REVIEW

c-MET inhibition: novel treatment for sporadic and MEN1-associated GEP NETs

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Abstract

Gastroenteropancreatic neuroendocrine tumors (GEP NETs) comprise a heterogeneous and diverse group of neoplasms arising from a common neuroendocrine cell origin. The majority of these tumors occur sporadically while ~20% manifest within the context of hereditary syndromes. Germline *MEN1* mutations cause a syndrome with an increased susceptibility to multifocal primary GEP NETs. In addition, somatic *MEN1* mutations also occur in these sporadic lesions. *MEN1* alterations are the most frequent somatic mutation found in pancreatic neuroendocrine tumors. In this review, we explore the implication of the loss of the *MEN1*-encoded protein menin as a key pathogenic driver in subsets of GEP NETs with downstream consequences including upregulation of the oncogenic receptor c-MET (hepatocyte growth factor receptor). Furthermore, the review will summarize the data related to the clinical presentation, therapeutic standards, and outcomes of these tumors in both sporadic and germline *MEN1* mutation-associated contexts. Finally, we present the data on c-MET expression in GEP NETs, clinical trials using c-MET inhibitors and provide an overview of the molecular mechanisms by which c-MET inhibition in these lesions represents a potential precision-medicine targeted approach.

Key Words

- ▶ neoplasia
- ▶ oncology
- ▶ pancreas
- ▶ digestive tract

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Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP NETs) represent a heterogeneous group of tumors with an unpredictable clinical course and varying degrees of malignancy. These neoplasms arise from neuroendocrine cells and are characterized by their ability to produce and secrete peptide hormones that can result in syndromes of hormonal excess. While they are rare, the incidence of NETs in the United States has increased 6.4-fold over the past 40 years (Dasari *et al.* 2017).

NET hereditary syndromes account for ~20% of all GEP NETs, including multiple endocrine neoplasia (MEN) syndrome types 1 and 4, von Hippel–Lindau (VHL) and neurofibromatosis type 1 (NF1). *MEN1* is caused by

heterozygous germline-inactivating mutations in the tumor-suppressor *MEN1* gene on chromosome 11q13 (Chandrasekharappa *et al.* 1997, Lemmens *et al.* 1997, Agarwal 2017). The *MEN1* gene encodes a ubiquitously expressed nuclear protein menin, which acts as a tumor suppressor in endocrine cells. Menin operates as a multi-functional protein that interacts with over 40 proteins and is implicated in many biological processes including the regulation of transcription, proliferation, differentiation, and genomic integrity (Agarwal 2017). GEP NETs are frequent in patients with *MEN1*, occurring in an estimated 80% of patients by age 80 years (de Laat *et al.* 2016). Metastatic GEP NETs increase the risk of death

by ~3.5-fold in this patient population, and therapeutic options are guided by clinical trials in sporadic GEP NETs (Goudet *et al.* 2010).

Tumor genomic profiling has elucidated that *MEN1* is frequently mutated in sporadic GEP NETs. The evidence is the strongest for sporadic non-functional pancreatic neuroendocrine tumors (NF PNETs) in which *MEN1* mutations are found in up to 30–44% of tumors (Jiao *et al.* 2011, Scarpa *et al.* 2017, Raj *et al.* 2018). Gastric, duodenal and small intestinal NETs may also harbor loss of 11q13 (Yang *et al.* 2017).

Our group has elucidated a downstream consequence of menin loss which results in an upregulation of c-MET, also known as hepatocyte growth factor receptor (Modali *et al.* 2015). Targeted therapies based on knowledge of the underlying genetics has proven beneficial in other tumor types, including BRAF inhibitors for melanoma or epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors for *EGFR* mutations in non-small-cell lung cancer treatment (Lynch *et al.* 2004, Flaherty *et al.* 2010). While mutations in *MET* have led to clinical trials in c-MET tumor-mutated malignancies with varying results, herein we explore an alternative pathway by which c-MET may be an actionable target for GEP NETs, with a particular focus on PNETs.

Clinical overview of MEN1 and sporadic GEP NETs

Clinical features

Factors that determine the clinical course and outcome of patients with GEP NETs are multifaceted and include the organ system of origin, hormone secretory properties, the size

of the primary tumor, the extent of disease, the tumor grade and the functional status/co-morbidities of the patient. Most sporadic GEP NETs are non-functional and may escape clinical detection until the tumor is large enough to exert a mass effect or to develop distant metastases. On the other hand, functional GEP NETs such as insulinoma, gastrinoma, glucagonoma, vasoactive intestinal peptide secreting tumor (VIPoma), and somatostatinoma, among other rare functional NETs, typically present symptomatically and the tumors are usually small at the time of diagnosis (Table 1). The cell of origin of these neuroendocrine tumors are varied and include β -cells for insulinomas, G-cells for gastrinomas, α -cells for glucagonomas, non- β pancreatic islet cells for VIPomas, among others. In patients with *MEN1*, functional and non-functional primary NETs often occur in the same gland (e.g. multiple primary pancreatic NF and gastrin-producing NET) and within different organs (e.g. duodenum and pancreas). The two most common functional GEP NETs seen in *MEN1* are gastrinomas (~40%) and insulinomas (10%) (Thakker *et al.* 2012).

GEP NETs within the *MEN1* patient population are often detected at an earlier age than patients with sporadic NETs. In addition to the inherited predisposition to early NETs, family members of *MEN1* patients typically undergo surveillance at a young age (starting at the age of 5 years) and symptoms of functional NETs such as gastrinoma or insulinoma may be identified during routine screenings (Hopper *et al.* 2019).

Diagnostic evaluation

A major challenge in the management of NET includes a lack of sensitive biomarkers to diagnose non-functional

Table 1 Functional pancreatic neuroendocrine tumors.

Tumor type	Sporadic prevalence (per million people)	Clinical symptoms	Mutational landscape	
			Germline (%)	Somatic (%)
Insulinoma	1–4 ^d	Whipple's triad: symptomatic hypoglycemia ameliorated by glucose administration with documented low plasma glucose level <50 mg/dL, dizziness, irritability, sweating, coma ^{a,b}	<i>MEN1</i> (10) ^h	<i>YY1</i> (0–30) ^f , <i>MEN1</i> (0–17) ^g
Gastrinoma	0.1–15 ^e	Gastroesophageal reflux disease, duodenal ulcers with bleeding and/or perforations, diarrhea, weight loss, amelioration with proton pump administration ^b	<i>MEN1</i> (40) ^h	<i>MEN1</i> (33) ^g
VIPoma	0.1 ^a	Severe diarrhea, weight loss, hypokalemia ^c	<i>MEN1</i> (<2) ⁱ	Unknown
Glucagonoma	0.001–0.01 ^a	Diabetes mellitus, necrolytic migratory erythema, diarrhea, stomatitis ^{a,b}	<i>MEN1</i> (<2) ⁱ	Unknown
Somatostatinoma	0.025 ^a	Gallstones, weight loss, diarrhea, steatorrhea, diabetes mellitus ^{a,b}	<i>MEN1</i> (<2) ⁱ	Unknown
ACTH	less than 10 case reports ^j	Cushing's syndrome, liver metastases ^j	Unknown	Unknown

References: ^a(Jensen *et al.* 2012); ^b(Lewis *et al.* 2017); ^c(Farina *et al.* 2019); ^d(Okabayashi *et al.* 2013); ^e(Zhang *et al.* 2016); ^f(Parekh *et al.* 2018); ^g(Zhuang *et al.* 1997); ^h(Agarwal 2017); ⁱ(Vargatu 2016); ^j(Byun *et al.* 2017).

GEP NETs. The 'NETest', a blood-based, multi-gene expression assay has been developed for use in sporadic NETs and has reported a higher degree of sensitivity and specificity (>95%), especially when compared to poor markers such as chromogranin A (Modlin *et al.* 2013). However, the utility of this test has not been evaluated in patients who may present with tumors in multiple endocrine and non-endocrine tissues, as is the case in MEN1. Similar to other liquid biopsy tests, this test is currently not routinely used in clinical practice due to cost and availability.

Without reliable and sensitive biochemical markers for non-functional NETs, various imaging modalities are available, including, but not limited to, endoscopic ultrasound (EUS), computerized tomography (CT), MRI, and ⁶⁸Ga-DOTATATE PET/CT. Sporadic NET patients typically undergo anatomic imaging (CT/MRI/EUS) in addition to ⁶⁸Ga-DOTATATE PET/CT given that most patients have one primary tumor and all other lesions are metastatic from the single original lesion. However, due to the frequent tumor multiplicity in MEN1, there is no universal consensus about which imaging techniques are best and/or most sensitive at detecting GEP NETs in MEN1. Expert guidelines from 2012 recommend surveillance imaging for GEP NETs with MRI, CT, or EUS every 1–2 years depending on manifestations. Newer agents, including ⁶⁸Ga-DOTATATE PET/CT are becoming more commonly used (and replacing ¹¹¹In-labeled octreotide scintigraphy), but expert opinion and data are lacking on the usefulness of this imaging modality for routine yearly screening. ⁶⁸Ga-DOTATATE has a 100-fold higher affinity for somatostatin receptor 2 (SSTR2), and about an equal affinity for somatostatin receptor 5 (SSTR5) compared to ¹¹¹In-pentetreotide scintigraphy which likely accounts for its superiority of localization and higher spatial resolution (Reubi *et al.* 2000). Other agents, such as ¹⁸F-FDOPA PET/CT and ⁶⁸Ga-DOTA-exendin-4 PET/CT have also been used to localize rare functional sporadic and MEN1 tumors such as pheochromocytoma and insulinoma (Luo *et al.* 2016, Tepede *et al.* 2019). These newer agents offer the possibility to identify a tumor based on receptor concentration for functional neuroendocrine tumors. Ideally, one would want to localize a functional tumor within a gland that has multiple NETs (or possibly identify a pheochromocytoma in a patient with bilateral, heterogenous adrenal nodules, for example).

Each imaging method has risks and benefits that must be considered when creating a comprehensive care plan for an MEN1 patient. For example, CT scans are widely available and affordable, with a sensitivity for

detecting MEN1-associated and sporadic GEP NETs of 70–94% (Challis *et al.* 2019). However, the repeated use of this modality exposes patients to increased cumulative radiation, which has been evaluated in other inherited endocrine syndromes such as von Hippel Landau (VHL) (Tirosh *et al.* 2019). MRI has an 88% sensitivity for visualizing GEP NETs in MEN1 patients and limits radiation exposure, but may be associated with the accumulation of gadolinium deposits within the nuclei of the brain. EUS has a reported NET detection rate of 90%, a sensitivity of 93%, and specificity of 95%, but it can miss areas of the pancreatic tail, is not as widely available, and is a more invasive test compared to the aforementioned imaging methods (Challis *et al.* 2019). A recent systematic review evaluating the diagnostic accuracy of different imaging modalities for MEN1-associated non-functional PNETs found that MRI is preferred over CT due to higher sensitivity and less radiation exposure (van Treijen *et al.* 2018). Future studies and consensus are needed to inform providers regarding the best surveillance and follow-up modality for GEP NETs in MEN1.

Pathologic classification and prognosis

All NETs are classified by the 2017 World Health Organization (WHO) Tumor Grading System (Rindi *et al.* 2018). NETs are categorized into grades 1 (G1), 2 (G2) and 3 (G3) based on the Ki-67 proliferation and/or mitotic indices. Ki-67 grades are classified as G1: <3%, G2: 3–20%, and G3: >20%, and mitotic index as G1: <2/10 high powered field (HPF), G2: 2–20/10 HPF, and G3: >20/10 HPF. Generally, well-differentiated NETs (G1) are indolent tumors and expresses typical markers of neuroendocrine differentiation. Poorly differentiated high-grade tumors (G3) are now classified as neuroendocrine carcinoma (NEC), which can be further characterized as small-cell or large-cell type and behave more aggressively than the typical indolent, well-differentiated NET (Choe *et al.* 2019). Finally, undifferentiated NETs are classified as G4 (Dasari *et al.* 2017).

For sporadic and MEN1-associated tumors, this updated grading system helps to predict overall patient prognosis. Poorly differentiated NECs are associated with increased risk of metastases and worse survival as compared to well-differentiated NETs (Conemans *et al.* 2017a). A review of the Surveillance, Epidemiology, and End Results (SEER) database of 50,000 US NET patients over 50 years by Dasari *et al.* confirms that G1 NETs have the highest median overall survival of 16.2 years, followed by G2 NETs at 8.3 years, and G3 and G4 (now called NEC)

NETs at 10 months (Dasari *et al.* 2017). Specifically for MEN1 patients, GEP NETs are most commonly G1 and G2, with only a few case reports demonstrating G3 NECs (Waldmann *et al.* 2008, Beijers *et al.* 2019). A large cohort study ($n=220$ MEN1 patients) demonstrated that 56% of patients had a GEP NET of which 15% developed liver metastases by an average age of 51 years old (range 31–74 years old) (Conemans *et al.* 2017b). Of the MEN1 patients with liver metastases, 50% had died after a median follow-up of 4 years, yielding an overall survival rate at 10 years of 50%. In MEN1, gastrinomas and non-functional PNETs are responsible for the most cancer-related deaths due to their metastatic potential (van Treijen *et al.* 2018, Vinault *et al.* 2018).

Management of sporadic and MEN1 GEP NETs

Surgical intervention

Surgical resection is the only possible curative intervention for both functional and non-functional GEP NETs (Ramage *et al.* 2005, Frost *et al.* 2018). For sporadic tumors, as many as 40% of NETs are metastatic at the time of diagnosis, limiting surgical intervention if the tumor is already widespread (Cives & Strosberg 2015). Another surgical challenge includes the inability to localize the culprit lesion (e.g. occult insulinoma), which requires an experienced NET center to localize the tumor and an experienced endocrine surgeon (Hirshberg *et al.* 2002). For functional NETs, the goal of surgical resection is to relieve symptoms associated with hormone hypersecretion and prevent metastasis.

On the other hand, treatment of non-functional PNETs in MEN1 patients often follows a conservative approach. Surgical resection is only recommended once the primary tumor is at or above 2 cm (Thakker *et al.* 2012). Additionally, the tendency of GEP NETs to be multifocal and recurrent in MEN1 patients must be considered when planning surgical interventions in order to optimize patient outcomes while minimizing surgical invasiveness (Demeure *et al.* 1991). Following surgery, continued screening and follow-up are important in MEN1 patients to assess their continued risk for new NETs in remnant gastroenteropancreatic tissue (Dralle *et al.* 2004). Such guidelines are internationally recognized and based on data which found a correlation between increased pancreatic tumor size (>2 cm) and increased risk of developing metastatic disease and/or death (Triponez *et al.* 2006). Surgical options depend on tumor location, size and extent of metastasis and may include distal

or total pancreatectomy, Whipple procedure, and/or tumor enucleation.

Medical management options

Well-differentiated NET treatment options include somatostatin analogues (SSAs), receptor tyrosine kinase inhibitors (TKIs), mechanistic target of rapamycin (mTOR) inhibitors, peptide receptor radionuclide therapy (PRRT), among other chemotherapies.

Somatostatin analogues

SSAs are typically the first line of treatment and were FDA approved in 1998. These agents target various isoforms of somatostatin receptors (SSTRs), which are a class of G-protein-coupled receptors present on the surface of GEP NETs. Well-differentiated tumors are known to express SSTRs at a higher density compared to poorly differentiated tumors. Within the gastrointestinal tract, low-grade NETs typically express a high density of SSTR2 (Reubi 2004). Lanreotide or octreotide long-acting release (LAR) acetate injections are two SSAs which have a high binding affinity for SSTR2 and have been utilized for their antisecretory and tumor stabilization effects. The PROMID study demonstrated that mid-gut NET treatment with 30 mg of octreotide LAR every 4 weeks significantly delayed time to tumor progression (TTP) (14.3 months vs 6 months, treatment vs placebo, respectively) (Rinke *et al.* 2019). Additionally, the treatment group had a significant delay in the worsening of symptoms such as fatigue, pain, insomnia, and diarrhea. In the Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET) study, patients with intestinal/pancreatic NETs were treated with 120 mg of lanreotide vs placebo every four weeks for almost 2 years, and progression-free survival (PFS) was found to be significantly increased with lanreotide treatment compared to placebo (65.1 vs 33% in treatment vs placebo at 1 year) (Caplin *et al.* 2014, Dromain *et al.* 2019). When tumor growth was analyzed against baseline CT and MRI imaging, the treatment group was observed to have a median tumor growth rate of 2.1% per month compared to 2.7% in the placebo group, which was significantly decreased ($P=0.008$) after 12 weeks of lanreotide treatment compared to placebo (Caplin *et al.* 2014). One challenge in the design of these studies includes the low rates of objective radiologic response of NETs, as noted above in the 0.6% difference, which is also subjected to subjective variability. However, given the typical slow

growth of low-grade NETs, tumor stabilization may be an alternative endpoint and should be considered in the design of clinical trials in NETs. Increased response rates of tumor stabilization, reported between 40–60% in NET patients with less disease progression at onset of treatment, supports this alternative trial endpoint (Cives & Strosberg 2015).

Receptor tyrosine kinase inhibitors (TKIs)

Tumor progression despite the administration of SSA requires escalation of medical treatment. Options include receptor TKIs, for which sunitinib has been FDA approved for metastatic NETs since 2006. TKIs target vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, which are crucial for tumor growth and survival. Specifically, sunitinib targets PDGF- α and PDGF- β receptors, as well as VEGF1 and VEGF2 receptors (Deeks & Raymond 2011). An early signal for efficacy in NET resulted from a phase I study of sunitinib in which 1/6th of tumors had a response to sunitinib (in highly vascularized gastrointestinal NETs) (Kulke *et al.* 2008). A non-randomized trial in advanced NET showed a 16.7% partial response rate (11/66 PNETs) and stable disease in 62% (limited by median treatment of 7.2 months). However, the quality of life was not significantly improved and the side effect profile was intolerable for some patients (Wiedmann & Mossner 2012). Ultimately, a phase III study of sunitinib for patients with advanced, well-differentiated PNETs was stopped early for efficacy, demonstrating a median PFS of 11.4 months as compared with 5.5 months with placebo. However, the side effect profile remained significant, and ~30% of patients reported diarrhea, nausea, asthenia, vomiting, while palmar-plantar erythrodysaesthesia and hypertension were present in 23 and 26% of patients, respectively (Deeks & Raymond 2011).

Mammalian target of rapamycin (mTOR) inhibitors

Everolimus is an oral inhibitor of mTOR that was FDA approved in 2016. The mTOR pathway regulates proliferation, cell growth, and angiogenesis of tumor cells (Faivre *et al.* 2006). Data for the use of everolimus mainly stem from the four RADIANT trials. The first RADIANT-1 study was a phase II trial evaluating metastatic PNETs which found that treatment with or without concomitant octreotide LAR was promising (Yao *et al.* 2008). Further evidence from RADIANT-2 evaluating octreotide plus everolimus or placebo did not meet the pre-specified overall survival endpoint in PNET patients (Pavel *et al.* 2011).

A number of design factors may have influenced these results, including a lower performance status, a higher incidence of lung NET and more frequent prior use of chemotherapy in the treatment arm. Nevertheless, the survival of the treatment subjects (~6.3 months) was not significantly different than that of the placebo group. Notably, serious adverse events led to discontinuation of the study in 21.1% of subjects in the treatment arm (compared to 5.9% of subjects in the placebo arm). RADIANT-3, the largest study at the time to be conducted in NETs, enrolled 410 patients with advanced, low-grade or intermediate-grade PNETs (Yao *et al.* 2011). Progression-free survival was improved in the treatment group, 11.0 months with everolimus vs 4.6 months with placebo, with a 65% reduced risk of progression or death (HR 0.35; 95% CI 0.27–0.45; $P < 0.001$). The final RADIANT-4 study was a phase III study on patients with G1, G2 advanced GEP NETs ($n = 175$) or lung NETs ($n = 90$) (Yao *et al.* 2016). There was a 44% benefit in PFS in GEP NET patients, and tumor shrinkage was observed in 64 vs 26% of patients (treatment vs placebo, respectively).

Peptide receptor radionuclide therapy (PRRT) and others

While the aforementioned therapies represent beneficial medical treatments for rare disease, options that offer patients improved survival or a significant delay in tumor progression over extended periods of time are limited. A promising new approach is the use of PRRT in NETs. To induce cellular damage, a radionuclide (^{90}Y or ^{177}Lu) is linked to a peptide (SSTR agonist, e.g. TOC-Tyr3 octreotide or TATE-Tyr3 octreotate) by means of a chelator (e.g. DOTA). The β -emitting radionuclide that results from the binding of the agents to the SSTRs on the tumor cell membrane results in ligand internalization which ultimately leads to cell death. Currently in the United States only ^{177}Lu -DOTATATE is FDA approved, although this agent has been used in Europe for over a decade (Frost *et al.* 2018). The NETTER 1 trial supported the FDA decision for approval (Strosberg *et al.* 2017). This study included 229 patients with well-differentiated, progressive, locally advanced, inoperable or metastatic SSTR-positive (determined by ^{68}Ga -DOTATATE PET/CT positive uptake in the tumor) midgut NET and found that the estimated rate of PFS was 65.2% in the treatment group compared to 10.8% in the control group at 20 weeks. Furthermore, response rate was significantly ($P < 0.001$) greater in the treatment group (18%) than the control group (3%).

Somatostatin antagonist treatment is another modality being investigated. As opposed to SSTR agonists which

bind to elicit a cellular response, antagonists block agonist binding and thus the agonist response. In 4 patients with progressive NETs, ^{177}Lu -DOTA-JR11 treatment resulted in partial remission in 2 patients, stable disease in 1 patient and a mixed response in the final patient (Wild *et al.* 2014). Somatostatin antagonists (e.g. ^{177}Lu -DOTA-JR11 or ^{177}Lu -OPS201) are also being investigated for theranostic use (Fani *et al.* 2017). Although the full side effect profile remains unknown, continued investigations, including the results of a preliminary study of the efficacy of ^{177}Lu -OPS201 are forthcoming (NCT02592707).

Other therapies beyond the scope of this review include combination treatment of capecitabine and temozolomide, interferon- α , and interventional radiofrequency (IR) ablation. Current ongoing studies of combination treatments and newer agents (NCT03049189, NCT02955069, NCT03375320) will help us better understand the relative benefits and disadvantages. However, there is still a need for randomized head-to-head clinical trials.

In addition, it is important to recognize that many trials do not include or do not report the number of patients with germline *MEN1* mutation-positive *MEN1* syndrome. Thus, we have an insufficient understanding of how these therapies affect this subset of patients. Mechanistic insights to guide therapeutic targets in *MEN1*-associated tumors is a critical step to improve outcomes for patients with *MEN1* and possibly patients with *MEN1*-mutated GEP NETs.

The role of c-MET in malignancy

Impact of c-MET alterations

c-MET is a tyrosine kinase receptor for hepatocyte growth factor (HGF). HGF ligand binding causes dimerization of the c-MET receptor and subsequent autophosphorylation of the intracellular domains, resulting in activation of downstream signaling pathways. These signals, including phosphoinositide 3-kinase (PI3K), GRB-associated-binding protein 1 (GAB1), and RAS, have been shown to be key regulators in cellular growth, survival, and motility (Puccini *et al.* 2019) (Fig. 1).

MET activating mutations were discovered by genome-wide analysis of families with hereditary papillary renal carcinoma (HPRC), and its role as a somatically mutated driver gene has been expanded to include papillary renal carcinomas, as well as brain, breast, colorectal, endometrial, esophageal, gastric, head and neck, hepatic, kidney, lymphomas, medulloblastoma, melanoma,

non-small-cell-lung, ovarian, and pancreatic cancers (Schmidt *et al.* 1997, Peters & Adjei 2012). Activating *MET* mutations are found in exons 18 and 19, as well as in the semaphorin domain (e.g. missense mutation E168D) and juxtamembrane domain (e.g. missense mutation T1010I, P1009S, and exon 14 skipping) of the receptor. Furthermore, c-MET overexpression is associated with poorer prognosis and increased peritoneal and liver metastasis in gastric cancer patients (Toiyama *et al.* 2012, Bradley *et al.* 2017).

MET mutations have not been observed in sporadic PNETs or other NETs such as lung and small intestine in whole genome or exome sequencing analyses (Jiao *et al.* 2011, Francis *et al.* 2013, Scarpa *et al.* 2017, Simbolo *et al.* 2017, 2019, Raj *et al.* 2018). Although receptor mutations have not been observed in NETs, c-MET has been found to be overexpressed in PNETs through regulation at the promoter level (as explained below) or other unknown mechanisms (Hansel *et al.* 2004, Modali *et al.* 2015, Krampitz *et al.* 2016, Chan *et al.* 2018). An in-depth profile of primary and metastatic PNETs implicated c-MET to be essential for tumor growth in NET xenograft models (Krampitz *et al.* 2016). Synthetic stimulation of the c-MET receptor in xenograft models with a monoclonal anti-c-MET antibody 3D6 (c-MET agonist) was shown to significantly increase the growth of transplanted NET tumor xenografts. None of the PNET samples lacking c-MET successfully became xenografts, supporting the role of c-MET activation and signaling in tumor cell proliferation and survival. Using a tissue microarray of well-differentiated PNETs ($n=74$), high c-MET expression correlated with decreased survival (Krampitz *et al.* 2016), similar to the data in gastric cancer patients above. Immunofluorescence analysis confirmed the co-staining of chromogranin A (a marker of NETs) and c-MET in a patient's liver and lymph node metastases, suggesting a c-MET inhibitor could additionally target metastasis. Based on these data, targeting c-MET for therapy has been intensively investigated for potential bench-to-bedside applications.

Current applications of c-MET inhibition in cancer therapy

Inhibition of c-MET signaling in cancer treatment is achieved via one of two mechanisms: monoclonal antibodies (MAB) that prevent HGF/c-MET interaction and/or c-MET dimerization or small-molecule kinase inhibitors which block the phosphorylation of c-MET after ligand binding. The small-molecule kinase inhibitor

Figure 1

HGF/c-MET interaction and associated inhibitors. Binding of the HGF ligand to the α -chain induces dimerization and subsequent autophosphorylation of the c-MET receptor. Monoclonal anti-HGF antibodies, such as ficlatuzumab and rilotumumab, and anti-c-MET receptor antibodies like SAIT301 and onartuzumab, inhibit downstream signaling by blocking ligand/receptor interactions. Upon ligand binding, phosphorylation events prompt the recruitment of several intracellular proteins. Cbl functions as a ubiquitinating effector to promote lysosomal recognition and subsequent degradation of c-MET. PI3K phosphorylates downstream agent protein kinase B (AKT), which activates mTOR pathways to promote cell survival. Signal transducer and activator of transcription (STAT) signaling also contributes to this pathway. GAB1 interacts with several downstream proteins, including STAT, to signal cell migration. Residing within the intracellular membrane, RAS induces a signaling cascade which promotes cell proliferation. Inhibitors that target phosphorylated intracellular domains of c-MET, such as cabozantinib, tivantinib, foretinib, MK-8033, golvantinib, crizotinib, and tepotinib, aim to block the downstream effects of HGF binding. The red highlighted inhibitors are not selective for c-MET. Cabozantinib, foretinib, MK-8033, golvantinib, crizotinib, and tepotinib all bind competitively with ATP (Classes I and II) while tivantinib does not (Class III).

interventions can be further subcategorized into Classes I, II and III. Classes I and II inhibitors are ATP-competitive and specifically bind to different locations of the ATP-binding domain on the c-MET receptor surface. Class III inhibitors are non-ATP-competitive small molecule inhibitors, that work via preventing the autophosphorylation of the intracellular domains of the receptor (Mughal *et al.* 2013) (Fig. 1).

c-MET inhibitors have proceeded through pre-clinical and clinical trials in different forms of solid tumors, including gastrointestinal cancers (Table 2). For example, tepotinib, an ATP competitive c-MET inhibitor, has been shown to suppress tumor growth and reduce the number of lung metastases from hepatic tumors and is currently in phase Ib clinical trials (Bladt *et al.* 2014). In another trial investigating the safety and efficacy of tepotinib treatment in patients with solid tumors, two patients with lung neuroendocrine carcinoma were treated in Regimen 1 (30–400 mg tepotinib once daily for 14 days), but no further data on efficacy of that subgroup is available (Falchook *et al.* 2019).

Tivantinib, a Class III c-MET inhibitor, was shown to successfully reduce c-MET signaling, induce apoptosis, and decrease angiogenesis of hepatocellular carcinoma

(Porta *et al.* 2015). However, during phase II clinical trials, toxic side effects were noted such as the development of neutropenia and anemia in some patients, and higher doses of tivantinib correlated to increased risk of adverse events. Other inhibitors such as SU11274, a Class I inhibitor, have only been tested in *in vitro* models. Rilotumumab, a MAB c-MET inhibitor which targets HGF, was found not to be an effective treatment for patients with advanced MET-mutation positive gastric or gastro-esophageal junction cancers (Catenacci *et al.* 2017).

In one of the only clinical trials relating PNETs with c-MET inhibition, cabozantinib (a c-MET and VEGFR2 inhibitor) treatment in patients with advanced carcinoids and PNETs showed partial responses in both tumor types (15% PNET, 14.6% carcinoids), and demonstrated that 75% of patients with PNETs achieved stable disease response, which was the primary endpoint (Chan *et al.* 2017). Median PFS achieved in the carcinoid cohort was 31.4 months, and 21.8 months in the PNETs cohort (placebo data pending full publication of results). The toxicity profile was consistent with previous observations in other trials (Chan *et al.* 2017). The efficacy of c-MET inhibitors as a potential treatment for GEP NETs and PNETs is still undefined, but shows promise.

Table 2. c-MET Inhibitors.

Tumor type	Agent used	Receptor(s) targeted	Reference	Patients (n)	IHC	Tumor genomics analyzed?	Responses (%)	Median progression free survival or time until progression (days)	Noted adverse effects
Solid tumors									
Metastatic or unresectable solid tumors	Foretinib	c-MET, VEGFR-2	Eder <i>et al.</i> (2010)	40	Yes	No	7.5 (partial)	NR	Elevated lipase, tumor hemorrhage, and hemorrhage into CNS, hypertension, proteinuria
Refractory advanced solid tumors	Rilotumumab	c-MET	Gordon <i>et al.</i> (2010)	40	Yes	No	NR	168	Fatigue, constipation, decreased appetite, nausea
Solid tumors	Tivantinib	c-MET, microtubule	Rosen <i>et al.</i> (2011)	79	Yes	No	NR	85	Fatigue, nausea, vomiting, diarrhea, anemia
Advanced solid tumors	Tivantinib	c-MET, microtubule	Yamamoto <i>et al.</i> (2013)	47	No	No	NR	71 (at least one WT CYP2C19 allele), 67 (both alleles are CYP2C19 variants)	Leukopenia, neutropenia, anemia, lymphopenia, fatigue, anorexia
Solid tumors	Golvatinib	c-MET and VEGFR2	Molife <i>et al.</i> (2014)	34	Yes	FISH analysis	NR	NR	Diarrhea, nausea, vomiting, fatigue, decreased appetite, elevated alanine aminotransferase, elevated aspartate aminotransferase
Metastatic solid tumors	Tivantinib + gemcitabine	c-MET (tivantinib), thymidylate synthetase (gemcitabine)	Pant <i>et al.</i> (2014)	74	No	No	1.4 (partial)	129	Thrombocytopenia, neutropenia, anemia, fatigue, nausea, vomiting, diarrhea, anorexia
Phosphorylated c-MET mutation-positive tumors	Ficlatuzumab	High specificity for HGF	Tabernero <i>et al.</i> (2014)	19	Yes	No	NR	43	Asthenia, peripheral edema, hepatic pain, cough
Advanced solid tumors	Tivantinib + tesolimus	c-MET (tivantinib), mTOR (tesolimus)	Kyriakopoulos <i>et al.</i> (2017)	29	No	No	3.4 (partial)	NR	Anemia, fatigue, anorexia, and hypoalbuminemia, hypophosphatemia, anemia, hypertension, hyponatremia, neutropenia
Advanced carcinoid or pNET	Cabozantinib	VEGFR2, c-MET	Chan <i>et al.</i> (2017)	41 (carcinoid), 20 (pNET)			15 (pNET), 14.6 (carcinoid) (both partial)	663 (pNET), 955 (carcinoid)	Hypertension, hypophosphatemia, diarrhea, lymphopenia, thrombocytopenia, fatigue, and increased lipase or amylase

Metastatic or locally advanced solid tumors	MK-8033	c-MET and RON	Keedy <i>et al.</i> (2018)	47	Yes	No	2.1 (partial)	57	Fatigue, nausea, alopecia, elevated alanine aminotransferase, anorexia
Solid tumors	Tepotinib	c-MET	Falchook <i>et al.</i> (2019)	149	Yes	ISH analysis	1.3 (partial)		Fatigue, peripheric edema, decreased appetite, nausea, vomiting, lipase increase
Gastrointestinal tumours									
Metastatic gastric carcinoma	Foretinib	c-MET, VEGFR-2	Shah <i>et al.</i> (2013)	74	Yes	FISH analysis	NR	52	Hypertension, diarrhea
Metastatic gastric cancer (MGC)	Tivantinib	c-MET, microtubule	Kang <i>et al.</i> (2014)	30	Yes	FISH analysis	NR	43	Nausea, anemia, decreased appetite
HCC	Tivantinib	c-MET, microtubule	Okusaka <i>et al.</i> (2015)	28	Yes	No	NR	113 (at least one WT CYP2C19 allele), 30 (both alleles are CYP2C19 variants)	Fatigue, anorexia, leukopenia, anemia, neutropenia, thrombocytopenia, lymphocytopenia, neutropenia, febrile neutropenia, cough, fatigue
HER2-negative, MET-positive gastroesophageal and stomach adenocarcinoma	Onartuzumab + mFOLFOX6	HGF (onartuzumab), DNA cross-linker (mFOLFOX6)	Shah <i>et al.</i> (2016)	123	Yes	No	NR	207	Neutropenia, hypoalbuminemia, peripheral edema, thrombocytopenia, PE, gastric perforation
Advanced pancreatic ductal adenocarcinoma	Cabozantinib + gemcitabine	c-MET, VEGFR, Axl (cabozantinib), thymidylate synthetase (gemcitabine)	Zhen <i>et al.</i> (2016)	12	No	No	37.5 (partial)	143	Neutropenia, AST/ALT elevations, fatigue, nausea, hypertension, diarrhea
Adenocarcinomas of esophagus, gastroesophageal junction, or stomach	Tivantinib + FOLFOX	c-Met (tivantinib), DNA cross-linker (FOLFOX)	Pant <i>et al.</i> (2017)	49	Yes	No	2 (complete), 26.5 (partial)	234 (low c-MET expressing tumors), 176 (high c-MET expressing tumors)	Nausea, thrombocytopenia, neutropenia, fatigue, diarrhea, nausea, peripheral neuropathy
MET-positive gastric or gastroesophageal junction adenocarcinoma	Rilotumumab + epirubicin, cisplatin, and capecitabine or placebo + epirubicin, cisplatin, capecitabine	c-MET (rilotumumab)	Catenacci <i>et al.</i> (2017)	609	Yes	FISH analysis	NR	170	Neutropenia, anemia, fatigue, anemia, vomiting, febrile neutropenia
Renal cell cancer and solid tumors	Axitinib + crizotinib	VEGFR1, -2, -3 (axitinib), ALK, c-MET, RON (crizotinib)	Michaelson <i>et al.</i> (2019)	22	No	No	NR	170	Hypertension, fatigue

(Continued)

Table 2. Continued.

Tumor type	Agent used	Receptor(s) targeted	Reference	Patients (n)	IHC	Tumor genomics analyzed?	Responses (%)	Median progression free survival or time until progression (days)	Noted adverse effects
Other tumours									
Recurrent or metastatic breast cancer	Tivantinib	c-MET, microtubule	Tolaney <i>et al.</i> (2015)	22	Yes	FISH analysis	4.5 (partial), 4.5 (overall), 4.5 (objective)	36	Fatigue, anemia, neutropenia
Previously treated malignant mesothelioma	Tivantinib	c-MET, microtubule	Maron <i>et al.</i> (2015)	18	Yes	MET mutational analysis, gene expression profiling, and serum HGF	NR	55 (pleural), 116 (peritoneal)	Leukopenia, lymphopenia, abdominal pain, fatigue
Advanced non-small cell lung cancer (NSCLC)	Crizotinib + panHER inhibitor	ALK, c-MET, RON, ROS1 (crizotinib), HER (panHER inhibitor)	Janne <i>et al.</i> (2016)	70	Yes	FISH analysis	1.5 (overall)	91 (escalation phase), 64 (expansion phases)	Alanine aminotransferase levels, mucosal inflammation, diarrhea, vomiting, decreased appetite, fatigue
Refractory multiple myeloma	Tivantinib	c-MET, microtubule	Baljevic <i>et al.</i> (2017)	16	No	Gene expression profiling, ELISA assay	NR	NR	Fatigue, decreased neutrophils, pain, myalgia, diarrhea, memory impairment, respiratory problems, rash, hypertension, neutropenia, syncope, infection, pain
Metastatic prostate cancer	Tivantinib	c-MET, microtubule	Monk <i>et al.</i> (2018)	78	No	No	1.3 (partial)	167	Fatigue
Colorectal cancer and non-small cell lung cancer	SAIT301	c-MET	Lee <i>et al.</i> (2018)	16	Yes	FISH analysis	6.3 (partial)	NR	Decreased appetite, hypophosphatemia, fatigue, dizziness, diarrhea, increased blood alkaline phosphate, dyspnea

ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate transaminase; Axl, tyrosine-protein kinase receptor UFO; c-MET, hepatocyte growth factor receptor; CNS, central nervous system; ELISA, enzyme-linked immunosorbent assay; FISH, fluorescence in situ hybridization; HER, human epidermal growth factor receptor; HGF, hepatocyte growth factor; IGH, in situ hybridization; mTOR, mammalian target of rapamycin; NR, no response; partial, partial response (decrease in tumor size or extent of cancer); PNET, pancreatic neuroendocrine tumor; RON, macrophage-stimulating protein receptor; ROS1, proto-oncogene tyrosine-protein kinase ROS; VEGFR, vascular endothelial growth factor receptor.

c-MET inhibition as a potential target in *MEN1* mutated GEP NET tumors

In vitro and *in vivo* data

A major obstacle in studying c-MET and the effects of c-MET inhibition in PNETs is the lack of suitable PNET pre-clinical models, particularly mouse models, with features of the more common non-functional tumors. The only human PNET cell line APL1, derived from a primary PNET, is very slow growing and not yet used extensively for *in vitro* experiments (Krampitz *et al.* 2016). The three other PNET cell lines QGP-1, BON1, and NT-3 do not truly represent PNETs. QGP-1 has a mutation in the *KRAS* oncogene which is not found in PNETs (Kaku *et al.* 1980, Vandamme *et al.* 2015). BON1 is not derived from a primary tumor, but is derived from a lymph node metastasis (Evers *et al.* 1991). Lastly, NT-3 is derived from the lymph node metastases of PNETs (Benten *et al.* 2018). There are various *in vivo* mouse models that develop insulin-secreting tumors, including (1) the germline *Men1*^{+/-} knockout in which over 80% develop insulin-secreting PNETs by 60 weeks (Crabtree *et al.* 2001, Bertolino *et al.* 2003a, Loffler *et al.* 2007, Harding *et al.* 2009), (2) β -cell specific *Men1* knockout where 100% of mice develop insulinoma by 40 weeks (Bertolino *et al.* 2003b, Crabtree *et al.* 2003, Biondi *et al.* 2004) and (3) RIP-Tag2 mice which develop invasive insulinoma (Hanahan 1985). The generation of reproducible, well-differentiated tumor xenografts from primary patient PNETs is challenging and is yet to be consistently achieved.

Studies in the RIP-Tag2 metastatic insulinoma mouse model of aggressive islet β -cell tumors found that anti-VEGF therapy reduced tumor burden, but increased hypoxia and c-MET expression and activation, and also increased tumor cell invasion and metastasis (Sennino *et al.* 2012). Initial inhibition of VEGF using either anti-VEGF antibodies or sunitinib showed decreased tumor size by 75 and 78%, respectively. Simultaneously, c-MET mRNA level increased 3-fold in the anti-VEGF treatment group and 6-fold in the sunitinib treatment group compared to control samples. While these tumors were smaller in size, irregular tumor borders and increased expression of proliferative markers showed their invasiveness had increased. To confirm that this enhanced invasiveness was related to increased c-MET expression, mice were treated with a c-MET inhibitor PF-04217903 together with sunitinib, or XL184 (cabozantinib) which simultaneously blocks c-MET and VEGF. Significant reductions were noted in the invasion index in both anti-VEGF and sunitinib

groups, showing tumor invasion was reduced by c-MET inhibition with simultaneous anti-VEGF treatment.

Additional studies also support the role of c-MET in tumorigenesis of *MEN1*-associated NETs. In the mouse MIN6 insulinoma cell line, menin was shown to target and upregulate MEG3, a long ncRNA that has tumor-suppressor properties in insulinoma (Miyazaki *et al.* 1990, Modali *et al.* 2015). Ectopic menin expression was observed to lead to an activating chromatin modification (H3K4me3) in the MEG3 promoter region. Subsequent MEG3 overexpression in MIN6 cells decreased proliferation and inhibited c-MET transcription (Modali *et al.* 2015) (Fig. 2). MIN6 cells with reduced c-MET expression had decreased migration and invasion. Furthermore, a reciprocal relationship between menin loss (i.e., MEG3 loss) and c-MET overexpression was detected in both human and mouse PNETs using immunohistochemical (IHC) staining, suggesting an oncogenic role of c-MET in *MEN1*-associated PNETs.

Also utilizing the MIN6 insulinoma line, the phosphorylated form of a β -cell specific transcription factor HLXB9 was shown to target the *Cblb* gene, which is an inhibitor of c-MET, thus controlling cell growth and proliferation (Desai *et al.* 2015). An increase in phospho-HLXB9 correlated with decreased *Cblb* expression and thus increased expression of c-MET, elucidating phospho-HLXB9's role as a pro-oncogenic agent with the potential to promote c-MET activation in an insulinoma cell line.

Using gene expression microarray assays, c-MET was found to be overexpressed by 4.9-fold in human metastatic PNETs ($n=7$) compared to nonmetastatic PNETs ($n=5$) (Hansel *et al.* 2004). In support of the role of c-MET in the progression and tumor invasion to metastatic sites, IHC staining of tissue microarrays to verify c-MET overexpression showed 33% of metastatic PNETs ($n=15$) had higher c-MET compared to 17% of nonmetastatic lesions ($n=24$). Increased c-MET expression was also observed in lymph node metastases (4/7, 57%) and in liver metastases (5/9, 56%). While c-MET expression was not found to be predictive of metastasis, the observation that expression was increased in metastases suggests that c-MET may play a role in the metastatic potential of PNETs (Hansel *et al.* 2004). Further support for this observation comes from a correlation between c-MET overexpression in 24 insulinomas and 3 hepatic metastases with the Ki-67 proliferative index (Murat *et al.* 2015).

MEN1, alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) and death domain-associated protein (*DAXX*) are among the most commonly mutated

Figure 2

Effect of menin loss on MEG3 and c-MET expression. The top panel represents effects in an islet cell that has normal menin expression. Menin facilitates an activating histone trimethylation mark (H3K4me3) in the promoter region of the long non-coding RNA (lncRNA) MEG3, leading to an increase in its expression. MEG3 interacts with the inhibitory multi-subunit polycomb repressive 2 protein complex (PRC2), to suppress the *c-MET* gene and thus decrease c-MET expression (the basal/normal level of c-MET). In islets with biallelic menin loss (lower panel), there is loss of the activating H3K4 trimethylation event at the MEG3 promoter, leading to decreased MEG3 expression, which increases c-MET expression due to loss of repressive chromatin marks in the *c-MET* gene associated with PRC2 recruitment.

genes in sporadic PNETs, found in 40, 10, and 20% of tumors, respectively (Jiao *et al.* 2011, Scarpa *et al.* 2017, Chan *et al.* 2018, Raj *et al.* 2018). In an analysis of whole exome sequencing of PNETs, 58% of 64 PNETs were found to carry mutations in these genes (Chan *et al.* 2018). In the same study, RNAseq analysis showed PNETs that carried mutations in either *MEN1*, *DAXX*, or *ATRX* had 7.3-fold lower MEG3 expression and 3-fold higher c-MET expression compared to wild-type PNETs, which also coincided with worse recurrence free survival according to Kaplan-Meier analysis. Interestingly, PNETs carrying mutated versions of these genes (*MEN1*, *DAXX*, or *ATRX*) had a gene expression signature very close to that of pancreatic α cells, supporting the possibility that PNETs either originate from or differentiate into a cell type that is similar to α cells, which express increased c-MET (Chan *et al.* 2018).

These findings suggest a possible mechanism whereby aggressiveness and metastasis of PNETs may be dependent on c-MET expression. The observed inverse relationship between c-MET vs menin and MEG3 expression supports the co-existence of tumor-suppressing roles of menin and MEG3. With this in mind, c-MET inhibitors represent an attractive targeted therapy for the management of aggressive GEP NETs in *MEN1* and similar sporadic tumors, warranting additional clinical trials and investigation.

Conclusions and future directions

GEP NETs are increasing in frequency and lack effective therapies once they become inoperable. In *MEN1* patients, multifocal GEP NETs possess malignant capacity, with the added challenge of definitively identifying the culprit primary tumor. While medical therapies exist for some non-operable tumors, there remains a paucity of options

that utilize molecularly identified targets. Mechanistic insights from recent studies show that menin loss may lead to subsequent upregulation of the HGF receptor c-MET, supporting c-MET inhibition as a therapeutic target. Similar overexpression of c-MET in sporadic PNETs shows a potential of c-MET inhibitors for the treatment of these tumors. Plausible biological mechanisms (e.g. menin loss correlating with the downregulation of MEG3, leading to increased expression of c-MET and increased migration/invasion), support an oncogenic role of c-MET in *MEN1*-associated tumorigenesis. Further clinical trials of c-MET inhibition in GEP NETs, specifically including patients with sporadic and *MEN1* syndrome-related NETs, would help further advance our understanding and potentially provide a precision medicine approach.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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