Expanding treatment options for diverse neuroendocrine tumors

Jane de Lartigue, PhD

Neuroendocrine tumors (NETs) are an extremely diverse group of cancers that have steadily increased in incidence in recent years. They can prove challenging to treat but, as we discuss here, a steady evolution in our understanding of NETs has significantly expanded the scope of therapeutic options.

A unique tumor type

NETs arise from neuroendocrine cells – cells with features of both nerve and endocrine cells that have important physiological functions, including the production and release of hormones. These tumors were first recognized by a German pathologist in the mid-1800s and were initially referred to as carcinoids in reference to their carcinoma-like appearance but lack of other malignant features.[1]

Unlike other solid tumors, which are associated with a particular primary location, NETs can arise anywhere in the body where neuroendocrine cells are found. They are also unique in their ability to oversecrete bioactive substances that regulate bodily functions, which results in an associated clinical syndrome, known as carcinoid syndrome, in up to 35% of patients.[2,3]

Although they are considered to be a relatively rare type of tumor, the incidence of NETs has been increasing in recent years. According to data from the Surveillance, Epidemiology and End Results (SEER) program, the age-adjusted incidence of NETs increased more than two-and-a-half fold during 1973-2004 and the rise is predicted to continue at an accelerated rate.[4]

Historically, NETs have been thought of as relatively benign because of their slow-growing nature, but it is now widely appreciated that they often metastasize. Furthermore, many patients are not symptomatic at first, so around half of all cases are not diagnosed until they have reached this more aggressive stage.[4]

The challenge of NET diversity

The most common type of NETs are those that arise in the gastrointestinal tract (GI-NET), representing more than 65% of cases, and for which the "carcinoid" terminology often is still applied. GI-NETs most frequently arise in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%).[4,5]

About a quarter of NETs originate in the bronchopulmonary system, including the lungs and the thymus. Thymic NETs are particularly aggressive and are associated with a poor prognosis. Pancreatic NETs (pNETs) make up the next largest group, although they represent less than 1% of total NETs. Compared with the most common type of pancreatic cancer, pancreatic ductal adenocarcinoma, they have a more favorable prognosis. pNETs are often grouped together with GI-NETs and referred to as gastroenteropancreatic NETs (GEP-NETs).[3-5] Other rarer types of NET include Merkel cell carcinoma (a type of skin cancer) and medullary thyroid cancers.

The classification network

NETs are classified according to the anatomic site from which they originate, as well as their histology, grade, and stage. Another important consideration is their level of hormone secretion. "Functional" and "nonfunctional" NETs both produce hormones, but only the former cause related symptoms.[3,4,6]

Functionality plays a particularly important role in the subclassification of GEP-NETs. Functional pNETs, for instance, are further divided according to the clinical syndromes associated with the hormones they produce, as insulinomas, glucagonomas, gastrinomas, somatostatinomas, and VIPomas (producing vasoactive intestinal peptide).[7,8]

In 2010, the World Health Organization developed a classification system for GEP-NETs that categorized these tumors as well differentiated (grade 1 or 2, depending on their rate of proliferation) and poorly differentiated (grade 3).[9] The WHO classification of bronchopulmonary NETs, published in 2015, is slightly different; broken down into 3 subgroups, typical carcinoid, atypical carcinoid (corresponding to grade 1 and 2 GEP-NETs), and large

TABLE 1 FDA-approved targeted therapies for NETs

Drug	Manufacturer	Approved indication (year approved)	Pivotal trial	Key data
Everolimus (Afinitor)	Novartis	Treatment of unresectable, locally advanced or metastatic pNETs (2011)	RADIANT-3 phase 3 trial of 410 patients with low- and intermediate-grade advanced or metastatic pNETs randomized to receive everolimus (10 mg/day) or placebo	Everolimus prolonged PFS compared with placebo; 11 vs 4.6 months (HR, 0.77; P = .026)[1]
		Treatment of adult patients with progressive, well-differentiated, nonfunctional NET of GI or lung origin with unresectable, locally advanced or metastatic disease (2015)	RADIANT-4 phase 3 trial of 285 patients with well-differentiated non-functioning GI or lung NET randomized to receive everolimus (10 mg/day) or placebo.	Everolimus prolonged PFS compared with placebo; 11 vs 3.9 months (HR, 0.48; P = .000001)[2]
Sunitinib (Sutent)	Pfizer	Treatment of progressive well-differentiated pNET in patients with unresectable, locally advanced or metastatic disease (2011)	Randomized controlled phase 3 trial of 171 patients with unresectable, locally advanced or metastatic well-differentiated pNET randomized to receive sunitinib (37.5 mg) or placebo	Sunitinib prolonged PFS compared with placebo; 10.2 vs 5.4 months HR, 0.42; P = .001)[3,4]
Lanreotide Depot (Somatuline)	Ipsen	Treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic GEP NETs to improve PFS (2014)	CLARINET phase 3 trial of 204 patients with locally advanced or metastatic non-functioning pancreatic or intestinal NETs randomized to receive lanreotide depot (120 mg) or placebo.	Lanreotide depot significantly improved PFS (not reached vs 18 months; HR, 0.47; P < .001)[5]
Octreotide-LAR (Sandostatin)	Novartis	Long-term treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid tumors and treatment of profuse watery diarrhea associated with VIP-secreting tumors (1986)	PROMID phase 3 trial of 85 patients with metastatic midgut NETs randomized to receive octreotide (30 mg) vs placebo	Octreotide LAR significantly lengthened the time to progression compared with placebo[a,6]
Avelumab (Bavencio)	EMD Serono/ Pfizer	Treatment of adult and pediatric patients over the age of 12 with metastatic Merkel cell carcinoma (2017)	JAVELIN Merkel 200 phase 2 trial of 88 previously treated patients with metastatic Merkel cell carcinoma given avelumab intravenously at a dose of 10 mg/kg every 2 weeks	Objective response rate with avelumab was 31.8%, including 9.1% complete response rate[7]
Vandetanib (Caprelsa)	Sanofi/ Genzyme	Treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced or metastatic disease (2011)	Randomized phase 3 trial of 331 patients with advanced medullary thyroid cancer randomized to receive vandetanib 300 mg/day or placebo	Vandetanib improved PFS compared with placebo (not yet reached vs 19.3 months; HR, 0.35; P < .0001)[8]
Cabozantinib (Cometriq)	Exelixis	Treatment of patients with advanced or metastatic medullary thyroid cancer (2012)	EXAM phase 3 trial of 330 patients with medullary thyroid cancer randomized to receive cabozantinib (140 mg/day) or placebo	Cabozantinib significantly improved PFS compared with placebo (11.2 vs 4 months; HR, 0.28; P < .0001)[9]

FDA, US Food and Drug Administration; GEP, gastroeseophageal; GI, gastrointestinal; HR, hazard ratio; LAR, long-acting release; NET, neuroendocrine tumor; PFS, progression-free survival; pNET, pancreatic NET.

[a]Currently only FDA approved to manage symptoms, not to Improve PFS

References

1. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. NEJM. 2011;364(6):514-523.
2. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387(10022):968-977.
3. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. NEJM. 2011;364(6):501-513.
4. Faivre S, Niccoli P, Castellano D, et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. Ann Oncol. 2017;28(2):339-343.
5. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. NEJM. 2014;371(3):224-233.
6. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR

Table continued from previous page

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(28):4656-4663.

7. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol.

2016;17(10):1374-1385.

8. Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30(2):134-141.

9. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31(29):3639-3646.

and small-cell NETs (equivalent to grade 3 GEP-NETs).[10]

Although NETs develop from the same cell type, they in fact comprise a spectrum of diseases that vary extensively in their underlying biology, histology, and clinical behavior. Both the diversity and unique nature of NETs have become increasingly evident in recent years with the application of next-generation sequencing technologies to this tumor type. In general, NETs seem to be more genetically stable than other tumor types from the same primary location, and have fewer somatic mutations. The classic tumor suppressors and oncogenes that drive other tumor types are not common in NETs.[6,11]

The diversity of NETs presents a diagnostic and therapeutic challenge and, until recently, there was a paucity of effective treatment options. In the past decade, an evolution in our understanding of the molecular mechanisms underlying these tumors has altered the treatment landscape for well-differentiated tumors as an expanding array of targeted therapies with proven efficacy have become available (Table 1). Their poorly differentiated counterparts, on the other hand, continue to present a significant unmet need.

Somatostatin analogs lead the charge

The fact that many NETs overexpress hormone receptors presents a significant therapeutic opportunity, and among the most successful targets to date are the somatostatin receptors (SSTRs). There are 5 main SSTRs that each bind to somatostatin with different effects on cell signaling and expression that varies according to the type of NET.

More stable synthetic analogs of the somatostatin hormone (somatostatin analogs [SSAs]), which has a very short half-life in the circulation, have been developed that act as SSTR agonists. Two long-acting SSAs, octreotide (Sandostatin LAR Depot) and lanreotide (Somatuline Depot), which bind SSTR2 and SSTR5, have been approved by the United States Food and Drug Administration (FDA), but were primarily used for the alleviation of the symptoms associated with NETs resulting from carcinoid syndrome.

In recent years, evidence has begun to emerge that SSAs also have an anti-tumor effect, which is thought to be both direct and indirect in nature. Direct effects result from the interaction between the SSA and SSTRs expressed on tumor cells, blocking the protumor cellular effects of SSTR signaling that are poorly understood but thought to involve the mitogen-activated protein kinase (MAPK) pathway. Indirect effects are fortuitous side effects mediated through off-target effects, such as the suppression of other cellular activities of SSTRs and the other growth factors that they bind to, which can impact processes such as angiogenesis and immune modulation.[7,12]
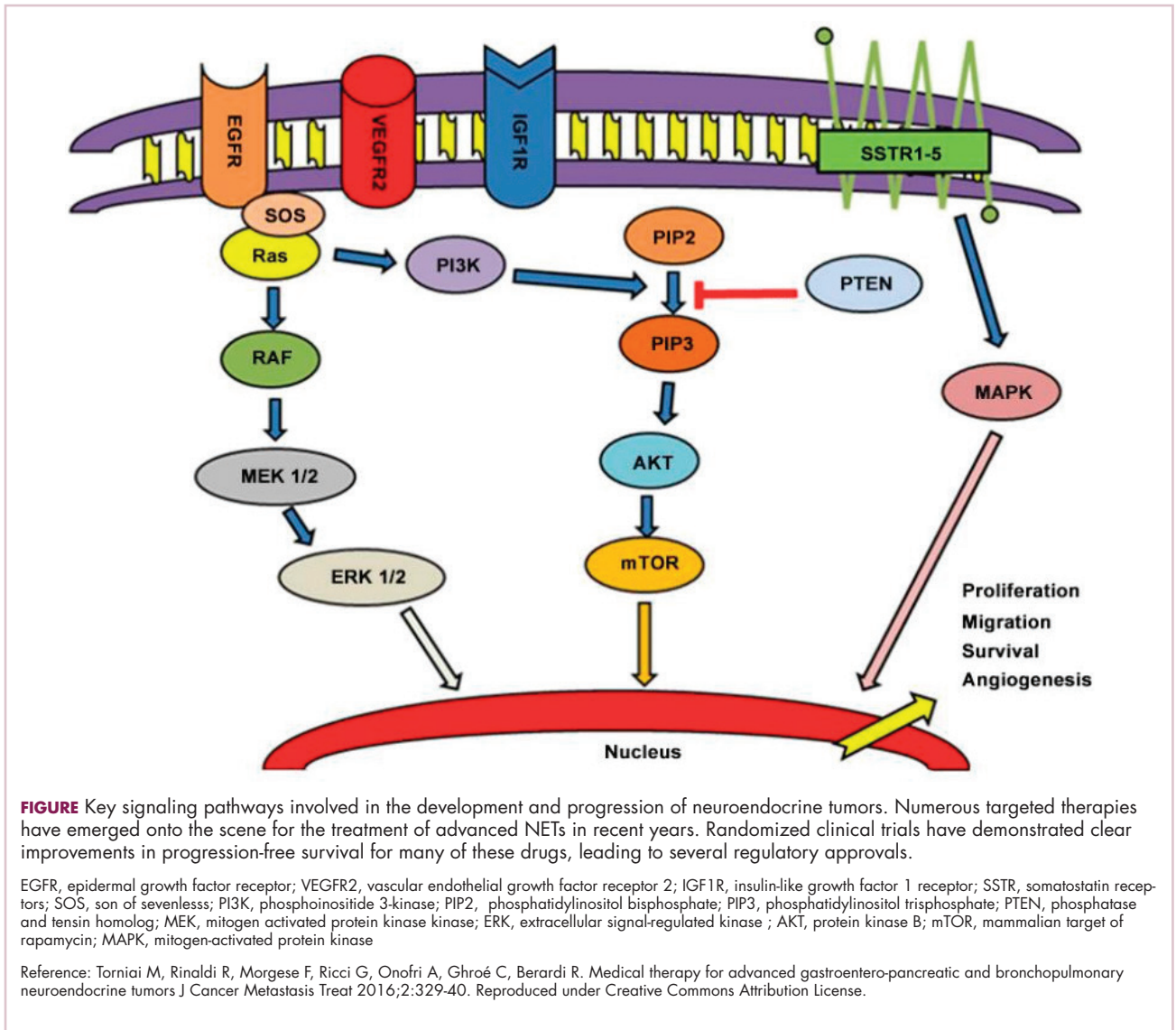
Several clinical trials have been designed to test the anti-tumor effects of NETs, including the PROMID trial of octreotide and the CLARINET trial of lanreotide, the latter leading to the 2014 approval of lanreotide for the improvement of progression-free survival (PFS) in patients with advanced GI- and pNETs.

The randomized phase 3 study compared lanreotide 120 mg with placebo in 204 patients with locally advanced or metastatic nonfunctioning pancreatic or intestinal NETs. Lanreotide treatment resulted in a significant improvement in PFS (Not yet reached vs 18 months for placebo; hazard ratio [HR], 0.47; P < .001).[13]

Meanwhile, the PROMID trial compared octreotide 30 mg with placebo in 85 patients with advanced midgut NETs and demonstrated that octreotide increased time to progression (TTP; 14.3 months vs 6 months for placebo; P = .000072) with no significant difference in side effects.[14]

Pasireotide is a second-generation SSA with improved binding affinity to SSTR1, 3, and 5. Despite its improved specificity, pasireotide has not proved more effective than other SSAs and its development for the treatment of NETs has been discontinued.

Coupling radioisotopes to SSAs provides another promising therapeutic option for NETs, known as peptide receptor radionuclide therapy, or PRRT, which uses SSAs to deliver therapeutic radiation directly to the tumor cells. Several variations have been studied with different radioactive isotopes, but most promising is lutetium-177 (^{177}Lu). A ^{177}Lu-labelled octreotide (^{177}Lu-Dotatate) recently demonstrated significant efficacy in the phase 3 NETTER-1 clinical trial in patients with advanced stage NETs of the small bowel. The trial randomly assigned 229 patients who were progressing on an SSA to either ^{177}Lu-Dotatate or high-dose octreotide LAR (long-acting release). There was a significant increase in PFS in the ^{177}Lu-Dotatate arm (Not yet reached vs 8.4 months; P < .0001). There was also a trend toward improved overall survival (OS), and longer follow-up is eagerly anticipated for confirmation. ^{177}Lu-Dotatate has been granted priority review by

FIGURE Key signaling pathways involved in the development and progression of neuroendocrine tumors. Numerous targeted therapies have emerged onto the scene for the treatment of advanced NETs in recent years. Randomized clinical trials have demonstrated clear improvements in progression-free survival for many of these drugs, leading to several regulatory approvals.

EGFR, epidermal growth factor receptor; VEGFR2, vascular endothelial growth factor receptor 2; IGF1R, insulin-like growth factor 1 receptor; SSTR, somatostatin receptors; SOS, son of sevenlesss; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol bisphosphate; PIP3, phosphatidylinositol trisphosphate; PTEN, phosphatase and tensin homolog; MEK, mitogen activated protein kinase kinase; ERK, extracellular signal-regulated kinase ; AKT, protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase

Reference: Torniai M, Rinaldi R, Morgese F, Ricci G, Onofri A, Ghroé C, Berardi R. Medical therapy for advanced gastroentero-pancreatic and bronchopulmonary neuroendocrine tumors J Cancer Metastasis Treat 2016;2:329-40. Reproduced under Creative Commons Attribution License.

the FDA, and a decision on its approval is expected in the next few months.[11,15-17]

Molecularly and immune-targeted therapies continue to take aim

The mammalian target of rapamycin, or mTOR, is a serine/threonine kinase that sits at the confluence of a number of different upstream signaling pathways and mediates key cellular processes including cell proliferation and survival (Figure 1). Alterations in nearly all members of the mTOR pathway, including upstream activators and downstream effectors, have been observed in NETs, in both sporadic disease and the genetic syndromes associated with the development of NETs.[18]

The involvement of the mTOR pathway in the pathogenesis of NETs first came into focus in pNETs and the mTOR inhibitor, everolimus (Afinitor) has been exten-

sively studied in this indication, culminating in its regulatory approval in 2011. In the pivotal trial (RADIANT-3), everolimus monotherapy was compared with placebo in 410 patients with low- and intermediate-grade pNETs. There was a statistically significant improvement in PFS from 4.6 months to 11 months (HR, 0.77; P = .026).[19] The final OS analysis for this trial also revealed a benefit of more than 6 months in the everolimus arm, although this was not statistically significant, which the study authors attribute to the high rate of crossover from the placebo arm after progression.[20]

More recently, the results of the RADIANT-4 trial, in which everolimus was compare with placebo in patients with advanced, well-differentiated, nonfunctioning NETs of the GI tract and lung, led to a new approved indication for the mTOR inhibitor and the first approved targeted therapy for advanced lung NETs. In the overall study pop-

TABLE 2 Ongoing clinical trials of targeted therapies in NETs

Drug	Manufacturer	Mechanism of action	Most advanced clinical trials (clinicaltrials.gov identifier)

Everolimus (Afinitor)	Novartis	mTOR inhibitor	Phase 2
			   Plus ribociclib (CDK4/6 inhibitor) in advanced NETs (NCT03070301)
			   As second-line therapy in poorly differentiated NETs (NCT02113800)
			   As maintenance therapy in pulmonary or GEP-NETs (NCT02687958)
			   Plus temozolomide in advanced GEP-NETs (NCT02248012)

Suntinib (Sutent)	Pfizer	Multi-targeted TKI	Phase 2
			   Rechallenge in patients with metastatic pNETs who have previously failed sunitinib therapy (NCT02713763)
			   Plus TH302 (hypoxia-activated prodrug in metastatic pNETs (NCT02402062)

Octreotide LAR (Sandostatin)	Novartis	SSA	Phase 2/3
			   Plus everolimus and metformin in advanced, well-differentiated pNETs (MetNET1; NCT02294006)
			   As maintenance therapy in GEP-NETs (NCT02409849)

Lanreotide Depot (Somatuline)	Ipsen	SSA	Phase 2/3
			   As maintenance therapy in non-resectable duodeno-pancreatic NETs (REMINET; NCT02288377)
			   In lung NETs (SPINET; NCT02689341)
			   Plus temozolomide in thoracic NETs (ATLANT; NCT02698410)

Pazopanib (Votrient)	Novartis	Multi-targeted TKI	Phase 1/2 Plus temozolomide in advanced, unresectable NETs (NCT01465659)
Axitinib (Inlyta)	Pfizer	Multi-targeted TKI	Phase 2/3 Plus octreotide in non-pancreatic NETs (NCT01744249)
Bevacizumab (Avastin)	Genentech	Anti-VEGF mAb	Phase 2 Plus FOLFIRI as second-line therapy in inoperable, poorly differentiated, advanced GEP-NETs (BEVANEC; NCT02820857)
Ramucirumab (Cyramza)	Eli Lilly	VEGFR2 inhibitor	Phase 2 Plus SSAs in advanced NETs (NCT02785858)
Ziv-aflibercept (Zaltrap)	Sanofi/ Genzyme	VEGF inhibitor	Phase 2 In advanced progressive NETs (NCT01782443)
Fosbretabulin	Mateon	Vascular-targeting agent	Phase 1 Plus everolimus in NETs with progression (NCT03014297)

Sulfatinib	Hutchison Medi	Multi-targeted TKI	Phase 3
			   In extrapancreatic NETs (NCT02588170)
			   In advanced pNETs (NCT02589821)

Pembrolizumab (Keytruda)	Merck	Immune check-point inhibitor	Phase 1/2 Plus lanreotide in GEP-NETs (PLANET; NCT03043664)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune check-point inhibitor	Phase 2 Plus ipilimumab in rare cancers, including NETs (NCT02923934)
Fosbretabulin	Mateon	Vascular-targeting agent	Phase 1 Plus everolimus in NETs with progression (NCT03014297)
Nintedanib (Ofev)	Boehringer Ingelheim	Multi-targeted TKI	Phase 2 Advanced/metastatic NETs (NCT02399215)
Ibrutinib (Imbruvica)	Pharmacyclics/ Janssen	BTK inhibitor	Phase 2 Advanced carcinoid and pancreatic NETs (NCT02575300)

Lutetium Lu 177 dototate (Lutathera)	Advanced Accelerator Applications	Radiolabelled octreotate	Phase 2/3
			   Versus octreotide LAR in unresectable, progressive, SSTR-positive midgut NETs (NETTER-1; NCT01578239)[a]
			   In metastatic, inoperable NETs (NCT02125474)
			   In SSTR-positive NETs (NAP; NCT01876771)

BTK, Bruton's tyroskine kinase; FOLFIRI, leucovorin, 5-fluorouracil, irinotecan combination chemotherapy; GEP, gastroenteropancreatic; LAR, long-acting release; mTOR, mammalian target of rapamycin; NET, neuroendocrine tumor; pNET, pancreatic NET; SSA, somatostatin analog; SSTR, somatostatin receptor; TKI, tyrosine kinase inhibitor

[a]Trial is ongoing, but no longer recruiting participants

ulation (n = 285), everolimus prolonged PFS by more than 7 months (11 months vs 3.9 months for placebo; HR, 0.48; *P* = .000001), corresponding to a 52% reduction in the risk of disease progression or death.[21,22]

Everolimus continues to be evaluated, with a particular focus on combination therapy to overcome the resistance that commonly occurs after treatment with molecularly targeted drugs (Table 2). For example, preclinical studies suggested that mTOR inhibitors and SSAs may have synergistic activity owing to combined inhibition of the mTOR and insulin-like growth factor pathways. In a phase 1 study, the combination of pasireotide and everolimus was found to be safe and to have preliminary anti-tumor activity. However, the subsequent phase 2 COOPERATE-2 study failed to show improved PFS.[23,24]

The observation that NETs are highly vascularized and frequently express vascular endothelial growth factor (VEGF) and its receptor (VEGFR), which play a key role in coordinating angiogenesis, led to the pursuit of anti-angiogenic therapies in NETs. Both the anti-VEGF monoclonal antibody bevacizumab and small molecule tyrosine kinase inhibitors that include among their targets VEGFRs and other receptors involved in angiogenesis, such as platelet-derived growth factor receptor, have been tested.

Sunitinib was approved for the treatment of pNETs in 2011, making it a banner year for this tumor type. Approval was granted on the basis of significantly improved PFS in the sunitinib arm of a phase 3 randomized trial, but long-term follow-up suggested that sunitinib also improved OS by 10 months. Like everolimus, the OS benefit was not statistically significant, and again this was thought to be the result of extensive crossover.

Two other multikinase inhibitors have received regulatory approval for a much rarer form of NET, medullary thyroid cancer. Vandetanib and cabozantinib were approved for this indication in 2011 and 2012, respectively. Early in 2017, the results of a single-arm phase 2 trial of cabozantinib suggested that this drug may also have sig-

nificant activity in other types of NET. In patients with advanced carcinoid and pNETs who received cabozantinib at 60 mg/day orally, partial responses were observed in 15% of patients and the median PFS was 21.8 months in the pNET cohort and >30 months in the carcinoid tumor cohort.[25] Confirmatory phase 3 trials are planned but not currently underway.

Sulfatinib is a novel kinase inhibitor that targets the VEGFRs and fibroblast growth factor receptor 1. It has recently shown significant promise in the treatment of patients with advanced NETs. According to data presented at this year's annual conference of the European Neuroendocrine Tumor Society in Barcelona, sulfatinib demonstrated an overall response rate of 17.1% in pancreatic NETs and 15% in extra-pancreatic NETs, with an overall disease control rate of 91.4%, and was well tolerated.[26] Based on these and other promising phase 1 and 2 data, 2 phase 3 trials are ongoing.

Meanwhile, earlier this year, Mateon Therapeutics presented data from a phase 2 trial of a different kind of anti-angiogenic drug in patients with GI- or pNETs. Fosbretabulin is a vascular disrupting agent that targets the existing tumor vasculature rather than preventing the formation of new blood vessels. They do this via a number of different mechanisms, in the case of fosbretabulin it specifically targets endothelial cells and inhibits the assembly of microtubules and, hence, blocks mitosis. In 18 patients, fosbretabulin treatment resulted in 1 partial response and 7 patients who had stable disease; more than half of the patients reported improved quality of life.[27] Fosbretabulin continues to be studied in NETs in combination with everolimus.

Finally, researchers are beginning to make a foray into the immunotherapy field that has revolutionized the treatment of many other tumor types. The immune checkpoint inhibitors nivolumab and pembrolizumab are being evaluated in ongoing phase 1 and 2 trials, while avelumab (Bavencio) was very recently approved by the FDA for the treatment of Merkel cell carcinoma.[28,29]

References

1. Pinchot SN, Holen K, Sippel RS, Chen H. Carcinoid tumors. Oncologist. 2008;13(12):1255-1269.
2. Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. J Surg Oncol. 2005;89(3):151-160.
3. The NET Alliance. Characterizing a challenging cancer. http://www.thenetalliance.com/hcp/facts-about-net/characterization/. Publishing date not provided. Accessed October 18, 2017.
4. Yao JC, Hassan M, Phan A, 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(18):3063-3072.
5. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934-959.
6. Spada F, Valente M. Review of recent advances in medical treatment for neuroendocrine neoplasms: somatostatin analogs and chemotherapy. J Cancer Metastasis Treat. 2016;2(8):313-320.

7. Kelgiorgi D, Dervenis C. Pancreatic neuroendocrine tumors: the basics, the gray zone, and the target. F1000Research. 2017;6:663.
8. Viudez A, De Jesus-Acosta A, Carvalho FL, Vera R, Martin-Algarra S, Ramirez N. Pancreatic neuroendocrine tumors: Challenges in an underestimated disease. Crit Rev Oncol Hematol. 2016;101:193-206.
9. World Health Organization, International Agency for Research on Cancer. Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). WHO classification of tumours of the digestive system. 2010, 4th ed (vol 3).
10. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors. J Thorac Oncol. 2015;10(9):1243-1260.
11. Lee A, Chan DL, Wong MH, et al. Systematic review of the role of targeted therapy in metastatic neuroendocrine tumors. Neuroendocrinology. 2017;104(3):209-222.
12. Theodoropoulou M, Stalla GK. Somatostatin receptors: from signal-

ing to clinical practice. Front Neuroendocrinol. 2013;34(3):228-252.

13. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224-233.

14. 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(28):4656-4663.

15. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125-135.

16. Falconi M, Partelli S. Neuroendocrine tumours in 2016: defining rules for increasingly personalized treatments. Nat Rev Clin Oncol. 2017;14(2):80-82.

17. Hutchinson L. Targeted therapies: widening the treatment NET. Nat Rev Clin Oncol. 2017;14(1):2-3.

18. Cingarlini S, Bonomi M, Corbo V, Scarpa A, Tortora G. Profiling mTOR pathway in neuroendocrine tumors. Target Oncol. 2012;7(3):183-188.

19. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514-523.

20. 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. http://ascopubs.org/doi/abs/10.1200/JCO.2016.68.0702?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed. September 12, 2016. E-pub ahead of print.

21. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387(10022):968-977.

22. Gajate P, Martínez-Sáez O, Alonso-Gordoa T, Grande E. Emerging use of everolimus in the treatment of neuroendocrine tumors. Cancer Manage Res. 2017;9:215-224.

23. Chan JA, Ryan DP, Zhu AX, et al. Phase I study of pasireotide (SOM 230) and everolimus (RAD001) in advanced neuroendocrine tumors. Endocr Relat Cancer. 2012;19(5):615-623.

24. Kulke MH, Ruszniewski P, Van Cutsem E, et al. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. Ann Oncol. 2017;28(6):1309-1315.

25. Chan JA, Faris JE, Murphy JE, et al. Phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumors (pNET). J Clin Oncol. 2017;35(4 suppl):228-228.

26. Xu J, Li J, Bai CM, et al. An open-label phase Ib/II study of sulfatinib in patients with advanced neuroendocrine tumors (NCT02267967). Paper presented at the 14th Annual European Neuroendocrine Tumor Society Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease; March 8-10, 2017, Barcelona, Spain.

27. Libutti SK, Anthony LB, Chaplin DJ, Sosa JA. A phase II study of combretastatin A4-phosphate (CA4P) in the treatment of well-differentiated, low- to intermediate-grade, unresectable, recurrent, or metastatic pancreatic, or GI neuroendocrine tumors/carcinoid (GI-NETs/PNETs) with elevated biomarkers. J Clin Oncol. 2017;35(4 suppl):432-432.

28. Cordes LM, Gulley JL. Avelumab for the treatment of metastatic Merkel cell carcinoma. Drugs Today (Barc). 2017;53(7):377-383.

29. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016;17(10):1374-1385.