Lanreotide depot/autogel before, during, and after peptide receptor radionuclide therapy in advanced neuroendocrine tumors: Data from the PRELUDE study

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INTRODUCTION

- Lanreotide depot/autogel (LAN) is an established anti-tumor therapy for metastatic neuroendocrine tumors (NETs)[1–3]
- Peptide receptor radionuclide therapy (PRRT) is an evolving treatment for well-differentiated metastatic NETs
- Somatostatin analogs as a combination and/or maintenance therapy with ^{177}Lu-DOTATATE has recently been shown to have a clinical benefit in patients with gastroenteropancreatic (GEP)-NETs[4,5]
- PRELUDE is a multicenter retrospective study, with central radiology reading, to describe the use of LAN with ^{177}Lu-PRRT (LAN–PRRT) in advanced NETs

METHODS

Study design

- PRELUDE (NCT02788578) was an international, retrospective, non-comparative analysis of medical records of patients receiving LAN with ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC and up to 12 months follow-up with LAN only
- Inclusion and exclusion criteria are shown in **Figure 1**

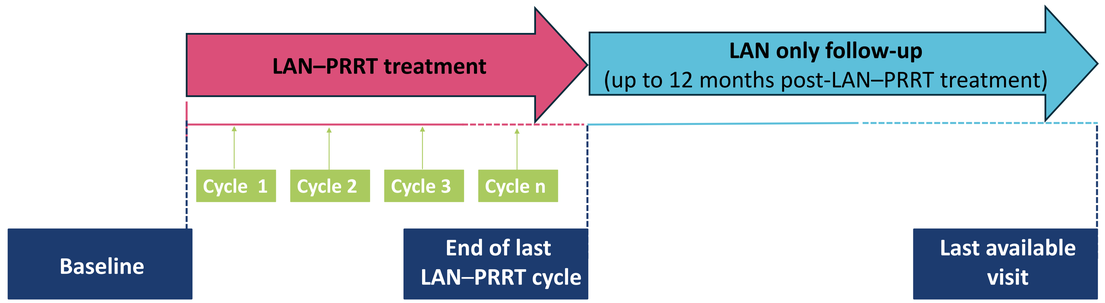
Assessments and endpoints

- Data were collected at 3 time points (**Figure 1**):
  - Baseline (before administration of treatment on day 1 of each patient's first LAN–PRRT cycle)
  - After the last LAN–PRRT cycle
  - At the last available follow-up visit
- The primary endpoint was progression-free survival (PFS) rate at the end of the last LAN–PRRT cycle (RECISTv1.1, centrally assessed)
- Secondary endpoints included best overall response (OR), objective response rate (ORR; both RECISTv1.1, centrally assessed) and changes from baseline in the presence and severity of diarrhea and flushing
- Safety endpoints included the incidence of nephro-, hemato- and hepatotoxicity and also vomiting during infusion

Statistical analysis

- No statistical testing was performed
- Two-sided 95% CI calculated for every relevant proportion, mean and median
- The analysis populations are:
  - Enrolled population: all informed and consenting patients who are willing to participate
  - Full analysis set (FAS): all enrolled patients with ≥1 measurable lesion at baseline and at the end of the last LAN–PRRT cycle
  - Safety population: all enrolled patients with ≥1 cycles of LAN–PRRT

Figure 1. Study design and key inclusion and exclusion criteria



Inclusion Criteria

- Consenting patients aged ≥18 years
- Grade 1 or 2 histopathologically confirmed metastatic or locally advance and well differentiated GEP- or lung-NET (WHO 2010 classification)
- SSTR-positive GEP- or lung-NET
- Radiologically documented disease progression (CT or MRI) within 12 and 6 months prior to first LAN–PRRT cycle
- ≥1 LAN injection in the 8 weeks prior to the first LAN–PRRT cycle
- Continuous LAN throughout the combination cycles (LAN–PRRT)
- Grade ≥2 on the Krenning scale or modified Krenning scale, confirming presence of SSTRs on all target lesions
- Karnofsky Performance Status ≥60 or ECOG Performance Status ≤2
- Cumulative PRRT activity of ≥500 mCi

Exclusion Criteria

- Missing information regarding LAN treatment: doses, start date, injection frequency
- Missing CT or MRI within 12 and 6 months preceding the baseline, and at the end of the last LAN–PRRT cycle
- Missing information on cumulative activity of PRRT
- Previous PRRT prior to the first combination cycle of LAN–PRRT

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; LAN, lanreotide depot/autogel; MRI, magnetic resonance imaging; PRRT, peptide receptor radionuclide therapy; SSTR, somatostatin receptor; WHO, World Health Organization

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RESULTS – BASELINE CHARACTERISTICS AND STUDY TREATMENT

Patients

- Enrollment was terminated early as a result of insufficient recruitment
- A total of 40 patients enrolled (enrolled population); 39 had a GEP-NET, 1 had a lung-NET

Baseline characteristics

- Tumor characteristics at baseline shown in **Table 1**
- At baseline, most patients with a GEP-NET:
  - Did not have progressive disease
  - Had a Ki-67 score between 2 and 20
  - Had a grade 4 global overall Krenning score (centrally assessed)
- The location of the primary tumor for patients with a GEP-NET (enrolled population, n=39) was:
  - 53.8% midgut (ileum and colon, right), 25.6% unknown, 10.3% pancreas, 5.1% stomach, 2.6% colon, sigmoid, 2.6% rectum

Study treatment

- LAN and PRRT administration and exposure are shown in **Table 2**
- Most patients with GEP-NET received:
  - 120 mg LAN last dose before PRRT
  - 4 LAN–PRRT cycles
  - Median cumulative administered activity of PRRT of 29.6 GBq (800 mCi) ranging from 21.2 to 31.7 GBq (573 to 857 mCi)

Table 1. Tumor characteristics at baseline (enrolled population)

	GEP-NETs (N=39)	All patients (N=40)
Progression at baseline*	30	31
Missing	9	9
Yes	1 (3.3)	1 (3.2)
Proliferation index Ki-67	32	33
Missing	7	7
≤2	15 (46.9)	16 (48.5)
>2 and ≤20	17 (53.1)	17 (51.5)
Global Overall Krenning Scale*	27	28
Missing	12	12
Grade 2	4 (14.8)	4 (14.3)
Grade 3	4 (14.8)	4 (14.3)
Grade 4	19 (70.4)	20 (71.4)

Table 2. LAN and PRRT administration and exposure (FAS)

	GEP-NETs (N=23)	All patients (N=24)
Last dose of LAN prior to the first LAN–PRRT cycle	23	24
60 mg	3 (13.0)	3 (12.5)
90 mg	2 (8.7)	3 (12.5)
120 mg	18 (78.3)	18 (75.0)
Number of LAN–PRRT cycles	23	24
3	1 (4.3)	1 (4.2)
4	17 (73.9)	18 (75.0)
>4	5 (21.7)	5 (20.8)
Median (range) cumulative administered activity of PRRT		
GBq	29.6 (21.2; 31.7)	29.6 (21.2; 31.7)
mCi	800 (573; 857)	799 (573; 857)
LAN exposure	23	24
Median (range) overall LAN exposure, months	37.0 (16.7; 90.0)	36.5 (13.2; 90.0)
Median (range) LAN exposure during LAN only follow-up, months	12.6 (6.1; 32.5)	12.6 (6.1; 32.5)

Data expressed as n (%) unless otherwise stated. *RECIST v1.1, centrally assessed. FAS, full analysis set; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; LAN, lanreotide depot/autogel; PRRT, peptide receptor radionuclide therapy; RECIST, response evaluation criteria in solid tumors.

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RESULTS - EFFECTIVENESS

- Effectiveness data (FAS) are shown in **Figure 2**
  - The high PFS rate at the end of the last LAN–PRRT cycle was sustained at the last available follow-up visit (**Figure 2A**)
  - Most patients reported stable disease and only 1 patient reported progressive disease (**Figure 2A**)
  - Most patients with a GEP-NET had stable or improved diarrhea and flushing at the end of the last LAN–PRRT cycle and at the follow-up visit (**Figure 2B** and **2C**)

Figure 2. Effectiveness data (FAS)

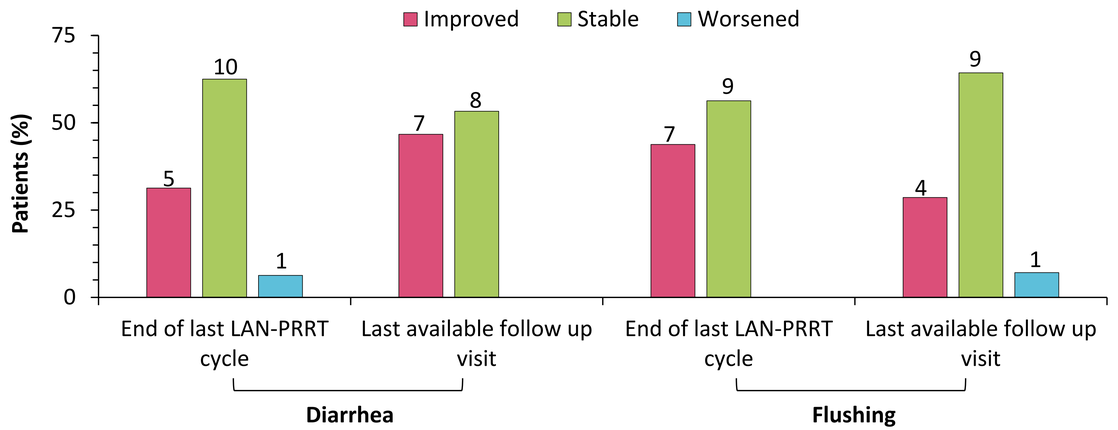
A) PFS rate, best OR, time point response, and ORR

Parameter	Patients with GEP-NETs (n=23; FAS)
PFS rate, % [95% CI]	
At end of last LAN–PRRT cycle*	91.7 [53.9; 98.8]
At the last available follow-up visit*	95.0 [69.5; 99.3]
Best OR*†, % [95% CI]	
PR	34.8 [18.8; 55.1]
SD	60.9 [40.8; 77.8]
PD	4.3 [0.8; 21.0]
Time point response at end of last LAN–PRRT cycle*, n (%) [CI 95%]	
PR	6 (27.3) [13.2; 48.2]
SD	15 (68.2) [47.3; 83.6]
PD	1 (4.5) [0.8; 21.8]
Time point response at the last available follow-up visit*, n (%) [CI 95%]	
PR	7 (36.8) [19.1; 59.0]
SD	11 (57.9) [36.3; 76.9]
PD	1 (5.3) [0.9; 24.6]
ORR*‡, n (%) [95% CI]	8 (34.8) [18.8; 55.1]
At time of last LAN–PRRT cycle*	6 (27.3) [13.2; 48.2]
At the last available follow-up visit*	7 (36.8) [19.1; 59.0]

B) Frequency of diarrhea and/ or flushing

Time point	N	Diarrhea or flushing	N	Diarrhea	N	Flushing
At day 1 of the first LAN–PRRT cycle, n (%)	21	17 (81.0)	20	11 (55.0)	20	12 (60.0)
At the end of the last first LAN–PRRT cycle, n (%)	18	11 (61.1)	19	8 (42.1)	19	7 (36.8)
At the last available follow-up visit, n (%)	17	12 (70.6)	17	7 (41.2)	16	6 (37.5)

C) Change from baseline in diarrhea or flushing



*RECIST v1.1, centrally assessed. †Best response recorded from the first LAN–PRRT cycle until disease progression or end of treatment period, whichever is earlier. ‡Rate of patients with complete response or PR. CI, confidence interval; FAS, full analysis set; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; LAN, lanreotide depot/autogel; N, number of patients with symptoms; OR, overall response; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease.

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RESULTS - SAFETY

- The most frequent reported toxicity was hematotoxicity (reported by only 3 patients in the safety population), contributing to 20 of 26 adverse events (AEs; 76.9%), mainly Grade 1 with three Grade 3 (Table 3)

Table 3. Incidence of nephro-, hemato- and hepatotoxicity events (safety population)

	From Day 1 of the first LAN–PRRT cycle to the end of the last LAN–PRRT cycle (N=31)		From the end of the last LAN–PRRT cycle to the last available follow-up (N=31)	
	N	n, %	N	n, %
Any events	26	2 (6.5)	5	2 (6.5)
Hematotoxicity/bone marrow toxicity	20	2 (6.5)	3	2 (6.5)
Grade 1	12	2 (6.5)	3	2 (6.5)
Grade 2	5	1 (3.2)	–	–
Grade 3	3	2 (6.5)	–	–
Hepatotoxicity	5	1 (3.2)	2	1 (3.2)
Grade 1	3	1 (3.2)	1	1 (3.2)
Grade 2	2	1 (3.2)	–	–
Grade 3	–	–	1	1 (3.2)
Renal toxicity	1	1 (3.2)	–	–
Grade 1	1	1 (3.2)	–	–

LAN, lanreotide depot/autogel; N, number of events; n, number of patients; PRRT, peptide receptor radionuclide therapy

CONCLUSIONS

- **Effectiveness data were encouraging in this selected population and highlight the potential effectiveness of the LAN–PRRT combination**
- **There was possible under-estimation of the incidence of AEs as a result of the limited number of patients in the study**
- **In clinical practice, LAN use is considered before, during and after PRRT**
- **Early recruitment termination in this study highlights the need for more standardized protocols for data collection, data reviewing and patient assessment**

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Disclosures

VP received: honoraria from and acted in a consulting/advisory role for Ipsen, ITG, Bayer; received remuneration for travel, accommodation, and expenses from Ipsen. RS has nothing to disclose. CT received honoraria from Ipsen, Novartis, and Advanced Accelerator Applications. CG received: remuneration for consulting/advisory role from Norginel; and remuneration for travel, accommodation, and expenses from Ipsen, Novartis, and Iason. SB has nothing to disclose. TS received: honoraria, remuneration for consulting/advisory role, and remuneration for travel, accommodation, and expenses from Ipsen. AL received remuneration for speaker's bureau, travel, accommodation, and expenses from Ipsen. FC received: remuneration for advisory board member/or board of directors from Nalgene; is a grant recipient from Advanced Accelerator Applications, and Bayer; received remuneration for speaker's bureau from GEHC, Bayer, Advanced Accelerator Applications, Novartis, and Ipsen; received re-imbursement for travel, accommodation, and expenses from GEHC, Bayer, Advanced Accelerator Applications, Novartis, Ipsen, Cyclopharma, and Norgine. KS received: honoraria from Ipsen and Shire; and remuneration for consulting/advisory role from Ipsen, Novartis, Shire, and Eisa. EB received honoraria, remuneration for a consulting/advisory role, and is a grant recipient from Ipsen, Novartis, Advanced Accelerator Applications and Pfizer. XMTT and AH are employees of Ipsen. LB received honoraria, remuneration for a consulting/advisory role, and is a grant recipient from Ipsen and Advanced Accelerator Applications.

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