^{177}Lu-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

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Summary

Background The primary analysis of the phase 3 NETTER-1 trial showed significant improvement in progression-free survival with ^{177}Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide alone in patients with advanced midgut neuroendocrine tumours. Here, we report the prespecified final analysis of overall survival and long-term safety results.

Methods This open-label, randomised, phase 3 trial enrolled patients from 41 sites in eight countries across Europe and the USA. Patients were 18 years and older with locally advanced or metastatic, well differentiated, somatostatin receptor-positive midgut neuroendocrine tumours (Karnofsky performance status score ≥60) and disease progression on fixed-dose long-acting octreotide. Patients were randomly assigned (1:1) via an interactive web-based response system to intravenous ^{177}Lu-Dotatate 7·4 GBq (200 mCi) every 8 weeks (four cycles) plus intramuscular long-acting octreotide 30 mg (^{177}Lu-Dotatate group) or high-dose long-acting octreotide 60 mg every 4 weeks (control group). The primary endpoint of progression-free survival has been previously reported; here, we report the key secondary endpoint of overall survival in the intention-to-treat population. Final overall survival analysis was prespecified to occur either after 158 deaths or 5 years after the last patient was randomised, whichever occurred first. During long-term follow-up, adverse events of special interest were reported in the ^{177}Lu-Dotatate group only. This trial is registered with ClinicalTrials.gov, NCT01578239.

Findings From Sept 6, 2012, to Jan 14, 2016, 231 patients were enrolled and randomly assigned for treatment. The prespecified final analysis occurred 5 years after the last patient was randomly assigned (when 142 deaths had occurred); median follow-up was 76·3 months (range 0·4–95·0) in the ^{177}Lu-Dotatate group and 76·5 months (0·1–92·3) in the control group. The secondary endpoint of overall survival was not met: median overall survival was 48·0 months (95% CI 37·4–55·2) in the ^{177}Lu-Dotatate group and 36·3 months (25·9–51·7) in the control group (HR 0·84 [95% CI 0·60–1·17]; two-sided p=0·30). During long-term follow-up, treatment-related serious adverse events of grade 3 or worse were recorded in three (3%) of 111 patients in the ^{177}Lu-Dotatate group, but no new treatment-related serious adverse events were reported after the safety analysis cutoff. Two (2%) of 111 patients given ^{177}Lu-Dotatate developed myelodysplastic syndrome, one of whom died 33 months after randomisation (this person was the only reported ^{177}Lu-Dotatate treatment-related death). No new cases of myelodysplastic syndrome or acute myeloid leukaemia were reported during long-term follow-up.

Interpretation ^{177}Lu-Dotatate treatment did not significantly improve median overall survival versus high-dose long-acting octreotide. Despite final overall survival not reaching statistical significance, the 11·7 month difference in median overall survival with ^{177}Lu-Dotatate treatment versus high-dose long-acting octreotide alone might be considered clinically relevant. No new safety signals were reported during long-term follow-up.

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Introduction

Neuroendocrine tumours (NETs) comprise a heterogeneous group of neoplasms arising from the neuroendocrine cell system.[1] Their reported clinical incidence has increased significantly in recent decades:[2] gastro-entero-pancreatic NETs (GEP-NETs) comprise about 70% of well differentiated NETs and now represent the second most prevalent gastrointestinal cancer in the

Research in context

Evidence before the study

Few systemic treatment options are available for advanced, midgut neuroendocrine tumours (NETs) beyond standard therapy with somatostatin analogues. During the past three decades, radiolabelled somatostatin analogues (a type of radioligand therapy called peptide receptor radionuclide therapy [PRRT]) have shown promise for the treatment of advanced, well differentiated, somatostatin receptor-positive NETs; however, no randomised phase 3 trials had been done. A key recommendation in the published consensus report of the NET Clinical Trials Planning Meeting in 2011 stated that randomised phase 3 trials comparing PRRT with standard systemic therapy were warranted, highlighting that many reported studies had suboptimal methods, lacked intention-to-treat analyses, and used non-standard endpoint definitions. This recommendation supported the development of the NETTER-1 trial; thus, a formal literature search for available evidence on PRRT in the treatment of NETs was not done before the study. The primary analysis of the NETTER-1 trial reported a clinically and statistically significant improvement in progression-free survival with ^{177}Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with advanced, progressive, well differentiated, somatostatin receptor-positive midgut NETs. These data supported regulatory approvals for ^{177}Lu-Dotatate.

Added value of the study

To our knowledge, these are the first reported long-term survival results from a randomised, controlled, phase 3 trial of PRRT in patients with NETs. In NETTER-1, the prespecified final analysis of the overall survival secondary endpoint was done 5 years after the last patient was randomly assigned in the study. With a long median duration of follow-up in each study group, the longer median overall survival with the ^{177}Lu-Dotatate group compared with the control group was clinically relevant, but was not statistically significant. The long follow-up in NETTER-1 allowed thorough evaluation of the long-term safety profile of ^{177}Lu-Dotatate, notably the risk of secondary haematological malignancies. The incidence of myelodysplastic syndrome was consistent with incidences of less than 3% reported in previous studies of ^{177}Lu-Dotatate, supporting the favourable benefit–risk profile of this treatment.

Implications of all the available evidence

The previously reported significant improvement in progression-free survival with ^{177}Lu-Dotatate treatment did not translate into a significant improvement in overall survival. These results highlight the challenges in demonstrating a significant overall survival benefit in patients with advanced, well differentiated NETs, given the extended survival in this indolent tumour type, heterogeneity of previous treatments, potential for crossover within the trial, and the availability of other further therapeutic options. Previous phase 3 trials of somatostatin analogues in similar patient populations have not shown improvements in overall survival, despite significant improvements in progression-free survival; thus, the longer median overall survival of 11·7 months with ^{177}Lu-Dotatate versus high-dose long-acting octreotide is clinically relevant, despite not reaching statistical significance. To increase the likelihood of showing a significant overall survival difference, randomised trials in NETs would probably need a larger sample size to enable observation of the required number of events earlier and thus reduce the potential effect of confounding factors. However, combined with the significant progression-free survival improvement, confirmed favourable safety profile, and associated quality-of-life benefits, the final overall survival results of NETTER-1 further support the use of ^{177}Lu-Dotatate as standard-of-care treatment in patients with advanced, well differentiated, grade 1 and 2 midgut NETs with disease progression on somatostatin analogues.

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See **Online** for appendix

USA.[3,4] Survival outcomes of patients with metastatic disease greatly depend on tumour grade and primary site, and can range from a median of approximately 2·3 years for patients with well differentiated colorectal NETs to nearly 6 years for those with well differentiated small-bowel NETs.[2] Despite recent improvements in survival outcomes, most patients with advanced disease eventually die from their cancer.[2]

Midgut NETs, formerly known as carcinoid tumours, originate in the jejunum, ileum, and caecum and represent the most common subtype of advanced, well differentiated GEP-NETs.[4] They often secrete serotonin and other vasoactive substances, and can cause carcinoid syndrome, which is associated with symptoms such as flushing and diarrhoea.[1] Nearly all midgut NETs express somatostatin receptors on cell surfaces, a property exploited for diagnostic and therapeutic purposes.[5]

Somatostatin analogues, including octreotide and lanreotide, are the standard first-line treatment for most patients with metastatic-grade, low-grade, or intermediate-grade GEP-NETs.[6] Somatostatin analogues, initially developed to control symptoms related to carcinoid syndrome and functioning pancreatic NETs, subsequently showed the ability to inhibit tumour progression in two placebo-controlled studies.[7,8] Retrospective studies of high-dose somatostatin analogues suggest some palliative benefit in patients with carcinoid syndrome, but their effect on tumour progression is largely unknown.[9] Everolimus, an oral mTOR inhibitor, demonstrated improved progression-free survival compared with placebo in patients with advanced non-functional gastrointestinal NETs.[10] By contrast, everolimus did not significantly improve progression-free survival when added to long-acting octreotide 30 mg in patients with metastatic NETs and a history of carcinoid syndrome.[11] Sunitinib, a VEGF inhibitor, has demonstrated activity only in pancreatic NETs and is thus only indicated for treatment of these specific NETs.[12] Cytotoxic drugs, such

as temozolomide and streptozocin, have demonstrable activity in pancreatic NETs, but are considered relatively ineffective in midgut NETs.[13,14] Furthermore, no additional single treatment has demonstrated improvement of overall survival versus somatostatin analogue alone in patients with advanced, progressive midgut NETs.[15] Thus, there are few treatment options for midgut NETs beyond standard somatostatin analogue therapy.

Radiolabelled somatostatin analogues represent a targeted approach to the treatment of GEP-NETs. This form of therapy, known as peptide receptor radionuclide therapy (PRRT; a form of radioligand therapy), involves the conjugation of a radionuclide to a somatostatin analogue using a chelator molecule to deliver targeted radiation to somatostatin receptor-expressing tumours.[5] Several radionuclides have been evaluated during the past three decades for the treatment of advanced, well differentiated NETs.[16–19] The radiolabelled somatostatin analogue ^{177}Lu-Dotatate consists of a β-emitting radionuclide, [^{177}Lu], coupled to a high-affinity somatostatin analogue (octreotate) via the DOTA chelator molecule.[20] The analogue has been associated with a particularly favourable therapeutic index and less collateral toxicity than [^{90}Y]-based compounds in single-arm trials.[21,22]

The use of ^{177}Lu-Dotatate was evaluated in the NETTER-1 trial, the first reported randomised, international, phase 3 trial of PRRT in NETs.[23] In this trial, patients with advanced, well differentiated, progressive midgut NETs were randomly assigned to receive four cycles of ^{177}Lu-Dotatate plus long-acting octreotide 30 mg every 8 weeks (every 4 weeks after completion of ^{177}Lu-Dotatate) or high-dose long-acting octreotide 60 mg alone every 4 weeks. The trial met the primary objective of significantly improved progression-free survival with ^{177}Lu-Dotatate, with a hazard ratio (HR) of 0·18 (95% CI 0·11–0·29; p<0·0001). ^{177}Lu-Dotatate received marketing authorisation from the European Medicines Agency in Europe on Sept 26, 2017, and from the US Food and Drug Administration in the USA on Jan 26, 2018. We report the final overall survival analysis and long-term safety in NETTER-1.

Methods

Study design and participants

NETTER-1 is an open-label, randomised, comparator-controlled, phase 3 trial that was done in 41 centres in eight countries across Europe and the USA (appendix p 2). Study site investigators enrolled patients. Patient eligibility criteria for NETTER-1 have been previously described in detail and are provided in the previously published trial protocol.[23] Briefly, eligible patients were aged 18 years and older, with advanced, inoperable, well-differentiated (Ki67 index ≤20%) midgut NETs with positive uptake on ^{111}In-DTPA-octreotide scintigraphy (OctreoScan) on all target lesions and centrally confirmed disease progression on CT or MRI (as per Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) while taking a fixed dose of long-acting octreotide 20–30 mg every 3–4 weeks for at least 12 weeks before randomisation. Patients had to have a Karnofsky performance status score of at least 60. Previous PRRT was not allowed, nor was any surgery, transarterial therapy, or chemotherapy within 12 weeks of randomisation. Key laboratory exclusion criteria included serum creatinine above 150 µmol/L (>1·7 mg/dL) or creatinine clearance below 50 mL/min as calculated by the Cockcroft–Gault method; haemoglobin concentration of less than 8·0 g/dL; white blood cell count below 2000 cells/mm^3; platelets below 75 000 cells/mm^3; total bilirubin above three times the upper limit of normal; and serum albumin below or equal to 3·0 g/dL (unless prothrombin time was within normal range). Comorbidities not permitted were congestive heart failure, uncontrolled diabetes, spontaneous urinary incontinence, and co-existing malignancies. At selected study sites, patients who met eligibility criteria for the main randomised study were enrolled separately into a non-randomised substudy to evaluate ^{177}Lu-Dotatate dosimetry and pharmacokinetics; this study will be published elsewhere (appendix p 3). All patients provided written informed consent. Independent ethical review boards approved the study protocol at each participating institution. The independent committee monitored safety throughout the study.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive study treatments. The allocation sequence was generated by Pierrel Research (Zurich, Switzerland). The interactive web-based response system module of the electronic case report form assigned a unique randomisation number, linked to a treatment group, to each patient. Randomisation was stratified by highest tumour uptake on OctreoScan (Krenning grade 2, 3, or 4; using the highest score measured among all target lesions in an individual patient) and by length of time on most recent fixed dose of long-acting octreotide (≤6 months or >6 months). The study was open-label, and both investigators and patients were aware of treatment allocation.

Procedures

Patients were randomly assigned to receive either four cycles of ^{177}Lu-Dotatate 7·4 GBq (200 mCi) every 8 weeks (or within 1 week of this timeframe) by intravenous infusions plus concomitant long-acting octreotide (30 mg) administered intramuscularly (then every 4 weeks after ^{177}Lu-Dotatate administrations were completed; ^{177}Lu-Dotatate group), or high-dose long-acting octreotide (60 mg) administered intramuscularly every 4 weeks (or within 3 days of this timeframe; control group). All patients could receive short-acting octreotide rescue injections for symptom control. An infusion of an amino acid solution (Aminosyn II 10% or VAMIN-18) was administered concomitantly with ^{177}Lu-Dotatate for renal protection. During the study treatment period,

patients could not receive any other systemic anticancer therapy.

Study treatments continued until centrally confirmed disease progression (as per RECIST version 1.1), unacceptable toxicity, non-adherence to trial procedures, withdrawal of informed consent, or completion of the 18-month treatment period.

After centrally confirmed disease progression, discontinuation of study treatment without confirmed progression, or completion of the 18-month treatment period, patients entered the long-term follow-up phase and could receive further anticancer treatment as recommended by their physicians. During long-term follow-up, local radiographic assessments with CT or MRI were done every 6 months, and adverse events were assessed every 6 months depending on treatment group (appendix p 4). Laboratory abnormalities were monitored every 6 months in both treatment groups. During long-term follow-up, the protocol only specified reporting of serious adverse events deemed related to ^{177}Lu-Dotatate treatment and adverse events of special interest (ie, haematotoxicity, cardiovascular events, and nephrotoxicity, regardless of causality) in the ^{177}Lu-Dotatate group. Thus, the protocol did not require reporting of all adverse events in both study groups during long-term follow-up. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Secondary malignancies (haematological and solid tumours) were reported regardless of causality during long-term follow-up in both study groups. Laboratory assessments (ie, urinalysis, haematology, and blood biochemistry) were done in both groups every 6 months. Long-term renal function was monitored in both study groups using calculated creatinine clearance (Cockcroft–Gault method; appendix p 4). Information on further anticancer treatments was collected.

Outcomes

The primary endpoint of progression-free survival, defined as the time from randomisation to documented disease progression or death due to any cause, whichever occurred first, the prespecified secondary endpoint of objective response rate, and additional prespecified secondary endpoints of health-related quality of life and on-treatment safety and tolerability, have been previously reported.[23,24] The originally published result for the progression-free survival primary endpoint (HR 0·21 [95% CI 0·13–0·33]; p<0·001) was subsequently updated during the health authority submission review using the same primary analysis data cutoff (July 24, 2015). Reassessment included prerandomisation baseline scans, rather than use of scans before treatment if there had been a delay (HR 0·18 [95% CI 0·11–0·29]; p<0·0001). Overall survival was a key secondary endpoint of the NETTER-1 trial and was defined as the time from the date of randomisation to the date of death due to any cause, or to the date of last contact (censored observation) at the time of data cutoff. The final analysis of overall survival was prespecified to occur either after 158 deaths had occurred or 5 years after the last patient was randomised, whichever occurred first. Safety was also a secondary endpoint. The safety and tolerability profiles of ^{177}Lu-Dotatate have been previously reported based on data collected up to the primary progression-free survival analysis data cutoff and the updated safety analysis cutoff (June 30, 2016, by which time all patients had completed treatment with ^{177}Lu-Dotatate).[23,25] The prespecified focus of the long-term follow-up safety analysis was renal function and secondary haematological malignancies.

Statistical analysis

The prespecified primary analysis of overall survival after 158 deaths would have provided 80% power to detect a statistically significant difference in overall survival, with a significance threshold of 0·049915, adjusted for 0·000085 type 1 error spent at the prespecified interim overall survival analyses using an O'Brien–Fleming alpha spending function. A hierarchical testing procedure-controlled family-wise type 1 error within multiple testing of the primary endpoint and two key secondary endpoints (objective response rate and overall survival). Progression-free survival and objective response rate were tested at the two-sided significance level of 0·05 at the primary analysis and were significant, allowing inferential statistical analysis of overall survival. The primary analysis of overall survival was done in all patients who were randomly assigned, according to the intention-to-treat principle (the full analysis set). The primary method of statistical comparison between the treatment groups was an unstratified log-rank test. The median, IQRs, 95% CIs, and prespecified yearly rates for overall survival were estimated using the Kaplan-Meier method. The HR and associated 95% CI were obtained using the unstratified Cox proportional-hazards regression model. The proportional-hazards assumption for the Cox analysis of overall survival was examined by both graphical and analytical methods (correlation between Schoenfeld residuals and rank-transformed time); this assumption was not fulfilled (Schoenfeld residuals test, p=0·03, two sided).

Analyses of overall survival were done in the following prespecified subgroups: randomisation stratification factors (time on fixed dose of long-acting octreotide [≤6 months or >6 months] and highest OctreoScan tumour uptake grade at baseline [grade 2, grade 3, or grade 4]); age (<65 years, <75 years, ≥65 years, or ≥75 years); sex (male or female); body-mass index (≤21 kg/m², 22–27 kg/m², or >27 kg/m²); region (European Union or USA); ethnicity and race (white and Caucasian or other); mean OctreoScan grade at baseline; Karnofsky performance status score at baseline (100, 90, or ≤80); previous therapies (with or without previous chemotherapy, radiotherapy, or surgery); OctreoScan tumour burden at baseline (limited, moderate,

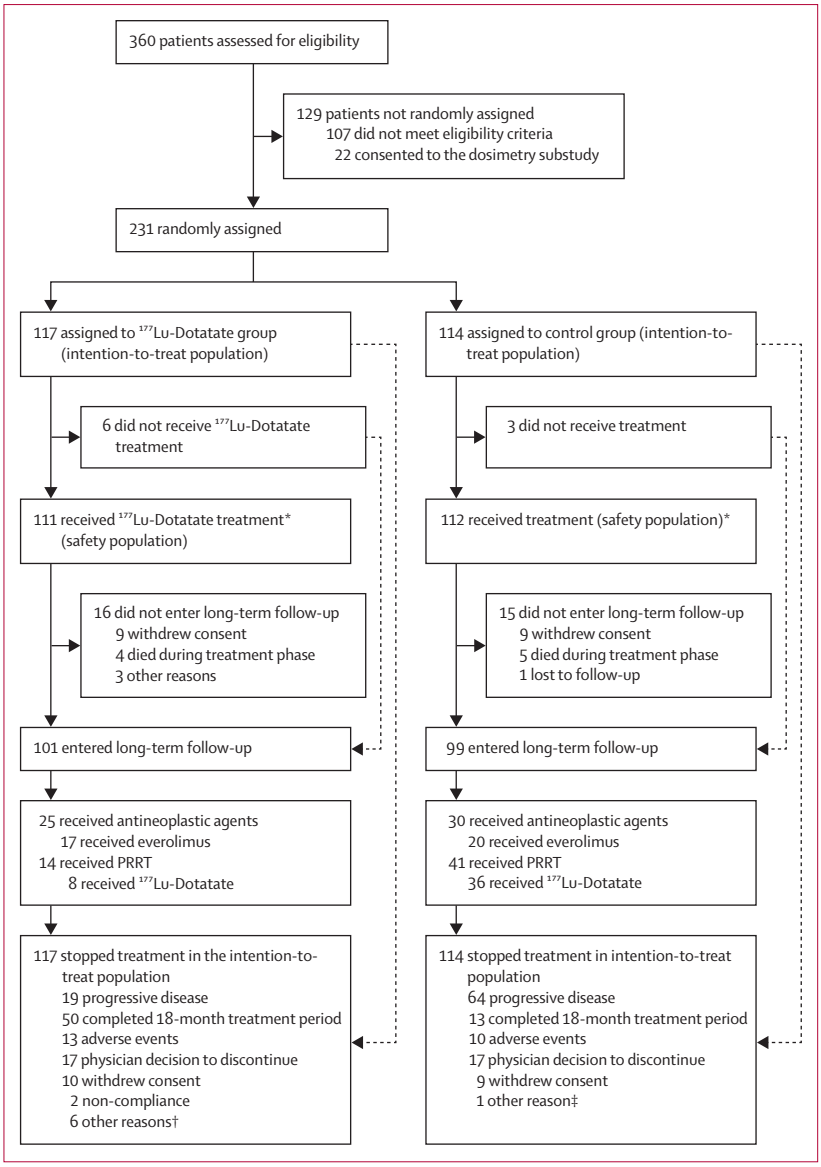

Figure 1: **Trial profile**
PRRT=peptide receptor radionuclide therapy. *One patient was randomly assigned to 177Lu-Dotatate but only received long-acting octreotide 60 mg before and after randomisation and therefore was included in the control group safety population. †Other reasons included: wrong central assessment of week 48 scan, wrong central assessment of week 12 scan (two patients), patient received long-acting octreotide 60 mg before and after randomisation, clinical deterioration, and patient request. ‡Patient requested change in treatment.

or extensive); tumour grade at baseline (grade 1 [Ki67 ≤2%] or grade 2 [Ki67 3–20%]), and tumour markers at baseline of chromogranin A (≤2×upper limit of normal [ULN] or >2×ULN) and of 5-hydroxyindoleacetic acid (≤2×ULN or >2×ULN).

An analysis of restricted mean survival time (the area under the survival curve up to a specific timepoint) at years 2, 3, 4, and 5 was specified in an amended statistical analysis plan before final data cutoff as an additional analysis in the intention-to-treat population if the proportional-hazards assumption was not met. A sensitivity analysis using the rank-preserving structural failure time method was also specified in the statistical analysis plan amendment to evaluate the treatment effect accounting for subsequent treatment with any PRRT in the control group (ie, accounting for crossover). All safety endpoints were evaluated in patients who were randomly assigned to a group and received at least one dose of study medication (the safety population).

Statistical analyses were done using SAS, version 9.3 on a Microsoft Windows Server 2008 R2 or subsequent platform.

This trial is registered with ClinicalTrials.gov, number NCT01578239.

Role of the funding source

This trial was sponsored by Advanced Accelerator Applications, a Novartis company, and was designed by representatives of the sponsor in collaboration with Dik Kwekkeboom; EPK from the Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, Netherlands; and Larry Kvols from the Moffitt Cancer Center, Tampa, FL, USA. Data were analysed by the sponsor and provided to all authors for further interpretation.

Results

Between Sept 6, 2012, and Jan 14, 2016, 231 patients were enrolled and randomly assigned for treatment at 41 sites (27 in Europe and 14 in the USA). This total included two patients who were randomly assigned after the primary progression-free survival analysis data cutoff (July 24, 2015).[23] 22 screened patients consented to separate enrolment in the dosimetry substudy and were not randomly assigned to the phase 3 trial. Eight patients did not receive study medication, so the safety population comprised 223 patients (figure 1). One patient was randomly assigned to 177Lu-Dotatate but received long-acting octreotide 60 mg and therefore was included in the control group safety population. As previously reported, demographic and baseline disease characteristics were generally well balanced between the study groups (appendix p 6). Median time since NET diagnosis was shorter in the 177Lu-Dotatate group than in the control group (3·8 years *vs* 4·8 years; appendix p 6). Although all patients were enrolled with disease progression while taking a fixed dose of long-acting octreotide, 90 (39%) of 231 patients had received additional previous treatment, including targeted therapy (ie, protein kinase inhibitors in 35 [15%] patients [19 (16%) of 117 in the 177Lu-Dotatate group and 16 (14%) of 114 in the control group]), systemic chemotherapy in 25 (11%) patients (ten [9%] in the 177Lu-Dotatate group and 15 [13%] in the control group), and antiangiogenics in 11 (5%) patients (seven [6%] in the 177Lu-Dotatate group and four [4%] in the control group). Most patients (216 [94%] of 231) had received octreotide 30 mg as the most recent constant dose of long-acting octreotide (109 in the 177Lu-Dotatate group and 107 in the

control group). Roughly a quarter of patients (60 [26%]) had been receiving a constant dose of octreotide for less than 6 months (31 [27%] in the ^{177}Lu-Dotatate group and 29 [25%] in the control group).

In total, 200 (87%) of 231 patients entered long-term follow-up, including 101 (86%) of 117 patients in the ^{177}Lu-Dotatate group and 99 (87%) of 114 patients in the control group. The most common primary reason for not entering long-term follow-up in both study groups was consent withdrawal (figure 1). The most common reason for entering long-term follow-up was completion of the 18-month treatment period (50 [43%] of 117 patients) in the ^{177}Lu-Dotatate group, and disease progression (64 [56%] of 114 patients) in the control group (figure 1).

During long-term follow-up, 14 (12%) of 117 patients in the ^{177}Lu-Dotatate group received further treatment with PRRT (figure 1, appendix p 7). Among these 14 patients, eight were treated further with additional cycles of ^{177}Lu-Dotatate (the other six patients received ^{177}Lu-Dotatoc or ^{90}Y-Dotatoc). In the control group, 41 (36%) of 114 patients had documented crossover to PRRT. Around a quarter of patients in the control group (26 [23%] of 114 patients) crossed over within 24 months of randomisation. 36 (32%) of 114 patients specifically received ^{177}Lu-Dotatate (the other five patients received ^{177}Lu-Dotanoc, ^{90}Y-Dotanoc, ^{90}Y-Dotatoc, or ^{90}Y-Dotatate). During long-term follow-up, 55 (24%) of 231 patients in both groups were documented as receiving other antineoplastic agents, including everolimus in 17 (15%) of 117 patients in the ^{177}Lu-Dotatate group and 20 (18%) of 114 patients in the control group (figure 1, appendix p 7).

Among the patients in the ^{177}Lu-Dotatate group who received their assigned treatment, 84 (76%) of 111 patients received the planned maximum of four administrations and nine (8%) of 111 patients received three administrations (appendix p 8). Five of these nine patients received fewer than four administrations because of death during treatment and four patients because of disease progression. Accounting for toxicity-related dose modification and small variations in the administered doses, 88 (79%) of 111 patients were exposed to more than 22·2 GBq (600 mCi) of ^{177}Lu-Dotatate (appendix p 8). Among the 36 patients in the control group who received subsequent ^{177}Lu-Dotatate treatment during long-term follow-up, 16 (44%) patients received four administrations (appendix p 9).

The prespecified final analysis of overall survival was done 5 years after the last patient was randomised because this occurred before the alternative cutoff of 158 deaths (data cutoff date, Jan 18, 2021). Median study follow-up was 76·3 months (range 0·4–95·0) in the ^{177}Lu-Dotatate group and 76·5 months (0·1–92·3) in the control group. At the time of the final analysis, 142 patients had died: 73 (62%) of 117 patients in the ^{177}Lu-Dotatate group and 69 (61%) of 114 patients in the control group. Death due to disease progression was the leading cause of death in

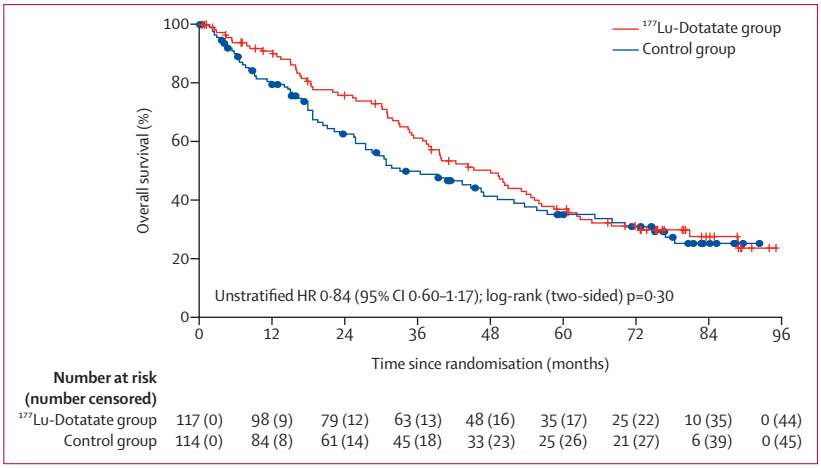

***Figure 2*: Overall survival**
Kaplan-Meier analysis of overall survival in the intention-to-treat population. Crosses and circles represent patients who are censored. HR=hazard ratio.

each group (57 [49%] of 117 patients in the ^{177}Lu-Dotatate group and 55 [48%] of 114 patients in the control group; appendix pp 4, 5). At final analysis, 20 (17%) of 117 patients in the ^{177}Lu-Dotatate group and 26 (23%) of 114 patients in the control group were either lost to follow-up or withdrew consent, and 24 (21%) of 117 patients and 19 (17%) of 114 patients in each respective group were alive at last contact. In total, 18 (15%) of 117 patients in the ^{177}Lu-Dotatate group and 25 (22%) of 114 patients in the control group were censored more than 12 months before the data cutoff date.

Final overall survival in the intention-to-treat population did not differ significantly between the study groups (HR 0·84 [95% CI 0·60–1·17]; two-sided p=0·30; figure 2). Median overall survival was 48·0 months (95% CI 37·4–55·2) in the ^{177}Lu-Dotatate group and 36·3 months (25·9–51·7) in the control group (figure 2). The yearly overall survival rates up to 5 years in the ^{177}Lu-Dotatate group versus the control group were: 1 year, 91·0% (95% CI 84·0–95·1) versus 79·7% (70·8–86·1); 2 years, 76·0% (66·7–83·0) versus 62·7% (52·6–71·2); 3 years, 61·4% (51·4–69·9) versus 50·1% (40·0–59·4); 4 years, 49·5% (39·5–58·6) versus 41·8% (31·8–51·4); and 5 years, 37·1% (27·8–46·4) versus 35·4% (25·7–45·2). The comparison of overall survival results between the treatment groups was generally consistent across stratification factors and the prespecified subgroups (figure 3).

An analysis of restricted mean survival time, which does not require the proportional hazards assumption to be met, was done to further evaluate the treatment effect. Restricted mean survival time was numerically longer in the ^{177}Lu-Dotatate group than in the control group at all timepoints after randomisation (table).

In a sensitivity analysis using the rank-preserving structural failure time method, which adjusted survival of those patients in the control group who crossed over to

	Number of events/ number of patients (%)		Median overall survival, months (95% CI)		Unstratified HR (95% CI)
	^{177}Lu-Dotatate group (n=117)	Control group (n=114)	^{177}Lu-Dotatate group (n=117)	Control group (n=114)	
Time on constant-dose octreotide					
≤6 months	17/31 (55%)	17/29 (59%)	55·9 (37·4–NE)	30·7 (16·2–78·3)	0·62 (0·32–1·23)
>6 months	56/86 (65%)	52/85 (61%)	42·2 (34·4–53·8)	40·9 (25·4–53·5)	0·93 (0·63–1·35)
OctreoScan highest tumour uptake grade					
Grade 2	8/11 (73%)	8/13 (62%)	36·8 (12·7–55·2)	70·0 (14·6–NE)	1·59 (0·59–4·26)
Grade 3	20/35 (57%)	21/34 (62%)	60·6 (25·8–88·8)	30·5 (17·5–65·2)	0·66 (0·35–1·21)
Grade 4	45/71 (63%)	40/67 (60%)	42·2 (34·9–54·7)	30·9 (25·7–51·7)	0·83 (0·54–1·27)
Age, years					
<65	34/65 (55%)	29/57 (51%)	53·1 (37·7–80·8)	40·9 (25·9–NE)	0·86 (0·53–1·42)
≥65	39/55 (71%)	40/57 (70%)	42·2 (30·0–50·8)	30·7 (18·9–46·8)	0·87 (0·56–1·36)
<75	62/104 (60%)	58/98 (59%)	50·0 (38·2–58·4)	39·4 (25·7–55·6)	0·83 (0·58–1·18)
≥75	11/13 (85%)	11/16 (69%)	33·1 (13·4–56·4)	36·3 (14·6–46·5)	1·07 (0·46–2·48)
Sex					
Female	31/54 (57%)	37/60 (62%)	48·0 (32·8–88·8)	31·7 (23·1–53·5)	0·70 (0·44–1·14)
Male	42/63 (67%)	32/54 (59%)	45·2 (34·9–55·2)	44·8 (20·9–57·3)	1·00 (0·63–1·59)
Body-mass index, kg/m²					
≤21	10/14 (71%)	18/21 (86%)	28·1 (2·8–80·8)	18·5 (6·6–33·1)	0·66 (0·30–1·48)
22–27	34/55 (62%)	31/47 (66%)	50·3 (34·6–60·6)	31·7 (20·9–51·7)	0·69 (0·42–1·13)
>27	20/35 (57%)	17/39 (44%)	55·9 (37·7–64·7)	70·0 (36·3–NE)	1·28 (0·67–2·46)
Region					
EU	28/50 (56%)	22/44 (50%)	55·2 (39·5–64·7)	46·5 (25·7–NE)	0·88 (0·50–1·55)
USA	45/67 (67%)	47/70 (67%)	39·6 (31·8–53·8)	30·9 (20·9–49·1)	0·84 (0·56–1·27)
Ethnicity or race					
Caucasian or white	60/93 (65%)	58/96 (60%)	42·2 (34·4–55·2)	33·1 (25·7–49·1)	0·91 (0·63–1·30)
Other	13/24 (54%)	11/18 (61%)	54·7 (39·5–NE)	46·5 (7·7–78·3)	0·64 (0·29–1·43)
Mean OctreoScan grade at baseline					
Grade 2	12/20 (60%)	17/27 (63%)	44·3 (17·6–55·2)	39·4 (16·2–75·0)	0·97 (0·46–2·03)
Grade 3	38/56 (68%)	35/56 (63%)	49·2 (34·4–60·6)	30·7 (22·2–51·7)	0·80 (0·50–1·27)
Grade 4	23/41 (56%)	17/31 (55%)	50·0 (32·8–NE)	40·9 (15·1–NE)	0·84 (0·45–1·58)
Baseline tumour burden (OctreoScan)					
Limited	64/100 (64%)	58/99 (59%)	44·3 (34·9–53·8)	39·4 (25·7–53·5)	0·94 (0·66–1·35)
Moderate	6/13 (46%)	10/13 (77%)	56·4 (22·0–NE)	27·4 (7·7–55·6)	0·28 (0·10–0·80)
Extensive	3/4 (75%)	1/2 (50%)	45·2 (5·4–88·8)	NE (2·5–NE)	0·81 (0·07–9·16)
Previous treatments					
Chemotherapy	4/10 (40%)	6/15 (40%)	54·7 (4·3–NE)	25·9 (4·2–NE)	0·59 (0·16–2·17)
Radiotherapy	4/4 (100%)	3/6 (50%)	30·6 (13·4–45·2)	7·7 (2·5–NE)	1·34 (0·29–6·21)
Surgery	55/94 (59%)	58/95 (61%)	50·3 (38·2–60·6)	31·7 (25·7–55·6)	0·77 (0·53–1·12)
Karnofsky performance status score					
≤80	26/32 (81%)	28/33 (85%)	38·2 (18·4–53·1)	11·9 (6·6–18·5)	0·45 (0·26–0·78)
90	30/51 (59%)	25/49 (51%)	50·0 (35·3–64·7)	65·2 (36·3–78·3)	1·04 (0·61–1·77)
100	16/33 (49%)	16/31 (52%)	58·4 (36·8–NE)	46·8 (30·5–NE)	0·89 (0·45–1·79)
Baseline chromogranin A					
≤2×ULN	2/18 (11%)	5/19 (26%)	NE (NE–NE)	NE (46·8–NE)	0·36 (0·07–1·85)
>2×ULN	47/61 (77%)	46/66 (70%)	37·4 (30·9–48·0)	33·1 (20·9–51·7)	1·08 (0·72–1·63)
Baseline 5-HIAA					
≤2×ULN	15/34 (44%)	13/28 (46%)	80·8 (39·6–NE)	75·0 (30·5–NE)	0·88 (0·42–1·85)
>2×ULN	42/55 (76%)	40/61 (66%)	38·2 (31·0–50·0)	27·4 (18·9–40·9)	0·86 (0·55–1·33)
Baseline Ki67					
≤2%	41/77 (53%)	44/81 (54%)	54·7 (39·5–80·8)	43·3 (29·7–68·1)	0·80 (0·52–1·38)
3–20%	32/40 (80%)	25/33 (76%)	37·4 (25·8–49·2)	19·5 (9·0–51·7)	0·81 (0·48–1·37)
All patients	**73/117 (62%)**	**69/114 (61%)**	**48·0 (37·4–55·2)**	**36·3 (25·9–51·7)**	**0·84 (0·60–1·17)**

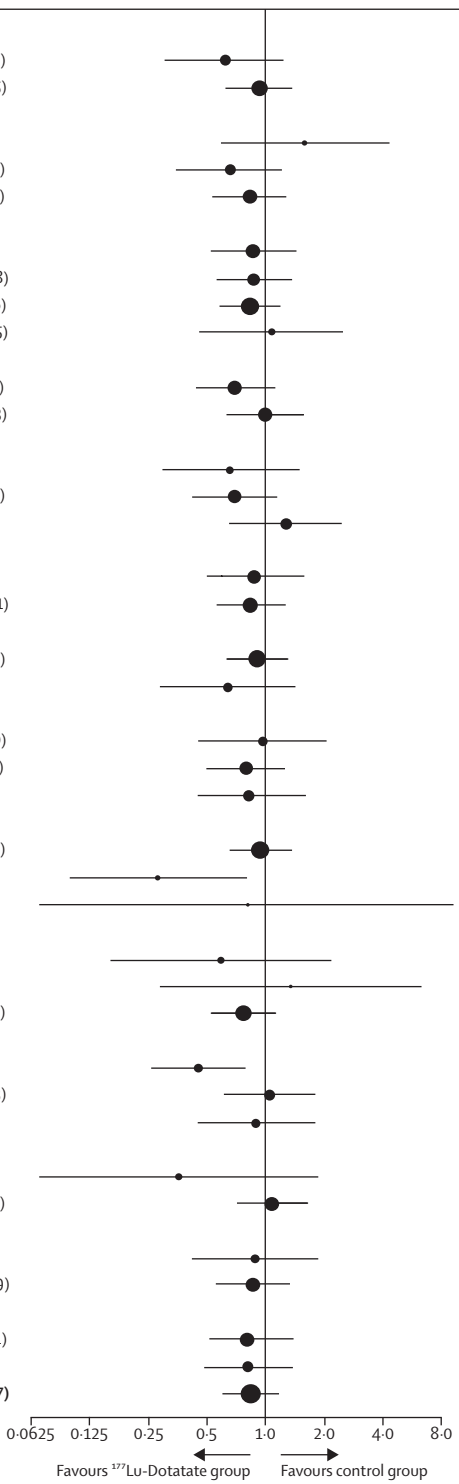

Figure 3: **Overall survival in key subgroups within the intention-to-treat population**
Point estimate circle diameter represents relative proportion of patients within subgroup. 5-HIAA=5-hydroxyindoleacetic acid. HR=hazard ratio. NE=not estimable. ULN=upper limit of normal.

PRRT (36%), the adjusted median overall survival was 30·9 months in the control group (figure 4).

During the whole study, seven (6%) of 111 patients in the ^{177}Lu-Dotatate group had a grade 3 or worse treatment-related serious adverse event; serious adverse events were not collected in the control group during long-term follow-up. The incidence of treatment-related serious adverse events was low during long-term follow-up (in three [3%] of 111 patients). One patient died from myelodysplastic syndrome (grade 5), one patient had grade 3 respiratory tract infection and grade 3 refractory cytopenia with multilineage dysplasia, which led to study discontinuation; one patient had grade 2 breast cancer. Notably, no new treatment-related serious adverse events were reported after the safety analysis cutoff (June 30, 2016). Two (2%) of 111 ^{177}Lu-Dotatate-treated patients developed myelodysplastic syndrome. One of these patients developed refractory cytopenia with unilineage dysplasia, confirmed as myelodysplastic syndrome (moderately hypercellular marrow with trilineage haematopoiesis and myeloid and megakaryocytic dysplasia), which occurred about 14 months after receiving the first of four doses of ^{177}Lu-Dotatate. This patient had a previous medical history of thrombocytosis and breast cancer, treated 18 years previously with an alkylating agent (cyclophosphamide). The patient was treated with azacitidine 60 mg (indicated for myelodysplastic syndrome) and died 33 months after randomisation because of myelodysplastic syndrome (the only reported ^{177}Lu-Dotatate treatment-related death). The other patient developed refractory cytopenia with multilineage dysplasia (morphological and phenotypical features consistent with plasma cell dyscrasia and erythroid and megakaryocytic dysplasia), occurring about 8 months after receiving the first of three doses of ^{177}Lu-Dotatate. The patient died roughly 18 months after randomisation due to NET disease progression. No cases of acute myeloid leukaemia were reported. One patient developed diffuse large B-cell lymphoma during long-term follow-up, deemed not related to ^{177}Lu-Dotatate treatment.

During the whole study, nephrotoxicity of grade 3 or worse, regardless of causality, was reported in six (5%) of 111 patients in the ^{177}Lu-Dotatate group and four (4%) of 112 patients in the control group (appendix p 10). Only one (1%) of 111 patients in the ^{177}Lu-Dotatate group had grade 3 increased serum creatinine. No additional patients in the ^{177}Lu-Dotatate group had any grade 3 or worse nephrotoxicity during long-term follow-up. One patient had grade 3 increased serum creatinine 2 years after resolution of an initial grade 1 event during treatment.

To clinically evaluate long-term renal function, creatinine clearance over time was analysed in both study groups. The estimated mean baseline creatinine clearance was 82·2 mL/min (SD 26·5) in the ^{177}Lu-Dotatate group and 86·9 mL/min (42·2) in the control group. Mean change from baseline in creatinine clearance over time was similar for both groups (figure 5).

	^{177}Lu-Dotatate group (n=117)	Control group (n=114)	Difference (95% CI)
2 years after randomisation			
Deaths	26 (22%)	39 (34%)	..
RMST, months	21·2 (20·2 to 22·3)	19·3 (18·0 to 20·7)	1·9 (0·1 to 3·6)
3 years after randomisation			
Deaths	41 (35%)	51 (45%)	..
RMST, months	29·7 (27·7 to 31·6)	26·0 (23·7 to 28·3)	3·7 (0·7 to 6·7)
4 years after randomisation			
Deaths	53 (45%)	58 (51%)	..
RMST, months	36·2 (33·4 to 39·0)	31·5 (28·3 to 34·8)	4·6 (0·3 to 8·9)
5 years after randomisation			
Deaths	65 (56%)	63 (55%)	..
RMST, months	41·2 (37·6 to 44·9)	36·1 (31·9 to 40·4)	5·1 (−0·5 to 10·7)

Data are n (%) or months (95% CI). RMST represents the area under the survival curve up to a specific timepoint. RMST=restricted mean survival time.

Table: **RMST analysis in the intention-to-treat population at specific timepoints since randomisation**

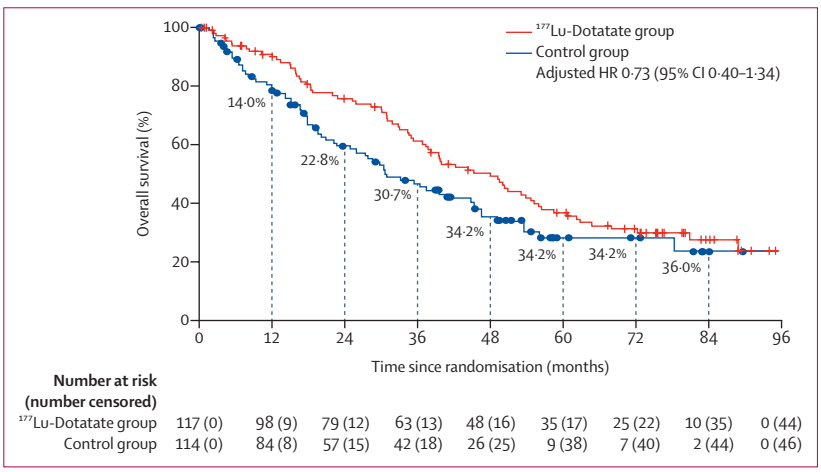

Figure 4: **Rank-preserving structured failure time analysis of overall survival accounting for crossover to any PRRT in the control group during long-term follow-up**

Percentages at each timepoint are cumulative proportions of patients crossing over from the control group to PRRT. HR=hazard ratio. PRRT=peptide receptor radionuclide therapy.

At 5 years (60 months) follow-up, mean change in creatinine clearance from baseline was −21·6 mL/min (SD 11·7) in the ^{177}Lu-Dotatate group (n=11 evaluable patients) and −24·7 mL/min (SD 22·14) in the control group (n=17 evaluable patients).

Discussion

To our knowledge, NETTER-1 is the first randomised, controlled, phase 3 study to report the comparative efficacy and safety of PRRT in patients with NETs. Previous analysis of the NETTER-1 trial has shown that ^{177}Lu-Dotatate significantly reduced the risk of disease progression or death and improved health-related quality of life compared with high-dose long-acting octreotide in patients with advanced, progressive, well differentiated

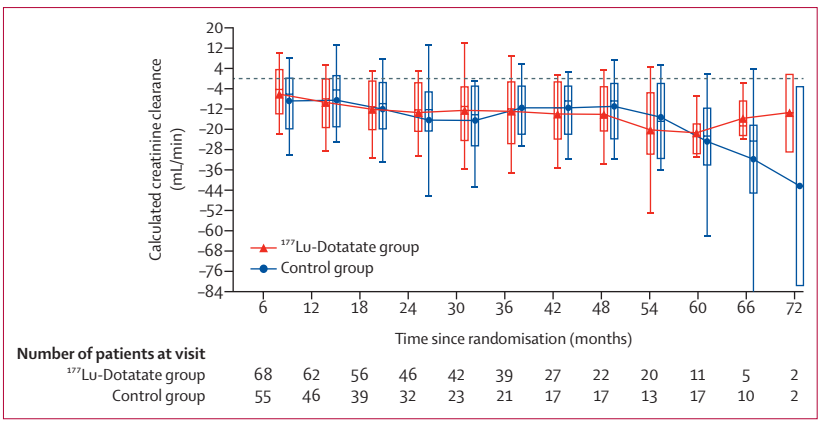

Figure 5: **Creatinine clearance mean change from baseline over time**
Baseline values are 82·2 mL/min (SD 26·5) in the ^{177}Lu-Dotatate group and 86·9 mL/min (42·2) in the control group. Plot shows boxes (IQR) with median as a horizontal line. Circles and triangles in the boxes represent mean values in each group. Whiskers (vertical lines) extend to the 10th–90th percentiles. Values outside this range are not displayed.

midgut NETs.[23,24] In this study, our prespecified final overall survival analysis, with a median duration of follow-up of more than 6·3 years in each group, showed that overall survival did not differ significantly between the study groups (HR 0·84 [95% CI 0·60–1·17]; two-sided p=0·30). Long-term survival analysis in this indolent tumour type is challenging because of the extended survival, potential for crossover to investigational treatment, and the use of other subsequent therapeutic options. For example, phase 3 trials of somatostatin analogues in similar patient populations have not shown a benefit with these agents in terms of overall survival, despite highly significant improvements in progression-free survival.[7,8,26] In NETTER-1, median overall survival was 48·0 months in the ^{177}Lu-Dotatate group and 36·3 months in the control group. Despite final overall survival not reaching statistical significance, the 11·7-month difference in median overall survival with ^{177}Lu-Dotatate might be considered clinically relevant. Additionally, at the time of this final analysis, no new safety signals had emerged, reaffirming the previously reported safety profile of ^{177}Lu-Dotatate.

A limitation of this analysis is that during long-term follow-up, 36% of patients in the control group received PRRT as subsequent treatment (primarily ^{177}Lu-Dotatate). Most of these patients received PRRT early during long-term follow-up (23% by 24 months after randomisation). The overall HR was adjusted to account for this crossover to PRRT, using the rank-preserving structural failure time approach. The method assumed a constant treatment effect regardless of when PRRT was received and adjusted the survival of patients who crossed over. The adjusted HR of 0·73 suggests that crossover to PRRT contributed to the overall survival results in the control group. However, other confounding factors clearly existed, which is another limitation of this analysis, including other subsequent anticancer treatments (24% patients received further antineoplastic agents); extended survival in a large subpopulation of patients regardless of their randomly assigned treatment (more than 35% of patients in each group survived for 5 years); and missing data (20% of patients were censored because of consent withdrawal or loss to follow-up).

The Cox regression analysis of treatment effect based on overall time-to-event comparison between the two groups requires the proportional-hazards assumption to be met. However, the proportional-hazards assumption for the Cox analysis of overall survival was not fulfilled in this trial. Therefore, we did a restricted mean survival time analysis, which does not require hazards to be proportional and can complement conventional statistical approaches. Restricted mean survival time was longer in the ^{177}Lu-Dotatate group than in the control group at all prespecified yearly time points, suggesting that, on average, patients survived longer with ^{177}Lu-Dotatate than with high-dose long-acting octreotide over the entirety of a 5-year period.

Overall survival was consistent across most prespecified subgroups, including regardless of age, sex, tumour grade (grade 1 or grade 2), and previous treatments. Interpretation of subgroup trends based on hazard ratios is restricted by the presence of non-proportional hazards. However, the finding of greater overall survival benefit with ^{177}Lu-Dotatate versus control treatment in patients with a low baseline Karnofsky performance status score of 60–80 (HR 0·45 [95% CI 0·26–0·78]) is supported by observed restricted mean survival time extension at the 2-year timepoint, which suggests a survival benefit with ^{177}Lu-Dotatate treatment in patients at high risk with a shorter life expectancy, in particular those with a low Karnofsky score. Notably, the median overall survival in the control group of this subgroup was less than 1 year. The overall survival result in this subgroup also corroborates the effect of subsequent treatments on final overall survival because it is likely that patients with shorter life expectancy in the control group were unable to subsequently benefit from crossover treatment or other therapies after progression on high-dose octreotide.

The survival outcomes in this controlled trial support previous findings in large prospective and retrospective institutional studies of ^{177}Lu-Dotatate treatment in patients with NETs.[19,21,22] The median overall survival of 48 months in the ^{177}Lu-Dotatate group in this phase 3 study establishes a new benchmark for survival in advanced, progressive, grade 1 or grade 2 midgut NETs. This finding is consistent with the median overall survival of 50 months in 94 patients with progressive midgut NETs who received a minimum cumulative dose of ^{177}Lu-Dotatate of 22·2 GBq (600 mCi) in a single-arm, phase 2 trial at the Erasmus Medical Center.[19] Almost 80% of patients in the ^{177}Lu-Dotatate group in NETTER-1 were exposed to ^{177}Lu-Dotatate 22·2 GBq or more. There are no data from prospective

head-to-head trials comparing PRRT with other treatments in patients with advanced GEP-NETs with disease progression on somatostatin analogue treatment. The ongoing phase 3 COMPETE trial (target enrolment of 300 patients) is evaluating the efficacy and safety of ^{177}Lu-Dotatoc compared with everolimus in patients with advanced, well differentiated, somatostatin receptor-positive, progressive GEP-NETs.[27] With a current paucity of direct comparison data, it is notable that the addition of everolimus to long-acting octreotide 30 mg for the treatment of patients with advanced, progressive, well differentiated, functional NETs was associated with a median overall survival of 29·2 months (95% CI 23·8–35·9) in the phase 3 RADIANT-2 study.[15] This finding did not represent an overall survival benefit versus long-acting octreotide alone (HR adjusted for baseline covariates 1·08 [95% CI 0·84–1·38]). The capecitabine and temozolomide regimen seems to be active in more aggressive NETs, including well differentiated grade 3 NETs,[28] but benefit in grade 1 and grade 2 midgut NETs is yet to be determined. The ongoing NETTER-2 study (NCT03972488) will evaluate the efficacy and safety of ^{177}Lu-Dotatate compared with high-dose long-acting octreotide as a first-line treatment for well differentiated, grade 2 and grade 3 (Ki67 10–55%) advanced GEP-NETs.

The long follow-up period in the present study allowed thorough evaluation of the long-term safety profile of ^{177}Lu-Dotatate, including serious adverse events considered to be related to ^{177}Lu-Dotatate treatment that emerged after completion of therapy, as well as the long-term risk of secondary haematological malignancies and nephrotoxicity. Two types of secondary malignancies have been reported in long-term studies of ^{177}Lu-Dotatate: myelodysplastic syndrome and acute myeloid leukaemia. Two (2%) of 111 patients in the ^{177}Lu-Dotatate group in this study developed myelodysplastic syndrome, with no new cases reported during long-term follow-up. This result is consistent with incidences of less than 3% in previous studies of ^{177}Lu-Dotatate.[19,29,30] No cases of acute myeloid leukaemia were reported in NETTER-1. Nephrotoxicity has been an important safety consideration with PRRT, although more toxicity has been associated with the [^{90}Y] than the [^{177}Lu] radionuclide.[29] The rate of severe nephrotoxicity in ^{177}Lu-Dotatate-treated patients was low (5%) and similar to that recorded in the control group (4%). Similar changes in creatinine clearance over time for both study groups suggest there was no long-term detrimental effect of ^{177}Lu-Dotatate on kidney function in the patients in this study. These results indicate that there was no apparent long-term nephrotoxicity with ^{177}Lu-Dotatate treatment.

The NETTER-1 study used baseline OctreoScans for assessment of somatostatin receptor expression, which were the standard functional imaging modality at the time of study enrolment. In current clinical practice, somatostatin receptor PET scans, such as ^{64}Cu-Dotatate or ^{68}Ga-Dotatate PET, are routinely used for patient selection, sometimes in combination with fluorodeoxyglucose PET. Although it is difficult to directly extrapolate OctreoScan eligibility criteria to PET criteria, it is likely that improved selection of patients for ^{177}Lu-Dotatate treatment, and exclusion of patients with highly aggressive, fluorodeoxyglucose-avid tumours, will result in improved outcomes.

In conclusion, final analysis of the NETTER-1 study showed that treatment with ^{177}Lu-Dotatate did not lead to a significant improvement in overall survival versus high-dose long-acting octreotide; however, an arguably clinically relevant differernce in median overall survival of 11·7 months with ^{177}Lu-Dotatate was recorded, and was accompanied by a favourable long-term safety profile, in patients with advanced, progressive, well-differentiated, grade 1 and grade 2 midgut NETs. Along with the significantly reduced risk of disease progression or death and the associated quality-of-life benefits,[24] these data further support the use of ^{177}Lu-Dotatate in this patient population with disease progression on somatostatin analogues.

Contributors

JRS, EPK, Dik Kwekkeboom (deceased), Larry Kvols, and MFM designed the study with representatives of the study sponsor. All authors contributed to data collection, analysis, and interpretation, as well as writing of the Article, critical review, and approval of the final version. All authors had access to the data. JRS, AD, and SM verified the underlying raw data in the study. JRS had the final responsibility to submit for publication.

Declaration of interests

JRS has provided consulting or advisory services for Novartis, speakers bureau services for Ipsen, Lexicon and has received research funding from Novartis. MEC has provided consulting or advisory services for Advanced Accelerator Applications (a Novartis company), Ipsen, Sirtex Medical, Novartis, speakers bureau services for Advanced Accelerator Applications, Ipsen, Sirtex Medical, and Pfizer, and has received research funding from Advanced Accelerator Applications. PLK has provided consulting or advisory services for Ipsen, Lexicon, and Advanced Accelerator Applications, and has received research funding from Advanced Accelerator Applications, Lexicon, Ipsen, Xencor, and Brahms. PLK owns stock in Guardant Health. PBR has provided consulting or advisory services for Ipsen, Advanced Accelerator Applications, ITM, and Novartis; has received research funding from Advanced Accelerator Applications, Ipsen, and ITM; and has received travel or accommodation expenses from Ipsen. LB has provided consulting services (non-remunerated) for Advanced Accelerator Applications, ITM, Clovis Oncology, Curium, and Iba; has provided speaker's bureau services (non-remunerated) for Advanced Accelerator Applications, ITM, and Iba; and has received research funding from Advanced Accelerator Applications. AH has provided consulting or advisory services for Novartis, Ipsen, Perthera, Celgene and AbbVie, and has received travel or accommodation expenses from Halozyme and research funding from Ipsen. EM has provided consulting or advisory services for Ipsen and Advanced Accelerator Applications, has received honoraria from Advanced Accelerator Applications and Curium, and has received research funding from Advanced Accelerator Applications and Nordic Nanovector. EMW has provided consulting or advisory services for Advanced Accelerator Applications, Lexicon, and Progenics. JCY has provided consulting or advisory services for Advanced Accelerator Applications, Ipsen, Chiasma, Crinetics, and Hutchinson Medi Pharma, and has received research funding from Advanced Accelerator Applications and Novartis. MEP has provided consulting or advisory services for Advanced Accelerator Applications and Ipsen, and has received honoraria from Ipsen, Hutchison

MediPharma, Advanced Accelerator Applications, Riemser, and Boehringer Ingelheim, and travel or accommodation expenses from Ipsen and Hutchison. EG has provided consulting or advisory services for MSD, Pfizer, Ipsen, Roche, and Bristol Myers Squibb; has received honoraria from Pfizer, Bristol Myers Squibb, Ipsen, Roche, Eisai, Eusa Pharma, MSD, Genzyme, Advanced Accelerator Applications, Novartis, Pierre Fabre, Lexicon, Celgene, Janssen-Cilag, Astellas Pharma, AstraZeneca, and Lilly; has received travel or accommodation expenses from Bristol Myers Squibb, Roche/Genentech, Pfizer, Janssen-Cilag, and Ipsen; and has received research funding from Roche, Pfizer, AstraZeneca, Ipsen, Molecular Templates, Lexicon, and Astellas Pharma. EVC has provided consulting or advisory services for Bayer, Lilly, Roche, Servier, Bristol Myers Squibb, Celgene, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca, Halozyme, Array BioPharma, Biocartis, GlaxoSmithKline, Daiichi Sankyo, Pierre Fabre, Sirtex Medical, Taiho Pharmaceutical, and Incyte, and has received research funding from Amgen, Bayer, Boehringer Ingelheim, Lilly, Novartis, Roche, Celgene, Ipsen, Merck, Merck KGaA, Servier, and Bristol Myers Squibb. GG is an employee of Novartis, owns stock in Novartis, and receives travel or accommodation expenses from Novartis. AB is an employee of Novartis, owns stock in Novartis, and receives travel or accommodation expenses from Novartis. MFM is an employee of Novartis and owns stock in Novartis. AD is an employee of Novartis and owns stock in Novartis. SM is an employee of Novartis and owns stock in Novartis. EPK has an employment interest in Cyclotron Rotterdam BV; has stock or other ownership interest in AstraZeneca, GlaxoSmithKline, Merck and Roche; has patent or intellectual property interest in Advanced Accelerator Applications; and receives travel or accommodation expenses from Advanced Accelerator Applications. ES and HD declare no competing interests.

Data sharing

Advanced Accelerator Applications and Novartis are committed to sharing, with qualified external researchers, patient-level data and supporting clinical documents from eligible studies. Requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymised. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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