 on a scale ranging from 0 to 4) and according to the length of time that a patient had been receiving a constant dose of octreotide (≤ 6 months or > 6 months). Treatment continued until central confirmation of radiographic progression, intolerable adverse events, or withdrawal of consent.

HRQoL Assessment

Patients in both arms of the study completed the EORTC QLQ C-30 and G.I.NET-21 questionnaires every 12 ± 1 weeks. Per protocol, patients were required to complete the questionnaires until progression or until a maximum of 72 weeks from random assignment had elapsed. As per the EORTC QOL scoring manual instructions for domains with multiple questions, if ≥ 50% but < 100% of questions were completed at a visit, then that visit was deemed evaluable for that domain, and the average of the remaining assessed questions was used in the analysis. Visits with > 50% of questions missing for a particular domain were excluded from the analyses.

The questionnaire results were converted to a 100-point scale per the EORTC manual. In the QLQ C30 questionnaire, the Global Health Status and five Function Scale domains (physical, role, emotional, cognitive, and social) are positive scales in which higher scores translate into higher QoL. The symptom scales are negative scales in which a higher score corresponds to a higher level of symptoms/problems. These include fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. The G.I.NET-21 domains include endocrine scale (flushing, sweats), GI scale (bloating, flatulence), treatment scale, social functioning scale, disease-related worries scale, muscle/bone pain, sexual function, information/communication function, and body image. All are negative scales in which higher scores correspond to increased symptoms/problems. The entire set of questions is listed in Appendix Table A1 (online only) by EORTC QLQ domain.

Time to Event Methodology

Time to deterioration (TTD) was defined as time from random assignment to the first deterioration ≥ 10 points (on a 100-point scale) compared with baseline score for the same domain. Patients with no deterioration were censored at the last QoL assessment date. Patients with no baseline and/or no follow-up were censored at random assignment.

For each question, or multiquestion domain, a Kaplan-Meier plot was produced showing time to event by treatment arm. Kaplan-Meier methods were used to generate a point estimate of the median time to event with corresponding 95% CI. The unstratified log-rank test was used to compare the time to event in the two groups. The HRs and corresponding 95% CIs were estimated from a Cox proportional hazards model including randomized treatment as a factor. A P value < .05 was considered statistically significant. No adjustments were made for multiple testing.

For sensitivity analysis purposes, the P value using a log-rank test stratified on randomization stratification factors (OctreoScan maximum tumor uptake score and length of time on the most recent constant dose of octreotide before random assignment [≤ 6 and > 6 months]) was also computed for the TTD analysis, and the HR was obtained from a Cox model adjusting for the same two factors. An additional sensitivity analysis of TTD was performed by censoring those patients with worst possible score at baseline (0 when a worsening is represented by a decrease in score and 100 when a worsening is represented by an increase in score) at random assignment.

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Table 1. Baseline HRQoL Scores by Randomly Assigned Group

HRQoL Domain	^{177}Lu-Dotatate (n = 117)				Octreotide LAR (n = 114)				*P**
	No.	Mean (SD)	Median	Q1-Q3	No.	Mean (SD)	Median	Q1-Q3	
Global health status/QoL	100	67.0 (22.3)	66.7	50.0-83.3	104	64.6 (23.3)	66.7	50.0-83.3	.577
Physical functioning	101	82.7 (19.5)	86.7	73.3,100.0	103	80.1 (19.3)	86.7	66.7-93.3	.178
Role functioning	101	75.4 (30.0)	83.3	66.7-100.0	103	75.4 (30.5)	83.3	66.7-100.0	.881
Emotional functioning	100	75.3 (23.7)	83.3	58.3-91.7	104	74.8 (24.9)	83.3	58.3-91.7	.721
Cognitive functioning	100	83.1 (22.4)	83.3	66.7.0-100.0	104	81.7 (22.5)	83.3	66.7-100.0	.433
Social functioning	100	76.5 (30.5)	91.7	66.7-100.0	104	76.6 (27.2)	83.3	66.7-100.0	.537
Fatigue	101	33.0 (26.4)	33.3	11.1-55.6	103	35.5 (27.7)	33.3	11.1-55.6	.437
Nausea and vomiting	101	8.9 (14.8)	0	0.0-16.7	103	8.9 (17.8)	0	0.0-16.7	.436
Pain	101	28.4 (29.9)	16.7	0.0-33.3	104	28.4 (28.7)	16.7	0.0-50.0	.900
Dyspnea	100	18.3 (26.5)	0	0.0-33.3	103	18.8 (26.7)	0	0.0-33.3	.843
Insomnia	100	27.7 (31.8)	33.3	0.0-33.3	103	31.1 (33.7)	33.3	0.0-66.7	.424
Appetite loss	101	15.2 (23.3)	0	0.0-33.3	103	19.1 (27.1)	0	0.0-33.3	.310
Constipation	100	5.7 (15.8)	0	0.0-0.0	102	9.8 (21.3)	0	0.0-0.0	.160
Diarrhea	100	43.3 (33.3)	33.3	33.3-66.7	104	41.7 (37.1)	33.3	0.0-66.7	.428
Financial difficulties	100	23.3 (33.0)	0	0.0-33.3	104	17.3 (29.4)	0	0.0-33.3	.120
Endocrine scale	101	22.0 (20.8)	22.2	0.0-33.3	104	20.9 (21.9)	11.1	0.0-33.3	.583
GI scale	101	22.8 (20.1)	20	6.7-33.3	104	23.8 (19.9)	20	6.7-33.3	.702
Treatment scale	68	11.6 (14.1)	11.1	0.0-19.4	62	11.9 (20.2)	0	0.0-11.1	.361
Social functioning scale	100	33.4 (25.5)	33.3	11.1-44.4	103	37.1 (27.4)	33.3	11.1-55.6	.440
Disease related worries scale	100	43.7 (27.7)	33.3	22.2-55.6	103	43.8 (30.5)	33.3	22.2-66.7	.861
Muscle/bone pain symptom	100	29.0 (30.6)	33.3	0.0-33.3	102	34.6 (31.8)	33.3	0.0-66.7	.164
Sexual function	74	30.6 (38.5)	0	0.0-66.7	72	28.2 (37.0)	0	0.0-66.7	.712
Information/communication function	99	5.4 (14.0)	0	0.0-0.0	103	12.3 (24.2)	0	0.0-33.3	.030
Body image	100	20.0 (32.1)	0	0.0-33.3	102	20.3 (30.8)	0	0.0-33.3	.774

Abbreviations: HRQoL, health-related quality of life; LAR, long-acting repeatable; Q, quartile; QoL, quality of life; SD, standard deviation.
*Wilcoxon rank sum test.

For domains where the univariable model showed a statistically significant effect of treatment, the Cox proportional hazards model was used to assess the impact of additional covariates on the estimated HR. The full model included randomized treatment as a binary indicator, the randomization stratification factors (OctreoScan maximum tumor uptake score and length of time on the most recent constant dose of octreotide before random assignment [$\leq$ 6 and $>$ 6 months]), and the following baseline characteristics: disease stage, tumor burden, Ki67 index, sex, body mass index, age, creatinine clearance, and relative QoL domain score. The final model was defined using a backward selection process, removing covariables that did not reach a significance level of .05. Randomized treatment was ineligible for removal from the model.

Alternate TTD Definitions

Self-assessment of HRQoL is dependent on the patient's internal standards and the definition of HRQoL used. Because patients adapt to their disease and treatment toxicities, their health and HRQoL expectations may also change over time. These changes may result in a response shift effect.

Several alternate definitions of TTD were explored to address the potential bias introduced by such response shifts.[10] TTD from highest score was defined as time from random assignment to first deterioration of 10 points in domain score compared with the best previous score for the same domain. Patients with no deterioration were censored at the last QoL assessment date. Time until definitive deterioration (TUDD) was defined as time from random assignment to deterioration of 10 points in domain score compared with baseline score with no further improvement of 10 points compared with the baseline score. Patients who died within 210 days after the last QoL survey was completed without a prior definitive deterioration were considered to have had an event at time of death. To avoid overestimating TUDD in the presence of missing data, patients who died more than 210 days after completion of their last QoL questionnaire (representing two or more consecutive missing assessments) were censored at the date of the last questionnaire.

RESULTS

Analysis cutoff date was June 30, 2016. In total, 231 patients were randomly assigned in the study (117 in ^{177}Lu-Dotatate arm and 114 in the high-dose octreotide LAR arm; Appendix Fig A1, online only). The analysis was conducted on all randomly assigned patients as per intent-to-treat principles. Overall compliance rates for patients completing questionnaires were high, with $>$ 80% return rates in both arms for all visits. Baseline HRQoL scores were well balanced (Table 1).

Using the definition of HRQoL deterioration ($\geq$ 10 points compared with baseline), TTD was significantly longer in the ^{177}Lu-Dotatate arm compared with the octreotide arm in the following domains (Fig 1; Table 2): global health, physical functioning, role functioning, diarrhea, pain, body image, disease-related worries, and fatigue. The HR for global health favoring ^{177}Lu-Dotatate was 0.41 (95% CI, 0.24 to 0.69; $P < .001$), with a 22.7-month difference in median TTD between both arms. The HR for physical functioning was 0.52 (95% CI, 0.30 to 0.89; $P = .015$), with a 13.7-month difference. The HR for role functioning was 0.58 (95% CI, 0.35 to 0.96; $P = .030$), the HR for diarrhea was 0.47 (95% CI, 0.26 to 0.85; $P = .011$), the HR for pain was 0.57 (95% CI, 0.34 to 0.94; $P = .025$), the HR for disease-related worries was 0.57 (95% CI, 0.36 to 0.91; $P = .018$), the HR for body image was 0.43 (95% CI, 0.23 to 0.80; $P = .006$), and the HR for fatigue was 0.62 (95% CI, 0.40 to 0.96; $P = .030$). There were no domains in which TTD analysis showed significant benefit for the control arm (octreotide LAR).

Cox multiple regression of the TTD end point was supportive of the main analysis. When adjusting for significant covariates,

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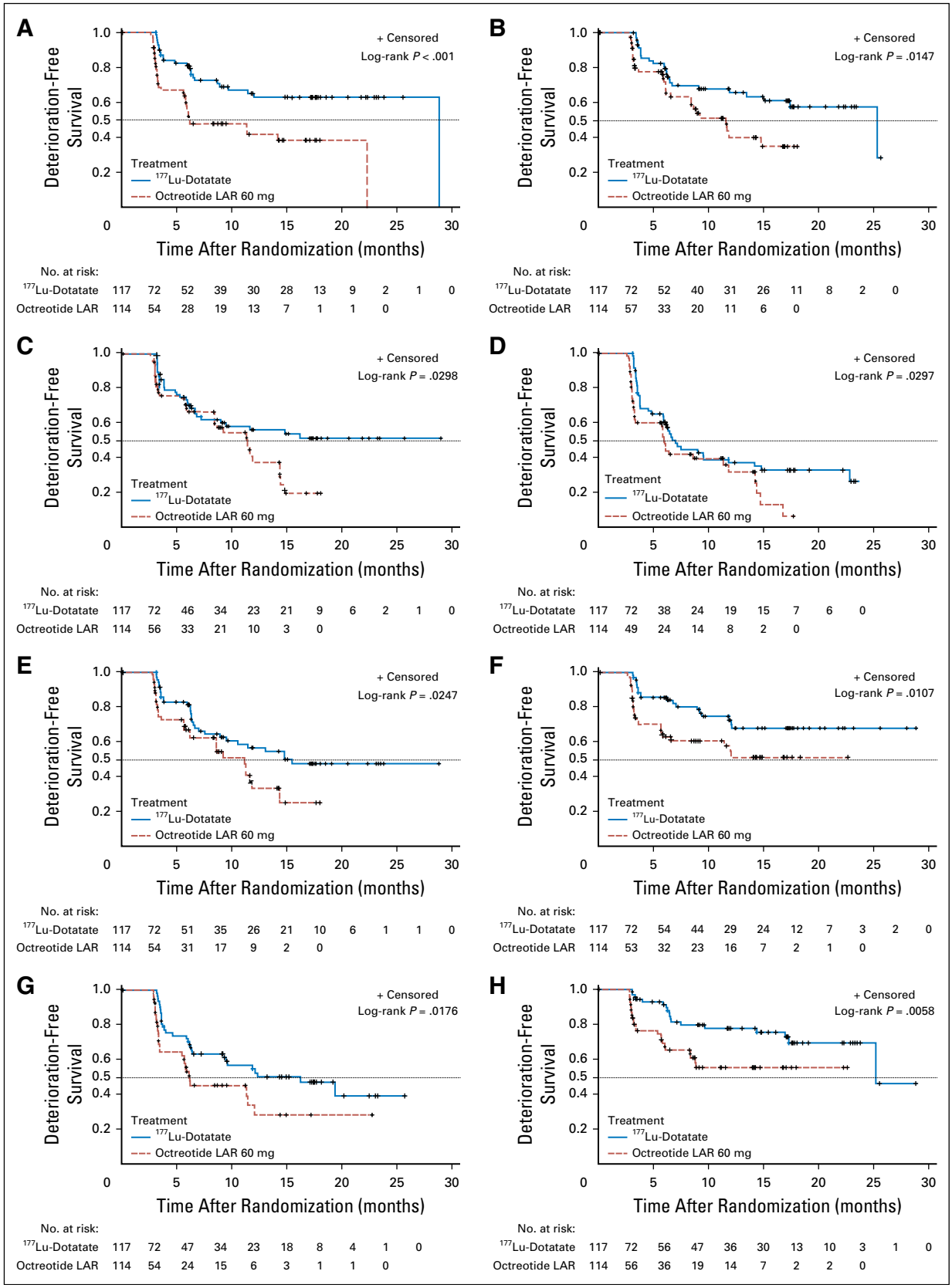

Fig 1. Kaplan-Meier plots showing European Organisation for Research and Treatment of Cancer quality of life questionnaire domains with significantly improved time to deterioration in the ^{177}Lu-Dotatate arm compared with the octreotide arm. (A) Global health status; (B) physical functioning; (C) role functioning; (D) fatigue; (E) pain; (F) diarrhea; (G) disease-related worries; (H) body image.

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Table 2. HR for Time to Deterioration, Time to Deterioration From Highest Score, and Time Until Definitive Deterioration: Comparison of Treatment Arms

Domain	Time to Deterioration From Baseline (primary analysis)		Time to Deterioration From Highest Score		Time Until Definitive Deterioration (or death)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Global health scale	0.41 (0.24 to 0.69)	< .001	0.41 (0.26 to 0.64)	< .001	0.39 (0.24 to 0.63)	< .001
Body image	0.43 (0.23 to 0.80)	.006	0.44 (0.25 to 0.78)	.004	0.44 (0.26 to 0.74)	.002
Diarrhea	0.47 (0.26 to 0.85)	.011	0.40 (0.25 to 0.64)	< .001	0.42 (0.25 to 0.70)	.001
Physical functioning	0.52 (0.30 to 0.89)	.015	0.69 (0.43 to 1.10)	.118	0.47 (0.29 to 0.78)	.002
Disease-related worries	0.57 (0.36 to 0.91)	.018	0.53 (0.35 to 0.80)	.002	0.46 (0.28 to 0.75)	.001
Pain	0.57 (0.34 to 0.94)	.025	0.62 (0.40 to 0.98)	.036	0.47 (0.28 to 0.77)	.002
Role functioning	0.58 (0.35 to 0.96)	.030	0.68 (0.43 to 1.08)	.100	0.41 (0.25 to 0.68)	< .001
Fatigue	0.62 (0.40 to 0.96)	.030	0.63 (0.43 to 0.93)	.017	0.70 (0.45 to 1.09)	.108
Constipation	0.55 (0.27 to 1.12)	.094	0.57 (0.30 to 1.11)	.092	0.56 (0.32 to 0.99)	.042
Social functioning	0.67 (0.41 to 1.09)	.100	0.63 (0.41 to 0.97)	.034	0.48 (0.30 to 0.76)	.001
GI scale	0.68 (0.40 to 1.15)	.147	0.65 (0.42 to 1.00)	.045	0.51 (0.31 to 0.82)	.005
Insomnia	0.70 (0.42 to 1.18)	.175	0.62 (0.39 to 1.00)	.042	0.59 (0.37 to 0.95)	.026
Treatment scale	0.70 (0.39 to 1.27)	.237	0.75 (0.43 to 1.30)	.297	0.42 (0.24 to 0.73)	.002
Muscle/bone pain symptoms	0.74 (0.42 to 1.28)	.276	0.61 (0.38 to 0.95)	.028	0.63 (0.38 to 1.04)	.067
Appetite loss	0.72 (0.38 to 1.35)	.300	0.67 (0.38 to 1.18)	.157	0.49 (0.28 to 0.85)	.009
Emotional functioning	0.73 (0.40 to 1.36)	.320	0.59 (0.37 to 0.95)	.027	0.52 (0.30 to 0.91)	.020
Social function scale	0.84 (0.51 to 1.39)	.494	0.68 (0.45 to 1.02)	.060	0.53 (0.32 to 0.87)	.011
Sexual function	0.79 (0.40 to 1.58)	.507	0.79 (0.41 to 1.50)	.470	0.63 (0.35 to 1.15)	.129
Nausea and vomiting	1.16 (0.66 to 2.04)	.613	1.28 (0.75 to 2.18)	.359	0.86 (0.51 to 1.44)	.560
Cognitive functioning	0.89 (0.53 to 1.49)	.649	0.71 (0.46 to 1.11)	.132	0.76 (0.46 to 1.26)	.284
Endocrine scale	0.89 (0.52 to 1.55)	.686	0.82 (0.52 to 1.27)	.366	0.78 (0.46 to 1.31)	.347
Financial difficulties	0.89 (0.46 to 1.72)	.737	0.75 (0.43 to 1.31)	.312	0.63 (0.37 to 1.10)	.099
Information/communication function	1.13 (0.47 to 2.74)	.780	0.98 (0.42 to 2.29)	.954	0.57 (0.30 to 1.08)	.079
Dyspnea	1.06 (0.59 to 1.91)	.844	1.06 (0.64 to 1.75)	.821	0.70 (0.41 to 1.19)	.188

Abbreviation: HR, hazard ratio.

including HRQoL baseline values, OctreoScan maximum tumor uptake score, and/or age, the impact of treatment remained statistically significant for global health status, physical functioning, diarrhea, and body image domains.

An additional sensitivity analysis of TTD was performed by censoring at random assignment those patients with worst possible score at baseline who could therefore not experience deterioration on subsequent time points. The analysis reconfirmed the significant benefits observed in global health status, role functioning, pain, diarrhea, disease-related worries, body image, and fatigue, even after censoring 2, 10, 6, 27, 16, 11, and 7 patients who met this criterion for each of these domains, respectively. For the physical function scale, no patients had the worst possible score at baseline; therefore, results were as for the main end point.

To compensate for a potential response shift, as described above, several alternatives were explored for defining deterioration. TTD from highest score was defined as time from random assignment to first deterioration of 10 points in domain score compared with the best previous score. Per this analysis, TTD from highest previous score was statistically significantly longer in the ^{177}Lu-Dotatate arm than in the control arm for the following domains: global health status (HR, 0.409; 95% CI, 0.263 to 0.636; $P < .001$), diarrhea (HR, 0.398; 95% CI, 0.246 to 0.643; $P < .001$), body image (HR, 0.437; 95% CI, 0.246 to 0.776; $P = .0038$), disease-related worries (HR, 0.532; 95% CI, 0.354 to 0.800; $P = .0019$), emotional functioning (HR, 0.590; 95% CI, 0.366 to 0.949; $P = .0273$), insomnia (HR, 0.622; 95% CI, 0.391 to 0.988; $P = .0419$), social functioning (HR, 0.630; 95% CI, 0.409 to 0.970; $P = .0339$), GI scale (HR, 0.647; 95% CI, 0.420 to 0.996; $P = .0452$), pain (HR, 0.622; 95% CI, 0.397 to 0.975; $P = .0361$), fatigue (HR, 0.630; 95% CI, 0.428 to 0.926; $P = .0170$), and muscle and bone pain (HR, 0.605; 95% CI, 0.384 to 0.952; $P = .0276$).

TUDD was defined as time from random assignment to deterioration of 10 points in domain score compared with baseline score for the same domain with no further improvement of 10 points as compared with the baseline score or death. Significant improvement in time to definitive deterioration was seen with ^{177}Lu-Dotatate in more than half of the domains. These included global health status (HR, 0.390; 95% CI, 0.243 to 0.626; $P < .001$), physical functioning (HR, 0.472; 95% CI, 0.287 to 0.775; $P = .0024$), role functioning (HR, 0.414; 95% CI, 0.253 to 0.678; $P < .001$), emotional functioning (HR, 0.519; 95% CI, 0.296 to 0.912; $P = .0203$), social functioning (HR, 0.476; 95% CI, 0.299 to 0.759; $P = .0014$), pain (HR, 0.467; 95% CI, 0.284 to 0.768; $P = .0021$), insomnia (HR, 0.591; 95% CI, 0.370 to 0.945; $P = .0259$), appetite loss (HR, 0.487; 95% CI, 0.280 to 0.847; $P = .0092$), constipation (HR, 0.560; 95% CI, 0.317 to 0.988; $P = .0422$), diarrhea (HR, 0.416; 95% CI, 0.246 to 0.703; $P < .001$), GI scale (HR, 0.505; 95% CI, 0.311 to 0.820; $P = .0048$), treatment scale (HR, 0.415; 95% CI, 0.236 to 0.730; $P = .0016$), social function scale (HR, 0.527; 95% CI, 0.319 to 0.870; $P = .0107$), disease-related worries scale (HR, 0.461; 95% CI, 0.284 to 0.746; $P = .0012$), and body image (HR, 0.435; 95% CI, 0.256 to 0.738; $P = .0015$).

All of the areas identified as having a significantly longer TTD with ^{177}Lu-Dotatate using the original definition of TTD (global health, physical functioning, role functioning, diarrhea, pain, body image, disease-related worries, and fatigue) were confirmed using at least one of the alternative definitions of TTD. All three definitions of TTD demonstrated a significant improvement in global health, diarrhea, pain, body image, and disease-related worries.

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DISCUSSION

QoL is a vital end point when evaluating the benefit versus risk of a new cancer treatment. In patients with advanced NETs, maintenance of an acceptable HRQoL is particularly important, given the relatively long durations of treatment and overall survival. TTD is an increasingly recognized and validated method used for analysis of longitudinal HRQoL data and enables comparison of study arms using Kaplan-Meier methodology.

In many analyses of randomized clinical studies, preservation of HRQoL with a new experimental treatment compared with a control is considered a favorable outcome. For example, a recent analysis of HRQoL in the RADIANT 4 study of everolimus versus placebo in GI and lung NETs reported no difference in TTD between patients receiving everolimus and placebo.[15] Within this context, it is notable that treatment with ^{177}Lu-Dotatate yielded significant improvement in time to deterioration of HRQoL compared with octreotide, a drug that has few adverse effects. The most clinically and statistically significant improvement was seen in the global health domain, in which patients are asked to rate their overall health and QoL. ^{177}Lu-Dotatate was associated with a striking 22.7-month prolongation in global health TTD compared with octreotide. Other important functional domains in which TTD analysis favored the ^{177}Lu-Dotatate arm were physical functioning (questions pertaining to activities of daily living) and role functioning (ability to participate in advanced activities of daily living, such as employment and leisure). Benefits in these domains indicate that patients treated with ^{177}Lu-Dotatate, on average, maintain a stable level of physical and social activity for a longer period of time than they would in absence of this treatment.

An important survey domain that is particularly relevant to patients with midgut NET is diarrhea, one of the hallmark symptoms of the carcinoid syndrome. It is therefore noteworthy that diarrhea was among the symptoms where ^{177}Lu-Dotatate demonstrated a significant benefit in TTD, with an HR of 0.43. Other important symptoms where patients experienced benefit included pain and fatigue. Benefit was not observed in few symptoms, such as constipation, which are not generally associated with NETs.

The Endocrine Scale of the G.I.NET 21 consists of questions related to flushing and sweats, also important features of carcinoid syndrome. Although no significant improvement was observed in TTD with ^{177}Lu-Dotatate in this domain, it is noteworthy that a substantial proportion of patients in both arms of the study experienced improvement in score in this domain. Therefore, it is likely that both ^{177}Lu-Dotatate and high-dose octreotide positively affected TTD in this domain, accounting for the inability to observe a difference in TTD between the two arms.

Moreover, when we assessed the absolute improvement rates in symptoms among patients with symptoms at baseline who were followed up for at least 24 weeks, the improvement rates post-treatment in the ^{177}Lu-Dotatate arm were clinically relevant (48% of the patients had an improvement in diarrhea, 50% in fatigue, 69% in pain, 63% in treatment scale and body image, 61% in the endocrine scale, 60% in the GI scale) and in line with the previous experience reported by Khan et al.[9]

One limitation of this HRQoL analysis is the fact that patients in the NETTER-1 study were not blinded to treatment, because of the significant differences in treatment modalities between the two trial arms. It is unclear whether knowledge of treatment assignment affected patient perception of HRQoL. The fact that clinically and statistically significant HRQoL benefits were observed predominantly in clinically relevant symptoms, such as pain, diarrhea, and fatigue, suggests that effect of perception bias on HRQoL survey results was likely minimal.

In conclusion, analysis of HRQoL from the phase III NETTER-1 study demonstrates that ^{177}Lu-Dotatate provides a statistically significant and clinically robust quality-of-life benefit for patients with progressive midgut NETs compared with high-dose octreotide. This improvement is seen across multiple clinically relevant symptom categories, including diarrhea, fatigue, and pain. Patients also experience benefits in functional HRQoL categories, including those pertaining to basic and advanced activities of daily living. Perhaps most importantly, patients report significant and sustained improvements in their global health. These data validate the overall benefit of ^{177}Lu-Dotatate in this patient population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With ^{177}Lu-Dotatate in the Phase III NETTER-1 Trial

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Appendix

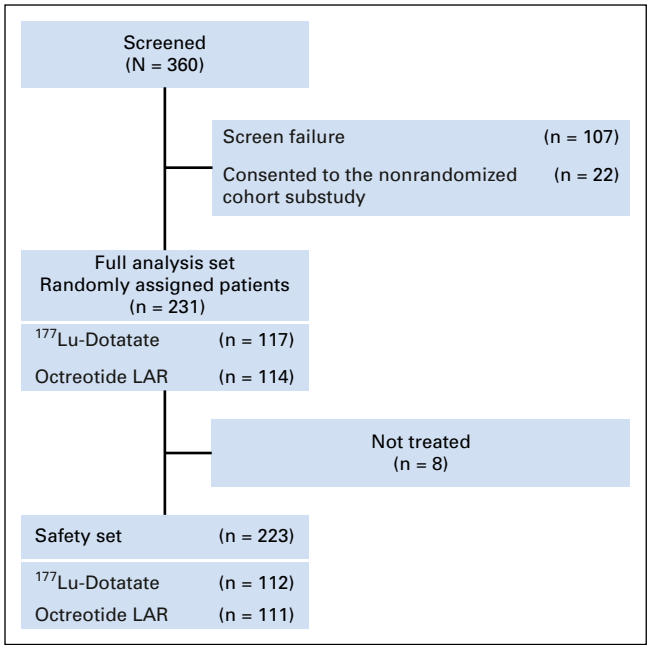

Fig A1. CONSORT diagram. LAR, long-acting repeatable.

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Table A1. List of EORTC-QLQ C-30 and EORTC-QLQ-G.I.NET-21 Questions by Domain

Questions by Domain
EORTC-QLQ-C30
Global health status/QoL (QL2)
29 How would you rate your overall health during the past week?
30 How would you rate your overall quality of life during the past week?
Functional scales
Physical functioning (PF2)
1 Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
2 Do you have any trouble taking a long walk?
3 Do you have any trouble taking a short walk outside of the house?
4 Do you need to stay in bed or a chair during the day?
5 Do you need help with eating, dressing, washing yourself or using the toilet?
Role functioning (RF2)
6 Were you limited in doing either your work or other daily activities?
7 Were you limited in pursuing your hobbies or other leisure time activities?
Emotional functioning (EF)
21 Did you feel tense?
22 Did you worry?
23 Did you feel irritable?
24 Did you feel depressed?
25 Have you had difficulty remembering things?
Cognitive functioning (CF)
20 Have you had difficulty in concentrating on things, like reading a newspaper or watching television?
Social functioning (SF)
26 Has your physical condition or medical treatment interfered with your family life?
27 Has your physical condition or medical treatment interfered with your social activities?
Symptom scales/items
Fatigue (FA)
10 Did you need to rest?
12 Have you felt weak?
18 Were you tired?
Nausea and vomiting (NV)
14 Have you felt nauseated?
15 Have you vomited?
Pain (PA)
9 Have you had pain?
19 Did pain interfere with your daily activities?
Dyspnea (DY)
8 Were you short of breath?
Insomnia (SL)
11 Have you had trouble sleeping?
Appetite loss (AP)
13 Have you lacked appetite?
Constipation (CO)
16 Have you been constipated?
Diarrhea (DI)
17 Have you had diarrhea?
Financial difficulties (FI)
28 Has your physical condition or medical treatment caused you financial difficulties?
EORTC-QLQ-GINET-21
Endocrine scale
31 Did you have hot flushes?
32 Have you noticed or been told by others that you looked flushed/red?
33 Did you have night sweats?
GI scale
34 Did you have abdominal discomfort?
35 Did you have a bloated feeling in your abdomen?
36 Have you had a problem with passing wind/gas/flatulence?
37 Have you had acid indigestion or heartburn?
38 Have you had difficulties with eating?
Treatment scale
39 Have you had side effects from your treatment?
40 Have you had a problem from repeated injections?
46 Has weight gain been a problem for you?
Social function scale
42 Were you concerned about disruption of home life?
44 How distressing has your illness or treatment been to those close to you?
49 Did you have any limitations in your ability to travel?

(continued on following page)

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Table A1. List of EORTC-QLQ C-30 and EORTC-QLQ-G.I.NET-21 Questions by Domain (continued)

Questions by Domain
Disease-related worries scale
41 Were you worried about the tumor recurring in other areas of the body?
43 Have you worried about your health in the future?
47 Did you worry about the results of your tests?
Single-item scales
Body image
45 Has weight loss been a problem for you?
Muscle/bone pain symptom
48 Have you had aches or pains in your muscles or bones?
Information/communication function
50 Have you had problems receiving adequate information about your disease and treatment?
Sexual function
51 Has the disease or treatment affected your sex life (for the worse)?

Abbreviations: EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer quality-of-life questionnaire, 30-question survey; EORTC-QLQ-G.I.NET-21, European Organisation for Research and Treatment of Cancer quality-of-life questionnaire, 21-question survey for patients with GI-related neuroendocrine tumors.

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