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SHORT REPORT

Efficacy and safety of lanreotide in Korean patients with metastatic, well-differentiated gastroenteropancreatic-neuroendocrine tumors: a retrospective analysis

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Summary
Lanreotide autogel is a long-acting somatostatin analogue with proven efficacy and safety in patients with well-differentiated (WD) gastroenteropancreatic-neuroendocrine tumors (GEP-NETs) in a prior randomized phase III trial (CLARINET). However, the CLARINET study only enrolled patients with Ki-67 index <10%, and few patients of Asian ethnicity were included. We retrospectively analyzed the efficacy and safety of lanreotide in Korean patients with GEP-NETs in the daily practice setting. Between January 2015 and May 2018, 64 patients with metastatic WD GEP-NETs received lanreotide at Asan Medical Center, Seoul, Korea. Of them, 45 (70.3%) patients who received lanreotide as monotherapy were included in the current analysis. The most common primary tumor site was the pancreas ($n = 22$, 48.9%), followed by the rectum (10, 22.2%) and the small bowel (7, 15.6%). According to RECIST v1.1, a partial response was achieved in one patient (2.2%) and stable disease was achieved in 40 patients (88.9%). The median progression-free survival (PFS) was 16.4 months (95% confidence interval, 9.5–23.3 months). There were no differences in PFS according to the primary tumor site ($p = 0.77$). Hepatic tumor volume > 25% and prior systemic therapy were significantly associated with poorer PFS in the multivariate analysis. Lanreotide is well-tolerated and effective for Korean patients with GEP-NETs in the daily practice setting.

Keywords Neuroendocrine tumor · Somatostatin analogue · Lanreotide

Introduction

Neuroendocrine tumors (NETs) are a rare, heterogeneous group of malignancies originating from neuroendocrine cells in various organs. More than half of NETs occur in the gastrointestinal tract and pancreas [1]. Surgery is a curative treatment for resectable NETs, but many patients have unresectable or metastatic tumors at the time of diagnosis, and medical therapy is often initiated to delay disease progression. Somatostatin analogues (SSAs), mTOR inhibitors, and multi-targeted vascular endothelial growth factor receptor (VEGFR) inhibitors have been tested and approved for treatment of metastatic gastroenteropancreatic (GEP)-NETs, based on positive results in randomized phase III trials [2–6]. Among these, SSAs such as lanreotide and octreotide are recommended as first-line systemic therapies for well-differentiated (WD) GEP-NETs, based on their proven antitumor activity and favorable toxicity profiles [7, 8].

Lanreotide autogel is a long-acting SSA with proven antiproliferative effects against WD GEP-NETs in the pivotal phase III CLARINET trial [9]. The CLARINET trial included more generalized GEP-NET patients than did the PROMID trial, the randomized phase III trial of octreotide, which included only patients with midgut NETs [2]. However, further

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evaluation of the efficacy of lanreotide in patients with GEP-NETs is needed in the real-world setting, as NETs are very heterogeneous, and the CLARINET trial excluded patients with Ki-67 index ≥10% and only included a small number of patients with tumors of foregut and hindgut origin [9]. Moreover, further clinical evidence of lanreotide activity in patients of Asian ethnicity is also needed, as the CLARINET study included only seven Asian patients, and there is only one phase II study that included 32 Japanese patients [9, 10].

In this study, we retrospectively analyzed the efficacy and safety of lanreotide in Korean patients with WD GEP-NETs treated in the daily practice setting.

Patients and methods

Patients

Between January 2015 and May 2018, a total of 64 patients with recurrent or metastatic WD GEP-NETs who received lanreotide autogel at Asan Medical Center, Seoul, Korea, were identified. Among them, 45 (70.3%) patients in whom lanreotide was used as monotherapy were included in this study. Patient characteristics and clinical outcomes were retrospectively assessed by a review of the medical records. The study was approved by the Institutional Review Board of Asan Medical Center. All histologic data were reviewed by two academic pathologists (HSW, SMH), and tumors were graded according to the 2017 World Health Organization (WHO) classification system [11].

Treatment and assessment

Lanreotide was given subcutaneously every 4 weeks, and the starting dose was chosen by the physician as either 90 or 120 mg. The anti-tumor response to lanreotide was assessed every 2–3 months using computed tomography (CT) or magnetic resonance imaging (MRI). Tumor response was graded according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The volume of hepatic metastases was assessed using baseline CT or MRI scans and was categorized as 0%–25% or > 25%.

Endpoints and statistical analysis

The primary endpoint of this study was progression-free survival (PFS). PFS was defined as the time from the initiation of lanreotide until the date of disease progression or death from any cause. Overall survival (OS) was defined as the time from the initiation of lanreotide to death from any cause. Survival probabilities were estimated using the Kaplan–Meier method and compared using log-rank testing. The Cox proportional hazards model was used for multivariate analyses to assess the influence of baseline characteristics on survival outcomes. The safety analysis included all patients who visited the clinic at least once after initiation of treatment. Toxicity was evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. A p value of <0.05 was considered statistically significant. SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

Patient characteristics

Baseline patient characteristics are summarized in Table 1. The median age was 58 years (range, 16–81), and 20 patients (44.4%) were male. The most common primary tumor site was the pancreas (n = 22, 48.9%), followed by the rectum (10, 22.2%) and the small bowel (7, 15.6%). Ten patients (22.2%) presented with carcinoid symptoms, the most common of which were abdominal pain (n = 6, 13.3%) and diarrhea (n = 5, 11.1%). The liver was the most frequent metastatic site (n = 38, 84.4%), and 17 patients (44.7%) had metastases occupying >25% of the liver. Lanreotide was given at 120 mg in 37 patients (82.2%) and at 90 mg in eight (17.8%) patients. ^{68}Gallium-DOTATOC positron emission tomography (PET)-CT was performed in 31 patients (68.9%), all of whom showed positive tumor uptake of tracer.

Tumor grading by the 2017 WHO classification was available in 43 patients (95.6%), and 10 (23.3%), 31 (72.1%), and 2 (4.7%) patients had grade 1, 2, and 3 tumors, respectively. The Ki-67 labeling index was available for 42 patients. The median Ki-67 index was 9.4% (range, 0.5–24.96%), and 20 patients (47.6%) had tumors with a Ki-67 index ≥10%.

Prior to lanreotide treatment, 19 (42.2%) patients had undergone surgery, 13 (28.9%) with curative intent. Liver-directed therapies including transarterial chemoembolization (TACE), transarterial embolization (TAE), or radiofrequency ablation (RFA) were performed in 10 (22.2%) patients. Most patients (n = 38, 84.4%) received lanreotide as a first-line systemic therapy. For patients who received prior systemic therapy (n = 7, 15.6%), the median time to progression of the first-line systemic therapy was 3.9 months (95% confidence interval (CI), 0.0–9.0 months). Platinum-containing chemotherapy,

Table 1 Baseline patient characteristics

Characteristics	Total, $n = 45$
Age, median (range), years	58 (16–81)
Gender	
Male	20 (44.4%)
Female	25 (55.6%)
ECOG performance status	
0–1	44 (97.8%)
2	1 (2.2%)
Primary site	
Pancreas	22 (48.9%)
Rectum	10 (22.2%)
Small bowel	7 (15.6%)
Stomach	2 (4.4%)
Unknown primary site	4 (8.9%)
Site of metastasis	
Liver	38 (84.4%)
Lymph node	21 (46.7%)
Bone	14 (31.1%)
Lung	6 (13.3%)
Peritoneum	4 (8.9%)
Hepatic tumor volume ($n = 33$)	
0–25%	16 (48.5%)
> 25%	17 (51.5%)
Differentiation	
Well-differentiated	45 (100%)
WHO grade ($n = 43$)	
1	10 (23.3%)
2	31 (72.1%)
3	2 (4.7%)
Ki-67 index ($n = 42$)	
≤ 2%	8 (19.0%)
> 2% and ≤ 10%	14 (33.3%)
> 10% and ≤ 20%	18 (42.9%)
> 20%	2 (4.8%)
Presence of Carcinoid symptoms	10 (22.2%)
Prior therapy (non-systemic)	
Surgery	19 (42.2%)
Liver-directed therapy (RFA, TACE or TAE)	10 (22.2%)
Prior systemic therapies	7 (15.6%)
1	5 (11.1%)
2–3	2 (4.4%)

RFA Radiofrequency ablation, *TAE* Transarterial embolization, *TACE* Transarterial chemoembolization, *ECOG* Eastern Cooperative Oncology Group

sunitinib, and everolimus were previously given in four (8.9%), one (2.2%), and two (4.4%) patients, respectively. In two patients (4.4%), two prior systemic therapies were given.

Efficacy

At the time of analysis, 21 patients (46.6%) had progressed on lanreotide and eight patients (17.8%) had died. Partial response was achieved in one patient (2.2%), and stable disease was achieved in 40 patients (88.9%) (Table 2). Progressive disease was the best response in four patients (8.9%). With a median follow-up duration of 16.1 months [95% CI, 13.2–19.0 months] in surviving patients, the median PFS was 16.4 months (95% CI, 9.5–23.3 months). The median OS was not reached at the time of analysis, and the 2-year OS rate was 67.5% (95% CI, 47.7–87.3%) (Fig. 1).

In patients who progressed on lanreotide ($n = 21$), 19 (90.5%) received subsequent systemic treatment [everolimus ($n = 16$, 84.2%), sunitinib ($n = 1$, 5.3%), or cytotoxic chemotherapy ($n = 6$, 31.6%)].

Prognostic factors

In the univariate analyses (Table 1), PFS was significantly associated with WHO grade [grade 1 vs. 2 vs. 3; median, 16.4 months (95% CI, 0.8–32.0) vs. 11.2 months (95% CI, 4.5–17.8) vs. 1.3 months (95% CI not available); $p = 0.048$; Fig. 2a] and hepatic tumor volume [0–25% vs. > 25%; median, 16.4 months (95% CI, 6.8–26.0) vs. 5.7 months (95% CI, 5.1–6.3); $p = 0.039$; Fig. 2b]. The median PFS did not differ according to the primary tumor site [pancreas vs. non-pancreatic gastrointestinal (except hindgut) vs. hindgut; median, 16.4 months (95% CI, 8.7–24.1) vs. not reached vs. 11.2 months (95% CI, 0.0–26.9); $p = 0.772$; Fig. 2c], prior systemic therapy [any number of prior systemic therapies vs. none; median, 5.4 months (95% CI, 3.9–6.9) vs. 16.4 months (95% CI, 9.5–23.3); $p = 0.41$; Fig. 2d], or Ki-67 index [Ki-67 index 0 to <10% vs. ≥10%; median, 21.8 months (95% CI, 9.0–34.6) vs. 10.3 months (95% CI, 2.1–18.4); $p = 0.131$; Fig. 2e].

In the multivariate analysis, a high hepatic tumor volume [> 25% vs. 0–25%, hazard ratio = 2.69 (95% CI, 1.03–7.02); $p = 0.044$] and prior systemic therapy [hazard ratio = 4.47 (95% CI, 1.09–18.38); $p = 0.038$] were significantly associated with poorer PFS (Table 3).

In the univariate analyses for OS, WHO grade and prior systemic therapy were significantly associated with OS ($p < 0.001$ and $p = 0.039$, respectively; Fig. 3). However, multivariate analyses were not available because of

Table 2 Efficacy outcomes with lanreotide

Variables	Total, $n = 45$
Response	
Partial response	1 (2.2%)
Stable disease	40 (88.9%)
Progressive disease	4 (8.9%)
Progression-free survival (median)	16.4 months (95% CI, 9.5–23.3 months)
Overall survival (median)	Not reached

insufficient power, due to the small number of deaths at the time of analysis.

Safety profile

Safety data were available for 37 patients (82.2%) who visited the clinic after the first injection of lanreotide (Table 4). Fifteen patients (40.5%) experienced adverse events of any grade. Abdominal pain ($n = 6$, 16.2%), flatulence ($n = 2$, 5.4%), diarrhea ($n = 1$, 2.7%), nausea ($n = 1$, 2.7%), injection site pain ($n = 1$, 2.7%), cholelithiasis ($n = 1$, 2.7%), and musculoskeletal pain ($n = 1$, 2.7%) were the most frequent adverse events. There were no grade 3–4 adverse events and no treatment delays or interruptions due to adverse events.

Discussion

In the current retrospective analysis of 45 patients with WD GEP-NETs, the efficacy of lanreotide was in line with that in prior studies [9, 10, 12], although the diverse baseline patient characteristics among the studies should be taken into consideration, as this may have an impact on clinical outcomes.

In this study, the median PFS was 16.4 months and the ORR was 2.2%. The 2-year OS rate was 67.5%, while the median OS was not reached at the time of analysis. The clinical outcomes in this study seem to be inferior to those presented in the CLARINET trial, the pivotal phase III trial for lanreotide, as the 2-year PFS rate was 65.1% in the primary analysis [9] and the median PFS was 32.8 months in the CLARINET open-label extension (OLE) study [13]. These discrepancies may be due to differences in baseline patient characteristics between the two studies. The CLARINET trial did not include patients with a Ki-67 index ≧10%, and 33% of patients had a hepatic tumor volume > 25%, while 47.6% of patients in this study had tumors with Ki-67 index ≧10% and 51.5% had hepatic tumor load >25%. The CLARINET study also excluded patients with recent liver-directed therapy, chemotherapy, or surgery. The fact that these characteristics have been proposed as poor prognostic factors may explain the numerically worse PFS in our cohort than in the CLARINET study [14]. Prior Spanish and Japanese multicenter phase II trials of lanreotide also showed comparable efficacy outcomes to our analysis (median PFS of 13 and 9.1 months, respectively) [10, 12]. These data, including ours, support the clinical activity of lanreotide for patients with WD GEP-NETs.

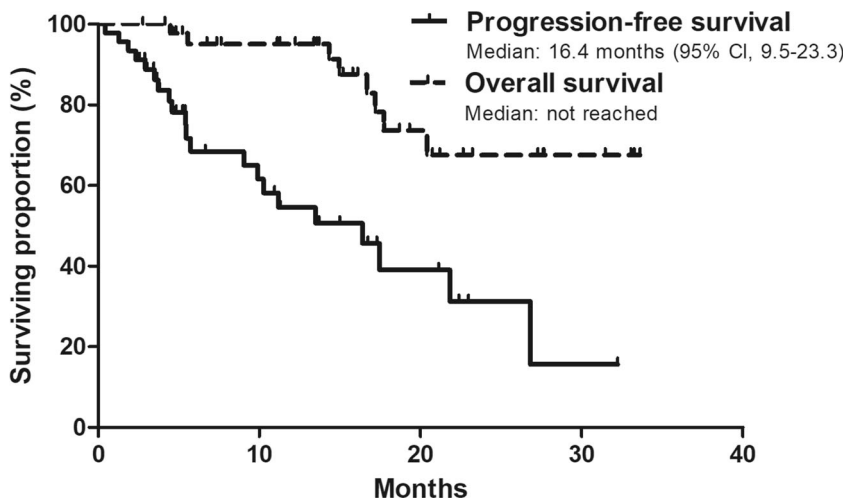

Fig. 1 Progression-free survival and overall survival

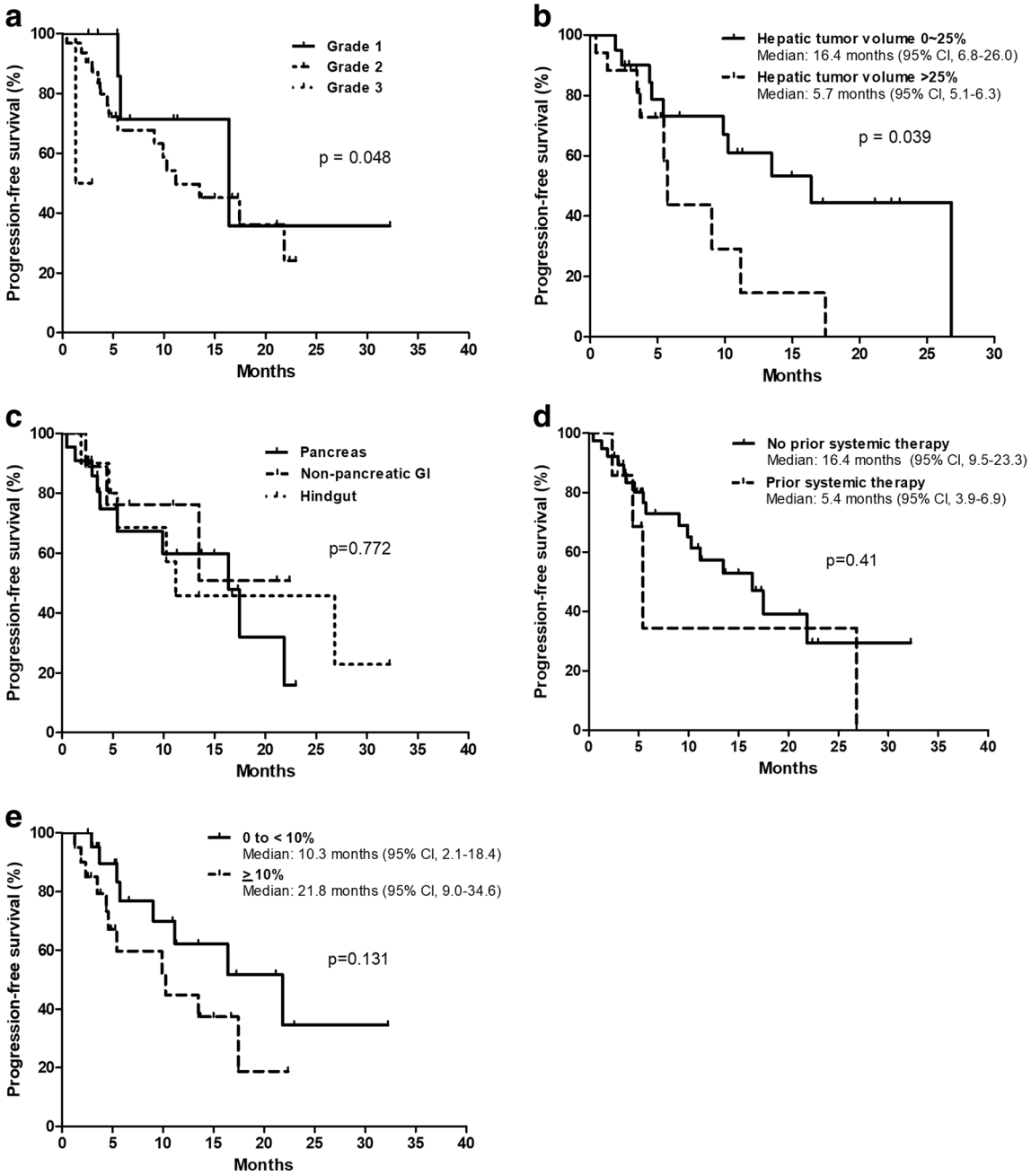

Fig. 2 Subgroup analysis for progression-free survival. WHO grade (**a**), hepatic tumor volume (**b**), primary tumor site (**c**), prior systemic therapy (**d**), and Ki-67 index (**e**)

Although the efficacy of SSAs in WD GEP-NETs has been demonstrated in randomized phase III trials, the efficacy of SSAs in patients with hindgut primary tumors has been rarely investigated. The PROMID trial of octreotide only included patients with midgut primary tumors [2], and only 14 patients (7% of total patients) had hindgut primary tumors in the CLARINET trial of lanreotide [9]. Furthermore, unlike in other subgroups in which lanreotide was strongly favored compared with the placebo, the subgroup of patients with hindgut primary tumors did not show a benefit from lanreotide (hazard ratio, 1.47) in the CLARINET study. The small sample size, which is insufficient for meaningful comparisons, may be the primary reason for these results, indicating that additional data on the efficacy of lanreotide in hindgut primary tumors are needed. Acquiring further data on lanreotide in hindgut primary tumors is particularly important in East Asian countries, where hindgut primary NETs occur more frequently than

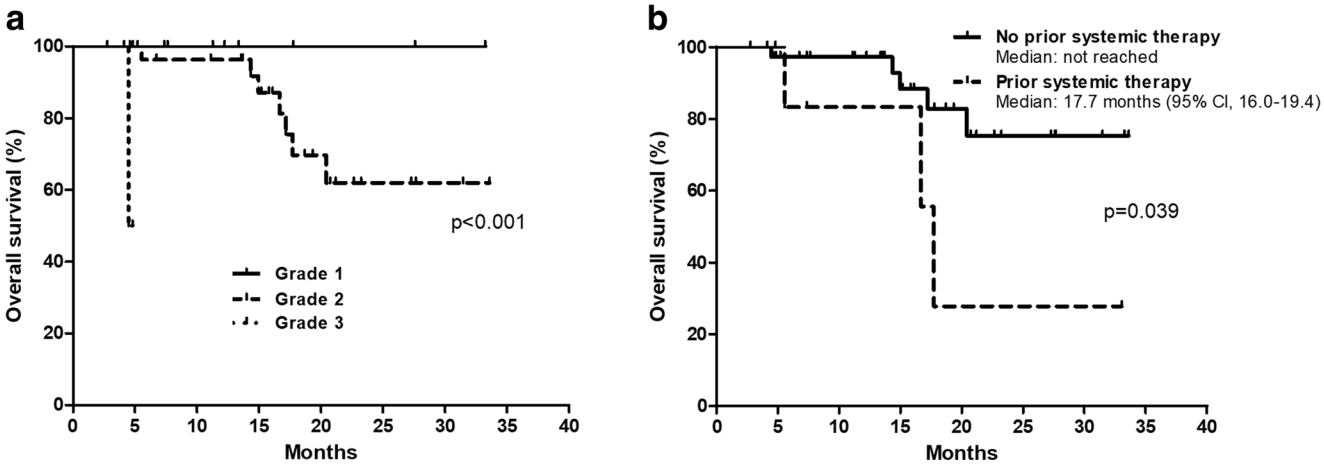

Fig. 3 Subgroup analysis for overall survival. WHO grade (**a**) and prior systemic therapy (**b**)

in Western countries [15–17]. In the previous Japanese phase II trial and in our retrospective analysis, which included eight (29% of total patients) and 10 (22% of total patients) patients with hindgut primary tumors, respectively, the PFS of patients with hindgut primary tumors was similar to that of patients with other primary tumor sites [10]. Although the number of analyzed patients is still too small to draw a clear conclusion on this issue, these findings suggest that lanreotide is an effective therapeutic agent in patients with hindgut primary tumors. Future prospective studies on hindgut primary tumors or large registry studies are needed.

A high hepatic tumor volume (> 25%) and prior systemic therapy were significantly associated with poorer outcomes in our study population. Patients who had Ki-67 index of ≥10% showed a trend towards poorer PFS compared with those with Ki-67 index of 0 to <10%; however, this was not statistically significant. Each of these factors has been suggested as a potential prognostic factor in prior studies [10, 14]. These may be prognostic factors that indicate the overall natural course of the disease, rather than predictive factors that may help guide the selection of therapeutic agents. Further imaging- or molecular-based studies are needed for this, and international, multi-center collaborations should be pursued, considering the small number of advanced GEP-NET patients and the heterogeneity of this disease.

The adverse events of lanreotide treatment in this study were consistent with those in prior studies [9, 10]. All adverse events were mild and easily manageable, and there were no grade 3 or 4 adverse events.

This study has limitations, as it was a retrospective analysis of a small number of patients treated at a single center.

Table 3 Univariate and multivariate analyses of progression-free survival (PFS)

Variables	Univariate analysis				Multivariate analysis		
	PFS, median	HR	95% CI	*p*	HR	95% CI	*p*
WHO grade							
Grade 1	16.4 months	Ref	–	–	–	–	–
Grades 2 and 3	11.2 months	1.82	0.53–6.23	0.34	–	–	–
Hindgut vs. others							
Others	16.4 months	Ref	–	–	–	–	–
Hindgut	11.2 months	0.84	0.31–2.33	0.74	–	–	–
Hepatic tumor volume							
0–25%	16.4 months	Ref	–	–	Ref		
> 25%	5.7 months	2.68	1.02–7.05	0.046	2.69	1.03–7.02	0.044
Prior systemic therapy treatment treatments							
No	16.4 months	Ref			Ref		
Yes	5.4 months	1.61	0.52–5.04	0.41	4.47	1.09–18.38	0.038

HR Hazard ratio, *CI* Confidence interval

Table 4 Adverse events

Adverse events	Total, $n = 37$ Grades 1–2*
Abdominal pain	6 (16.2%)
Flatulence	2 (5.4%)
Nausea	1 (2.7%)
Diarrhea	1 (2.7%)
Injection site pain	1 (2.7%)
Hyperglycemia	1 (2.7%)
Headache	1 (2.7%)
Dizziness	1 (2.7%)
Musculoskeletal pain	1 (2.7%)
Cholelithiasis	1 (2.7%)
Constipation	1 (2.7%)

*There was no grade 3–4 adverse events in this study population

However, considering the lack of data in patients of Asian ethnicity, our results provide clinical evidence of treatment outcomes for GEP-NETs in the Asian real-world setting.

In conclusion, lanreotide is well-tolerated and effective in Korean patients with WD GEP-NETs in the daily practice setting. Future studies are needed to identify subgroups that show the best outcomes with lanreotide.

Compliance with ethical standards

Conflicts of interest The authors have no competing financial interests to declare.

Statement of ethics All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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