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NETTER-1 study Abstracts

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First author : Professor Lisa Bodei

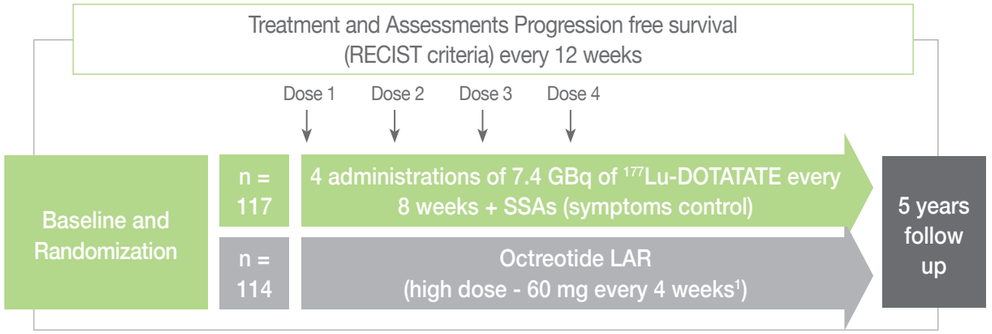
AAA-Lu177-GL-0048

NETTER-1 PROTOCOL OUTLINE

The NETTER-1 trial is an international phase III study which enrolled patients with progressive, somatostatin receptor positive midgut neuroendocrine tumors. Patients were randomized to receive treatment with ^{177}Lu-DOTATATE (^{177}Lu) versus high-dose (60 mg) Octreotide LAR (Oct). EORTC questionnaires QLQC-30 and G.I.NET-21 were assessed during the trial to determine the impact of treatment on HRQoL.

NETTER -1 Study Objectives and Design

Aim	Evaluate the efficacy and safety of ^{177}Lu-DOTATATE + SSAs (symptoms control) compared to Octreotide LAR 60 mg in patients with inoperable, somatostatin receptors positive, midgut NET, progressive under Octreotide LAR 30 mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group



1. As requested by the EMA and the FDA for this Phase III trial.

Secondary objectives

- Compare the Objective Response Rate between study arms
- Compare the Overall Survival between study arms
- Compare the Time to Progression between study arms
- Evaluate the safety and tolerability of ^{177}Lu-DOTATATE
- Evaluate the health related quality of life (QoL) as measured by the EORTC questionnaires QLQC-30 and G.I.NET-21

Main Inclusion Criteria

- Patients ≥18 years of age
- Metastatic or locally advanced, inoperable, histologically proven, well-differentiated midgut NET
- Ki67 index ≤ 20% (Grade 1-2)
- Progressive disease (RECIST Criteria 1.1 centrally confirmed) on uninterrupted fixed dose of Octreotide LAR (20-30 mg every 3-4 weeks)
- Somatostatin receptors positive disease
- Karnofsky Performance Score ≥ 60
- Including functioning and non-functioning

1 IMPACT OF BASELINE LIVER TUMOR BURDEN ON TREATMENT OUTCOMES WITH LUTATHERA® IN THE NETTER-1 STUDY

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Background

The liver is the most common site of metastasis in patients with midgut neuroendocrine tumors (NET). We assessed the impact of hepatic tumor burden on treatment efficacy in the NETTER-1 study population.

Methods

Patients on the phase III NETTER-1 study were randomized to receive either ^{177}Lu-DOTATATE (Lu) (n=117) or high-dose octreotide (Oct) (n=114). Progression-free survival (PFS) was assessed based on liver tumor burden at baseline. The tumor burden was defined as tumor volume/total liver volume by CT, and categorized as low (<25%), moderate (25-50%), and high (>50%), as assessed by central radiology review. Rates of grade 3 or 4 hepatotoxicity were also assessed based on initial tumor burden.

Results

In total, 141 patients (61%) had low tumor burden (71 Lu, 70 Oct), 50 (22%) had moderate burden (19 Lu, 31 Oct), and 40 (17%) patients had high burden (27 Lu, 13 Oct).
Hazard ratios (HR) of PFS were similar across the low, moderate and high liver burden subgroups. Median PFS (months) was 28.35 vs. 11.04 in low (HR= 0.218, 95% confidence interval [CI] 0.120 to 0.394); Not Reached (NR) vs. 8.67 in moderate (HR=0.202, 95% CI 0.077 to 0.525); 19.38 vs. 5.52 in high liver burden (HR= 0.193, 95% CI 0.079 to 0.474), respectively.
In the ^{177}Lu-DOTATATE arm, grade 3/4 (CTCAE v 4.03) AST and ALT toxicities occurred in the low burden group in 2 and 3 patients, respectively and in the high burden group in 3 and 1 patients, respectively. Grade 3/4 hyperbilirubiniemia occurred in one patient from the low burden group and one from the moderate burden group. All hepatic toxicities were resolved without sequelae. In the high-dose octreotide arm, there were no treatment-related grade 3/4 AST, ALT or bilirubin toxicities.

Conclusion

Treatment with ^{177}Lu-DOTATATE resulted in significant PFS improvement regardless of baseline liver tumor burden in patients with well-differentiated, metastatic midgut NET.

Aim

This study assesses whether baseline liver tumor burden alters the response to ^{177}Lu-DOTATATE administration..

Method

- Kaplan-Meier PFS stratified by liver tumor burden
- Kaplan-Meier PFS stratified by baseline ALP (≤ULN vs >ULN)
- Kaplan-Meier PFS stratified by lesion (>30 mm diameter) at baseline (0 vs ≥1)

Tumor burden in NETTER-1 patients

Tumor burden	Patient number (%)	^{177}Lu-DOTATATE	Oct LAR 60 mg
Low (<25%)	141 (61%)	71	70
Moderate (25-50%)	50 (22%)	19	31
High (>50%)	40 (17%)	27	13

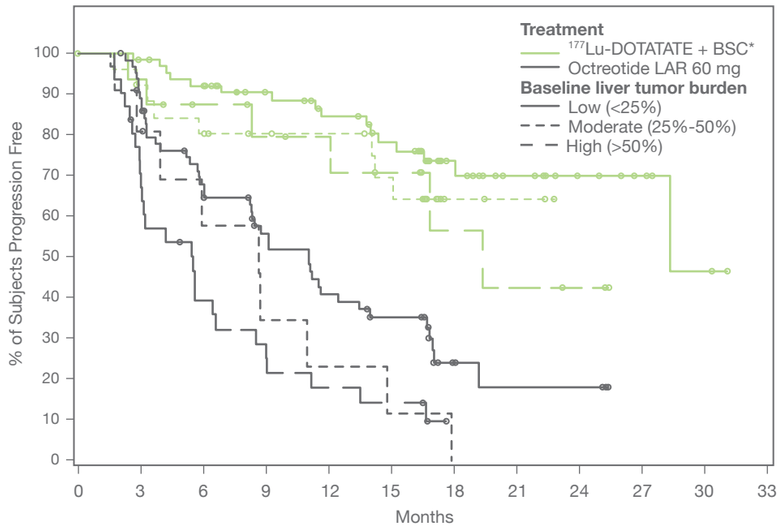
PFS improvement regardless of baseline liver tumor burden

^{177}Lu-DOTATATE infusion was associated with an ~80% reduction in the estimated risk of tumor progression or death vs octreotide LAR 60 mg, regardless of baseline liver tumor burden.

Baseline Liver Tumor Burden (%)	Treatment	N	Events, n (%)	Median PFS (months)	Hazard ratio (95% CI)	P-value
<25	^{177}Lu-DOTATATE	71	16 (22.5)	28.35	0.218 (0.120-0.394)	**<0.0001**
	Octreotide LAR 60 mg	70	43 (16.4)	11.04		
25-50	^{177}Lu-DOTATATE	27	8 (29.6)	NR	0.202 (0.077-0.525)	**0.001**
	Octreotide LAR 60 mg	13	9 (69.2)	8.67		
>50	^{177}Lu-DOTATATE	19	6 (31.6)	19.38	0.193 (0.079-0.474)	**0.0003**
	Octreotide LAR 60 mg	31	26 (83.9)	5.52		

1. Impact of baseline liver tumor burden on treatment outcomes with LUTATHERA® in the NETTER-1 study

PFS by baseline liver tumor burden



Liver function abnormalities were not associated with baseline liver tumor burden and resolved without sequela

Grade 3/4 liver function abnormalities by baseline liver tumor burden

Baseline Liver Tumor Burden (%)	Treatment	N	↑ AST	↑ ALT	↑ ALP	↓ Albumin	↑ Bilirubin
<25	^{177}Lu-DOTATATE	69	2	3	4	0	1
	Octreotide LAR 60 mg	69	0	0	3	0	0
25-50	^{177}Lu-DOTATATE	25	0	0	0	0	1
	Octreotide LAR 60 mg	12	0	0	0	0	0
>50	^{177}Lu-DOTATATE	18	3	1	2	0	0
	Octreotide LAR 60 mg	30	0	0	7	0	0

NCI CTCAE v4.03 grade 3/4 increases in AST, ALT, and ALP are defined as >5 × ULN; grade 3/4 increase in bilirubin is defined as >3 × ULN; grade 3/4 decrease in albumin is defined as <2 g/dL.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

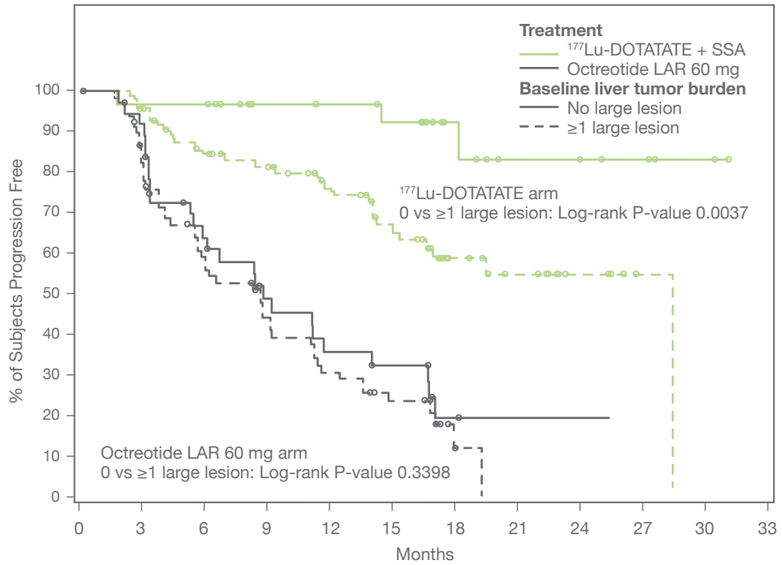
1. Impact of baseline liver tumor burden on treatment outcomes with LUTATHERA® in the NETTER-1 study

PFS improvement regardless of presence of a large lesion at baseline

Number of Large lesions at Baseline (>30mm)	Treatment	N	Events, n (%)	Median PFS (months)	Hazard ratio (95% CI)	P-value
N= 0	^{177}Lu-DOTATATE	37	3 (8.1)	NR	0.069 (0.021, 0.233)	<0.0001
	Octreotide LAR 60 mg	39	26 (66.7)	8.74		
N ≥1	^{177}Lu-DOTATATE	80	27 (33.8)	28.35	0.266 (0.165, 0.429)	<0.0001
	Octreotide LAR 60 mg	75	52 (69.3)	8.44		

Medians are generated using Kaplan-Meier estimates, HRs, their corresponding 95% CIs, and p-values are estimated using a Cox regression model with randomized treatment, 1 or more large lesions at baseline (yes or no) and (1 or more large lesions at baseline*randomized treatment) as covariates.

PFS by baseline liver tumor burden



Conclusions

The extent of baseline liver tumor burden does not affect ^{177}Lu-DOTATATE efficacy, as demonstrated by significant longer PFS compared to octreotide LAR 60 mg.

2 RENAL PROTECTION DURING LUTATHERA® TREATMENT USING LYSINE AND ARGININE SOLUTIONS

Lisa Bodei[1], Marta Cremonesi[2], Mahila Ferrari[2], Eric Krenning[4], Maribel Lopera Sierra[5], Jack L. Erion[5], Paola Santoro[5], Daniela Chicco[6], Maurizio F. Mariani[7].

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Background

Radioactive somatostatin analogs used in Peptide Receptor Radionuclide Therapy (PRRT) are partially reabsorbed by proximal tubular cells in the kidney after glomerular filtration. Co-administration of positively charged amino acids (AA) is effective in decreasing the kidney absorbed radiation dose and risk for toxicity, increasing the dose limiting threshold.
Published clinical experience and ENETs guidelines recommend lysine and arginine (25g each) as optimal AA composition for renal protection infused over 4 h.
Kidney dosimetry findings and short to long-term monitoring of renal function following treatment with ^{177}Lu-DOTATATE in the Phase III NETTER-1 study and Phase I/II Erasmus MC study (published data) were evaluated in relation to different AA solutions for renal protection: 2.5% lysine–arginine in 1L vs commercially available solutions containing similar amounts of these two AA in 2L.

Methods

Patients treated with ^{177}Lu-DOTATATE (7.4 GBq x4 treatments at 8-week intervals) were co-administered AA solutions from 30 minutes before ^{177}Lu-DOTATATE onset for 4 hours. Erasmus MC patients (n=223) received 2.5% lysine-arginine in 1L of 0.225% NaCl, whereas NETTER-1 patients received 2L of Aminosyn II 10% (Hospira, Inc) (n=66) or Vamin 18 (Fresenius Kabi) (n=50) solutions for parenteral nutrition with 18-24g of lysine and arginine content.

Results

Mean kidney absorbed doses estimated for a cumulative ^{177}Lu-DOTATATE administered activity of 29.6 GBq was 19±9 Gy in the NETTER-1 dosimetry substudy (n=20 patients) and 20±5 Gy in the Erasmus MC study (n=223 patients), suggesting that the different AA solutions used in the two studies provided an equivalent kidney radiation exposure. This is also confirmed by the low incidence of renal function toxicities, as determined by creatinine clearance values during treatment and follow-up period (up to 21 months for NETTER -1 and up to 3 years for Erasmus patients), with no treatment-related Grade 3 or 4 kidney toxicity observed in these two studies.
Aminosyn II 10% or Vamin 18 were associated with increased incidence of nausea or vomiting compared to 2.5% lysine-arginine solution (25% and 10% of nausea and vomiting respectively reported in Erasmus MC, vs 59% and 46% in NETTER -1).

Conclusion

Solutions containing lysine and arginine used for renal protection in PRRT with ^{177}Lu-DOTATATE effectively decrease the kidney absorbed radiation dose. The absence of unnecessary components, adequate osmolality, lower infused volume (1L versus 2L) and lower incidence of nausea and vomiting, make 2.5% lysine–2.5% arginine solution the best option for patients receiving ^{177}Lu-DOTATATE.

Aim

The aim of this investigation was to evaluate kidney dosimetry findings and the outcome of short to long-term renal function monitoring following treatment with ^{177}Lu-DOTATATE in the Phase III NETTER-1 study and Phase I/II Erasmus MC study (published data), in relation to different AA solutions for renal protection: 2.5% lysine–arginine in 1L vs commercially available solutions containing similar amounts of these two AA in 2L.

Materials & Methods

Assessment of kidney radio-dosimetry and longterm toxicity under infusion of different admino acid solutions.

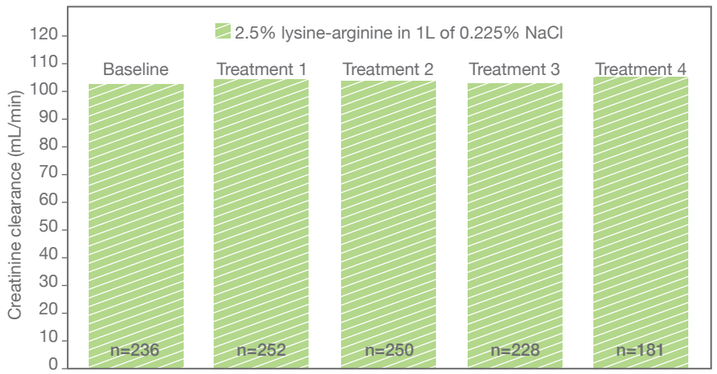
Results

All patients have been administered with 7,4 GBq X 4 times (29,6 GBq) with ~8 weeks interval ^{177}Lu-DOTATATE injection started 30 minutes after the amino acid infusion.

	Aminosyn II 10%	Vamin 18	2.5% lysine-arginine
Patients	66	50	223
Absorbed dose (Gy) in kidney	19±9		20±5
Median follow-up (months)	22.44 (0.4-41.1)		25 (0-142)
Adverse events (nausea and vomiting)	59% and 46%		25% and 10%

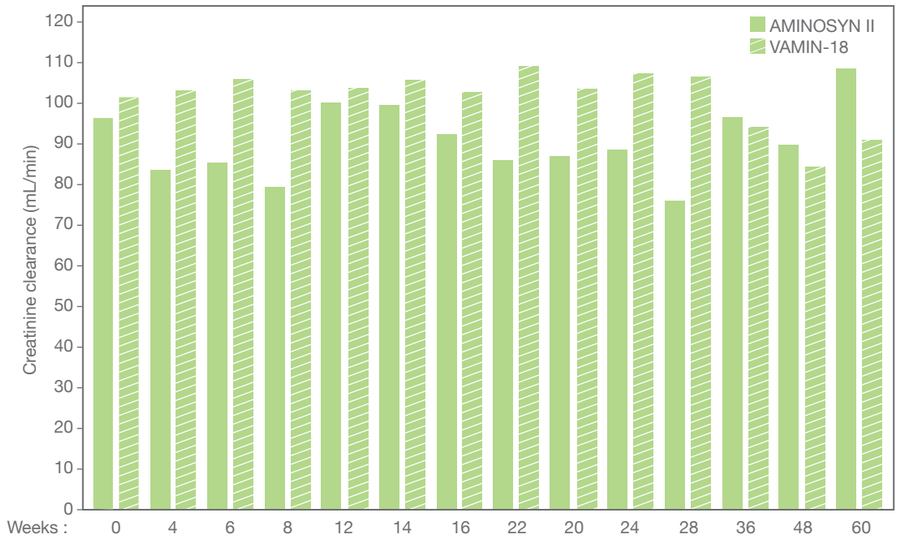
Indirect assessment of kidney absorbed dose via evaluation of kidney potential toxicity measured by creatinine clearance. ^{177}Lu-DOTATATE has been injected in all patients in 4 cycles at 8 +/- week interval and patients have been coinjected with 3 different amino acids solutions.

Creatinine clearance at baseline and under ^{177}Lu-DOTATATE treatment for patients pretreated with 2.5% lysine-arginine in 1L of 0.225% NaCl



2. Renal protection during LUTATHERA® treatment
using lysine and arginine solutions

Creatinine clearance at baseline and under ^{177}Lu-DOTATATE treatment for patients pretreated with Aminosyn II or Vamin-18



Conclusions

The amino acid solution containing 2.5% lysine–2.5% arginine is suitable to protect renal cells in a similar way as the Viamin 18 and Aminoyin II.
Viamin-18 and Aminosyn II are related to higher incidence of nausea and vomiting, therefore 2.5% lysine–2.5% arginine solution confers a better quality of life to the patients.

3 DOSIMETRY OF LUTATHERA® IN PATIENTS WITH ADVANCED MIDGUT NEUROENDOCRINE TUMORS: RESULTS OF THE PHASE III NETTER-1 SUB-STUDY

Lisa Bodei[1], Marta Cremonesi[2], Mahila Ferrari[2], Eric Krenning[3], Maribel Lopera Sierra[5], Jack L. Erion[5], Paola Santoro[5], Daniela Chicco[6], Maurizio F. Mariani[6].

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Background

High levels of somatostatin receptors in NETs are the basis for Peptide Receptor Radionuclide Therapy, a treatment that uses a somatostatin analogue coupled with a beta emitting radionuclide. This report summarizes dosimetry and pharmacokinetic (PK) findings from the Phase III NETTER-1 trial.

Methods

Dosimetry and PK evaluations were performed in a subgroup of 20 patients (mean age 58 years, range 30-74) in which ^{177}Lu-DOTATATE treatment (7.4 GBq x4 infusions at 8-week intervals) was administered in association with a commercial amino acid solution for renal protection.
PK evaluation of ^{177}Lu-DOTATATE blood time-activity concentrations was performed using non-compartmental analysis.
Whole body planar images were acquired for ≥5 time-points for up to 7 days following ^{177}Lu-DOTATATE administration. Venous blood and urine samples up to day 8 and 48 hours post-administration respectively were also collected. Regions of interest were drawn and used to derive time integrated activity coefficients. Absorbed dose values in target organs were calculated by OLINDA/EXM software.

Results

PK/biodistribution: blood clearance profiles were biphasic, with serum levels at 8 hours being ~5% Cmax. Systemic clearance was 4.52±1.40 L/h, mean terminal phase volume of distribution was 460±246L, indicating rapid and broad distribution. This is consistent with whole body image data, showing biodistribution in kidney (main elimination route), spleen, liver and tumor.
Dosimetry: estimated mean absorbed doses for cumulative activity of 29.6 GBq were 19±9 Gy for kidneys, 9±7 Gy for liver, 25±24 Gy for spleen, 13±5 Gy for urinary bladder wall, 1.0±0.8 Gy for red marrow and 1.5±0.8 Gy for total body. High tumor absorbed doses in target lesions resulted from the high uptake and long-term retention of ^{177}Lu-DOTATATE in tumors.
Considering the threshold absorbed doses, 23 Gy for kidneys exceeded in 7 patients, 2 Gy for red marrow would have been exceeded in 1 patient who did not complete the 4 cycles.
The treatment was well tolerated, with no clinically significant renal toxicity and mild-transient hematological toxicity, not correlated with bone marrow absorbed radiation dose, indicating that laboratory values monitoring during PRRT intervals (WBC, PLT, Hb) to be the method of choice to assess toxicities rather than absorbed dose.

Conclusion

These results are in agreement with previous findings of Erasmus MC, demonstrating that renal doses are below commonly accepted thresholds in most cases, and confirm the favorable safety profile of ^{177}Lu-DOTATATE treatment scheme used in NETTER-1 trial. This dosimetry analysis did not identify predictive factors that would warrant patient-individual dosing.

Aim

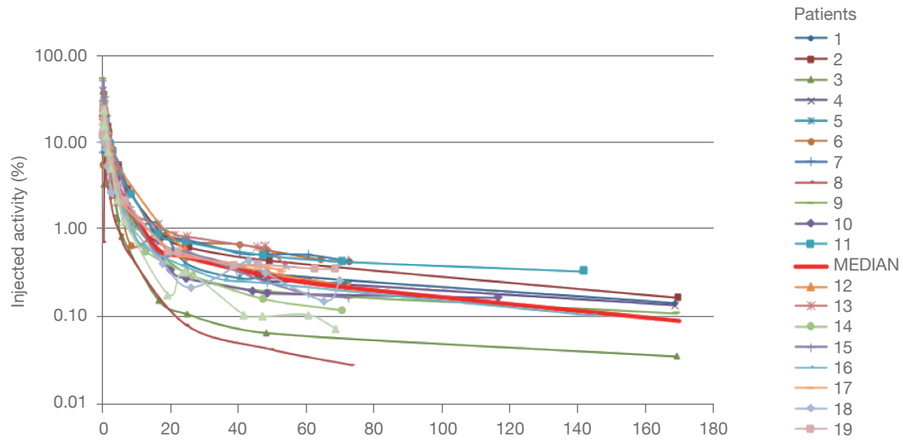
Assessment of organ dosimetry and pharmacokynetics of ^{177}Lu-DOTATATE in patients.

Methods

Radioactivity was assessed through imaging and blood sampling over time after ^{177}Lu-DOTATATE injection in 20 patients.

Results

Blood clearance following ^{177}Lu-DOTATATE 7.4 GBq administration



- Polyphasic behavior
- Systemic clearance = 4.52 ± 1.40 L/h
- Volume of distribution = 460 ± 246L, indicating rapid and broad distribution

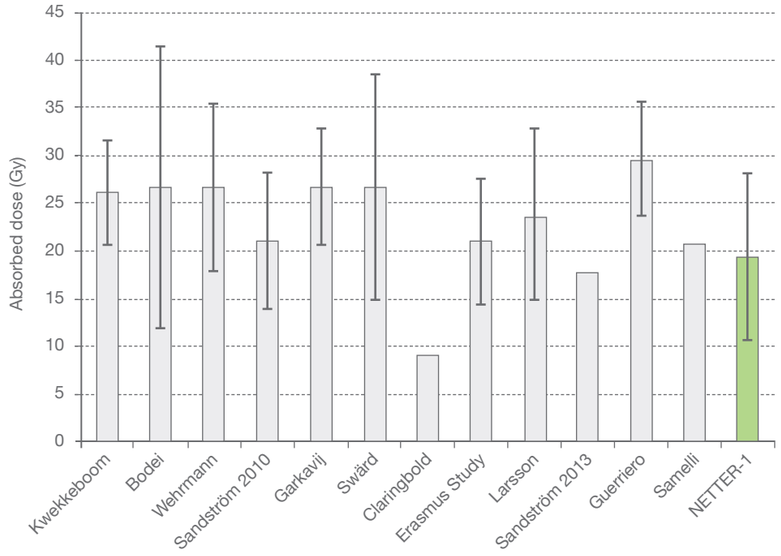
Estimated mean absorbed doses (Gy) for cumulative activity of 29.6 GBq of ^{177}Lu-DOTATATE

Organs	Estimated activity (Gy)
Kidneys	19±9
Liver	9±7
Spleen	25±24
Urinary bladder wall	13±5
Red marrow	1.0±0.8
Total body	1.5±0.8

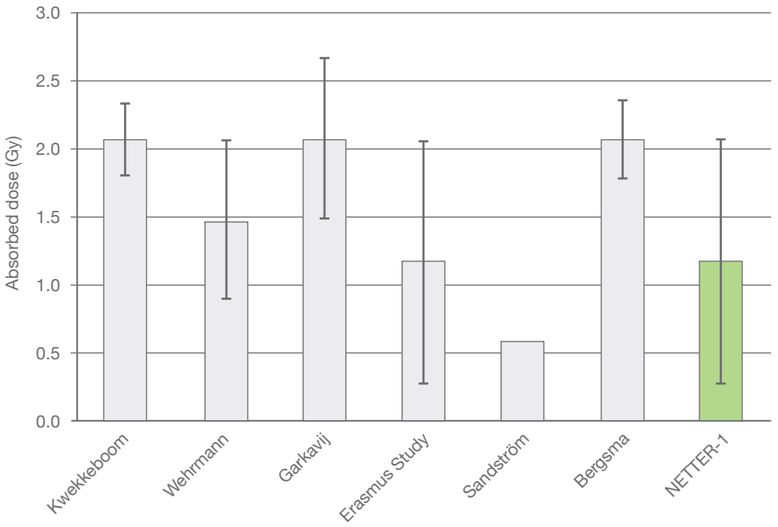
The treatment was well tolerated, with no clinically significant renal toxicity and mild-transient hematological toxicity.

Comparison of kidney and bone marrow dosimetry after ^{177}Lu-DOTATATE administration with literature data

Kidney absorbed doses (Gy) resulting from a cumulative activity of 29.6 GBq in 4 administrations.



Bone marrow dose (Gy) resulting from a cumulative activity of 29.6 GBq in 4 administrations.



3. Dosimetry of LUTATHERA in patients with advanced midgut neuroendocrine tumors: results of the Phase III NETTER-1 sub-study

Tumor Dosimetry

Cumulative absorbed dose in tumor masses selected as target lesions indicate that ^{177}Lu-DOTATATE has a generally high and prolonged uptake in tumor lesions.
This dosimetry analysis did not identify predictive factors that would warrant patient-individual dosing.

Safety

The treatment was well tolerated, with no clinically significant renal toxicity and mild-transient hematological toxicity, not correlated with bone marrow absorbed radiation dose.
The monitoring of laboratory values during PRRT intervals (WBC, PLT, Hb) is the method of choice to assess acute toxicities as the calculation of the absorbed dose is not the most suitable way to predict the occurrence of adverse events.

Conclusions

- **Pharmacokinetic analysis** shows that blood clearance and urinary elimination curves are fully consistent with the literature.
- **Dosimetry evaluation** indicates that absorbed doses for normal tissues are in agreement with previous publications.
- **Toxicity analysis** are in agreement with previous findings of Erasmus MC, and confirm the **favorable safety profile of ^{177}Lu-DOTATATE** treatment scheme used in NETTER-1 trial.

NOTES

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