Curr. Treat. Options in Oncol. (2019) 20:87
DOI 10.1007/s11864-019-0690-x

Neuroendocrine Cancers (JR Strosberg, Section Editor)

Systemic Therapies for Metastatic Pancreatic Neuroendocrine Tumors

Haley Hauser, BA[1]
Daniela Shveid Gerson, MD[2]
Diane Reidy-Lagunes, MD[3]
Nitya Raj, MD[1,*]

Address
[*,1]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 300 E66th Street, New York, NY, 10065, USA
Email: Rajn@mskcc.org
[2]ABC Medical Center, Sur 136 # 116, Colonia Las Américas, Delegación Álvaro Obregón, 01120, Ciudad de México, Mexico
[3]Chief of Clinical Operations, Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 300 E66th Street, New York, NY, 10065, USA

This article is part of the Topical Collection on *Neuroendocrine Cancers*

Keywords Pancreatic neuroendocrine tumors (panNETs) · Somatostatin analogs (SSAs) · Targeted agents · Chemotherapy

Opinion statement

Over the years, there have been significant advances in systemic treatments for metastatic pancreatic neuroendocrine tumors (panNETs). Despite these advancements, uncertainty remains regarding how to best sequence available therapies. For well-differentiated and metastatic panNETs that are somatostatin receptor (SSTR) avid on functional imaging, first-line therapy typically consists of somatostatin analogs (SSAs), given their favorable toxicity profile and overall low burden for patients. When progression of disease is observed on an SSA, multiple treatment options are available, including the targeted agents everolimus and sunitinib, peptide receptor radionuclide therapy (PRRT), as well as chemotherapy, with the latter often preferred for those panNETs of heavy tumor burden, higher grade, and/or more aggressive behavior clinically and/or radiographically. Here, we review panNET classification, currently available systemic treatments, therapy sequencing, and areas of active investigation to further our treatments for the disease.

Published online: 27 November 2019

Introduction

Neuroendocrine tumors (NETs) represent a heterogeneous group of cancers originating from the diffuse neuroendocrine cell system throughout the body, and most commonly arise from either the lung or gastrointestinal tract [1]. PanNETs comprise of those NETs originating in the pancreas, and are the second most common tumor arising from the pancreas, representing 1–2% of all pancreatic cancers [2, 3]. PanNETs have the potential to secrete hormones (insulin, gastrin, glucagon, vasoactive intestinal peptide, somatostatin) that can sometimes lead to debilitating symptoms for patients. In the presence of metastases, treatment of panNETs is with palliative intent, and while survival for patients with metastatic and progressive panNETs can be measured on the order of years, most patients will die of the disease [4–6].

Many systemic treatments have become available for metastatic panNETs over the years. Most of these therapies have been discovered through the rigorous completion of phase III clinical trials, providing level one evidence of support for use in the disease. The current treatment landscape for metastatic panNETs is diverse, and includes somatostatin analogs (SSAs), targeted agents, chemotherapy, and radiolabeled therapies.

Pathology

PanNETs are classified according to the 2017 World Health Organization (WHO) classification for pancreatic neuroendocrine neoplasms (NENs) [7••]. The WHO pathologic classification remains the most significant prognostic tool for the treating clinician, offering important information to help predict tumor behavior and guide treatment selection for patients.

Consistent with the 2010 WHO criteria, in the 2017 classification, pancreatic NENs are stratified by both differentiation (well or poorly differentiated) and grade (grade 1, low; grade 2, intermediate; grade 3, high), classified by proliferative index measured by Ki-67 and/or mitotic count [8]. Importantly, however, the 2017 updates recognize the heterogeneity of grade 3 pancreatic NENs, including well-differentiated NETs and poorly differentiated neuroendocrine carcinomas (NECs) within the grade 3 category as distinct disease subtypes [8]. Changes in the WHO classification schema for pancreatic NENs evolved from our understanding of distinct treatment responses as well as clinical outcomes for pancreatic primary grade 3 NETs in comparison to grade 3 NECs [9–13].

Genetic basis of panNETs

Some panNETs develop in the setting of inherited, autosomal dominant, genetic disorders (multiple endocrine neoplasia type 1, von Hippel-Lindau disease, neurofibromatosis 1, tuberous sclerosis complex) [14]. The majority of panNETs, however, develop sporadically. In recent years, there have been significant advances in our understanding of the genetic basis of sporadic panNETs.

In one of the earliest efforts, whole exome sequencing was performed in 10 nonfamilial panNETs, and the most commonly mutated genes in these 10 tumor samples were screened in an additional 58 tumor specimens [15]. In the tested tumors, an increased number of mutations were identified in chromatin remodeling genes (MEN1, DAXX, ATRX), as well as along the mammalian target of rapamycin (mTOR) pathway (particularly in PTEN, TSC2, and PIK3CA).

Subsequently, whole genome sequencing was performed in 102 primary panNETs [16•]. In this investigation, a larger than anticipated germline contribution was identified, with previously unreported germline mutations noted in the DNA repair genes MUTYH, CHEK2, and BRCA2. Additionally, somatic point and gene fusion mutations were observed along four main pathways (chromatin remodeling, DNA damage repair, mTOR, and telomere maintenance), in line with the prior findings from whole exome sequencing.

Additional efforts have assessed a role for real-time sequencing in the clinic setting. The benefits of prospective next-generation sequencing (NGS) in predicting tumor biology and characterizing genomic evolution in the routine clinic setting were recently assessed in 96 tumor samples from 80 patients with metastatic panNETs [17]. In this study, somatic alterations were identified in 95% of patients, with the most commonly altered genes, consistent with prior findings, being MEN1 (56%), DAXX (40%), ATRX (25%), and TSC2 (25%). In this analysis, sequencing of pre- and post-treatment samples revealed progression in tumor grade as well as clonal evolution in panNETs, and germline alterations were also observed in high-penetrance autosomal dominant cancer susceptibility genes (MEN1, TSC2, and VHL).

Somatostatin analogs

The majority (80%) of well-differentiated NETs express SSTRs, most commonly subtype 2, on their surface. These tumors are SSTR avid on functional imaging (octreoscan or gallium-68 dotatate PET/CT).

In the setting of SSTR avidity, SSAs (octreotide and lanreotide) are typically considered for first-line for treatment of advanced and progressive panNETs. Support for a role for SSAs in cytostatic control was provided through two phase III randomized, double blind, placebo controlled studies: PROMID and CLARINET.

In the PROMID study, 85 patients with well-differentiated, functioning and nonfunctioning, metastatic midgut NETs were randomly assigned, 42 to receive octreotide long-acting-release (LAR) and 43 to receive placebo intramuscularly monthly with a primary endpoint of progression-free survival (PFS) [18]. At 6 months, 66.7% of octreotide recipients and 37.2% of placebo recipients had stable disease with a significant difference in median time to tumor progression (14.3 and 6 months, respectively, $p < 0.001$).

The CLARINET study demonstrated a similar benefit of prolonged PFS with use of the SSA lanreotide [19]. In CLARINET, 204 patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, low or intermediate grade enteropancreatic NETs were randomly assigned, 101 to receive lanreotide and 103 to receive placebo monthly. At 24 months, 65.1% of lanreotide recipients and 33% of placebo recipients were estimated to be progression free (median PFS not reached versus 18 months, hazard ratio [HR] 0.47; $p < 0.001$).

Taken together, the findings from PROMID and CLARINET were aligned in affirming clinically relevant antiproliferative effects with SSA's in patients with NETs. Based on these findings, the National Comprehensive Cancer Network (NCCN) guidelines recommend use of either octreotide LAR or lanreotide in

the first-line for relief of symptoms (in the setting of hormone release) as well as for tumor control in patients with SSTR avid NETs [20, 21].

Targeted therapies

Given the highly vascular nature of panNETs, targeted therapies that inhibit angiogenesis have been investigated as treatments for the disease. Sunitinib, a multi-targeted receptor tyrosine kinase inhibitor that blocks VEGFR as well as PDGFR, and everolimus, an mTOR inhibitor, both have demonstrable activity and are approved for the treatment of advanced panNETs.

Sunitinib

The efficacy of sunitinib for advanced panNETs was demonstrated in a randomized, multinational, phase III study, in which 171 patients with advanced and well-differentiated panNETs were randomized to receive best supportive care with either daily sunitinib or placebo [22]. The study was stopped early after more serious adverse events and deaths were observed in the placebo group with PFS favoring sunitinib (median PFS 11.4 months in the sunitinib arm versus 5.5 months in the placebo arm; HR 0.42; $p < 0.001$). A notable difference was also seen in objective overall response (9.3% in the sunitinib arm and 0% in the placebo arm). These findings led to the US Food and Drug Administration (FDA) approval of sunitinib in panNETs. In a more recent analysis, a five-year overall survival (OS) difference of 9.5 months was confirmed for the sunitinib arm versus the placebo arm in the aforementioned study [23•].

Everolimus

A role for and FDA approval of everolimus in the treatment of panNETs were established through the phase III RADIANT-3 study [24]. In RADIANT-3, 410 patients with advanced, progressive panNETs were randomly assigned to receive daily everolimus (207 patients) or placebo (203 patients) in conjunction with best supportive care. In this study, treatment with everolimus was associated with an improvement in median PFS by 6.4 months (11 months versus 4.6 months; HR 0.35; $p < 0.001$) and response rate (5% versus 2%) when compared with placebo. In a more recent analysis, those patients randomly assigned to everolimus had a median OS of 44 months, the longest OS reported in a phase III study for this population [25•]. Crossover from placebo to open label everolimus was allowed at disease progression and 172 patients (85%) initially randomized to the placebo arm did crossover to receive everolimus, with a 37.7-month OS reported for the placebo cohort.

Chemotherapy

Most often, chemotherapy is considered for treatment of panNETs in the setting of a heavy tumor burden, high grade disease, and/or an aggressive behavior pattern. The role for chemotherapy in the management of

panNETs has been examined in several single and combination-drug studies. Chemotherapy agents that have been investigated and commonly used in the treatment of panNETs include alkylating agents as well as platinum-based chemotherapy regimens.

Alkylating agents

Alkylating agents investigated in advanced panNETs include streptozocin, dacarbazine, as well as temozolomide. The earliest evidence for use of alkylating agents in the management of panNETs came from a case report describing relief of hormonal symptoms as well as cytostatic control in a patient with insulinoma treated with streptozocin [26]. A randomized study through the Eastern Cooperative Oncology Group (ECOG) later demonstrated notable activity with use of streptozocin; however, it was appreciated that streptozocin therapy was associated with significant nausea and vomiting, compromising both quality of life (QOL) and compliance to therapy [27]. Follow-up retrospective efforts demonstrated mixed findings with regard to a role for treatment with streptozocin in the disease [28, 29].

The alkylating agent dacarbazine was first studied in carcinoid tumors, with both tumor shrinkage as well as improvement in QOL noted [30, 31]. A role for use of dacarbazine in the treatment of panNETs came from a phase II ECOG study (E6282) which included 50 patients. A response rate of 34% was observed in the treated cohort; however, notable adverse events were seen [32].

Temozolomide was investigated as a therapy for panNETs in an effort to identify a less toxic alternative to dacarbazine [33]. Notable phase II data has demonstrated a role for both single-agent temozolomide, as well as temozolomide in combination with capecitabine (CAPETEM), in the treatment of metastatic panNETs [34–38]. The most notable toxicity with temozolomide containing regimens is myelosuppression; given the potential myelosuppressive effects of this drug, these studies illustrated the need to carefully monitor blood counts during the course of treatment.

The question regarding the benefit of single versus combination temozolomide therapy was recently addressed in the first prospective randomized trial of temozolomide alone versus CAPETEM conducted by ECOG (E2211) [39•]. In this study, 144 patients with advanced low or intermediate grade panNETs who had disease progression were enrolled into this two arm, phase II trial, and were randomized to receive temozolomide alone or CAPETEM. Median PFS in the temozolomide and CAPETEM arms were 14.4 months and 22.7 months, respectively. Median OS in the temozolomide arm was 38 months and not yet reached in the CAPETEM arm. Data review is ongoing at this time but CAPETEM was associated with significantly improved PFS (HR 0.58 $p = 0.023$) and OS (HR 0.41; $p = 0.012$) compared with temozolomide alone.

Platinum agents

Chemotherapy regimens incorporating platinum drugs have been investigated in panNETs, with these efforts demonstrating that the benefit of cisplatin and carboplatin-based regimens may be limited to those patients with higher grade tumors [40, 41]. In the largest retrospective study, which included 305 advanced gastrointestinal NENs, it was concluded that tumors with Ki-67 < 55% were less responsive to platinum-based chemotherapy; however importantly, patients

with tumors of Ki-67 < 55% did still experience longer survival, speaking to a varying biology within the high grade cohort of NENs [9].

Oxaliplatin-based regimens have also been investigated and show some activity in advanced panNETs. Two prospective phase II studies suggested antitumor activity based on radiographic responses and prolonged disease stability in previously progressing NETs [42]. One study evaluated treatment with oxaliplatin, leucovorin, and 5-flurouracil (FOLFOX) plus bevacizumab every 14 days in progressing and advanced carcinoid, panNETs, and poorly differentiated NECs; 12 panNET patients were eligible for response assessment with a response rate at twelve cycles of 41.7% (5/12) and median PFS of 21 months. The second study evaluated advanced NET patients treated with oxaliplatin and capecitabine plus bevacizumab for four 21-day cycles with the option to continue bevacizumab plus or minus capecitabine thereafter; 40 patients were eligible for response assessment with a response rate of 18% and a median PFS of 16.7 months.

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) targets and treats NETs with radiolabeled SSAs. In PRRT, a radioisotope is attached to an SSA via a chelator allowing for the systemic delivery of targeted radiation to tumors [43]. When the radiolabeled SSA binds to the surface of the tumor, targeted radiation is emitted resulting in cytotoxicity [44]. Given the mechanism of action, it is well recognized and has been demonstrated that SSTR expression on functional imaging predicts response to PRRT [45, 46].

Multiple radioisotopes have been investigated in PRRT. The initial first-generation radionuclide used was gamma-emitting ^{111}Indium, which had short particle ranges of Auger electrons and weak therapeutic (cytotoxic) effects [47]. Next-generation radionuclides included beta-emitting ^{90}Yttrium (^{90}Y) and ^{177}Lutetium (^{177}Lu), both which have intermediate particle ranges, killing neighboring tumor cells and offering improved cytotoxic effects [48].

Several studies have demonstrated a role for PRRT in the treatment of advanced and metastatic panNETs, with the most notable observed toxicities with PRRT being suppression of the blood counts and nephrotoxicity [49]. The largest efforts have utilized ^{177}Lu-based radiolabeled SSAs, with results demonstrating a benefit in reduction of tumor size, survival, as well as QOL [48, 50]. In a large study of 504 advanced NETs treated with four cycles of ^{177}Lu-DOTATATE at 6- to 10-week intervals, the median OS observed from treatment start was 46 months (128 months from diagnosis), with a survival benefit of 40 to 72 months from time of diagnosis when compared with historical controls [51]. In an even larger study, the efficacy, survival, and toxicity results were reported in a group of over 1200 patients treated at Erasmus Medical Center since the year 2000 with ^{177}Lu-DOTATATE infusion for four treatments at 8-week intervals [52]. In the treated cohort, an objective response rate of 39% was observed with 43% of patients achieving stable disease. PFS and OS were 29 months and 63 months, respectively. Long-term toxicities were primarily hematologic, and included acute leukemia in 4 patients (0.7%) and myelodysplastic syndrome in 9 patients (1.5%).

The phase III NETTER-1 trial is the only prospective, randomized trial of PRRT [53••]. In NETTER-1, 229 patients with progressive, well-differentiated metastatic midgut NETs were randomized in a 1:1 ratio to receive either ^{177}Lu-DOTATATE (116 patients) for four infusions every 8 weeks plus octreotide LAR or octreotide LAR alone (113 patients). At the time of primary analysis, the PFS at 20 months was 65.2% and 10.8% in the ^{177}Lu-DOTATATE group and control group, respectively. The observed overall response rate was 18% in the ^{177}Lu-DOTATATE group versus 3% in the control group, and at the time of analysis, there were 14 deaths in the ^{177}Lu-DOTATATE group versus 26 deaths in the control group. Grade 3/4 toxicities observed in the ^{177}Lu-DOTATATE group included neutropenia (1%), thrombocytopenia (2%), and lymphopenia (9%). The data from NETTER-1, as well as that from Erasmus Medical Center, led to the 2018 FDA approval of ^{177}Lu-DOTATATE for the treatment of advanced gastroenteropancreatic NETs [52, 53••].

Future directions

There are many avenues of ongoing investigation for the treatment of advanced panNETs. In recent years, immunotherapy has been studied while interest in and investigation into immunotherapy has been quite extensive; unfortunately, little activity has been demonstrated from this class of drugs to date [54–56]. Additional investigation of cabozantinib, a targeted agent that inhibits the tyrosine kinase receptors MET, VEGFR2, AXL, and RET, has offered promising data; in a phase II study of cabozantinib, which included both advanced panNETs and carcinoid tumors, many who had progressed on prior therapy, a 15% response rate and PFS of 21.8 months were noted in the treated cohort of panNETs [57, 58]. Based on these results, investigation of cabozantinib in NETs has expanded, with the phase III CABINET trial (ALLIANCE A021602) underway and actively accruing patients. The CABINET study includes patients with advanced NETs that have progressed on everolimus, with this cohort randomized to treatment with either cabozantinib or placebo. Areas of ongoing investigation in PRRT include studies of somatostatin antagonists well as intraarterial PRRT [59, 60].

In addition, there are ongoing studies attempting to clarify sequencing of the available therapies. These include SEQTOR (NCT02246127), a randomized and prospective study evaluating the efficacy and safety of chemotherapy (fluorouracil and streptozotocin) followed by everolimus versus everolimus followed by chemotherapy in progressive, advanced panNETs, as well as COMPETE (NCT03049189), a randomized and prospective study evaluating the efficacy and safety of PRRT (^{177}Lu-DOTATOC) versus everolimus in advanced and progressive GEP-NETs that are SSTR avid.

Compliance with Ethical Standards

Conflict of Interest

Haley Hauser, Daniela Shveid Gerson, Diane Reidy-Lagunes, and Nitya Raj declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas. 2013;42:557–77.
2. Dumlu EG, Karakoc D, Ozdemir A. Nonfunctional pancreatic neuroendocrine tumors: advances in diagnosis, management, and controversies. Int Surg. 2015;100:1089–97.
3. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135:1469–92.
4. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–72.
5. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol. 2008;19:1727–33.
6. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. Jama Oncol. 2017;3:1335–42.
7. •• Lloyd RV, Osamura RY, Klöppel G, et al. WHO classification of tumours of endocrine organs. International Agency for Research on Cancer, 2017.

The WHO pathologic classification remains the most significant prognostic tool. The 2017 classification of pancreatic neuroendocrine neoplasms (NENs) remains consistent with the previous 2010 WHO classification by stratifying by both differentiation and grade but offers important updates recognizing the heterogeneity of grade 3 pancreatic NENs.

8. Inzani F, Petrone G, Rindi G. The new World Health Organization classification for pancreatic neuroendocrine neoplasia. Endocrinol Metab Clin N Am. 2018;47:463–+.
9. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol. 2013;24:152–60.
10. Raj N, Valentino E, Capanu M, Tang LH, Basturk O, Untch BR, et al. Treatment response and outcomes of grade 3 pancreatic neuroendocrine neoplasms based on morphology well differentiated versus poorly differentiated. Pancreas. 2017;46:296–301.
11. Basturk O, Yang ZH, Tang LH, Hruban RH, Adsay V, McCall C, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogeneous and includes both well differentiated and poorly differentiated neoplasms. Am J Surg Pathol. 2015;39:683–90.
12. Tang LH, Untch BR, Reidy DL, et al. Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas (vol 22, pg 1011, 2016). Clin Cancer Res. 2016;22:4273–3.
13. Crippa S, Partelli S, Bassi C, Berardi R, Capelli P, Scarpa A, et al. Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: morphology matters. Surgery. 2016;159:862–71.
14. Jensen RI, Berna MJ, Bingham DB, et al. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer. 2008;113:1807–43.
15. Jiao YC, Shi CJ, Edil BH, de Wilde RF, Klimstra DS, Maitra A, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science. 2011;331:1199–203.
16. • Scarpa A, Chang DK, Nones K, et al. Whole-genome landscape of pancreatic neuroendocrine tumours. Nature. 2017;543:6.

A comprehensive molecular analysis of 102 clinically sporadic panNETs to describe the mutational landscape and the mutational signatures that underlie pathogenesis. Importantly, this study identified a larger than anticipated germline contribution including previously unreported germline mutations in DNA repair genes.

17. Raj N, Shah R, Stadler Z, et al. Real-time genomic characterization of metastatic pancreatic neuroendocrine tumors has prognostic implications and identifies potential germline actionability. JCO Precis Oncol. 2018;2018:1–18.
18. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol. 2009;27:4656–63.
19. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371:224–33.
20. Clark OH, Benson AB 3rd, Berlin JD, et al. NCCN clinical practice guidelines in oncology:

neuroendocrine tumors. J Natl Compr Cancer Netw. 2009;7:712–47.
21. Raj N, Reidy-Lagunes D. Systemic therapies for advanced pancreatic neuroendocrine tumors. Hematol Oncol Clin North Am. 2016;30:119–33.
22. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:501–13.
23.• Raymond E, Niccoli P, Castellano D, et al. Sunitinib (SU) in patients with advanced, progressive pancreatic neuroendocrine tumors (pNET): final overall survival (OS) results from a phase III randomized study including adjustment for crossover. Proc Am Soc Clin Oncol. 2016;
The 5 year follow up results to a pivotal randomized, multinational, phase III study that led to the FDA approval of sunitinib in panNETs.
24. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:514–23.
25.• Yao JC, Pavel M, Lombard-Bohas C, et al. Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 Study. J Clin Oncol. 2016;34:3906–13
The final overall survival data from the RADIANT-3 study that led to the FDA approval of everolimus in panNETs.
26. Murray-Lyon IM, Eddleston AL, Williams R, Brown M, Hogbin BM, Bennett A, et al. Treatment of multiple-hormone-producing malignant islet-cell tumour with streptozotocin. Lancet. 1968;2:895–8.
27. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin–doxorubicin, streptozocin–fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med. 1992;326:519–23.
28. Cheng PN, Saltz LB. Failure to confirm major objective antitumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. Cancer. 1999;86:944–8.
29. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol. 2004;22:4762–71.
30. Altimari AF, Badrinath K, Reisel HJ, Prinz RA. DTIC therapy in patients with malignant intra-abdominal neuroendocrine tumors. Surgery. 1987;102:1009–17.
31. Kessinger A, Foley J, Lemon H. Use of DTIC in the malignant carcinoid syndrome. Cancer Treat Rep. 1977;61:101.
32. Ramanathan RK, Cnaan A, Hahn RG, Carbone PP, Haller DG. Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the eastern cooperative oncology group-E6282. Ann Oncol. 2001;12:1139–43.
33. Stevens MF, Hickman JA, Langdon SP, Chubb D, Vickers L, Stone R, et al. Antitumor activity and pharmacokinetics in mice of 8-carbamoyl-3-methyl-imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (CCRG 81045; M & B 39831), a novel drug with potential as an alternative to dacarbazine. Cancer Res. 1987;47:5846–52.
34. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol. 2006;24:401–6.
35. Varker KA, Campbell J, Shah MH. Phase II study of thalidomide in patients with metastatic carcinoid and islet cell tumors. Cancer Chemother Pharmacol. 2008;61:661–8.
36. Ekeblad S, Sundin A, Janson ET, Welin S, Granberg D, Kindmark H, et al. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. Clin Cancer Res. 2007;13:2986–91.
37. Fine RL, Gulati AP, Krantz BA, Moss RA, Schreibman S, Tsushima DA, et al. Capecitabine and temozolomide (CAPTEM) for metastatic, well-differentiated neuroendocrine cancers: the pancreas Center at Columbia University experience. Cancer Chemother Pharmacol. 2013;71:663–70.
38. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117:268–75.
39.• Kunz PL, Catalano PJ, Nimeiri H, et al: A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: a trial of the ECOG-ACRIN Cancer research group (E2211). Am Soc Clin Oncol. 2018.
The first prospective randomized trial to evaluate the benefit of single agent temozolomide versus combination temozolomide plus capecitabine in advanced panNETs.
40. Moertel CG, Kvols LK, Oconnell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer. 1991;68:227–32.
41. Turner NC, Strauss SJ, Sarker D, Gillmore R, Kirkwood A, Hackshaw A, et al. Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. Br J Cancer. 2010;102:1106–12.
42. Kunz PL, Balise RR, Fehrenbacher L, Pan M, Venook AP, Fisher GA, et al. Oxaliplatin-fluoropyrimidine chemotherapy plus bevacizumab in advanced neuroendocrine tumors: an analysis of 2 phase II trials. Pancreas. 2016;45:1394–400.
43. Cives M, Strosberg J. Radionuclide therapy for neuroendocrine tumors. Curr Oncol Rep. 2017;19:9.
44. Waldherr C, Pless M, Maecke HR, et al. Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq 90Y-DOTATOC. J Nucl Med. 2002;43:610–6.
45. Kwekkeboom DJ, Kam BL, van Essen M, Teunissen JJ, van Eijck C, Valkema R, et al. Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer. 2010;17:R53–73.

46. Stefanova M, Kratochwil C, Mavriopoulou E, et al. SUV of 68Ga-DOTATOC PET/CT predicts response probability of PRRT in neuroendocrine tumors. J Nucl Med. 2014;55:1446–6.
47. Capello A, Krenning EP, Breeman WA, et al. Peptide receptor radionuclide therapy in vitro using [111In-DTPA0] octreotide. J Nucl Med. 2003;44:98–104.
48. Van Der Zwan WA, Bodei L, Mueller-Brand J, et al. GEP–NETs UPDATE: radionuclide therapy in neuroendocrine tumors. Eur J Endocrinol. 2015;172:R1–8.
49. Ramage J, Naraev BG, Halfdanarson TR. Peptide receptor radionuclide therapy for patients with advanced pancreatic neuroendocrine tumors, Seminars in oncology, Elsevier, 2018.
50. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med. 2011;52:1361–8.
51. Kwekkeboom DJ, de Herder WW, Kam BL, et al: Treatment with the radiolabeled somatostatin analog [^ 1^ 7^ 7Lu-DOTA^ 0, Tyr^ 3] octreotate: toxicity, efficacy, and survival. 26:2124–2130, 2008.
52. Brabander T, Van der Zwan WA, Teunissen JJ, et al. Long-term efficacy, survival, and safety of [177Lu-DOTA0, Tyr3] octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Clin Cancer Res. 2017;23:4617–24.
53.•• Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of (177)Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125–35
The phase III NETTER-1 randomized prospective trial led to FDA approval of 177Lu-DOTATATE for the treatment of advanced gastroenteropancreatic NETs.
54. Yao J, Strosberg J, Fazio N, et al. 1308O Activity & safety of spartalizumab (PDR001) in patients (pts) with advanced neuroendocrine tumors (NET) of pancreatic (Pan), gastrointestinal (GI), or thoracic (T) origin, & gastroenteropancreatic neuroendocrine carcinoma (GEP NEC) who have progressed on prior treatment (Tx). 29:mdy293. 001, 2018.
55. Mehnert J, Rugo H, O'neil B, et al. 427O Pembrolizumab for patients with PD-L1–positive advanced carcinoid or pancreatic neuroendocrine tumors: results from the KEYNOTE-028 study. 28, 2017.
56. Strosberg JR, Mizuno N, Doi T, et al. Pembrolizumab treatment of advanced neuroendocrine tumors: results from the phase II KEYNOTE-158 study. American Society of Clinical Oncology, 2019.
57. Chan JA, Faris JE, Murphy JE, et al. Phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumors (pNET). American Society of Clinical Oncology, 2017.
58. Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011;10:2298–308.
59. Reubi JC, Waser B, Macke H, et al. Highly increased 125I-JR11 antagonist binding in vitro reveals novel indications for sst2 targeting in human cancers. J Nucl Med. 2017;58:300–6.
60. SINGH A, Zhang J, Kulkarni H, et al. Intra-arterial PRRT of SSTR-expressing tumors in patients with hepatic only versus extrahepatic tumor: efficacy and safety evaluation. J Nucl Med. 2019;60:625–5.

Publisher's note