^{177}Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine tumors: Results of the Phase III NETTER-1 Trial

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Introduction

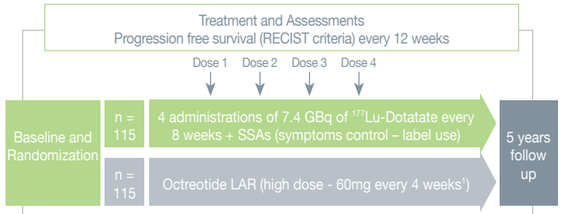
- There are limited therapeutic options for patients with advanced midgut neuroendocrine tumors (20-45% of NETs) progressing on first-line somatostatin analogue therapy.
- Thousands of patients have been treated with ^{177}Lu-Dotatate, peptide receptor radionuclide therapy (PRRT), with promising results.
- NETTER-1 is the first prospective phase III study assessing efficacy and safety of ^{177}Lu-Dotatate in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg

Methods and Design

- Protocol consists of treatment with a cumulative dose of 29.6 GBq of ^{177}Lu-Dotatate (4 x 7.4 GBq every 8 weeks) + symptom control treatment with 30 mg Octreotide LAR compared to 60 mg Octreotide LAR every 4-weeks.
- Design objective was 230 patients randomized in the 2 arms (1:1).
- Tumor response is centrally assessed in both arms, every 12 +/-1 week(s) from the randomization date, according to the RECIST criteria. Efficacy is blindly and independently assessed through image review by qualified readers.
- Patients remain under treatment until disease progression or unacceptable toxicity or inability/unwillingness to comply with study requirements or consent withdrawal.

NETTER -1 Study Objectives and Design

Objective	Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg
Design	International, multicenter, randomized, comparator-controlled, parallel-group



1. FDA and EMA recommendation

Study Endpoints

Primary objective

Compare Progression Free Survival (PFS) after treatment with ^{177}Lu-Dotatate + 30 mg Octreotide LAR vs treatment with high dose (60 mg) Octreotide LAR

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 QLQ-G.I.NET21 questionnaire

Once the primary endpoint has been reached, patients who have completed the treatment phase according to the study protocol will enter the long term follow up assessment phase. End-of-Study (EOS) is expected to take place after 158 deaths or the 5-year follow up period, whichever occurs first. OS analysis will be performed at this time.

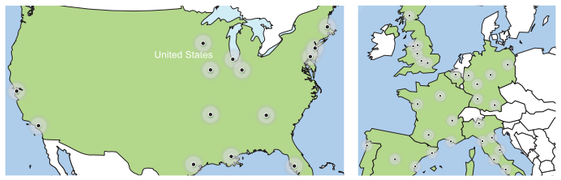
Main Inclusion Criteria

- Patients ≥18 years of age
- Metastatic or locally advanced, inoperable, histologically proven, well-differentiated midgut NET, functioning or not
- 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 receptor positive disease
- Karnofsky Performance Score ≥ 60

Main Exclusion Criteria

- Serum creatinine >150 µmol/L, or creatinine clearance <50 mL/min
- Hb concentration <5.0 mmol/L
- WBC <2x10^9/L , Platelets <75x10^9/L
- Treatment with >30 mg Octreotide LAR at 3-4 weeks intervals within 12 weeks prior to randomization
- Surgery, radioembolization, chemoembolization, chemotherapy and RF ablation within 12 weeks prior to randomization

Participating Sites in 51 Centers - 8 Countries



Results

Patients

- Most patients had liver as a primary site of metastasis (84% vs. 83% in the ^{177}Lu-Dotatate vs. comparator arm, respectively). 66% vs. 72% had grade 1 tumors and 34% vs. 28% grade 2 tumors.
- The majority of patients had prior resection (78% vs. 82%), ablation (5% vs. 10%) or chemo-embolization (12% vs. 10%). Part of the patients received prior chemotherapy (27% vs. 30%) or radiotherapy (4% vs. 5%).
- 76% of the patients in the ^{177}Lu-Dotatate treatment arm received the 4 administrations of the drug as per protocol.
- Among 111 treated patients in the ^{177}Lu-Dotatate arm, only 5% (5 patients) experienced DMT (Dose Modifying Toxicity).

Population Characteristics at Enrolment (ITT population, N=229)

	^{177}Lu-Dotatate (n=116)	Octreotide LAR 60mg (n=113)
Gender, n (%)		
Male	53 (46%)	60 (53%)
Female	63 (54%)	53 (47%)
Age (years), mean (SD)	63 (±9)	64 (±10)
BMI (Kg/sqm), mean (SD)	25 (±5)	26 (±7)
Primary tumor site, n (%)		
Jejunum	6 (5%)	9 (8%)
Ileum	86 (74%)	82 (73%)
Appendix	1 (1%)	2 (2%)
Right colon	3 (3%)	1 (1%)
Other	20 (17%)	19 (17%)
Site of metastasis, n (%)		
Liver	97 (84%)	94 (83%)
Lymph nodes	77 (66%)	65 (58%)
Bone	13 (11%)	12 (11%)
Lungs	11 (10%)	5 (4%)
Other	40 (35%)	37 (33%)
ENETS Grading, n (%)		
G1/G2	76/40 (66/34%)	81/32 (72/28%)
SRS, Krenning scale, n (%)		
Grade 2	13 (11%)	14 (12%)
Grade 3	34 (29%)	32 (28%)
Grade 4	69 (60%)	67 (59%)
Chromogranin A (µg/L), mean (SD)	649 (420)	670 (422)
5-HIAA (mg/24h), mean (SD)*	100 (183)	77 (83)

*Only available in 98 patients

Prior Cancer Treatments at Enrolment (ITT population, N=229)

	^{177}Lu-Dotatate (n=116)	Octreotide LAR 60mg (n=113)
Prior resection, n (%)	90 (78%)	93 (82%)
Prior ablation, n (%)	6 (5%)	11 (10%)
Chemo-embolization, n (%)	14 (12%)	11 (10%)
Time since last intervention, yrs (SD)	4.7 (±3.3)	5.7 (±3.6)
Previous treatment		
Radiotherapy	7 (4%)	8 (5%)
PRRT	1 (1%)	0 (0%)
Chemotherapy	47 (27%)	51 (30%)
Other	48 (28%)	40 (24%)

^{177}Lu-Dotatate Exposure

Patients who completed trt phase, N=102*	Nb of Patients
Number of administrations, n (%)	
4	78 (76%)
3	5 (5%)
2	11 (11%)
1	4 (4%)
0	4 (4%)
All treated patients – N=111	**Nb of Patients**
Dose modifying toxicity, n (%)	
No DMT	105 (95%)
DMT	6 (5%)

*14 patients still under treatment.

Treatment effects

Enrolment was completed in February 2015, with a target of 230 patients randomized (1:1) in 35 European and 15 sites in the United States.
Data status at the time of statistical analysis:

- PFS: final analysis
- ORR : final analysis
- OS: interim analysis

- The number of centrally confirmed disease progressions or deaths was 23 in the ^{177}Lu-Dotatate group and 67 in the Octreotide LAR 60 mg group.
- The median PFS was not reached for ^{177}Lu-Dotatate and was 8.4 months with 60 mg Octreotide LAR [95% CI: 5.8-11.0 months], p<0.0001, with a hazard ratio of 0.21 [95% CI: 0.13-0.34]. This means a 79% reduction in the risk of disease progression/death could be obtained by treatment with ^{177}Lu-Dotatate. All progressions were centrally confirmed and independently reviewed for eligibility (SAP).
- Within the currently evaluable patient dataset for tumor responses (n=201), the number of CR + PR was 19 (ORR=19%) in the ^{177}Lu-Dotatate group and 3 (3%) in the Octreotide LAR 60 mg group (p=0.00043).
- The number of deaths was 13 in the ^{177}Lu-Dotatate group and 22 in the Octreotide LAR 60 mg group (p=0.0186 at interim analysis), which suggests an improvement in overall survival.

Safety analysis

Treatment-related serious adverse events (n=111) :

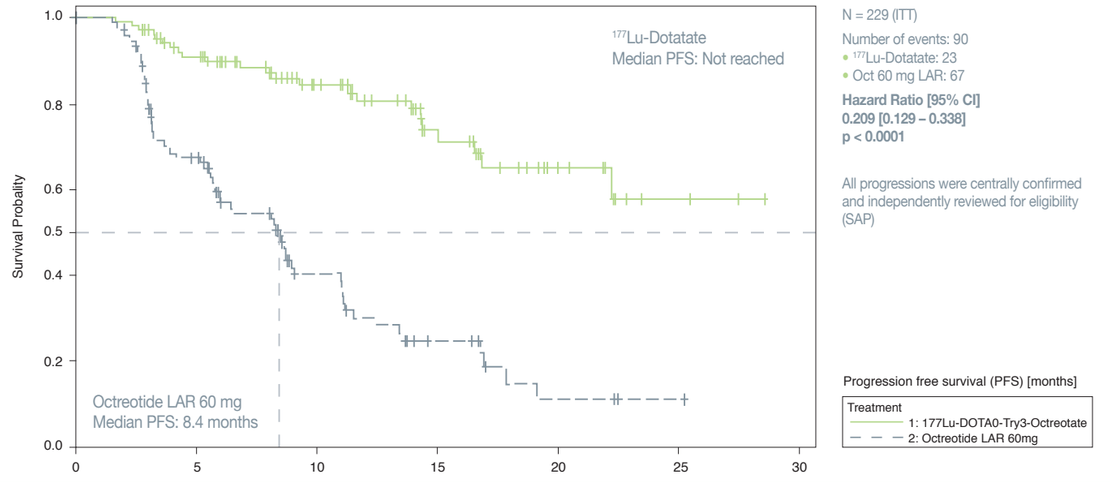
- 10 SAEs
- 5 patient withdrawals

Currently available safety data confirms the results of the previous phase I-II study.

Safety and Tolerability (Nb of patients (%), Safety Set; n=221)

	^{177}Lu-Dotatate (n=111)	Octreotide LAR 60mg (n=110)
Any adverse event	106 (96%)	95 (86%)
Related to treatment	95 (86%)	34 (31%)
Serious adverse events	29 (26%)	26 (24%)
Related to treatment	10 (9%)	1 (1%)
Withdrawals due to adverse events	7 (6%)	10 (9%)
Related to treatment	5 (5%)	0 (0%)

Progression-Free Survival

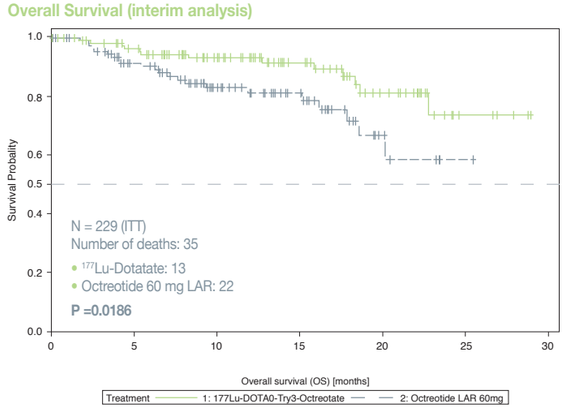


Tumor Response Rate (currently evaluable patients)

	^{177}Lu-Dotatate (n=101)	Octreotide LAR 60mg (n=100)
Complete Response (n)	1	0
Partial Response (n)	18	3
Objective Response Rate (CI 95%)	19% (11-26%)	3% (0-6%*)
Progressive Disease (n, %)	5 (4%)	27 (24%)
Stable Disease (n, %)	77 (66%)	70 (62%)

*P=0.00043

Overall Survival (interim analysis)



Summary and Conclusions

- In this first prospective randomized study in patients with progressive metastatic midgut NETs, ^{177}Lu-Dotatate was superior to Octreotide 60 mg in terms of PFS (NR vs 8.4 months, p<0.0001) and ORR (19% vs 3%)
- Patients treated with ^{177}Lu-Dotatate have a 79% risk reduction of disease progression or death
- Interim analysis suggests increased overall survival (13 vs 22 deaths), to be confirmed by final analysis
- Currently available safety data confirms the results from the phase I-II, i.e. a favorable safety profile
- While few treatment options were up to now available, ^{177}Lu-Dotatate appears as a major advance in this patient population

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