Real-World Analysis of Long-Term Treatment Patterns in Patients with Advanced Gastrointestinal Neuroendocrine Tumors (GI NET): A Multicenter Study

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Matthew H. Kulke, MMSc, MD[1], Al B. Benson, MD[2], Arvind Dasari, MD[3], Lynn Huynh, MPH, MBA, DrPH[4], Beilei Cai, PhD[5], Todor Totev, BSc[4], Nina Roesner, BA[4], Mei Sheng Duh, MPH, ScD[4], Maureen P. Neary, MS, PhD[5], Emily K. Bergsland, MD[6]

[1]Dana-Farber Cancer Institute and Section of Hematology/Oncology, Boston Medical Center and Boston University Cancer Center, Boston, MA, USA; [2]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA; [3]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [4]Analysis Group, Boston, MA, USA; [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [6]UCSF Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA

Background and Study Objective

- Neuroendocrine tumors of gastrointestinal origin (GI NETs) arise from endocrine cells in the digestive tract and represent approximately 67% of all well-differentiated NETs[1]
  - About half of patients with GI NET are diagnosed at an advanced stage[1]
- There are a growing number of treatment options available to manage advanced GI NET
  - First-line treatment for metastatic NETs of the GI tract typically consists of somatostatin analogs (SSAs)[2]
  - Other recommended treatments include everolimus, interferon-alpha, cytotoxic chemotherapy, and liver-directed therapy (LDT) for hepatic-predominant disease[2]
- Limited data are available on real-world treatment patterns and treatments spanning the NET disease course
- The objective of this study was to assess long-term, real-world treatment patterns and clinical outcome of GI NET patients at four tertiary cancer centers

Methods

Study Design and Data Sources

- This study is a multi-center, non-interventional, retrospective medical records review, conducted at four large tertiary cancer centers: Dana-Farber Cancer Institute, MD Anderson Cancer Center, Helen Diller Family Comprehensive Cancer Center, and Robert H. Lurie Comprehensive Cancer Center
  - Eligible patients were diagnosed with advanced, well differentiated (grade 1/2) GI NET at age ≥18 years
  - Tumors of unknown primary site were eligible provided the treating physician did not suspect medullary thyroid cancer, pancreatic NET, paraganglioma, or pheochromocytoma.
  - Patients who received SSAs, targeted therapy, chemotherapy, peptide receptor radiotherapy, non-surgical liver-directed therapy, or interferon between July 2011 and December 2014 were included
  - The follow-up period for a given patient was the time from the date of advanced GI NET diagnosis (index date) until the date of last contact or death. The earliest recorded diagnosis was in March 1987, and the latest recorded date was in May 2017
- Data collected included demographic characteristics, clinical characteristics, treatment and dosing patterns, and clinical endpoints
- Data were de-identified and complied with the patient confidentially requirements of the Health Insurance Portability and Account Act
  - All study materials were approved by the Institutional Review Board or Ethics Committee at each clinical site

1. Modlin IM, Lye KD, Kidd M. *Cancer* . 2003 Feb 15;97(4):934-59.
2. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors.* Version 3.2017 (2017).

Statistical Analyses

- Data collected from all centers were pooled for the analysis
- Descriptive statistics were calculated using frequencies and proportions for categorical variables and means, standard deviations, and medians for continuous variables
  - Baseline characteristics were examined for heterogeneity across sites using *P*-values computed with a global chi-squared test (or Fisher's exact test as appropriate) for categorical variables and Kruskal-Wallis test for continuous variables
- Time to treatment discontinuation and overall survival were estimated using Kaplan-Meier analysis, where patients who did not have an event were censored at the date of death or the date of last contact
  - Time to treatment discontinuation was defined as time from treatment initiation to treatment discontinuation. Discontinuation was considered as the first one-month gap between treatments for the same therapy with the exception of LDT, for which the gap was six months between LDT treatments
  - Overall survival was defined as the time from treatment initiation to death

Results

Demographic and Clinical Characteristics

- Among the 273 patients included in this study, half were female (50%) and the majority were Caucasian (83%), with mean age of 59 years at advanced NET diagnosis (**Table 1**)

Table 1. Demographic Characteristics

	All Patients (N=273)
Age at advanced NET diagnosis (years), mean (SD)	59.0 (11.6)
Female, N (%)	137 (50.2%)
Race, N (%)[1]	
Caucasian	226 (82.8%)
Black or African American	18 (6.6%)
Hispanic or Latino	17 (6.2%)
Asian/Pacific Islander	5 (1.8%)
Native American/American Indian	1 (0.4%)
Unknown/not sure	7 (2.6%)

Abbreviations: NET, neuroendocrine tumor; SD, standard deviation.
[1]Multiple responses were allowed, so counts and percentages may not sum to the total N or 100%.

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Results (contd.)

- 70% (N=191) of patients had comorbidities, the most common being hypertension (42%, N=114), other non-pancreatic cancers (13%, N=35), diabetes with or without end-organ damage (12%, N=34), and hyperlipidemia (11%, N=31); 3% (N=7) had confirmed or suspected hereditary cancer syndrome or family history of NET
- The majority of patients were diagnosed with functional NET 64% (N=174), of whom 99% (N=173) had carcinoid syndrome and 1% (N=1) had gastrinoma
  - Most common carcinoid syndrome symptoms were diarrhea 87% (N=150) and flushing 73% (N=127)
- The most common primary site of NET was ileum (57%), and the most common sites of metastases were liver (86%) and lymph nodes (45%) (**Table 2**)
- The mean number of metastases at advanced NET diagnosis was 1.4 (**Table 2**)
  - Ki-67 proliferation index was available for 45% (N=124) of patients, with a median proliferation index of 2% (interquartile range: 1%–5%)
  - Mitotic rate was available for 50% (N=137) of patients, with a median rate of 1 (interquartile range: 1–2) mitosis per 10 high power fields
  - KI-67 and mitotic rate were not available for 34.4% of the patients, but their charts specified the histologic differentiation or tumor grade

Table 2. Clinical Characteristics

	All Patients (N=273)
Primary site of NET, N (%)[1]	
Ileum	156 (57.1%)
Rectum	9 (3.3%)
Jejunum	8 (2.9%)
Duodenum	5 (1.8%)
NET of unknown origin	3 (1.1%)
Other GI[2]	85 (31.1%)
Unknown	7 (2.6%)
Metastasis sites at advanced NET diagnosis (number of sites), mean (SD)	1.4 (0.8)

Abbreviations: NET, neuroendocrine tumor; SD, standard deviation.
[1]Multiple responses were allowed, so counts and percentages may not sum to the total N or 100%.
[2]Other primary NET sites include ampulla, appendix, cecum, colon, small bowel (exact site unknown), small bowel mesentery, small intestine, and stomach.

Treatment Sequences

- Majority of patients were treated with SSAs: octreotide alone (88%) or in combination (2%) with LDT, targeted therapy, or chemotherapy, and pasireotide alone (0.4%; 60-120 mg/month) as *first-line* therapy (**Table 3**)
  - No patients received lanreotide in first line, which may have been due to the study eligibility period (July 1, 2011-December 31, 2014) that occurred prior to lanreotide's approval on December 16, 2014
  - Other first-line treatments included LDT (8%) and cytotoxic chemotherapy or interferon (2%)
- Of the 155 patients on *second-line*, 93% were treated with SSAs: octreotide alone or in combination (89%), lanreotide (3%; 90-120 mg/4 weeks), and pasireotide (1%) (**Table 3, next slide**)
  - Other second-line therapies included LDT (4%) and targeted therapy, cytotoxic chemotherapy, or external-beam radiation therapy (3%)

Table 3. Treatment Regimens Received in the First Two Lines of Treatment

	All Patients with Treatment Information[1]
First line, N (%)	**(N=272)**
SSA	246 (90.4%)
Octreotide	240 (88.2%)
Octreotide combinations	5 (1.8%)
Octreotide, everolimus, and other	1 (0.4%)
Octreotide and LDT[2]	1 (0.4%)
Octreotide and other	3 (1.1%)
Pasireotide	1 (0.4%)
Cytotoxic chemotherapy	4 (1.5%)
Interferon alpha	1 (0.4%)
LDT[2]	21 (7.7%)

Abbreviations: LDT, liver-directed therapy; SSA, somatostatin analog.
[1]Any overlap of individual treatments was identified as a combination treatment. Treatments that were less than 14 days in duration (other than procedures) were excluded. Only patients who had information about when treatment was started and ended/discontinued or on going were included.
[2]LDT includes radioembolization, liver resection, transarterial chemoembolization, transarterial embolization, bland embolization, radiofrequency ablation, liver ablation, hepatic arterial embolization, and microwave ablation.
[3]Patients receiving octreotide and pasireotide as second-line therapy are not receiving these treatments concurrently, but rather receive them in close succession within the same time period.

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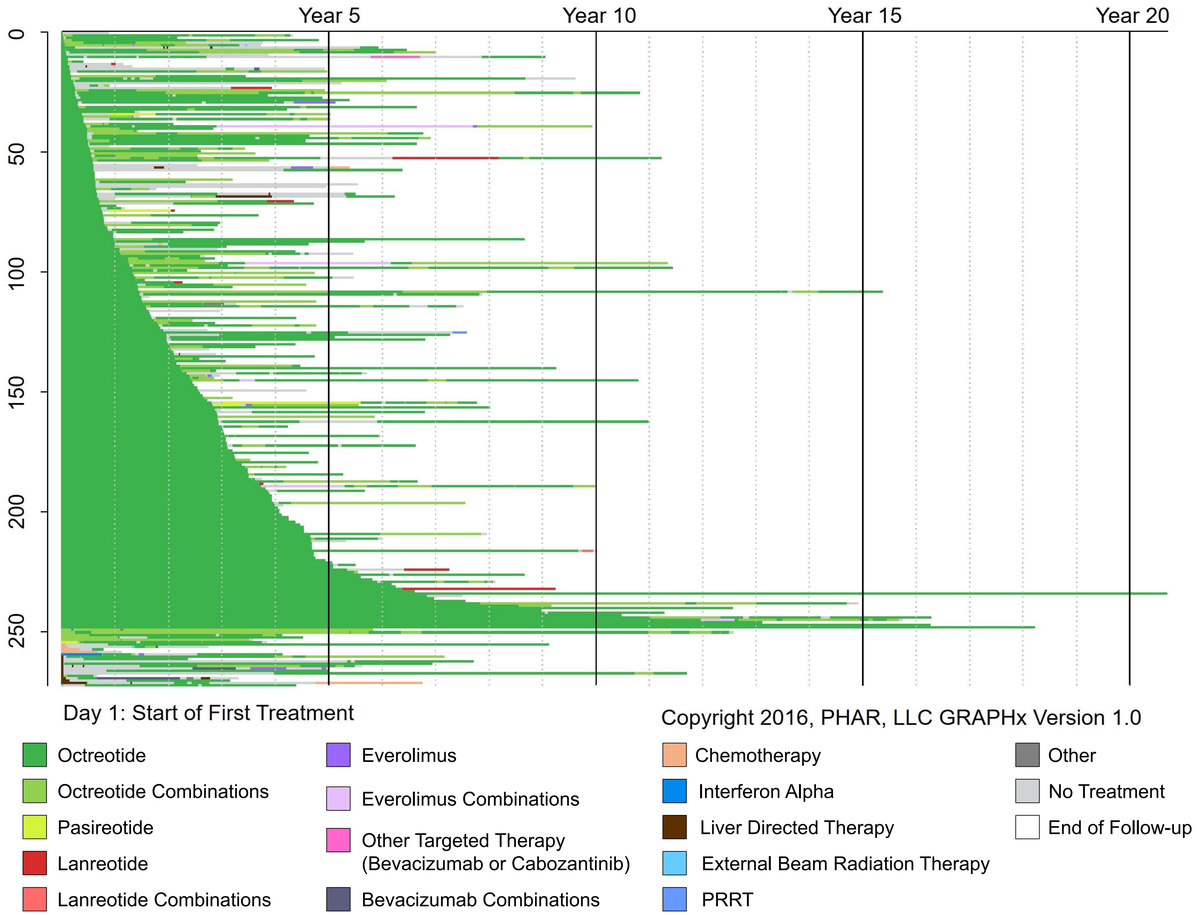
Table 3. Treatment Regimens Received in the First Two Lines of Treatment (contd.)

	All Patients with Treatment Information[1]
Second line, N (%)	**(N=155)**
SSA	144 (92.9%)
Octreotide	17 (11.0%)
Octreotide combinations	117 (75.5%)
Octreotide and bevacizumab	4 (2.6%)
Octreotide and cabozantinib	6 (3.9%)
Octreotide and cytotoxic chemotherapy	12 (7.7%)
Octreotide and everolimus	23 (14.8%)
Octreotide and external beam radiation	2 (1.3%)
Octreotide and interferon alpha	6 (3.9%)
Octreotide and LDT[2]	57 (36.8%)
Octreotide and PRRT	4 (2.6%)
Octreotide and other	13 (8.4%)
Octreotide and pasireotide[3]	4 (2.6%)
Lanreotide	5 (3.2%)
Pasireotide	1 (0.6%)
Bevacizumab and cytotoxic chemotherapy	2 (1.3%)
Everolimus	1 (0.6%)
External beam radiation	2 (1.3%)
LDT[2]	6 (3.9%)

Abbreviations: LDT, liver-directed therapy; PRRT, peptide receptor radiotherapy; SSA, somatostatin analog.
[1]Any overlap of individual treatments was identified as a combination treatment. Treatments that were less than 14 days in duration (other than procedures) were excluded. Only patients who had information about when treatment was started and ended/discontinued or on going were included.
[2]LDT includes radioembolization, liver resection, transarterial chemoembolization, transarterial embolization, bland embolization, radiofrequency ablation, liver ablation, hepatic arterial embolization, and microwave ablation.
[3]Patients receiving octreotide and pasireotide as second-line therapy are not receiving these treatments concurrently, but rather receive them in close succession within the same time period.

- **Figure 1** illustrates the long-term treatment duration of octreotide (median treatment duration of 12.0 years [min:0.2, max: 20.7 years]). Duration of therapies are shown for individual patients over their entire course of treatment

Figure 1. Treatment Sequences



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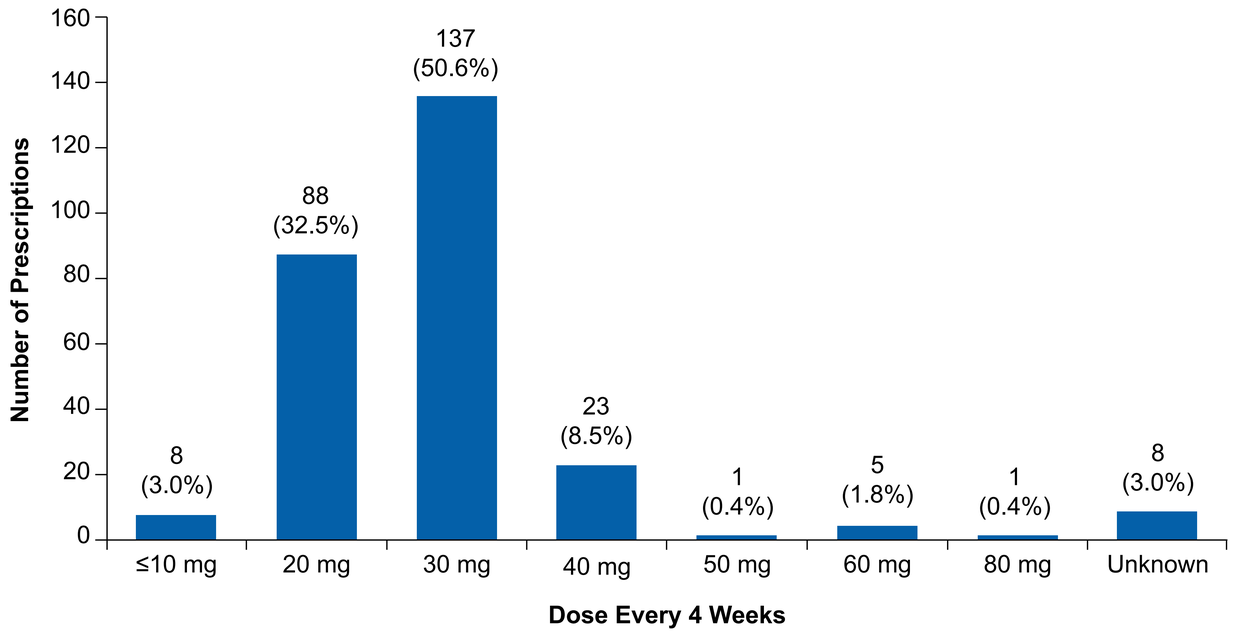
Dose Patterns of Octreotide Use

- In evaluating octreotide dosages administered during the observation period, most patients (86%) initiated octreotide with a dose of 30 mg/4 weeks or less (**Figure 2**)

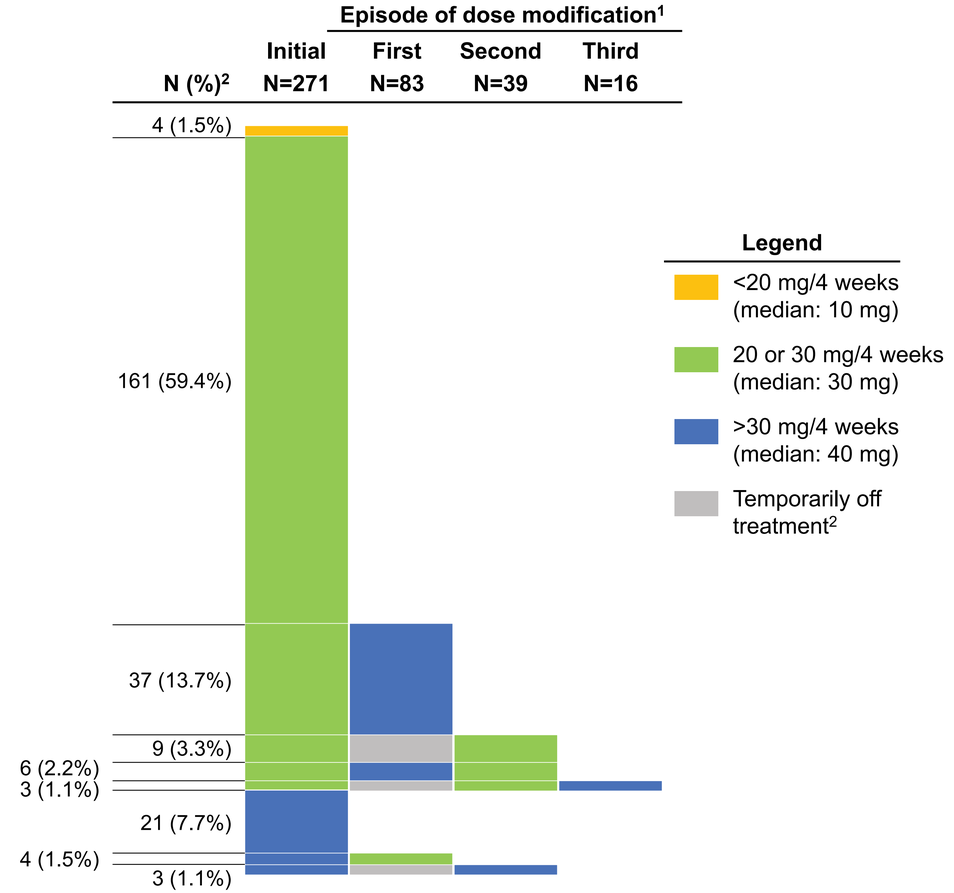
Figure 2. Octreotide Dose at Treatment Initiation[1] (N=271)



Abbreviation: MG, milligram.
[1]Reported dose includes dosage of short-acting or long-acting octreotide, standardized to milligrams per 4 weeks, rounded to the nearest multiple of 10.

- Dose modification occurred in 83 patients (31%), with a maximum of 5 instances of modification (**Figure 3**)
  - The majority of octreotide-treated patients (65%, N=177) never received a dose greater than 30 mg/4 weeks of octreotide throughout the disease course

Figure 3. Octreotide Dose Modifications



Abbreviation: MG, milligram.
[1]Dose modification patterns reflecting less than 1% of the patient population are not shown. In total, this includes 23 patients.
[2]Temporarily off treatment denotes lapses in treatment longer than 60 days.

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Treatment Discontinuation

- The median time to treatment discontinuation for first-line treatments was 154.0 (95% confidence interval [CI]: 95.1-not reached) months for SSAs and was 144.5 (95% CI: 83.0-177.4) months for octreotide alone, specifically (functional NET: 144.5; non-functional NET: 117.1)
  - For cytotoxic chemotherapy, median time to first-line discontinuation was 3.8 (95% CI: 2.0-9.2) months

Overall Survival

- Median overall survival among patients with advanced GI NET following first-line therapy was 151.8 (95% CI: 95.5-188.9) months
  - 28% of patients died
- Patients who received first-line treatment with octreotide had median overall survival of 178.9 (95% CI: 95.5-188.9) months (functional NET: 178.9; non-functional NET: 115.4)

Limitations

- Treatment sequences and discontinuation information are based on data recorded in patient medical charts
- Short- and long-acting octreotide could not be distinguished in the data, and so they were reported combined
- Results reported in this study are based on data collected at four cancer referral centers and may not be reflective of practice patterns observed in other institutions
- Lack of information about patients' care at outside institutions may result in underreporting of treatments received (i.e., patients may have received additional therapy at another institution that was not captured at institution participating in this study)
- This study is descriptive; no statistical comparisons were performed

Conclusions

- This study showed that SSAs, specifically long-acting octreotide observed in this study, are widely used in treating advanced GI NET in first- and second-line therapy
- Patients remain on SSA long-term
- Multiple lines of therapy are commonly used
- Patients with advanced GI NET have relatively long overall survival

Disclosures

- This study was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
- MPN and BC are employees of Novartis Pharmaceuticals Corporation (NPC), the sponsor of this study. LH, TT, NR, and MSD are employees of Analysis Group, Inc., which has received funding for this and other studies from NPC. MHK, ABB, AD, and EKB are employees of institutions, which have received research funding from NPC

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Text: Qdcb53
To: 8NOVA (86682) US Only
+18324604729 North, Central and South Americas; Caribbean; China
+447860024038 UK, Europe & Russia
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