[^{177}Lu]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

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Summary

Background There are currently no standard first-line treatment options for patients with higher grade 2–3, well-differentiated, advanced, gastroenteropancreatic neuroendocrine tumours. We aimed to investigate the efficacy and safety of first-line [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate) treatment.

Methods NETTER-2 was an open-label, randomised, parallel-group, superiority, phase 3 trial. We enrolled patients (aged ≥15 years) with newly diagnosed higher grade 2 (Ki67 ≥10% and ≤20%) and grade 3 (Ki67 >20% and ≤55%), somatostatin receptor-positive (in all target lesions), advanced gastroenteropancreatic neuroendocrine tumours from 45 centres across nine countries in North America, Europe, and Asia. We used interactive response technologies to randomly assign (2:1) patients to receive four cycles (cycle interval was 8 weeks ± 1 week) of intravenous ^{177}Lu-Dotatate plus intramuscular octreotide 30 mg long-acting repeatable (LAR) then octreotide 30 mg LAR every 4 weeks (^{177}Lu-Dotatate group) or high-dose octreotide 60 mg LAR every 4 weeks (control group), stratified by neuroendocrine tumour grade (2 *vs* 3) and origin (pancreas *vs* other). Tumour assessments were done at baseline, week 16, and week 24, and then every 12 weeks until disease progression or death. The primary endpoint was progression-free survival by blinded, independent, central radiology assessment. We did the primary analysis at 101 progression-free survival events as the final progression-free survival analysis. NETTER-2 is registered with ClinicalTrials.gov, NCT03972488, and is active and not recruiting.

Findings Between Jan 22, 2020, and Oct 13, 2022, we screened 261 patients, 35 (13%) of whom were excluded. We randomly assigned 226 (87%) patients (121 [54%] male and 105 [46%] female) to the ^{177}Lu-Dotatate group (n=151 [67%]) and control group (n=75 [33%]). Median progression-free survival was 8·5 months (95% CI 7·7–13·8) in the control group and 22·8 months (19·4–not estimated) in the ^{177}Lu-Dotatate group (stratified hazard ratio 0·276 [0·182–0·418]; p<0·0001). During the treatment period, adverse events (of any grade) occurred in 136 (93%) of 147 treated patients in the ^{177}Lu-Dotatate group and 69 (95%) of 73 treated patients in the control group. There were no study drug-related deaths during the treatment period.

Interpretation First-line ^{177}Lu-Dotatate plus octreotide LAR significantly extended median progression-free survival (by 14 months) in patients with grade 2 or 3 advanced gastroenteropancreatic neuroendocrine tumours. ^{177}Lu-Dotatate should be considered a new standard of care in first-line therapy in this population.

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Introduction

Radioligand therapy delivers cytotoxic radiation directly to the tumour and, unlike most other systemic therapies, adverse events are generally minimal.[1] [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate) is a ^{177}Lu-labelled somatostatin analogue that binds to somatostatin receptors,[2] which are highly expressed in neuroendocrine tumours (NETs) and have been used diagnostically and therapeutically for decades.[3] The groundbreaking phase 3 NETTER-1 trial established the efficacy and safety of ^{177}Lu-Dotatate plus octreotide 30 mg long-acting repeatable (LAR) for the treatment of patients with advanced somatostatin receptor-positive grade 1 or grade 2 midgut NETs who had progressed on somatostatin analogues.[4,5]

In the first-line advanced or metastatic setting, international guidelines recommend somatostatin

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See **Online** for appendix 1

Research in context

Evidence before this study

In 2017, grade 3 well-differentiated neuroendocrine tumours were formally classified as a separate entity from the poorly differentiated neuroendocrine carcinomas by WHO. Following the phase 3 PROMID and CLARINET studies, somatostatin analogues are the recognised first-line treatment for advanced grade 1–2 (Ki67 <10%) gastroenteropancreatic neuroendocrine tumours and the role of platinum-based chemotherapy is generally accepted for neuroendocrine carcinomas, but there are limited robust data to support first-line treatment options for patients with advanced higher grade 2 (Ki67 ≥10% and ≤20%) and grade 3 (Ki67 >20% and ≤55%) well-differentiated gastroenteropancreatic neuroendocrine tumours. To our knowledge, at the time of the NETTER-2 study design, no randomised phase 3 studies had been done in this population of patients with newly diagnosed, advanced or metastatic disease. This represents an unmet need and has been identified as an evidence gap in treatment guidelines. The pivotal, phase 3, NETTER-1 study showed that treatment with the radioligand therapy [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate) plus best supportive care (octreotide 30 mg long-acting repeatable [LAR]) provided a significant increase in progression-free survival to patients with progressive midgut grade 1–2 neuroendocrine tumours compared with patients treated with high-dose octreotide 60 mg LAR and led to regulatory approvals for ^{177}Lu-Dotatate.

Added value of this study

NETTER-2 is the first randomised trial in any metastatic solid tumour to investigate a radioligand therapy in a first-line metastatic setting. Among patients with higher grade 2 (Ki67 ≥10% and ≤20%) and grade 3 (Ki67 >20% and ≤55%) well-differentiated gastroenteropancreatic neuroendocrine tumours, ^{177}Lu-Dotatate plus octreotide 30 mg LAR showed a significant progression-free survival benefit versus high-dose octreotide 60 mg LAR (median progression-free survival 22·8 months *vs* 8·5 months), with a high and durable response (overall response rate 43%; median duration of response 23·3 months) without deterioration in quality of life. Our results will help to fill the evidence gap for high-grade gastroenteropancreatic neuroendocrine tumours that has been highlighted in treatment guidelines and aid treatment decision making for these patients who currently have a worse prognosis compared with patients with lower-grade disease.

Implications of all the available evidence

NETTER-2 provides the first robust, randomised, phase 3 data for patients with newly diagnosed high-grade gastroenteropancreatic neuroendocrine tumours. These results have clinical practice-changing implications and support the use of ^{177}Lu-Dotatate earlier within the disease course of higher grade 2–3 gastroenteropancreatic neuroendocrine tumours.

analogues for almost all patients with low-grade and intermediate-grade (grade 1–2) gastroenteropancreatic NETs.[6-8] Two phase 3, randomised, placebo-controlled trials (CLARINET[9] and PROMID[10]) have established somatostatin analogues as standard of care in grade 1–2 NETs. The CLARINET study included patients with lower grade 2 NETs (Ki67 <10%), and excluded higher grade 2 NETs (Ki67 ≥10%).[9] Historically, high-grade neuroendocrine neoplasms were universally described as poorly differentiated and often thought to be similar to small-cell malignancies. In 2017, grade 3 well-differentiated NETs were formally recognised by WHO as a distinct entity from the poorly differentiated neuroendocrine carcinomas. There is a paucity of high-quality evidence with respect to gastroenteropancreatic-NET treatments, especially for higher grade 2 (Ki67 ≥10% and ≤20%) and grade 3 (Ki67 >20% and ≤55%) in the first-line setting.[11] In patients with Ki67 greater than 55%, the role of platinum-based therapy is generally accepted,[12,13] but no randomised phase 3 studies have yet investigated the most appropriate treatment strategy for these patients.[6,12] The lack of a defined first-line therapy represents an unmet need for these patients with metastatic disease. Retrospective analyses of treatment outcomes for patients with grade 3 well-differentiated gastroenteropancreatic NETs have reported on various therapeutic strategies, including chemotherapy, high-dose somatostatin analogues, targeted therapy, radioligand therapy, and local therapies, highlighting the need for robust, prospective, randomised data to inform optimal treatment selection.[14,15]

We present the primary results of the ongoing phase 3 NETTER-2 trial, which aimed to investigate whether ^{177}Lu-Dotatate plus octreotide 30 mg LAR, at the same dose and schedule as established in the NETTER-1 trial,[4] would prolong progression-free survival compared with high-dose octreotide 60 mg LAR, in patients with newly diagnosed, advanced higher grade 2–3, well-differentiated gastroenteropancreatic NETs.

Methods

Study design and participants

NETTER-2 was an international, multicentre, randomised, parallel-group, superiority, open-label study done at 45 centres in nine countries across North America, Europe, and Asia. Eligible patients were aged 15 years or older with metastasised or locally advanced, histologically proven, higher grade 2 (Ki67 ≥10% and ≤20%) and grade 3 (Ki67 >20% and ≤55%), well-differentiated gastroenteropancreatic NETs that were considered inoperable and had been diagnosed within 6 months before screening. Histological confirmation and Ki67 assessment were done locally by each study site. Cytology was not an acceptable method of gastroenteropancreatic-NET

diagnosis in this study. Patients were required to have a Karnofsky Performance Scale score of at least 60, bodyweight greater than 40 kg at screening, and somatostatin receptor expression on all target lesions, assessed by any somatostatin receptor imaging modality, within 3 months before randomisation. Somatostatin receptor uptake was scored according to a visual semi-quantitative scale.[16] Eligible patients were required to have an uptake score of 3 (greater than liver but lower than spleen) or 4 (greater than spleen). We excluded patients with creatinine clearance below 40 mL/min. Patients were also ineligible if they had received any previous peptide receptor radionuclide therapy, hepatic artery embolisation, or radiofrequency ablation for gastroenteropancreatic NETs. Previous systemic therapy for gastroenteropancreatic NETs was not allowed unless it was administered for less than 1 month and not within 12 weeks before randomisation. Patients who had received short-term (<6 months) somatostatin analogues with no evidence of progression were eligible for enrolment. Full eligibility criteria are listed in the protocol (appendix 2). Patients self-reported sex data (female or male). All patients provided written informed consent.

See Online for appendix 2

The trial protocol was approved by the institutional review board or independent ethics committee at each participating centre. The trial was done in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable regulations. The protocol, with amendments, is available in appendix 2. No changes occurred to the methods after the study commencement. NETTER-2 is registered with ClinicalTrials.gov, NCT03972488.

Randomisation and masking

We used interactive response technologies (web and voice; Calyx, Nottingham, UK) to randomly assign patients (2:1) to the ^{177}Lu-Dotatate group or control group

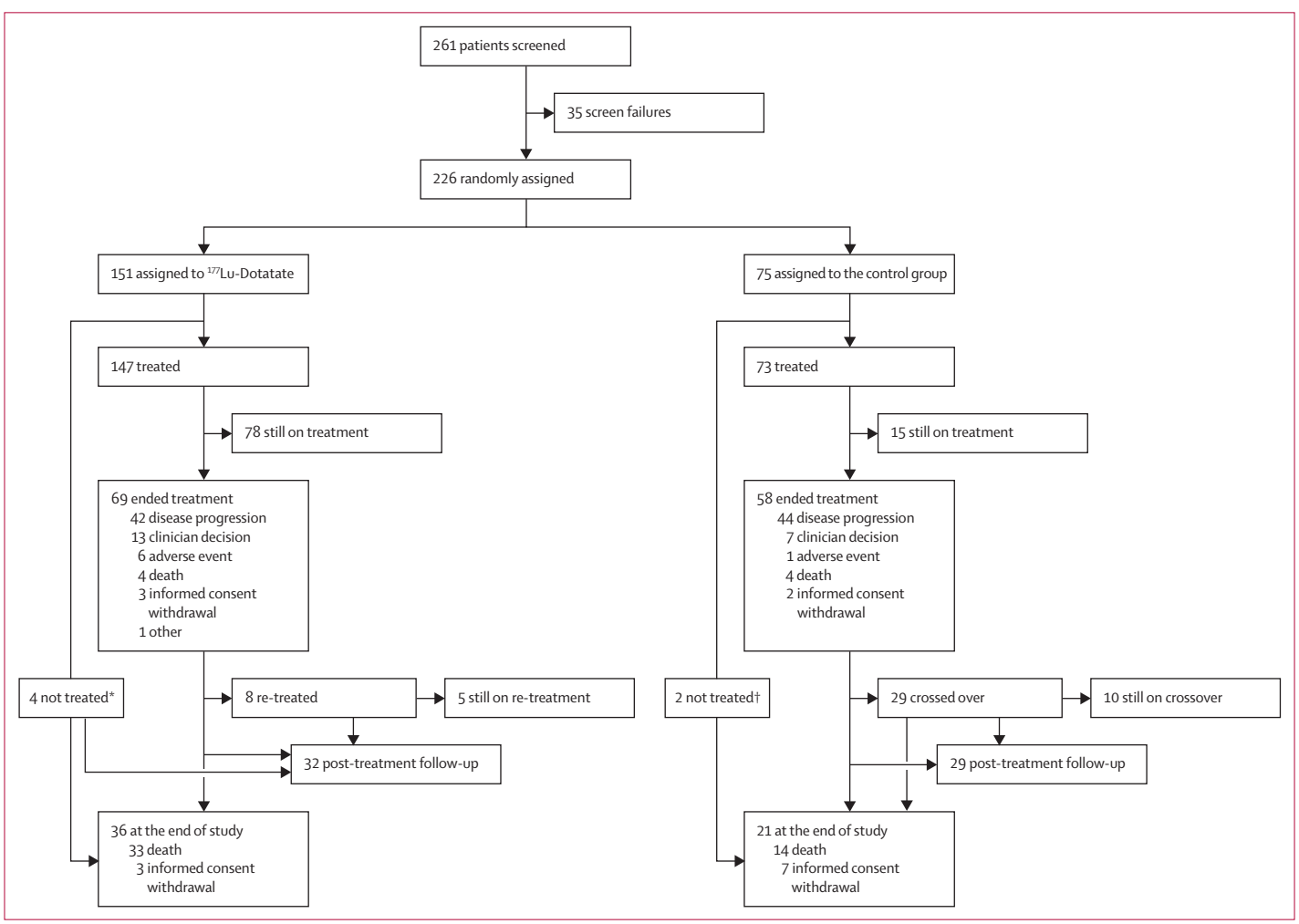

Figure 1: **Trial profile**
^{177}Lu-Dotatate=[^{177}Lu]Lu-DOTA-TATE. *Reasons for not being treated were surgery before first treatment (n=1), randomisation mistake (n=1), informed consent withdrawal (n=1), and adverse event (n=1). †Reasons for not being treated were surgery before first treatment (n=1) and informed consent withdrawal (n=1).

stratified by tumour grade (2 *vs* 3) and tumour origin (pancreas *vs* other). We chose a 2:1 randomisation design to increase patients' chances of receiving ^{177}Lu-Dotatate. To minimise a potentially high dropout rate in the control group, patients were offered to cross over to ^{177}Lu-Dotatate after centrally confirmed radiological progression. The randomisation list contained 240 pre-allocated records for each of the four strata in the study (960 records in total). The first patient in a specific stratum was assigned the first randomisation entry from the randomisation schedule pre-allocated to that stratum. Subsequent patients in the same stratum were assigned to the next available randomisation entry from the randomisation schedule pre-allocated to that stratum. We used a block size of six within each stratum. Forced randomisation was not allowed in this study. Tumour grade and origin are both important prognostic factors for gastroenteropancreatic NETs and thus were used as stratification factors.[17,18] The trial was open label, so masking of treatments was not applicable.

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=151)	High-dose octreotide 60 mg LAR (control group; n=75)	All patients (n=226)
Age, years	61 (51–72)	60 (51–69)	61 (51–70)
Sex			
Male	81 (54%)	40 (53%)	121 (54%)
Female	70 (46%)	35 (47%)	105 (46%)
Race			
White	115 (76%)	50 (67%)	165 (73%)
Asian	23 (15%)	11 (15%)	34 (15%)
American Indian or Alaska native	1 (<1%)	0	1 (<1%)
Black or African American	3 (2%)	2 (3%)	5 (2%)
Other	9 (6%)	12 (16%)	21 (9%)
Karnofsky Performance Scale score at baseline			
60	0	1 (1%)	1 (<1%)
70–80	28 (19%)	10 (13%)	38 (17%)
90–100	123 (81%)	64 (85%)	187 (83%)
Time since initial diagnosis, months	1·8 (1·2–3·7)	2·1 (1·4–3·9)	1·9 (1·3–3·7)
Primary tumour site			
Pancreas	82 (54%)	41 (55%)	123 (54%)
Small intestine	45 (30%)	21 (28%)	66 (29%)
Rectum	7 (5%)	4 (5%)	11 (5%)
Stomach	6 (4%)	4 (5%)	10 (4%)
Other	11 (7%)	5 (7%)	16 (7%)
Presence of metastases			
Yes	150 (99%)	74 (99%)	224 (99%)
No	1 (<1%)	1 (1%)	2 (<1%)
Site of metastases (>10% patients)			
Bone	37 (25%)	18 (24%)	55 (24%)
Liver	134 (89%)	69 (92%)	203 (90%)
Lymph nodes*	101 (67%)	34 (45%)	135 (60%)
Peritoneum	26 (17%)	9 (12%)	35 (15%)
Neuroendocrine tumour grade at diagnosis			
Grade 2 (Ki67 ≥10% and ≤20%)	99 (66%)	48 (64%)	147 (65%)
Grade 3 (Ki67 >20% and ≤55%)	52 (34%)	27 (36%)	79 (35%)
Ki67 index	17% (12–25)	16% (12–25)	16% (12–25)
Previous therapy with somatostatin analogues†	24 (16%)	18 (24%)	42 (19%)
Highest somatostatin receptor tumour uptake score‡			
Score 3	56 (37%)	25 (33%)	81 (36%)
Score 4	95 (63%)	50 (67%)	145 (64%)

Data are median (IQR) or n (%). LAR=long-acting repeatable. *Distant plus regional combined. †Most patients who received previous therapy with somatostatin analogues received only a single dose. No patients had disease progression before study enrolment. ‡Based on local assessment.

Table 1: **Baseline demographic and clinical characteristics (full analysis set)**

Procedures

Patients were randomly assigned to receive ^{177}Lu-Dotatate plus octreotide 30 mg LAR or high-dose octreotide 60 mg LAR (control group; appendix 1 p 3). In the ^{177}Lu-Dotatate group, four cycles of ^{177}Lu-Dotatate (7·4 GBq [200 mCi]) were administered intravenously over 30 min every 8 weeks (cumulative dose 29·6 GBq [800 mCi]). For renal protection, an intravenous infusion of 2·5% lysine-arginine amino acid solution was started 30 min before ^{177}Lu-Dotatate infusion and continued for 4 h.[19] Octreotide 30 mg LAR was administered intramuscularly after each ^{177}Lu-Dotatate infusion every 8 weeks until completion of four ^{177}Lu-Dotatate cycles, and then every 4 weeks. In the control group, octreotide 60 mg LAR was administered intramuscularly every 4 weeks. We assessed tumours in both groups at baseline, week 16, and week 24, and then every 12 weeks until centrally confirmed disease progression or death. Somatostatin receptor imaging was not required for follow-up imaging. European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30) were completed by patients every 12 weeks from initiation of treatment until end of treatment. We assessed safety throughout the trial, including adverse events and laboratory toxicities (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 5.0). Randomised treatment was allowed to continue until centrally confirmed disease progression or treatment discontinuation for another reason. Patients with disease progression were able to enrol for post-progression crossover (control group) or re-treatment (^{177}Lu-Dotatate group) upon meeting protocol criteria.

Outcomes

The primary endpoint was progression-free survival, defined as time from randomisation to first-line progression (as assessed by independent blinded central review according to the Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1[20]) or death from any cause. Key secondary endpoints were objective response rate, defined as the rate of best overall response of complete or partial response (as assessed by independent central review according to RECIST 1.1), and time to deterioration by 10 points from baseline in quality-of-life (QoL) scores for global health status, diarrhoea, fatigue,

and pain as measured by EORTC QLQ-C30. Other secondary endpoints were disease control rate, duration of response, safety, and overall survival. The assessment timing of patient outcomes corresponds to the schedule described in the protocol (appendix 2). The NETTER-2 study is ongoing for long-term patient follow-up and overall survival analysis.

Statistical analysis

The statistical analysis plan is available in appendix 3. We did the primary analysis at 101 progression-free survival events as the final progression-free survival analysis. We estimated that 99 progression-free survival events would be required to achieve 90% power using a one-sided log-rank test at the overall 2·5% level of significance, to detect a 50% reduction in hazard rate, corresponding to a doubling of median progression-free survival from an assumed 15 months for the control group to 30 months for the ^{177}Lu-Dotatate group. These assumptions were based on the results from NETTER-1 (progression-free survival was 28·4 months with ^{177}Lu-Dotatate).[19] We conservatively selected a hazard ratio (HR) of 0·5 and, therefore, a progression-free survival of 15 months for control was used for the sample size calculations. Assuming that enrolment would continue for approximately 22·2 months at a rate of ten patients per month and a 15% dropout rate by the time of primary progression-free survival analysis, we estimated that approximately 222 patients would need to be randomly assigned in a 2:1 ratio to the ^{177}Lu-Dotatate versus control groups.

To control for the overall type I error, we tested the primary and key secondary endpoints hierarchically at the time of the primary analysis. The order of the hypothesis testing was progression-free survival followed by objective response rate, time to deterioration in QoL by EORTC QLQ-C30 for global health scale, time to deterioration for diarrhoea, time to deterioration for fatigue, and time to deterioration for pain. An endpoint would be tested only if all endpoints tested before it showed statistical significance.

We used the full analysis set for efficacy analyses and summary for demographic and baseline characteristics, which comprised all randomly assigned patients, and patients were analysed according to the randomised treatment. All safety analyses were based on the safety set, which included all patients who received at least one administration of study treatment. We compared progression-free survival using a log-rank test stratified by randomisation stratification factors (tumour grade and origin). We calculated the rank statistic and its variance separately for each stratum, then calculated the final statistic as the sum of rank statistics from all four strata divided by the square root of the sum of variances from all four strata, and compared the result with the normal distribution to obtain the p value. We estimated the survival distribution of progression-free survival using the Kaplan–Meier method. We estimated HRs with 95% CIs using a stratified Cox model. We compared objective response rate between treatment groups, and the corresponding odds ratio along with 95% CIs was calculated using the stratified Cochran–Mantel–Haenszel method. We analysed time to deterioration in QoL using the same method as progression-free survival. Unless specified otherwise, we summarised categorical data as n (%) and continuous data as median (IQR).

See Online for appendix 3

All safety analyses were done in the safety set, which included all patients who received at least one administration of study treatment, and patients were analysed according to the study treatment received. We summarised adverse events by number and percentage of patients having at least one adverse event by preferred term using the Medical Dictionary for Regulatory Activities (version 26.0) and CTCAE (version 5.0). In the AE summary tables, patients with multiple CTCAE grades for the same preferred term were summarised under the maximum CTCAE grade recorded for the event.

Role of the funding source

The trial was designed and sponsored by Advanced Accelerator Applications, a Novartis Company. Data were analysed by the sponsor's statistical team and provided to all authors for interpretation.

Results

Between Jan 22, 2020, and Oct 13, 2022, we screened 261 patients, 35 (13%) of whom were excluded. We randomly assigned 226 (87%) patients (151 [67%] to the ^{177}Lu-Dotatate group and 75 [33%] to the control group), of whom 147 (97%) in the ^{177}Lu-Dotatate group and

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=147)	High-dose octreotide 60 mg LAR (control group; n=73)
Duration of exposure, weeks		
Any study treatment	71·1 (47·9–100·0)	40·3 (21·0–64·1)
^{177}Lu-Dotatate	32·0 (31·7–33·0)	NA
Octreotide LAR	71·0 (47·7–100·0)	40·3 (21·0–64·1)
Number of ^{177}Lu-Dotatate cycles		
1 cycle*	1 (<1%)	NA
2 cycles*	10 (7%)	NA
3 cycles*	7 (5%)	NA
4 cycles	129 (88%)	NA
Dose of ^{177}Lu-Dotatate		
Cumulative dose, GBq	29·2 (28·0–29·8)	NA
Dose per administration, GBq/cycle	7·3 (7·2–7·5)	NA

Data are median (IQR) or n (%). LAR=long-acting repeatable. NA=not applicable. *Reasons for not receiving all four cycles were disease progression (n=11), adverse events (n=4), death (n=2), and informed consent withdrawal (n=1).

Table 2: **Treatment exposure in the randomised treatment period**

73 (97%) in the control group received at least one dose of study treatment (figure 1). Of the 226 randomly assigned patients, 121 (54%) patients were male, 105 (46%) were female, and 165 (73%) were White (table 1). The primary tumour site was the pancreas in 123 (54%) patients and the small intestine in 66 (29%) patients; 147 (65%) patients had grade 2 NETs and 79 (35%) had grade 3 NETs. Two (1%) patients had locally advanced unresectable

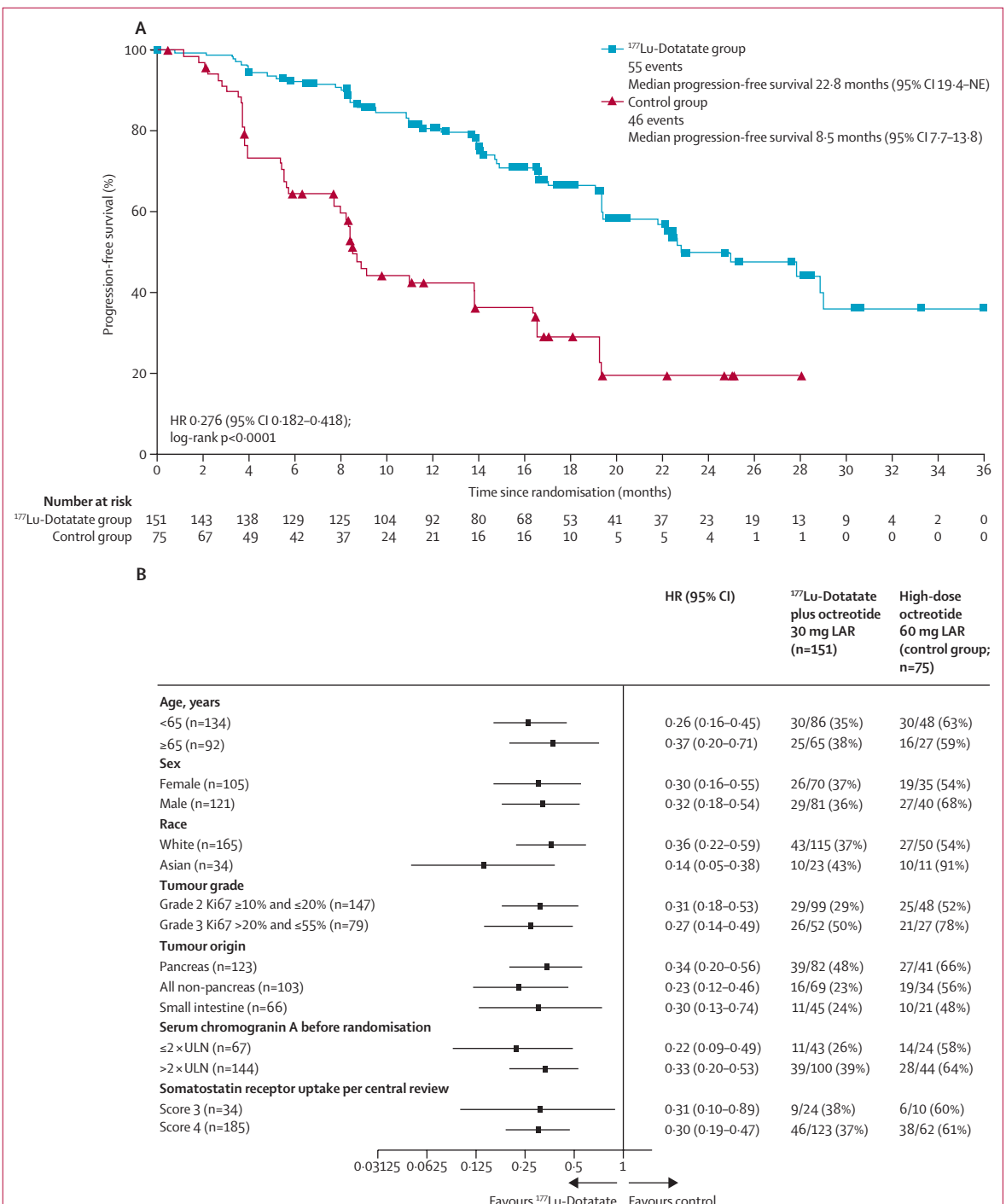

Figure 2: **Progression-free survival (full analysis set)**
(A) Kaplan–Meier curves for centrally assessed progression-free survival. (B) Subgroup analysis for progression-free survival based on central review and analysed by unstratified Cox model. HR=hazard ratio. LAR=long-acting repeatable. NE=not estimated. ULN=upper limit of normal as scored using the Common Terminology Criteria for Adverse Events.

disease; the remaining 224 (99%) patients had distant metastatic disease. Most patients had liver metastases (203 patients [90%]), followed by lymph node metastases in 135 patients (60%), bone metastases in 55 patients (24%), and peritoneal metastases in 35 patients (15%).

Tumour somatostatin receptor uptake score was 3 in 81 (36%) patients and 4 in 145 (64%) patients, as per local assessment (table 1). The median time since initial diagnosis was 1·9 months (IQR 1·3–3·7).

In total, 129 (88%) patients in the ^{177}Lu-Dotatate group received all four cycles of ^{177}Lu-Dotatate (table 2). The median dose per cycle was 7·3 GBq (IQR 7·2–7·5; 198 mCi), with a median cumulative dose of 29·2 GBq (28·0–29·8; 789 mCi; table 2). Patients in the ^{177}Lu-Dotatate group remained on study treatment (^{177}Lu-Dotatate plus octreotide 30 mg LAR) for a median of 71·1 weeks (47·9–100·0) compared with 40·3 (21·0–64·1) weeks for the control group (table 2). At the cutoff date of the primary analysis (July 20, 2023), 78 (52%) patients remained on study treatment in the ^{177}Lu-Dotatate group and 15 (20%) remained on octreotide 60 mg LAR in the control group. The median duration of patient follow-up from randomisation to data cutoff was 23·2 months (16·4–28·8).

The study met its primary objective of progression-free survival. At data cutoff, progression-free survival events had occurred in 55 (36%) patients in the ^{177}Lu-Dotatate group and 46 (61%) in the control group. The median progression-free survival, as per blinded central assessment according to RECIST 1.1, was 22·8 months (95% CI 19·4–not estimated [NE]) in the ^{177}Lu-Dotatate group versus 8·5 months (7·7–13·8) in the control group. We found a reduction in the risk of disease progression or death by around 72% in the ^{177}Lu-Dotatate group compared with the control group (HR for progression-free survival with ^{177}Lu-Dotatate *vs* control 0·276 [0·182–0·418]; p<0·0001; figure 2A). The progression-free survival benefit observed in the ^{177}Lu-Dotatate group was consistent across all prespecified subgroups (figure 2B). Progression-free survival results based on local tumour response assessment by investigators were in agreement with the centrally reviewed data (median progression-free survival 22·6 months [17·7–NE] in the ^{177}Lu-Dotatate group and 8·2 months [5·6–11·1] in the control group).

The objective response rate was significantly higher in the ^{177}Lu-Dotatate group (43·0% [95% CI 35·0–51·3]) than in the control group (9·3% [3·8–18·3])—ie, an improvement of 33·7% (23·4–44·0) and a stratified odds ratio of 7·81 (3·32–18·40; p<0·0001; table 3). Eight (5%) patients in the ^{177}Lu-Dotatate group had a complete response versus none in the control group (table 3). The median duration of response was 23·3 months (18·4–NE) based on 65 responders in the ^{177}Lu-Dotatate group and was NE (2·3–NE) with seven responders in the control group. The disease control rate as assessed by central review was higher in the ^{177}Lu-Dotatate group (90·7% [84·9–94·8]) compared with the control group (66·7% [54·8–77·1]).

Overall survival data were immature at the time of primary progression-free survival analysis. Median overall survival was not reached for either treatment group, and we found no difference in overall survival between treatment groups at the time of follow-up. By the cutoff date, 36 (48%) patients in the control group had progressed and crossed over to ^{177}Lu-Dotatate treatment (n=29 during the crossover phase) or received ^{177}Lu-Dotatate or ^{177}Lu-Dotatoc (n=7 during the follow-up phase), which might have confounded the overall survival results in addition to the data immaturity. Overall survival monitoring is ongoing in the long-term follow-up and will be analysed at the final analysis.

We found no significant difference between treatment groups for the key secondary endpoint of time to deterioration in QoL, as per EORTC QLQ-C30 scores (appendix 1 p 4).

Overall, 136 (93%) patients in the ^{177}Lu-Dotatate group and 69 (95%) in the control group experienced an adverse event in the randomised treatment period (ie, up to the last randomised study treatment date plus 30 days), with the most common (≥20% in either group) being nausea (40 [27%] *vs* 13 [18%]), diarrhoea (38 [26%] *vs* 25 [34%]), and abdominal pain (26 [18%] *vs* 20 [27%]; table 4; appendix 1 p 5). Adverse events of grade 3 or worse were observed in 52 (35%) patients in the ^{177}Lu-Dotatate group and 20 (27%) in the control group, with the most common (>3% in either group) being lymphocyte count decreased (eight [5%] *vs* 0), gamma-glutamyltransferase increased (seven [5%] *vs* two [3%]), small intestinal obstruction (5 [3%] *vs* 0), and abdominal pain (four [3%] *vs* three [4%]; table 4; appendix 1 p 5). Adverse events of special interest of CTCAE grade 3 or worse occurred in three

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=151)	High-dose octreotide 60 mg LAR (control group; n=75)
Best overall response		
Complete response	8 (5%)	0
Partial response	57 (38%)	7 (9%)
Stable disease	72 (48%)	42 (56%)
Non-complete response or non-progressive disease	0	1 (1%)
Progressive disease	8 (5%)	14 (19%)
Unknown*	6 (4%)	11 (15%)
Objective response rate	65 (43·0%; 95% CI 35·0–51·3)	7 (9·3%; 95% CI 3·8–18·3)
Stratified odds ratio (95% CI)	..	7·81 (3·32–18·40)
Stratified one-sided p value	..	<0·0001
Disease control rate	137 (90·7%; 95% CI 84·9–94·8)	50 (66·7%; 95% CI 54·8–77·1)

Data are n (%) unless otherwise indicated. LAR=long-acting repeatable. *In the ^{177}Lu-Dotatate group, two patients had no valid post-baseline assessment and four patients had new anticancer therapy before post-baseline assessment. In the control group, six patients had no valid post-baseline assessments, three patients had new anticancer therapy before post-baseline assessment, and two patients had a scan with stable disease early after randomisation and started new anticancer therapy.

Table 3: **Objective tumour response (full analysis set)**

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=147)		High-dose octreotide 60 mg LAR (control group; n=73)	
	All grades	Grade ≥3	All grades	Grade ≥3
Adverse events	136 (93%)	52 (35%)	69 (95%)	20 (27%)
Related to any treatment	101 (69%)	23 (16%)	43 (59%)	3 (4%)
Related to ^{177}Lu-Dotatate	96 (65%)	22 (15%)	NA	NA
Related to octreotide	55 (37%)	2 (1%)	43 (59%)	3 (4%)
Serious adverse events	30 (20%)	24 (16%)	15 (21%)	13 (18%)
Related to any treatment	8 (5%)	6 (4%)	1 (1%)	1 (1%)
Related to ^{177}Lu-Dotatate	8 (5%)	6 (4%)	NA	NA
Related to octreotide	0	0	1 (1%)	1 (1%)
Fatal serious adverse events	3 (2%)	3 (2%)	2 (3%)	2 (3%)
Related to any treatment	0	0	0	0
Adverse events leading to discontinuation				
^{177}Lu-Dotatate	3 (2%)	1 (<1%)	NA	NA
Octreotide	5 (3%)	3 (2%)	2 (3%)	2 (3%)

Data are n (%). Table includes time from randomisation up to the last randomised study treatment date plus 30 days. LAR=long-acting repeatable. NA=not applicable.

Table 4: **Safety summary during the randomised treatment period (safety set)**

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=147)		High-dose octreotide 60 mg LAR (control group; n=73)	
	All grades	Grade ≥3	All grades	Grade ≥3
Immediate haematotoxicities*	30 (20%)	20 (14%)	1 (1%)	1 (1%)
Anaemia	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
Thrombocytopenia†	17 (12%)	3 (2%)	0	0
Leukopenia‡	3 (2%)	3 (2%)	0	0
Neutropenia§	3 (2%)	3 (2%)	0	0
Nephrotoxicities¶	13 (9%)	3 (2%)	4 (5%)	1 (1%)
Cardiovascular and electrolyte disorder‖	11 (7%)	11 (7%)	10 (14%)	10 (14%)
Secondary haematological malignancies	1 (<1%)	1 (<1%)	0	0

Data are n (%). Table includes time from randomisation up to the last randomised study treatment date plus 30 days. LAR=long-acting repeatable. MedDRA=Medical Dictionary for Regulatory Activities. *The search included Standardised MedDRA Query for grade ≥3 events under the following categories: granulocytosis, haematopoietic cytopenias affecting more than one type of blood cell, haematopoietic erythropenia, and haematopoietic leukopenia and for grade ≥2 events under the category of haematopoietic thrombocytopenia. †Includes preferred terms of platelet count decreased and thrombocytopenia. ‡Includes preferred terms of white blood cell count decreased and leukopenia. §Includes preferred terms of neutrophil count decreased and neutropenia. ¶The search included Standardised MedDRA Query categories of acute renal failure, chronic kidney disease, and tubulointerstitial diseases of any grade and any duration. ‖Includes two grade 5 events. Both reported disease under study as primary reason for death (dyspnoea [n=1] in the ^{177}Lu-Dotatate group and tumour lysis syndrome [n=1] in the control group).

Table 5: **Adverse events of special interest during the randomised treatment period (safety set)**

(2%; leukopenia), one (<1%; anaemia), and three (2%; thrombocytopenia) patients in the ^{177}Lu-Dotatate group versus 0 (leukopenia), one (1%; anaemia), and 0 (thrombocytopenia) in the control group (table 5). One case of myelodysplastic syndrome was observed in the ^{177}Lu-Dotatate group by the time of data cutoff (at approximately 14 months from the first dose).

Six deaths occurred during the randomised treatment period (two in the ^{177}Lu-Dotatate group and four in the control group), all attributed to disease progression under study. Discontinuation rates due to adverse events were low for ^{177}Lu-Dotatate (three [2%]) and for octreotide LAR (five [3%] in the ^{177}Lu-Dotatate group and two [3%] for octreotide LAR in the control group; table 4). Few patients required dose reduction (three [2%] *vs* one [1%]) and the frequency of dose interruptions was similar in both groups (23 [16%] *vs* 11 [15%]).

Discussion

NETTER-2 is the first phase 3 study to report results for radioligand therapy administered first line to patients in any cancer population. It is also the first randomised study of any therapy for patients with grade 3 well-differentiated gastroenteropancreatic NETs. In this study, patients with newly diagnosed higher grade 2–3, somatostatin receptor-positive, metastatic, gastroenteropancreatic NETs were shown to significantly benefit from radioligand therapy. The study met its primary objective, with ^{177}Lu-Dotatate plus octreotide 30 mg LAR reducing the risk of disease progression or death by around 72% compared with high-dose octreotide 60 mg LAR. Consistent benefit was observed across all subgroups, including grade 2–3 NETs, and pancreatic as well as non-pancreatic primary origin. In this patient population with grade 2–3 NETs, the objective response rate was 43·0% (one of the highest reported in the literature) with ^{177}Lu-Dotatate plus octreotide 30 mg LAR compared with 9·3% for octreotide 60 mg LAR. No new safety concerns were observed. Myelodysplastic syndrome is a recognised risk of radioligand therapy with ^{177}Lu-Dotatate.[19,21] In this study, one case of myelodysplastic syndrome was observed in the ^{177}Lu-Dotatate group. However, the follow-up time was limited at the time of primary analysis; long-term safety follow-up and data collection on secondary haematological malignancies are ongoing.

Before this study, little evidence existed to support treatment decisions in this patient population, and outcomes were generally poor. Although somatostatin analogues have been used as first-line treatment for advanced grade 1–2 gastroenteropancreatic NETs (Ki67 <10%) following the phase 3 PROMID[10] and CLARINET studies,[9,22] such robust data do not exist for higher grade 2 tumours (Ki67 ≥10%) or grade 3 well-differentiated NETs.[23] Small retrospective studies[14,15,24,25] have reported median progression-free survival durations of 4–8 months in patients with grade 3 NETs treated with first-line somatostatin analogues. Other potential options for higher grade 2–3 NETs include alkylating chemotherapy regimens, such as 5-fluorouracil plus streptozotocin and capecitabine plus temozolomide.[8,15] Multicentre, retrospective analyses of temozolomide regimens for grade 3 NETs have shown response rates between 27·3% and 51·0%.[26,27] All of these retrospective analyses were done after the design and initiation of NETTER-2, and complement the evidence presented here to aid in treatment decisions for patients with higher grade 2 or 3 gastroenteropancreatic NETs. Although there is no defined standard of care and robust data for this

patient population, randomised data in patients with progressive pancreatic lower-grade NETs (Ki67 cutoff ≤20%) showed a response rate of 40% with capecitabine plus temozolomide (phase 2 ECOG-ACRIN E2211 study).[28] The 60 mg dose of octreotide in the control group was selected following the NETTER-1 study design, which was developed following guidance from the US Food and Drug Administration. The high dose of octreotide did not have notable side-effects, suggesting that this regimen is well tolerated.[4] According to guidelines,[6] somatostatin analogues may be used in high-grade gastroenteropancreatic NETs, according to individual patient characteristics. Considering that all recruited patients in NETTER-2 had a high level of somatostatin receptor expression, this choice is rational.

In our study, time to deterioration in QoL was not significantly different between the treatment groups. This finding is perhaps not surprising given that patients in both groups received a backbone of somatostatin analogue therapy. Lack of QoL detriment with treatment by a radioligand therapy compared with a generally well-tolerated somatostatin analogue is encouraging.

Until NETTER-2, no randomised studies had investigated first-line radioligand therapy for any solid tumour. The data from NETTER-2 add to evidence that early molecular imaging could help optimise treatment selection and sequencing for patients with somatostatin receptor-positive primary tumours of gastroenteropancreatic origin.

Our study has some limitations. Because of differences in administration methods between treatments, and the need for radiation-exposure precautions, this study was designed to be open label. Bias was mitigated through the blinded central review of imaging data. Although this study was open to patients aged 15 years or older, no accrual of adolescent patients aged 15–17 years occurred; therefore, these data relate to adults only. Relative effectiveness to other available therapies, sequencing, cost-effectiveness, and access issues should all be considered in future research.

Radioligand therapy is a promising new frontier in the treatment of cancers, which has previously been limited to surgery and systemic therapy. Our results will help to fill the evidence gap for high-grade gastroenteropancreatic NETs that has been highlighted in treatment guidelines.[6,12] The significant improvement in progression-free survival and response with ^{177}Lu-Dotatate plus octreotide LAR compared with somatostatin analogues alone was observed across tumour site and grade and will have clinical practice-changing implications in support of first-line radioligand therapy as standard of care for advanced higher grade 2 and grade 3, well-differentiated, gastroenteropancreatic NETs.

Contributors

SS, PLK, IF, YZ, and WWdH were involved in the study design. SS, DH, SM, KH, BC, JC, AG-B, D-YO, IF, PA, WWdH, and DF vouch for the accuracy and integrity of the data. All authors were involved in data collection, had access to and contributed to the analysis or interpretation of the data, and were involved in the writing, reviewing, and amending of the manuscript with the assistance of a medical writer funded by the sponsor. All authors approved the final draft and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Novartis is committed to sharing (with qualified external researchers) access to patient-level data and supporting clinical documents from eligible studies. This trial data availability is according to the criteria and process described on https://www.clinicalstudydatarequest.com. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

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