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Authors

Hendifar, Andrew E
Dhall, Deepti
Strosberg, Jonathan R

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Endocrinology

The Evolving Treatment Algorithm for Advanced Neuroendocrine Neoplasms: Diversity and Commonalities Across Tumor Types

Andrew E. Hendifar,[a] Deepti Dhall,[a] Jonathan R. Strosberg[b]

[a]Department of Medicine and Pathology, Cedars-Sinai Medical Center, Los Angeles, California, USA; [b]H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neuroendocrine • Carcinoid • Gastrointestinal • Lung • Pancreas

Abstract

Neuroendocrine neoplasms (NEN) most commonly arise in the gastroenteropancreatic system and lungs. The incidence of NEN is increasing globally, with improved diagnostic techniques identifying patients with early-stage disease. The number of approved therapies for the treatment of advanced disease has grown substantially in the past decade. The treatment algorithm for advanced NEN is evolving from one that is directed by primary site–specific classification to one that is directed by biologic classification, as evidenced by overlapping systemic treatments across the primary tumor sites. Commonalities in biologic characteristics across primary sites include functional status, differentiation status, grade, level of somatostatin receptor expression, and genetic alterations. In this review, we discuss current clinical evidence and available therapies for the treatment of advanced NEN and highlight the need for prospective trials in patients with well-differentiated, high-grade NEN. ***The Oncologist*** 2019;24:54–61

Implications for Practice: This review raises awareness of the evolution of the treatment algorithm for advanced neuroendocrine neoplasms (NEN) from one that is directed by primary tumor site–specific classification to one that is directed by biologic classification. In addition, this review promotes understanding of the new pathologic category of well-differentiated G3 pancreatic neuroendocrine tumors and highlights the need for prospective trials in this patient population, for whom there is currently no standard of care. This review further provides a conceptual treatment schematic that categorizes the recommendations for systemic treatments for advanced disease by biologic classification, including the new and established categories of NEN.

Introduction

Neuroendocrine neoplasms (NEN) most commonly arise in the gastroenteropancreatic (GEP) system and lungs [1,2]. The term NEN encompasses both well-differentiated (WD) neuroendocrine tumors (NET) and poorly differentiated (PD) neuroendocrine carcinomas (NEC). Many symptoms associated with NEN are nonspecific, such as abdominal pain, diarrhea, flushing, and bowel obstruction, which may lead to delays in diagnosis [3]. The rates of NEN diagnosed each year have increased steadily since the early 1970s [1,2,4], possibly as a result of improvements in diagnostic techniques and the increased detection of asymptomatic early-stage disease [1].

NEN are currently classified by functional status, tumor cell differentiation and grade, somatostatin receptor (SSTR) expression, and, more recently, their genetic alterations. In this review, we present recent epidemiologic data and summarize the biologic characteristics of NEN. We also review pivotal clinical evidence regarding systemic treatments for advanced disease and provide a conceptual schematic of systemic treatments based on tumor classification for advanced NEN.

Epidemiology

Recent estimates of the incidence and prevalence of NEN in the United States are based on nationally representative data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which includes comprehensive data from 64,971 patients diagnosed with NEN between 1973 and 2012 (excluding small-cell lung carcinoma [SCLC] and large-cell neuroendocrine carcinoma [LCNEC] of the lung, pheochromocytoma, paraganglioma, and medullary carcinoma of the thyroid) [1,5].

Correspondence: Andrew E. Hendifar, M.D., Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, California 90033, USA. Telephone: 310-423-2217; e-mail: andrew.hendifar@cshs.org Received March 26, 2018; accepted for publication June 5, 2018; published Online First on August 13, 2018. http://dx.doi.org/10.1634/theoncologist.2018-0187

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Although the total incidence of malignant neoplasms has remained relatively stable over the past 40 years, the incidence of NEN has increased—by 6.4-fold between 1973 and 2012, from 1.09 to 6.98 per 100,000 persons [1]. This increase in incidence occurred across all sites and stages, although localized disease was markedly increased, from 0.21 to 3.15 per 100,000 persons [1]. The greatest increases in incidence for individual primary tumor sites occurred in the stomach (15-fold) and rectum (9-fold); the increased incidence at these sites may be associated with the increased use of endoscopic procedures in clinical practice [1]. The prevalence of NEN has also increased significantly in the past 20 years, from 0.006% in 1993 to 0.048% in 2012, which may be explained by the increased incidence of NEN and the increased diagnosis of early-stage disease [1]. For NEN diagnosed in the U.S. between 2000 and 2012, the highest incidences were for lung carcinoid tumors (1.49 per 100,000 persons), gastroenteropancreatic (GEP) sites (3.56 per 100,000), and unknown primary site (0.84 per 100,000) [1]. The small intestine (1.05 per 100,000 persons) and rectum (1.04 per 100,000) were the most common GEP primary sites, and the pancreas had an incidence of 0.48 per 100,000 [1].

Survival

Recent epidemiologic analyses of SEER data have demonstrated a decreased risk of death for those diagnosed with NEN from 2005 to 2012 versus those diagnosed from 2000 to 2004 in the U.S. [1]. Those diagnosed between 2005 and 2008 had a 17.1% lower risk of death (hazard ratio [HR] = 0.83, 95% confidence interval [CI] = 0.78–0.89), and those diagnosed in the 2009–2012 period had a 21.3% lower risk of death (HR = 0.79, 95% CI = 0.74–0.85). This improvement in survival for patients with NEN of all grades/stages in recent years may be due to increased diagnosis of more indolent NEN identified by improved imaging procedures, which would have previously gone undetected until a later stage [1]. Decreased risk of death was particularly notable ($p < .001$ vs. 2000–2004) in the subgroup with metastatic gastrointestinal (GI) NEN (2009–2012: HR = 0.71, 95% CI = 0.63–0.82) and metastatic pancreatic NEN (2009–2012: HR = 0.56, 95% CI = 0.44–0.71). Improvement in survival for patients with metastatic NEN likely reflects improvements in therapies [1].

Functional Status

Neuroendocrine cells can produce a variety of amine and peptide secretory products, which may produce clinical syndromes in NEN [6]. Classification of NEN as functional or nonfunctional is based on the presence or absence of symptoms related to these hypersecretory syndromes [7].

Carcinoid syndrome results from hypersecretion of vasoactive amines, including serotonin, histamine, tachykinins, and prostaglandins [7]. The cardinal features of carcinoid syndrome are diarrhea (frequency 60%–80%) and flushing (frequency 60%–85%), and a severe complication of carcinoid syndrome is carcinoid heart disease (frequency ≤20%). Carcinoid syndrome is a common functional syndrome in WD-NET originating in the ileum [8]. A recent analysis of the SEER registry linked with Medicare claims data identified 1,786 patients diagnosed with both NET and carcinoid syndrome between 2000 and 2011 in the United States; 19% of these patients received a diagnosis of carcinoid syndrome within 6 months of being diagnosed with NET [9]. Carcinoid syndrome was most common in patients with WD G1/2, distant metastatic disease originating in the small intestine (56%; 242/436) or the cecum (52%; 28/54).

Carcinoid syndrome occurring in patients with a pancreatic primary tumor is very rare [10], owing to the absence of serotonin-producing cells in the normal pancreas [9]. Common functional syndromes occurring in pancreatic NET are insulinoma and Zollinger-Ellison syndrome [10]. Although the majority (70%) of Zollinger-Ellison syndrome cases have a duodenal primary tumor location, 25% are associated with a pancreatic primary [10]. Less common functional syndromes include VIPoma, glucagonoma, and somatostatinoma, named after the biologically active peptide that is secreted [10]. In recent studies, between 60% and 90% of pancreatic NEN have been classified as nonfunctional [10,11]. SEER data analyzed from 1973 to 2000 demonstrated that only 10% (137/1483) of pancreatic NEN were functional, and this frequency did not increase in metastatic disease (8.4%; 75/893) [12].

Cell Differentiation and Grading

Grading of GEP NEN is assessed by mitotic rate and/or Ki-67 index [13]. According to the World Health Organization (WHO) classification, NEN are separated into WD and PD tumors based on their cell morphology [13,14]. PD tumors are further classified as small-cell or large-cell morphology [13]. Previously, the differentiation of GEP NEN was assumed to be directly correlated with grade—all low- to intermediate-grade (G1 or G2) NEN were classified as WD-NET, and all high-grade (G3) NEN were classified as PD-NEC [13]. However, G3 NEN are now known to be heterogeneous, comprising both WD-NET with elevated proliferative index (Ki-67 >20%) and PD-NEC (Fig. 1A) [15,16]. Accordingly, a new category of G3 WD-NET has been recognized in the WHO classification of tumors of endocrine organs, which refers specifically to pancreatic NEN [17]. Although these tumors have a somewhat worse prognosis than G2 WD-NET, they are less aggressive than G3 PD-NEC [17]. Distinguishing G3 WD-NET from G3 PD-NEC based on cell morphology can be difficult and may require correlation with clinical history, imaging findings, and molecular phenotype [18,19].

Lung and thymic NEN are currently classified by the WHO classification into four major categories: typical carcinoid (TC; low grade); atypical carcinoid (AC; intermediate grade), SCLC (high grade), and LCNEC (high grade) [20,21]. Key criteria for the differential diagnosis of lung NEN include mitotic rate, necrosis, and Ki-67 index, although the utility of Ki-67 to discriminate TC from AC is not currently established [20]. Ki-67 proliferation indices provided by the classification are as follows: TC, up to 5%; AC, up to 20%; LCNEC, 40%–80%; and SCLC, 50%–100% [20]. Preliminary evidence suggests that lung NEN, like GEP NEN, may

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include G3 WD-NET with a Ki-67 index exceeding 20% (or mitotic count >10 per 2 mm^2), and these patients have a poorer prognosis than those with G2 WD-NET [22,23].

Preliminary evidence suggests that lung NEN, like GEP NEN, may include G3 WD-NET with a Ki-67 index exceeding 20% (or mitotic count >10 per 2 mm^2), and these patients have a poorer prognosis than those with G2 WD-NET.

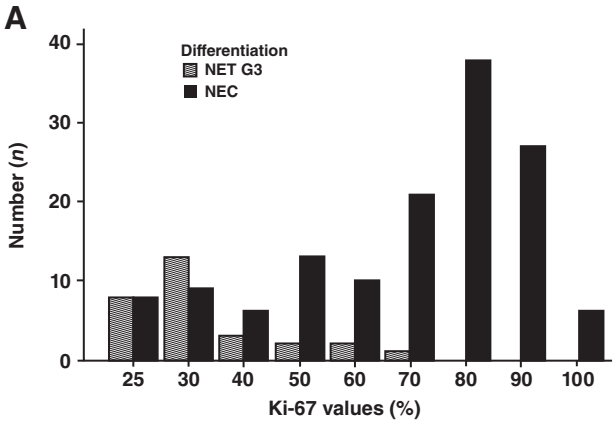
SSTR Expression

SSTRs are highly expressed in NET, with approximately 80% of GEP NET expressing SSTRs [24]. There are five subtypes of SSTR, and the protein/mRNA expression of these SSTRs differ among GEP and lung NET [24,25]. Using receptor subtype antibodies, $SSTR_2$ is expressed by 86% of GEP NET and 40% of lung carcinoids [24,25]. Recent evidence has also demonstrated high expression of $SSTR_{2A}$ in G3 WD-NET (80%), whereas G3 PD-NEC lacks significant expression (16%) [19].

Given the high expression of SSTRs in NET, they are useful for diagnostic imaging. The radiopeptide ^{111}In-pentetreotide binds to $SSTR_{2A}$ and has been the mainstay for diagnostic imaging of NET [26]. This technique has a sensitivity of 60%–80% [26]. Newer SSTR-based positron emission tomography (PET) scans, including ^{68}Ga-DOTA-TATE, -TOC, and -NOC, offer substantially higher sensitivity and improved spatial resolution compared with ^{111}In-pentetreotide-based somatostatin receptor scintigraphy [27]. ^{68}Ga-DOTA PET/computed tomography (CT) has therefore replaced ^{111}In-pentetreotide as the method of choice to localize and stage NET, with a sensitivity of 88%–93% and a specificity of 88%–95% [26]. This has resulted in a significantly higher overall accuracy with ^{68}Ga-DOTA PET/CT (0.94, 95% CI = 0.89–1.00) versus ^{111}In-pentetreotide (0.82, 95% CI = 0.74–0.90) [28].

Genetic Landscape

Most NEN are sporadic; fewer than 5% of GEP NEN have inherited mutations [6]. No activating mutations have been identified, with inherited mutations resulting in a loss of tumor suppressor genes. Somatic alterations are identified in 1%–50% of GEP NEN; these typically involve mutations, loss of heterozygosity, and chromosomal changes that lead to activated signaling pathways such as PI3K/AKT/mTOR [6]. In pancreatic NET, the *MEN1* gene is somatically inactivated in 45% of patients, alterations in mTOR pathway genes are evident in 15% [17], and loss of *DAXX* or *ATRX* occurs in 43% [29]. The loss of *DAXX/ATRX* is associated with chromosome instability and reduced survival [30]. The genetic alterations in pancreatic PD-NEC are considerably different from those in pancreatic WD-NET; there are often mutations in *TP53* and *RB1*, whereas *MEN1*, *ATRX*, and *DAXX* are not altered [17,31]. Conversely, *RB1* and *TP53* mutations have not been identified in pancreatic WD-NET [31]. The genetic landscape of pancreatic G3 WD-NET is more similar to that of G1/G2 NET than to PD-NEC [18]. It has been proposed that G3 WD-NET arises from progression of G1/G2 WD-NET and is a biologically different entity from G3 PD-NEC (Fig. 1B) [32]. Differential diagnosis of G3 WD-NET from G3 PD-NEC may be assisted by application of molecular markers *TP53, RB1, ATRX,* and *DAXX* [18] in conjunction with Ki-67 proliferation index and $SSTR_{2A}$ expression [19].



Neuroendocrine neoplasm	Morphology (differentiation)	Grading G1–G3 (Ki-67 index)
Neuroendocrine tumor grade 1	Well differentiated	G1 (≤2%)
Neuroendocrine tumor grade 2	Well differentiated	G2 (3%–20%)
Neuroendocrine tumor grade 3	Well differentiated	G3 (>20%)
Neuroendocrine carcinoma	Poorly differentiated (large or small cell)	G3 (>20%)

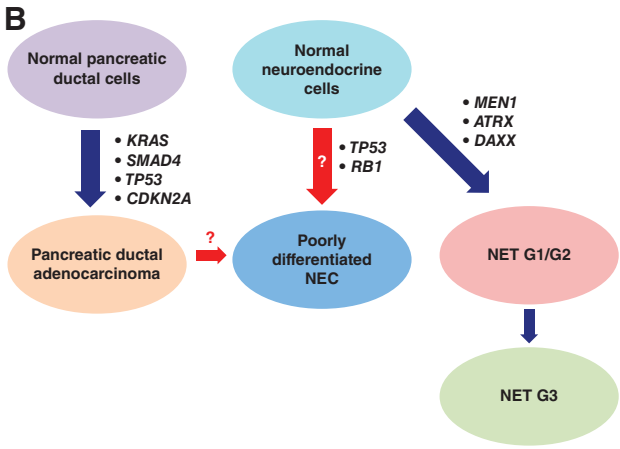


Figure 1. Grade 3 NEN: classification according to cell morphology, tumor grade, and genetic alterations. **(A):** Ki-67 distribution according to differentiation in G3 gastroenteropancreatic neuroendocrine neoplasms and division into two groups based on cell morphology and tumor grade. (Reproduced from Heetfeld M et al. Endocr Relat Cancer 2015;22:657–664. © 2015 Society for Endocrinology. Copyright material reproduced under a license from the Society for Endocrinology. All rights reserved.) **(B):** Conceptual diagram showing the putative genetic development of pancreatic G3 WD-NET or G3 PD-NEC. (Adapted with changes from Ohmoto A, Rokutan H, Yachida S. Pancreatic neuroendocrine neoplasms: Basic biology, current treatment strategies and prospects for the future. Int J Mol Sci 2017;18:143, and licensed under the Creative Commons Attribution License [CC BY 4.0], https://creativecommons.org/licenses/by/4.0/.)
Abbreviations: G, grade; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumors; PD, poorly differentiated; WD, well-differentiated.

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Lung carcinoid tumors display a very low somatic mutation rate (0.4 per Mbps), whereas SCLC and LCNEC have the highest rates (>7 per Mbps) in human tumors [20]. *TP53* and *RB1* mutation and inactivation are rare in TC (<5%) but more frequent in AC (20%). TC and AC may contain *MEN1* mutations in sporadic cases (40%). SCLC and LCNEC are driven by inactivating mutations in the *RB* and *TP53* genes and never harbor *MEN1* somatic mutations [20]. Although double genetic inactivation of *TP53* and *RB* is universal in SCLC [20], it is not in LCNEC, with *TP53* altered in 78% of cases and *RB1* in 38% [33]. Current data support the notion that lung carcinoid tumors are genetically distinct from high-grade lung tumors and are therefore not early progenitors of SCLC or LCNEC, whereas TC and AC have no genetic segregation and appear to derive from the same progenitor [20]. Molecular markers for WD G3 lung NET have not been examined at this time.

Pivotal Clinical Evidence: Treatments for Tumor Control in Advanced NET

An overview of the patient characteristics and primary endpoint results from each prospective randomized clinical trial are provided in Table 1 [34–40]. Two key studies have demonstrated the antiproliferative effect of somatostatin analogues (SSAs) in advanced GEP NET: PROMID and CLARINET. The PROMID trial showed a significant prolongation in the median time to tumor progression with long-acting octreotide 30 mg every 28 days (q28d) versus placebo (14.3 vs. 6.0 months, HR = 0.34, 95% CI = 0.20–0.59, p = .000072) in patients with midgut NET. Patients with functional or nonfunctional tumors had similar responses, whereas the antiproliferative response was more pronounced in those with a low hepatic tumor load (≤10%) (p = .0023) [34]. The CLARINET trial demonstrated a significant prolongation in median progression-free survival (PFS) with lanreotide 120 mg q28d versus placebo (not reached vs. 18.0 months, HR = 0.47, 95% CI = 0.30–0.73, p < .001) [35]. Patients appeared to experience a PFS benefit from lanreotide treatment regardless of hepatic tumor volume or grade. Hazard ratios for disease progression in patients with primary tumor sites in the midgut (0.35, 95% CI = 0.16–0.80) and pancreas (0.58, 95% CI = 0.32–1.04) also appeared to favor lanreotide over placebo; however, the benefit of lanreotide for patients with a hindgut primary NET is unclear due to the small sample size of this subpopulation (n = 14) [35].

Sunitinib is approved for the treatment of advanced progressive WD pancreatic NET [41], based on the demonstration of an extended PFS with sunitinib versus placebo (median 11.4 vs. 5.5 months, HR = 0.42, 95% CI = 0.26–0.66, p < .001) [39]. Patients with nonfunctional tumors appeared to experience a greater PFS benefit (HR = 0.26, 95% CI = 0.13–0.54) versus those with functional tumors (HR = 0.75, 95% CI = 0.30–1.84) [39].

Everolimus is approved for the treatment of advanced, progressive, nonfunctional NET of the pancreas, GI tract, and lung [42,43], due to positive results from RADIANT-3 and RADIANT-4; a significant benefit in median PFS was demonstrated with everolimus in patients with advanced progressive pancreatic NET in RADIANT-3 (11.0 vs. 4.6 months, HR = 0.35, 95% CI = 0.27–0.45; p < .001) [37] and in patients with advanced progressive nonfunctional NET of the GI tract or lung in RADIANT-4 (11.0 vs. 3.9 months, HR = 0.48, 95% CI = 0.35–0.67, p < .00001) [38]. In RADIANT-4, the PFS benefit with everolimus compared with placebo was observed regardless of tumor grade or primary site [38]. Furthermore, health-related quality of life was preserved with everolimus treatment versus placebo [44].

RADIANT-2 compared everolimus and placebo, both in combination with long-acting octreotide 30 mg q28d, in patients with progressive, low- or intermediate-grade NET and a history of secretory symptoms attributed to carcinoid syndrome [36]. This trial did not lead to the approval of everolimus plus long-acting octreotide for functional NET. RADIANT-2 demonstrated a PFS benefit with everolimus versus placebo (median 16.4 vs. 11.3 months, HR = 0.77, 95% CI = 0.59–1.00, p = .026); however, the prespecified significance boundary of p = .0246 was not met [36]. A subgroup analysis indicated a potentially higher PFS benefit for everolimus in patients with NET originating in the colon (median 29.9 vs. 13.0 months, HR = 0.39) in comparison with those with NET originating in the small intestine (median 18.6 vs. 14.0 months, HR = 0.77) [36]. A subsequent analysis of the colorectal subgroup (n = 39) in RADIANT-2 confirmed this benefit in patients with hindgut NET, with a significant prolongation in median PFS with everolimus versus placebo (29.9 vs. 6.6 months, HR = 0.34, 95% CI = 0.13–0.89, p = .011) [45]. These findings suggest that the overall PFS benefit provided by everolimus may be lower in patients with slow-growing midgut NET and higher in those with the more aggressive hindgut NET. A RADIANT-4 subgroup analysis also provides support for a higher PFS benefit with everolimus in patients with nonmidgut NET (median 8.11 vs. 1.94 months; HR = 0.27, 95% CI = 0.15–0.51) versus midgut NET (median 17.28 vs. 10.87 months, HR = 0.71, 95% CI = 0.40–1.26) [46]. Importantly, a consistent positive treatment effect of everolimus was demonstrated in the jejunal (median PFS 17.3 vs. 4.5 months, HR = 0.37, 95% CI = 0.08–1.64) but not the ileal subgroup (median PFS 16.6 vs. 16.7 months, HR = 1.22, 95% CI = 0.56–2.65) of the RADIANT-4 trial.

^{177}Lu-Dotatate peptide receptor radionuclide therapy has demonstrated efficacy in many clinical studies of GEP NET in the past decade [47]. ^{177}Lu-Dotatate was recently approved by the European Medicines Agency and the U.S. Food and Drug Administration for advanced GEP NET based on the phase III NETTER-1 trial [40]. Treatment with ^{177}Lu-Dotatate (plus best supportive care of long-acting octreotide 30 mg every 4 weeks [q4w]) resulted in a markedly longer PFS versus the control group (long-acting octreotide 60 mg q4w) in patients with advanced midgut NET and radiologic progression on a standard dose of long-acting octreotide. At the time of data cutoff for the primary analysis, median PFS was not yet reached with ^{177}Lu-Dotatate versus 8.4 months in the control group (HR = 0.21, 95% CI = 0.13–0.33, p < .001) [40]. A single-arm trial of ^{177}Lu-Dotatate in patients with radiologic progression at baseline demonstrated a median PFS of 31 months in patients with pancreatic NET and 29 months in patients with midgut NET [48].

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Table 1. Pivotal clinical trials in the treatment of advanced G1/G2 NET

Characteristic	PROMID [34] (*n* = 85)	CLARINET [35] (*n* = 204)	RADIANT-2 [36] (*n* = 429)	RADIANT-3 [37] (*n* = 410)	RADIANT-4 [38] (*n* = 302)	Sunitinib phase III [39] (*n* = 171)	NETTER-1 [40] (*n* = 229)
Treatment arms	Long-acting octreotide 30 mg q28d (*n* = 42) vs. placebo (*n* = 43)	Lanreotide 120 mg q28d (*n* = 101) vs. placebo (*n* = 103)	Everolimus 10 mg daily (*n* = 216) vs. placebo (*n* = 213); both with long-acting octreotide 30 mg q28d	Everolimus 10 mg daily (*n* = 207) vs. placebo (*n* = 203)	Everolimus 10 mg daily (*n* = 205) vs. placebo (*n* = 97)	Sunitinib 37.5 mg daily (*n* = 86) vs. placebo (*n* = 85)	^{177}Lu-Dotatate plus long-acting octreotide 30 mg q4w (*n* = 111) vs. long-acting octreotide 60 mg q4w (*n* = 110)
Primary sites	Midgut	Pancreas (45%), midgut (36%), hindgut (7%), or unknown origin (13%)	Small intestine (52%), lung (10%), colon (7%), pancreas (6%), liver (4%), and other NET sites (21%)	Pancreas	Lung (30%), jejunum/ileum (31%), colon/rectum (15%), unknown origin (12%), and other GI sites	Pancreas	Midgut
Tumor grade/differentiation	Well-differentiated; 95.3% had Ki-67 ≤2%	Well- to moderately differentiated (defined as Ki-67 <10% [or ≤2 mitoses per 10 HPF]); 69% had Ki-67 ≤2%, and 29.9% had Ki-67 3%–10%	Low- to intermediate-grade; well-differentiated (79%), moderately differentiated (16%), poorly differentiated (<0.5%), or unknown (4%)	Low- to intermediate-grade; well-differentiated (83%) and moderately differentiated (32.5%)	Well- to moderately differentiated; grade 1 (64.2%) and grade 2 (35.4%)	Well-differentiated	Well-differentiated (defined as Ki-67 ≤20%)
Tumor functional status	Functional or nonfunctional; carcinoid syndrome in 38.8% patients	Nonfunctional	Functional—history of secretory symptoms attributed to carcinoid syndrome	Not specified	Nonfunctional	Functional or nonfunctional; functional (26.9%), nonfunctional (50.3%), or not specified (22.8%)	Not specified
SSTR imaging	74.1% Octreoscan-positive	SRS grade ≥2 (on scale from 0 to 4)	Not specified	Not specified	Not specified	Not specified	SSTR present on all target lesions using SRS
Baseline tumor progression	Not specified	Not specified; approximately 5% had baseline tumor progression	Within 12 months	Within 12 months	Within 6 months	Within 12 months	Within 3 years during treatment with long-acting octreotide (20–30 mg q3–4w for at least 12 weeks)
Primary endpoint	Time to tumor progression: median 14.3 months vs. 6.0 months (HR = 0.34; 95% CI = 0.20–0.59; *p* = .000072)	Progression-free survival: median not reached vs. 18.0 months (HR = 0.47; 95% CI = 0.30–0.73; *p* < .001)	Progression-free survival: median 16.4 months vs. 11.3 months (HR = 0.77; 95% CI = 0.59–1.00; *p* = .026 [NS])	Progression-free survival: median 11.0 months vs. 4.6 months (HR = 0.35; 95% CI = 0.27–0.45; *p* < .001)	Progression-free survival: median 11.0 months vs. 3.9 months (HR = 0.48; 95% CI = 0.35–0.67; *p* < .00001)	Progression-free survival: median 11.4 months vs. 5.5 months (HR = 0.42, 95% CI = 0.26–0.66, *p* < .001)	Progression-free survival: median not reached vs. 8.4 months (HR = 0.21; 95% CI = 0.13–0.33; *p* < .001)

Abbreviations: CI, confidence interval; G, grade; GI, gastrointestinal; HPF, high-power field; HR, hazard ratio; NET, neuroendocrine tumors; NS, not significant; q4w, every 4 weeks; q28d, every 28 days; SRS, somatostatin receptor scintigraphy; SSTR, somatostatin receptor.

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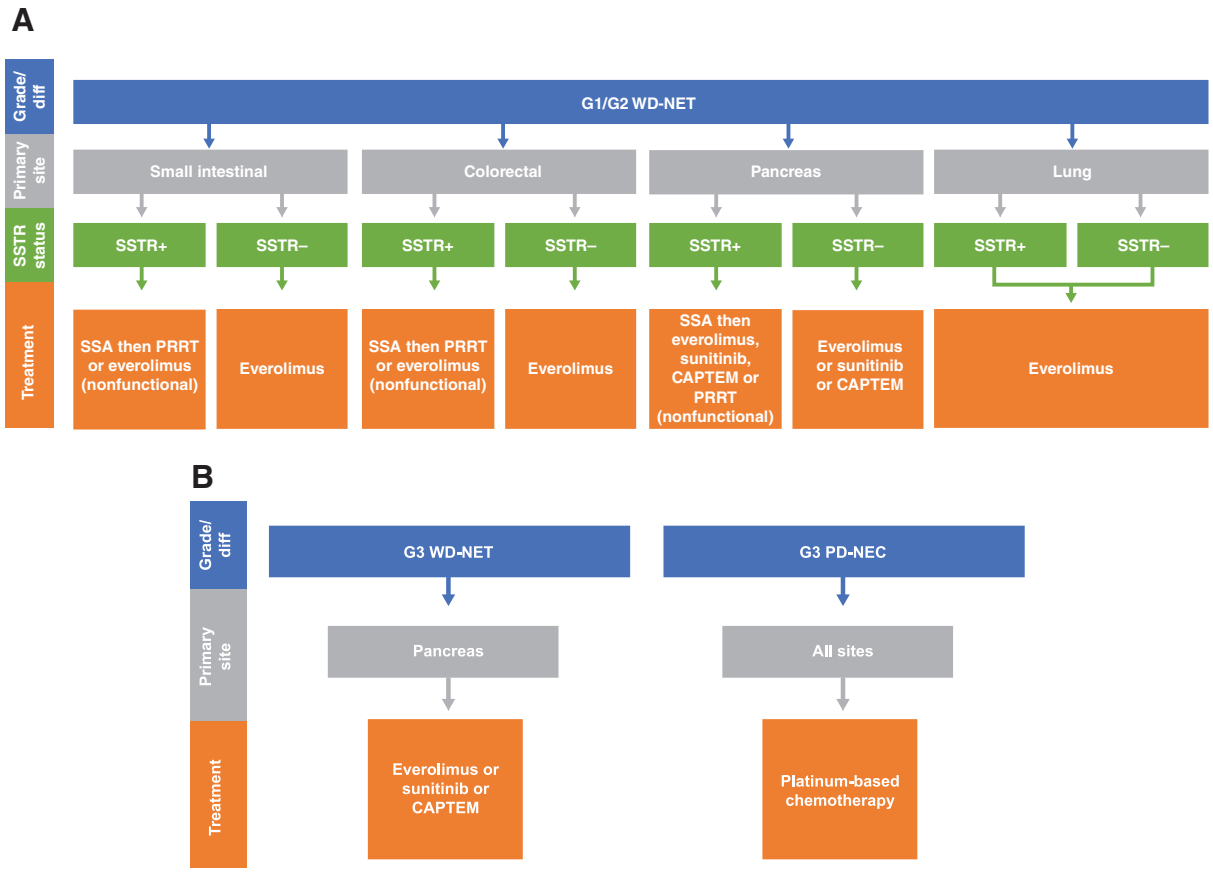

Figure 2. Conceptual systemic treatment schematic for advanced, progressive NET. **(A):** G1/G2 WD-NET. **(B):** G3 WD-NET and G3 PD-NEC. Abbreviations: CAPTEM, capecitabine plus temozolomide; diff, differentiation status; G, grade; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumors; PD, poorly differentiated; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues; SSTR, somatostatin receptor; WD, well-differentiated.

Treatment with capecitabine combined with temozolomide chemotherapy has shown efficacy in recent retrospective clinical studies of pancreatic NET, with an objective response rate (ORR) ranging from 53% to 70% and a median PFS of 16.5 to >18 months [49]. The efficacy of this treatment approach is undergoing validation in a phase II study of capecitabine + temozolomide versus temozolomide monotherapy in patients with advanced low- to intermediate-grade pancreatic NET (NCT01824875).

Pivotal Clinical Evidence: Treatments for Carcinoid Syndrome

Long-acting octreotide is approved for the treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid tumors [50], based on the results of the randomized clinical trial by Rubin et al., in which complete (no rescue medication) or partial (rescue medication on >2 occasions for ≤5 days) treatment success was demonstrated in 66.7%, 71.4%, and 61.9% of participants treated with long-acting octreotide 10 mg, 20 mg, or 30 mg, respectively [51]. In the recent ELECT clinical trial, lanreotide was found to be effective for the control of carcinoid syndrome symptoms [52]. The adjusted mean percentage of days in which rescue octreotide was used during the 16-week double-blind phase was significantly lower for participants who received lanreotide than for those who received placebo (33.7% vs. 48.5%).

In early 2017, telotristat ethyl was approved for the treatment of carcinoid syndrome diarrhea in combination with SSAs in adults inadequately controlled with SSA therapy alone [53], based on the results of the TELESTAR trial, which assessed the safety and efficacy of telotristat ethyl + SSA therapy in patients with WD metastatic NET and carcinoid syndrome refractory to SSA therapy [54]. Telotristat ethyl at either dose (250 mg t.i.d. or 500 mg t.i.d.) was associated with statistically significant reductions in bowel movement frequency over time compared with placebo; 44% and 42% of participants treated with 250 mg t.i.d. and 500 mg t.i.d., respectively, were classified as responders versus 20% of patients receiving placebo [54].

Evidence for Treatment of G3 PD-NEC

Evidence supports the use of platinum-based chemotherapy in the first-line treatment for G3 PD-NEC regardless of primary site. Median PFS with this first-line treatment is approximately 5.0–5.8 months for patients with G3 PD GEP NEC, SCLC, and LCNEC [15,55,56]. The ORR reported with first-line platinum-based chemotherapy is highest in SCLC (~67%) [55] compared with LCNEC (47%) [56] or G3 PD GEP NEC (35%) [15]. However, high disease control rates

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are reported for both LCNEC (80%) and G3 PD-NEC (68%) [15].

Evolving Treatment Algorithm for Advanced NEN

We present a conceptual treatment schematic for systemic therapy based on tumor classification for advanced NEN (Fig. 2). There is currently no established standard treatment for the new classification of G3 WD-NET, which have a significantly worse response to platinum-based chemotherapy than G3 PD-NEC [15]. Systemic treatments for tumor control in G2 WD-NET should also be considered for G3 WD-NET, given their high SSTR2 expression [19] and consistent molecular profile [32]. An analysis of sunitinib efficacy in a phase II trial reported preliminary evidence of activity in G3 WD-NET [57], indicating that targeted therapies may be appropriate in this clinical situation. Prospective randomized trials are required to determine the effectiveness of therapies for these patients.

There is currently no established standard treatment for the new classification of G3 WD-NET, which have a significantly worse response to platinum-based chemotherapy than G3 PD-NEC. Systemic treatments for tumor control in G2 WD-NET should also be considered for G3 WD-NET, given their high SSTR2 expression and consistent molecular profile.

Conclusion

During recent years, the treatment algorithm for advanced NEN has evolved from one that is directed by primary site–specific classification to one that is directed by biologic classification, with overlapping treatments across the primary sites. Commonalities in biologic characteristics across primary tumor sites include functional/nonfunctional status, WD/PD status, high/low grade, SSTR+/SSTR− status, and genetic alterations, with biologic characteristics guiding treatment decisions in some circumstances. It is therefore important to understand the diversity of and commonalities in biologic characteristics across primary tumor sites as the conception of NET continues to evolve, with new classifications and clinical evidence becoming available.

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Author Contributions

Conception/design: Andrew E. Hendifar
Collection and/or assembly of data: Andrew E. Hendifar, Deepti Dhall, Jonathan R. Strosberg
Data analysis and interpretation: Andrew E. Hendifar, Deepti Dhall, Jonathan R. Strosberg
Manuscript writing: Andrew E. Hendifar, Deepti Dhall, Jonathan R. Strosberg
Final approval of manuscript: Andrew E. Hendifar, Deepti Dhall, Jonathan R. Strosberg

Disclosures

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