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Updates in Neuroendocrine Tumor Genomic Studies and Systemic Therapies

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Abstract

Neuroendocrine tumors (NET) are a mysterious group of malignancies that can form throughout the diffuse neuroendocrine system and produce biological effects distant from their primary location. They have an increasing incidence and can also behave more aggressively than previously recognized. These heterogeneous features have interfered with a more fundamental understanding of tumor biology. Over the past several years, systematic genetic surveys NETs from the major sites of origin have revealed important genomic changes, with potential driver mutations, that have an impact on prognosis and clinical development of targeted therapies. We will take a focused approach in reviewing this data and its impact on clinical medicine.

Keywords: Neuroendocrine tumor; Carcinoid; Small molecule targeted therapy; PRRT; NTRK fusion

Introduction

Neuroendocrine tumors (NETs) originate from the enterochromaffin cells of the neuroendocrine system located throughout the body. NETs are rare but have increasing incidence and prevalence [1]. The annual age-adjusted incidence of NETs in the United States was 6.98 per 100,000 persons in 2012, compared to 1.09 per 100,000 persons in 1973 [2]. Historically, NETs have been perceived as an indolent disease however they can behave aggressively and their heterogeneity has been appreciated more lately [3,4]. In this article, we summarize current molecular and genetic data of NETs, provide a concise review on how approved treatments interact with these pathways, and highlight emerging small molecule targeted therapies.

NETs are currently classified by primary location, stage, and histologic grade. Foregut NETs include tumors of lung, bronchi, gastric, duodenal, and pancreatic origins. Midgut NETs cover ileum to ascending colon. Lastly, hindgut NETs are composed of distal large bowel and rectum primary sites. The TNM staging system is used in NETs [5]. Present World Health Organization (WHO) grading system of NETs is based on two proliferation markers, Ki-67 score and mitotic index (MI). WHO 2010 classification of digestive NETs defines both grade 1 (Ki-67 <= 2%, MI<2/10 per high-power filed, HPF) and grade 2 (Ki-67 3-20%, MI 2-20/10 HPF) tumors as well-differentiated neuroendocrine tumors, whereas grade 3 (Ki-67 > 20%, MI > 20/10 HPF) neuroendocrine carcinoma (NEC) are poorly-differentiated [6]. In 2017, WHO updated its grading system of pancreatic NETs to broaden grade 1 tumor to include Ki-67 <3% [7]. A second change in WHO 2017 classification was to subdivide grade 3 cancers (Ki-67 >20%) to well-differentiated NET G3 and poorly differentiated NEC. When compared to NET G3, NEC G3 is rarely involved in hereditary syndromes, has a poor prognosis, but is more responsive to platinum agents [8]. A recent study by French researchers suggests that perhaps using 5% Ki-67 cut-off to differentiate grade 1 and grade 2 tumors can provide more accurate risk stratification [9].

Literature Review

Part I – Molecular genetic updates

In the past decade, molecular analysis has assumed a critical role in understanding NETs and in uncovering potential treatment targets. Despite the majority of NETs being sporadic, there are hereditary syndromes associated with NETs, including multiple endocrine neoplasia type 1 (MEN 1), von Hippel-Lindau syndrome, neurofibromatosis type 1, and tuberous sclerosis complex [10-13]. All four diseases have autosomal-dominant inheritance and are caused by the tumor suppression genes, MEN1, VHL, NF1, and TSC1/TSC2, respectively. Whole-genome landscape analysis of pancreatic NETs was published in Nature in 2017 [14]. In this pivotal study, genome sequencing was performed on 102 cases of sporadic pancreatic NETs and noted a higher than expected prevalence of germline mutations in patients with presumed clinically sporadic pancreatic NETs as 17% of patients studied had germline mutations such in *MUTYH, CHEK2, BRCA2, MEN1* and *VHL*. This result reinforces the role of genetic changes and potential driver mutations in the pathogenesis and treatments for NETs.

Four common pathways of somatic mutations have been identified in pancreatic NETs. These include chromatin remodeling, DNA damage repair, mTOR (mammalian target of rapamycin) signaling activation, and telomere maintenance (Table 1) [15]. Nearly half (43%) of pancreatic NETs have altered telomeres associated with inactivating mutations in the ATRX (ATRX chromatin remodeler) or DAXX (death-domain associated protein) genes [16]. The exact prognostic value of these mutations is unclear [17]. Mutations in the mTOR pathway were found in 14% of pancreatic NETs. Retrospective and observation studies have shown abnormal mTOR pathway in small intestinal NETs along with other primary sites. High immunohistochemical expression of mTOR or its downstream targets is associated with adverse clinical outcomes [18]. The product of PTEN (phosphatase and tensin homolog) gene normally inhibits the P13K-AKT-mTOR pathway. Loss of PTEN results in increased phosphorylated AKT expression and is associated with metastatic potential of low-grade NETs [19]. Similarly, low-grade lung NETs often have high PTEN expression and is associated with markedly better prognosis than their gastroenteropancreatic counterparts.

Targeted next-generation sequencing of NETs from a variety

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of primary sites provide a better understanding of the genetic heterogeneity of NETs. In a study looking at 148 lung NETs, MEN1 alterations were found almost exclusive in low grade bronchial NETs whereas mutations in *TP53, RB1,* and *PI3K/AKT/mTOR* pathway were more common in large-cell NECs and small cell lung carcinomas [20]. Targeted NGS done in 84 well-differentiated rectal, gastric, and appendiceal NETs showed a trend of higher mutation variants association with higher grade, lymphovascular invasion, and increased recurrence, but this did not reach statistical significance [21]. The researchers noted rectal NETS tend to have more unpredictable malignant behavior despite small size. They found repetitive mutations in *TP53, PTEN, CDKN2A, FBXW7, IDH1, AKT1* and *KIT* however it is inconclusive whether any of the mutation is exclusive to rectal NETs. In another study of nine primary renal well-differentiated NETs, all were negative for ATRA and DAXX mutations [22]. There were 56 variants identified in this study of 9 cases with an average of 5 variants per sample. Repeated mutations included *CHD1, TET2, AKT3, ROS1, PIK3R2, BCR*, and *MYC*. Renal NETs are rare with only approximately one hundred case reports published, but this reflects the challenges of defining the genetics of NETs.

Part II – Treatment development

Somatostatin analogues: Well-differentiated NETs are known to overexpress somatostatin receptors, especially somatostatin receptor type 2. The somatostatin analogue octreotide has been FDA approved for symptom control in carcinoid syndrome since the 1980s. Somatostatin was first identified and isolated from hypothalamic extracts in 1973 at the Salk Institute [23]. Therapeutic usage of somatostatin was limited due to its short half-life that required continuous intravenous infusion. Long-acting somatostatin analogue SMS 201-995, later known as octreotide, was therefore developed by Sandoz. In 1986, Mayo Clinic was the first to report octreotide effectiveness in carcinoid syndrome symptoms control among a group of 25 patients [24]. The antitumor effect of octreotide was long suspected and eventually confirmed by a phase III double-blinded control trial (PROMID study; NCT00171873) published in 2009 with an improved median time to tumor progression when compared with placebo (14.3 months vs 6 months, p=0.000072) [25]. However, long term follow up on overall survival was not statically different and was thought related to crossover of the majority of placebo patients to octreotide treatment in this small cohort of 85 patients [26]. In 2014, interim results of the CLARINET trial (NCT00353496) was published. This double-blinded, placebo-controlled, multinational Phase III trial of somatostatin analogue lanreotide enrolled 204 patients with progressive, advanced, well-to-moderately differentiated, grade 1-2, nonfunctioning, somatostatin receptor-positive NETs. Lanreotide was found to significantly prolong median progression-free survival (PFS) in patients with gastroenteropancreatic NETs when compared to placebo (median not reached vs 18 months, p<0.001) [27]. Subsequently, lanreotide was approved by the FDA for gastroenteropancreatic NETs based on the improved PFS endpoint, whereas octreotide only has labeling approved for symptomatic control.

Peptide receptor radionuclide therapy (PRRT): The NETTER-1 trial (NCT01578239) was an international open-labeled Phase III study that evaluated Lutetium-177(^{177}Lu)-Dotatate in well-differentiated metastatic midgut NETs. The ^{177}Lu-Dotatate radioisotope emits β particles with 2mm range and a short half-life of 160 hours. Linking ^{177}Lu-Dotatate to a somatostatin analogue, a type of PRRT, enables precise delivery of radioactive therapy to tumor sites throughout the body. Since the initial report report of PRRT usage, a number of Phase I and II studies have been identified a more effective radionuclide (^{177}Lu vs ^{111}In and ^{90}Y) and more specific peptide (octreotate vs octreotide) approaches, paving the road for the high-quality, prospective NETTER-1 trial [28-31]. Patients in the ^{177}Lu-Dotatate group (n=116) had a response rate of 18% compared to 3% in the control group using octreotide alone (p<0.001). The primary endpoint of this trial was PFS, and although the median PFS had not yet been reached, the estimated rate of PFS at 20 months was 65.2% in the ^{177}Lu-Dotatate group and 10.8% in the control group (p=0.004). Study follow-up is still ongoing and more mature survival outcomes are awaited.

mTOR kinase inhibitors. Yao and colleagues first reported antitumor activity of everolimus in pancreatic NETs in 2008 [32]. The subsequent open-labeled phase III RADIANT-3 study of 410 patients with advanced pancreatic NETs met its primary endpoint ofe improved median PFS (11.0 months vs 4.6 months, p<0.001) using everolimus compared to placebo [33]. Everolimus was associated with a median OS of 44 months, translating to a 6.3 months of survival benefit over placebo, however it did not reach statistical significance (p=0.30) likely due to significant crossover of patients in this study [34]. The RADIANT-2 study was a double-blinded phase III trial that enrolled patients with carcinoid syndrome from advanced NETs of various primary sites. In this study, everolimus plus octreotide improved median PFS by 5.1 months compared with placebo plus octreotide [35]. The *P*-value (0.026) was marginally above the pre-specified threshold for statistical significance (P <= 0.0246). Even though this study did not meet its primary endpoint, it suggested a potential antitumor effect of everolimus in non-pancreatic NETs. The follow-up Phase III RADIANT-4 study noted that everolimus monotherapy had significant improvement in median PFS (11 months vs 3.9 months in placebo group, p<0.0001) in advanced, non-functional NETs of lung and gastrointestinal tract [36]. The data from RADIANT-3 and RADIANT-4 studies support the use of everolimus in a broader range of NETs. Another mTOR inhibitor that has been studied in NETs is temsirolimus. In a single-arm phase II study (NCT01010126) of pancreatic NETs, temsirolimus and vascular endothelial growth factor antibody bevacizumab combination demonstrated an encouraging response rate of 41% with relatively tolerable side effect profile [37].

Multitargeted tyrosine kinase inhibitors (MTKIs): Sunitinib exhibits antitumor and antiangiogenic activities by blocking all three vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFRα and PDGFRβ), stem cell factor receptor KIT, and fetal liver tyrosine kinase receptor 3 (FLT3) [38]. When studied against placebo in a double-blind phase III trial in patients with advanced well-differentiated pancreatic NETs, sunitinib was associated with statistically significant median PFS improvement compared to placebo (11.4 months vs 5.5 months, p<0.001) [39]. The response rate was 9% compared to 0% in placebo group. A number of MTKIs, including axitinib, lenvatinib, pazopanib, and surafatinib, have also shown potential efficacy in NETs in Phase II studies [40-43]. Levatinib produced radiological response in pretreated patients including those progressed on other TKIs. Phase III trials are ongoing for cabozantinib (NCT03375320) and surafatinib (NCT02589821 and NCT02588170).

Tropomyosin receptor kinase (TRK) inhibitors: Entrectinib (RXDX-101), an oral tyrosine kinase inhibitor of TRK A/B/C, C-ros oncogene 1 (ROS1) proteins, and anaplastic lymphoma kinase (ALK), was reported to have significant activity against a newly identified driver mutation in NET. The TrK receptor family are expressed in neuronal tissue and regulate nervous system development and function by activating neurotrophins [44,45]. It is composed of 3 transmembrane

Pathogenic pathways		Associated mutations
Chromatin remodeling	*MEN1*	*SETD2* *MLL3*
Altered telomere length		*DAXX* *ATRX*
mTOR signaling		*PTEN* *TSC1, TSC2 DEPDC5* ⊥ ⊥ ⊥ *PI3K AKT* → *mTOR* → cell growth proliferation
DNA damage repair		*MUTYH* *CHEK2* *BRCA2*

Table 1: Main pathways and their associated mutations in pancreatic NETs. *MEN1* encodes menin which is a histone modifier and its inactivation leads to widespread transcriptional dysregulations that affect all four processes. Inactivating mutation in apoptotic regulator *DAXX* or chromatin modifier *ATRX* promotes alternative lengthening of telomeres and chromosomal instability. Loss of suppressive function of *PTEN, TSC1, TSC2*, or *DEPDC5* results in overactivation of mTOR pathway.

proteins referred to as *Trk A, Trk B,* and *Trk C* which are coded by the *NTRK1, NTRK2* and *NTRK3* genes, accordingly. Fusion of Trk with other genes leads to a constitutively activated kinase trigging uncontrolled downstream proliferation. There are a wide variety of NTRK gene fusion partners however they all share similar tyrosine kinase domains of Trk protein and can be targeted by a tyrosine kinase inhibitor [46]. NTRK fusions were identified in approximately 0.3% of NETs, across all subtypes [47]. Entrectinib produced rapid, profound, and protracted tumor response in a patient with a small intestinal NET [48]. The U.S. Food and Drug Administration (FDA) has granted Priority Review for entrectinib in treatment of NTRK fusion-positive advanced solid tumors and is expected to have a decision regarding approval by August 2019.

Alkylating agents: Streptozocin (STZ) was approved in pancreatic NETs in 1982 and STZ based chemotherapy is still the standard of care for advanced pancreatic NETs in the European Union. Oral chemotherapy combination capecitabine-temozolomide has also demonstrated effectiveness in metastatic well-differentiated NETs, but now often reserved for intermediate to high grade NETs due to the effectiveness of somatostatin analogues and small targeted therapies [49,50]. The SEQTOR study (NCT02246127) is a phase III trial current recruiting in hope to answer what is the best therapy sequence for advanced pancreatic NETs, whether everolimus followed by STZ-fluorouracil or vice versa.

Immunotherapy: At the moment, there is minimal data supporting usage of checkpoint inhibitor immunotherapy in well-differentiated NETs [51]. Phase 2 studies are ongoing evaluating safety and efficiency of nivolumab, nivolumab/ipilimumab, and pembrolizumab in metastatic NETs (NCT03591731, NCT02834013, NCT02939651). Early data from SWOG S1609 (NCT02834013) revealed antitumor activity (either a complete or partial response) in 44% of high-grade extrapancreatic NETs but no (0%) response in low-to-intermediate-grade NETs [52]. In this prospective, open-label, multicenter phase 2 trial, ipilimumab (1mg/kg IV every 6 weeks) and nivolumab (240mg IV every 2 weeks) are used which are at a lower dose than those in melanoma treatment but comparable to the FDA-approved dosage in other solid tumors.

Discussion and Conclusion

Neuroendocrine tumors composed a heterogeneity group of disease with variable aggressiveness and responses to therapy. Advancements in molecular diagnostic studies have enabled researches to begin uncovering underlying genomic mutations that differentiated different type of NETs and identifying actionable target for specific tumors. Over the past decade, treatment options for NET patients has expanded from toxic and relatively ineffective older chemotherapy regimens and somatostatin analogues to effective targeted therapies, including tyrosine kinase inhibitors and PRRT. With this range of new treatment options, considerations of tumor differentiation and treatment sequencing are paramount. Sequencing studies are currently ongoing.

References

1. Tsikitis VL, Wertheim BC, Guerrero MA (2012) Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: A SEER analysis. J Cancer 3: 292-302.
2. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, et al. (2017) Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United State. JAMA Oncol 3: 1335-1342.
3. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, et al. (2008) One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 26: 3063-3072.
4. Solorzano CC, Lee JE, Pisters PW, Vauthey JN, Ayers GD, et al. (2001) Non-functioning islet cell carcinoma of the pancreas: Survival results in a contemporary series of 163 patients. Surgery 130: 1078-1085.
5. American Joint Committee on Cancer (2017) AJCC Cancer Staging Manual, (8th edn). Springer International Publishing, United Kingdom.
6. Hamilton SR, Aaltonen LA (2010) WHO classification of Tumours of the digestive system. IARC Press, United Kingdom.
7. Lloyd RV, Osamura RY, Kloppel G, Rosai J (2017) WHO classification of tumours of endocrine organs (4th edn). IARC Press, UK.
8. Velayoudom-Cephise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, et al. (2013) Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer 20: 649-657.
9. Foubert F, Salimon M, Dumars C, Regenet N, Girot P, et al. (2019) Survival and prognostic factors analysis of 151 intestinal and pancreatic neuroendocrine tumors: A single center experience. J Gastrointest Oncol 10: 103-111.
10. Capelli P, Martignoni G, Pedica F, Falconi M, Antonello D, et al. (2009) Endocrine neoplasms of the pancreas: pathologic and genetic features. Arch Pathol Lab Med 133: 350-364.
11. Francalanci P, Diomedi-Camassei F, Purificato C, Santorelli FM, Giannotti A, et al. (2003) Malignant pancreatic endocrine tumor in a child with tuberous sclerosis. Am J Surg Pathol 27: 1386-1389.
12. Lodish MB, Stratakis CA (2011) Endocrine tumours in neurofibromatosis type 1, tuberous sclerosis and related syndromes. Best Pract Res Clin Endocrinol Metab 24: 439-449.
13. Jensen RT, Berna MJ, Bingham DB, Norton JA (2008) Inherited pancreatic endocrine tumor syndromes: Advances in molecular pathogenesis, diagnosis, management and controversies. Cancer 113: 1807-1843.
14. Scarpa A, Chang DK, Nones K, Corbo V, Patch AM, et al. (2017) Whole-genome landscape of pancreatic neuroendocrine tumours. Nature 543: 65-71.
15. Scarpa A, Mafficini A (2017) Genomic landscape of pancreatic neuroendocrine tumours: The International Cancer Genome Consortium. J Endocrinol 236: R161 to R167.
16. Jiao Y, Shi C, Edil BH, De Wilde RF, Klimstra DS, et al. (2011) DAXX/ATRX, MEN1 and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science 331: 1199-1203.
17. Chan CS, Laddha SV, Lewis PW, Koletsky MS, Robzyk K, et al. (2018) *ATRX, DAXX,* or *MEN1* mutant pancreatic neuroendocrine tumors are a distinct alpha-cell signature subgroup. Nat Commun 9: 4158.
18. Qian ZR, Ter-Minassian M, Chan JA, Imamura Y, Hooshmand SM, et al. (2013) Prognostic significance of MTOR pathway component expression in neuroendocrine tumors. J Clin Oncol 31: 3418-3425.
19. Jayakumar R, Lanjewar S, Axiotis CA (2018) Loss of PTEN and increased pAKT expression distinguishes aggressive low-grade neuroendocrine tumors. Ann Clin Lab Sci 48: 565-572.

20. Simbolo M, Mafficini A, Sikora KO, Fassan M, Barbi S, et al. (2016) Lung neuroendocrine tumours: Deep sequencing of the four World Health Organization histotypes reveals chromatin-remodelling genes as major players and a prognostic role for *TERT, RB1, MEN1,* and *KMT2D*. J Pathol 241: 488-500.

21. Park HY, Kown MJ, Kang HS, Kim YJ, Kim NY, et al. (2019) Target next-generation sequencing of well-differentiated rectal, gastric, and appendiceal neuroendocrine tumors to identify potential targets. Human Pathol 87: 83-94.

22. Pivovarcikova K, Agaimy A, Martinek P, Alaghebandan R, Perez MD, et al. (2019) Primary renal well-differentiated neuroendocrine tumor (carcinoid): Next-generation sequencing study of 11 cases. Histopathol 75: 104-117.

23. Brazeau P, Vale W, Burgus R, Ling N, Butcher M, et al. (1973) Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 179: 77-79.

24. Kvols LK, Moertel CG, O'Connell MJ, Schutt A, Rubin J, et al. (1986) Treatment of the malignant carcinoid syndrome. N Engl J Med 315: 663-666.

25. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, et al. (2009) Placebo-controlled, double-blinded, 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 27: 4656-4663.

26. Rinke A, Wittenberg M, Schade-Brittinger C, Aminossadati B, Ronicke E, et al. (2017) Placebo-controlled, double-blinded, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): Results of long-term survival. Neuroendocrinology 104: 26-32.

27. Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, et al. (2014) Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 371: 224-233.

28. Krenning EP, Kooij PP, Bakker WH, Breeman WA, Postema PT, et al. (1994) Radiotherapy with a radiolabeled somatostatin analogue, [111In-DTPA-D-Phe1]-octreotide. A case history. Ann N Y Acad Sci 733: 496-506.

29. Kwekkeboom DJ, Mueller-Brand J, Paganelli G, Anthony LB, Pauwels S, et al. (2005) Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. J Nucl Med 46: 62S-66S.

30. Kwekkeboom DJ, Teunissen JJ, Bakker WH, Kooij PP, De Herder WW, et al. (2005) Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotide in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 23: 2754-2762.

31. Esser JP, Krenning EP, Teunissen JJ, Kooij PP, Van Gameren AL, et al. (2006) Comparison of [(177)Lu-DOTA(0),Tyr(3)]octreotate and [(177)Lu-DOTA(0),Tyr(3)]octreotide: which peptide is preferable for PRRT? Eur J Nucl Med Mol Imaging 33: 1346-1351.

32. Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, et al. (2008) Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: Results of a Phase II study. J Clin Oncol 26: 4311-4318.

33. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, et al. (2011) Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 364: 514-523.

34. Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, et al. (2016) Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, phase III RADIANT-2 study. J Clin Oncol 34: 3906-3913.

35. Pavel ME, Baudin E, Oberg KE, Hainsworth JD, Voi M, et al. (2017) Efficacy of everolimus plus octreotide LAR in patients with advanced neuroendocrine tumor and carcinoid syndrome: Final overall survival from the randomized, placebo-controlled phase 3 RADIANT-2 study. Ann Oncol 28: 1569-1575.

36. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, et al. (2015) 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 387: 968-977.

37. Hobday TJ, Qin R, Reidy-Lagunes D, Moore M, Strosberg J, et al. (2015) Multicenter phase II trial of temsirolimus and bevacizumab in pancreatic neuroendocrine tumors. J Clin Oncol 33: 1551-1556.

38. Le Tourneau C, Raymond E, Faivre S (2007) Sunitinib: A novel tyrosine kinase inhibitor. A brief review of its therapeutic potential in the treatment of renal carcinoma and gastrointestinal stromal tumors (GIST). Ther Clin Risk Manag 3: 341-348.

39. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, et al. (2011) Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 364: 501-513.

40. Strosberg JR, Cives M, Hwang J, Wever T, Nickerson M, et al. (2016) A phase II study of axitinib in advanced neuroendocrine tumors. Endocrine-Related Cancer 23: 411-418.

41. Capdevila J, Fazio N, Lopez CL, Teule A, Valle JW, et al. (2019) Final results of the TALENT trial (GETNE 1509): A prospective multicohort phase II study of lenvatinib in patients with with G1/G2 advanced pancreatic and gastrointestinal neuroendocrine tumors. J Clin Oncol 37: 4106.

42. Phan AT, Halperin DM, Chan JA, Fogelman DR, Hess KR, et al. (2015) Pazopanib and depot octreotide in advanced, well-differentiated neuroendocrine tumours: a multicentre, single-group, phase 2 study. Lancet Oncol 16: 695-703.

43. Xu J, Li J, Bai C, Xu N, Zhou Z, et al. (2019) Surufatinib in advanced well-differentiated neuroendocrine tumors: a multicenter, single-arm, open-label, phase Ib/II trial. Clin Cancer Res 2: 1-4.

44. Klein R, Jing SQ, Nanduri V, O'Rourke E, Barbacid M (1991) The trk proto-oncogene encodes a receptor for nerve growth factor. Cell 65: 189-197.

45. Nakagawara A (2001) Trk receptor tyrosine kinase: A bridge between cancer and neural development. Cancer Lett 169: 107-114.

46. Bertrand T, Kothe M, Liu J, Dupuy A, Rak A, et al. (2012) The crystal structure of TrkA and TrkB suggest key regions for achieving selective inhibition. J Mol Biol 423: 439-453.

47. Sigal DS, Bhangoo MS, Hermel JA, Pavlick DC, Frampton G, et al. (2018) Comprehensive genomic profiling identifies novel NTRK fusions in neuroendocrine tumors. Oncotarget 9: 35809-35812.

48. Sigal D, Tartar M, Xavier M, Bao F, Foley P, et al. (2017) Activity of entrectinib in a patient with the first reported NTRK fusion in neuroendocrine cancer. J Natl Compr Canc Netw 15: 1317-1322.

49. Saif MW, Kaley K, Brennan M, Garcon MC, Rodriguez G, et al. (2013) A retrospective study of capecitabine/temozolomide (CAPTEM) regimen in the treatment of metastatic pancreatic neuroendocrine tumors (pNETs) after failing previous therapy. J Oncol 14: 498-501.

50. Sahu A, Jefford M, Lai-Kwon J, Thai A, Hicks RJ, et al. (2019) CAPTEM in metastatic well-differentiated intermediate to high grade neuroendocrine tumors: A single centre experience. J Oncol 1: 1-7.

51. Chauhan A, Horn M, Magee G, Hodges K, Evers M, et al. (2018) Immune checkpoint inhibitors in neuroendocrine tumors: A single institution experience with review of literature. Oncotarget 9: 8801-8809.

52. Patel SP, Othus M, Chae YK, Giles F, Hansel D, et al. (2019) A Phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) S1609: The neuroendocrine cohort. 2019 AACR Annual Meeting Abstract CT039.