

Everolimus for the treatment of advanced pancreatic neuroendocrine tumors

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Pancreatic neuroendocrine tumors (pNETs) account for 1–2% of all pancreatic tumors. Approximately two-thirds of patients have an advanced disease with metastases at diagnosis. Surgery is still the gold-standard treatment in most cases, while few medical options exist for inoperable tumors. A new potential therapeutic approach for advanced pNETs results from targeting intracellular molecular pathways. Rapalogs – rapamycin analogs including everolimus – target the mTOR signaling cascade, inhibit cell proliferation and evoke apoptosis. Recent Phase II and III clinical trials demonstrated that everolimus is effective in advanced pNETs as it increases progression-free survival of treated patients. Everolimus appears to be promising for advanced pNETs and is usually tolerated with mainly mild adverse events. Future studies will establish whether everolimus, alone or in combination with other compounds (e.g., new somatostatin analogs, cytotoxic agents and anti-angiogenic drugs), will also prove to be a valid option for patients with other forms of advanced neuroendocrine tumors.

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Neuroendocrine tumors (NETs) are increasingly recognized in clinical practice, likely due to an improved knowledge of their manifestations and increased availability of reliable imaging techniques used for their detection. The management of advanced, metastatic NETs is still challenging owing to the variety of diagnostic and therapeutic issues that these patients pose to clinicians. Nonetheless, recent advances have clearly shown that the prognosis of NET patients has improved thanks to newly developed agents, including somatostatin analogs, various chemotherapeutic agents, radiolabeled drugs and newly developed targeted therapies [1]. Drugs such as bevacizumab and sunitinib represent the forefront of targeted therapies for cancer treatment due to their selective action on intracellular pathways involved in tumor cell proliferation [1].

The purpose of this review is to provide a summary of current knowledge on pancreatic NETs (pNETs) and their established medical treatment with a special focus on the use of the recently approved mTOR inhibitor, everolimus.

General aspects of pNETs

NETs are rare neoplasms arising in various sites of the gut, pancreas and lungs. The incidence of these tumors has increased over the past two decades from 1.09 in 100,000 in the 1970s to 5.25 in 100,000 in 2004. The refinement of diagnostic procedures and better knowledge acquired on these tumors, are plausible reasons to explain, at least in part, the increased frequency of NETs. These findings are based on the survey database from the Surveillance Epidemiology and End

Result Program registry [2]. pNETs represent 1.3% of all pancreatic tumors in incidence and 10% of cases in prevalence [2]. The prevalence may well be over 1% of the population with the vast majority of pNET patients lacking an early diagnosis. As a result, approximately two-thirds of patients with well-differentiated pNETs have distant metastases at diagnosis [2]. In most cases, they occur sporadically and tend to affect elderly patients, with males having a slightly increased risk over females. Many pNETs are associated with genetic cancer syndromes, such as multiple endocrine neoplasia type 1, von Hippel-Lindau, neurofibromatosis type 1 and tuberous sclerosis. These patients are often younger at diagnosis, found to have multiple synchronous lesions and a family history of endocrine disorders or associated cancers [3,4].

NETs are often classified into functional (i.e., those producing endocrine hormones/mediators and leading to related clinical syndromes) and nonfunctional tumors (NF tumors; i.e., those not secreting hormones or releasing biologically inactive mediators unable to evoke clinical symptoms). The natural course of the disease varies according to the type of primary tumor, and survival correlates with tumor size, stage of the disease and histological grade at diagnosis. Patients with functional tumors usually show a better prognosis as compared with those with NF tumors [3]. NF tumors represent the majority (90%) of pNETs [3]. Their clinical presentation is characterized by symptoms such as bleeding and abdominal pain and weight loss related to increased tumor mass and/or metastatic locations. Functional pNETs (Table 1) are characterized by a syndrome related to excessive hormonal mediators (usually peptides) and a clinical picture associated with their location and extension [5,6].

A histopathology-based rationale for pNET treatment

Current treatment of pNETs is strictly dependent on accurate definition of tumor histopathology (i.e.,

grading) and evaluation of extension (staging), which are crucial pieces of information influencing treatment options. Concerning grading, this aspect has been revised by the WHO classification established in 2010 (Table 2), which classified NETs into well-differentiated tumors (G1), well-differentiated carcinomas (G2) and poorly differentiated neuroendocrine carcinomas (G3). While G1 and G2 tumors show the concomitant expression of the neuroendocrine markers chromogranin A and synaptophysin, G3 displays positive immunostaining only for synaptophysin. Other tumors that combine both exocrine and endocrine morphological features have been referred to as mixed adenoneuroendocrine carcinoma [7]. The grading depends on the proliferative activity, which can be determined by counting the number of mitoses per high-power field and/or by assessing Ki67 (MIB1) antigen, which is expressed in the nucleus (Table 3) [7]. The staging parameter was proposed by Rindi *et al.* in 2006 for pNETs and is now routinely applied in clinical practice as a tumor-node-metastases classification [8,9].

Currently available medical options for advanced pNETs

In recent years, the diagnosis and management of pNETs has dramatically improved, with a significant prolongation of life expectancy as well as quality of life. Surgical treatment remains the only curative strategy for pNETs; however, it depends on the stage of tumor (3). In patients with advanced or recurrent disease, cytoreductive or palliative surgery is also a key modality, but other locoregional and systemic therapies may be considered. Currently, the medical management of functioning pNETs includes the use of somatostatin analogs to control the symptoms produced by excessive production and release of hormones and biologically active peptides. While the efficacy of somatostatin analogs in controlling tumor-associated symptoms has been proven, the

Table 1. Gastroenteropancreatic tumor and clinical features.

Tumor	Major hormone produced	Symptoms or signs
Insulinoma	Insulin, proinsulin	Hypoglycemic symptoms
Gastrinoma	Gastrin	Abdominal pain, peptic ulcers, esophageal symptoms, diarrhea
Glucagonoma	Glucagon	Diabetes/glucose intolerance, necrolytic migratory erythema, weight loss
VIPoma	VIP	Severe watery diarrhea, hypokalemia
Somatostatinoma	Somatostatin	Diabetes, cholelithiasis, diarrhea, steatorrhea
ACTHoma	ACTH	Cushing's syndrome
Nonfunctioning	CgA, PP, NSE	Occasionally asymptomatic; weight loss, hepatomegaly, abdominal mass

CgA: Chromogranin A; NSE: Neuron specific enolase; PP: Pancreatic polypeptide; VIP: Vasoactive intestinal polypeptide.

Table 2. Classifications of gastroenteropancreatic neuroendocrine tumors by the WHO.

WHO 1980	WHO 2000	WHO 2010
Carcinoid	Highly differentiated neuroendocrine tumor Highly differentiated neuroendocrine carcinoma	Neuroendocrine tumor G1–G2
	Poorly differentiated neuroendocrine carcinoma	Neuroendocrine carcinoma G3
Mucocarcinoid mixed carcinoid–adenocarcinoma	Mixed endocrine–exocrine carcinoma	Mixed adenoneuroendocrine carcinoma

effect of these drugs on tumor growth remains controversial. However, octreotide has a demonstrated antitumor effect in approximately 50% of patients. Recent data by Rinke *et al.* from the PROMID study demonstrated significant evidence that the long-term administration of octreotide inhibits tumor growth [10]. However, it should be emphasized that these data have been obtained in patients with midgut NETs and not in pNETs. There is no prospective study demonstrating the effect of somatostatin analogs on pNET growth.

Traditional cytotoxic agents (e.g., streptozotocin, 5-fluorouracil and doxorubicin alone or more commonly in combination) yielded little beneficial effect upon tumor shrinkage or symptom control of pNETs [11]. Indeed, only 39–40% of pNET inoperable patients treated with streptozocin and 5-fluorouracil with/without doxorubicin showed an objective response [12,13]. This limited efficacy of chemotherapy can be explained by the usual low mitotic rate of pNETs [14] and the distinct gene expression pattern related to chemoresistance [15]. Currently, in addition to G2 foregut extrapancreatic NETs and G3 neuroendocrine carcinomas, chemotherapy is recommended for pNETs if there are tumor-related local symptoms, advanced metastatic disease or tumor progression after a first-line therapy (i.e., surgery, somatostatin analogs or other options) [16]. The lack of a well-defined Ki67 cut-off value may also represent a possible reason hampering the clinical efficacy of conventional chemotherapeutic agents.

The high rate of somatostatin receptor expression in pNETs provides a rationale for peptide receptor radionuclide therapy (PRRT) in patients with inoperable or metastatic disease. The most frequently used radionuclides for targeted therapy in both functioning and nonfunctioning pNETs are yttrium (⁹⁰Y) and lutetium (¹⁷⁷Lu). A retrospective, Phase II study by Kwekkeboom *et al.* has shown that ¹⁷⁷Lu yielded a partial remission rate in up to 37% of patients with pNETs [17]. It should be noted, however, that PRRT may determine side effects such as renal function impairment

and bone marrow toxicity [18]. Prospective studies are currently in progress and the results will establish the actual safety and efficacy of this therapeutic approach in advanced pNETs.

Recently, the availability of new molecules targeting the cellular pathways involved in cancer-cell proliferation, has emerged as an option for patients with advanced forms of pNETs. This review will highlight the basic knowledge and clinical experience recently obtained with the mTOR inhibitor, everolimus, which has emerged as an efficacious compound in the treatment of patients with advanced/metastatic pNETs.

The mTOR signaling pathway

In vivo and *in vitro* studies have shown the antitumor effects of everolimus, an mTOR-pathway inhibitor. The mTOR; a 289 kDa serine–threonine protein kinase, shows a highly conserved sequence from yeast to mammals [19]. It plays a major role in the regulation of cell growth and proliferation, sensing nutritional status and mitogens, thereby allowing for progression from the G1 to S phase of the mitotic cycle. Overall, mTOR acts as a master switch of cellular catabolism and anabolism, regulating cell growth and proliferation [20].

The mTOR is a central controller, integrating a plethora of signaling pathways that respond to growth factors, such as erythroblastic leukemia viral (v-erb-b) oncogene homolog-1 family, IGF and PDGF receptors as well as amino acids, ATP and O₂ levels, and possibly mitochondrial stress. All these factors activate the PI3K/AKT-dependent mTOR signaling,

Table 3. Grading proposal for gastroenteropancreatic neuroendocrine tumors.

Grade	Ki67 index (%)
1	≤2
2	3–20
3	>20

thereby contributing to the regulation of cell-cycle progression, translational processes, transcriptional stress responses, protein stability, survival and autophagy [21,22]. How mTOR is regulated by PI3K or by its effector AKT is still unclear; however, PI3K and AKT are key elements of the upstream pathway leading to mTOR activation.

Activated mTOR induces the translation of subsets of mRNAs that encode the proteins required for progression from the G1 cell-cycle phase to S phase initiation. Therefore, mTOR inhibition results in a prolonged transit through, or an arrest in, G1 phase. The mTOR can be considered as the gatekeeper of cell proliferation and since many cancers are characterized by deregulation of G1 phase, mTOR inhibition should be considered a potential target for anticancer therapy [21].

It should be noted that there are two mTOR complexes:

- A rapamycin sensitive complex, mTORC1, defined by interaction with the accessory regulatory-associated protein of mTOR (raptor); and
- A rapamycin insensitive complex (mTORC2), defined by its interaction with the rapamycin-insensitive companion of mTOR (riCTOR) [23].

The activation of mTORC1 results in the phosphorylation of the ribosomal S6 kinase 1 (S6K1) and the eukaryotic initiation factor 4E binding protein 1, two key messengers for protein translation [24–26]. While the phosphorylation of S6K1 increases mRNA translation, the activation of 4E binding protein 1 elicits the cap-dependent translation of several mRNAs encoding critical regulators of G1 phase progression. As a result, the deregulated mTOR signaling pathway in cancers represents a molecular target for pharmacological intervention based on mTOR inhibitors, leading to tumor growth suppression (Figure 1).

The PI3K/AKT signaling pathway is deregulated by a variety of mechanisms in cancer cells, including overexpression of tyrosine kinase receptors, constitutively activated mutant receptors (e.g., HER2, IGF receptor) or mutation/amplification of AKT [27,28]. The tumor suppressor PTEN is a negative regulator of PI3K signaling. In many types of cancer, PTEN expression is decreased through several mechanisms resulting in the mTOR activation [29,30]. Furthermore, the tuberous sclerosis complex inhibits mTOR indirectly by inactivating RHEB protein, which is proposed to be a direct mTOR activator [31]. Activated p53 acts as a negative regulator of the mTOR pathway and its loss of function in cancer might favor mTOR activation [32]. Evidence indicates that the PI3K/AKT/mTOR pathway activation is not sufficient to induce cancer,

rather it requires other oncogenic events. However, because of its key role in this pathway, mTOR remains one of the most important targets in novel anticancer therapies [33].

Rapamycin & its analogs

Rapamycin is a macrocyclic lactone produced by *Streptomyces hygroscopicus* that was initially developed as an antifungal drug. Further data indicated that this drug had immunosuppressive properties revealed by its ability to inhibit T-cell proliferation. As a result, rapamycin is now used along with steroids and cyclosporine as an immunosuppressive strategy to prevent the rejection of renal and liver transplantation. Subsequent *in vitro* and *in vivo* studies demonstrated that rapamycin had prominent cytostatic activity against several human cancers [34]. Recently, rapamycin has been shown to induce, in a concentration-dependent manner the inhibition of several murine and human cancer cell-line growth in tissue cultures and in xenograft models [33]. In addition to the prototype agent rapamycin, a number of analogs have been developed for research and therapeutic purposes.

The inhibition of cell proliferation is mediated by the downstream signaling blockade induced by rapamycin and its analogs. These compounds, also referred to as ‘rapalogs’, act by binding the 12 kD immunophilin FK506 binding protein and this complex in turn inhibits mTOR [35], causing cell-cycle arrest. In addition, another important effect of mTOR inhibition exerted by rapamycin is the induction of apoptosis, which results in cancer-cell death. The underlying molecular mechanisms leading to apoptosis have not been completely defined. Likely, rapamycin leads to the mTOR downstream target S6K1 inactivation, inducing a proapoptotic signal mediated by the BCL-2 family member, BAD [36]. Indeed, high levels and/or the aberrant pattern of BCL-2 expression have been correlated with resistance to commonly used anticancer agents [37].

These data provided the conceptual basis to use rapalogs as potential anticancer agents in the clinical setting. They have recently been approved by the US FDA as second-line treatment for sunitinib- or sorafenib-unresponsive renal cell carcinoma. Phase II studies have shown that objective response rates with rapamycin and analogs ranged from 38 to 41% in mantle-cell lymphomas [38], and 35% in non-mantle-cell non-Hodgkin lymphomas [39]. In Phase II trials, rapalogs have shown promising effects in patients with sarcoma and endometrial cancer [40,41]. Finally, rapamycin has also been evaluated in other proliferative syndromes, such as angiofibromas, renal angiomyomas and lymphangiomyomatosis and conditions

associated with mutations of the tuberous sclerosis genes [42,43]. Three rapalogs/mTOR inhibitors, temsirolimus (CCI-779), ridaforolimus (AP23573) and everolimus (RAD001), either alone or in combination, are currently available and approved for clinical purposes in a variety of cancers [35]. Amongst these novel compounds, everolimus is an oral mTOR inhibitor that has been recently tested in the treatment of advanced NETs.

Everolimus for pNETs

The PI3K/AKT/mTOR signaling pathway has recently emerged as a potential therapeutic target for cancers, including NETs. Beginning in 2008, research data in NETs have demonstrated the antitumor effects exerted by rapamycin either alone or in combination with octreotide. Using human pancreatic and bronchial carcinoid cell lines (BON-1 and NCL-H727, respectively), Moreno *et al.* showed that rapamycin significantly inhibited cell proliferation [44]. In contrast, the somatostatin analog octreotide did not show any effect and its association with rapamycin did not yield any adjunctive improvement on cell proliferation [44]. These *in vitro* results prompted the first clinical open-labeled study in 60 patients with moderately and well-differentiated advanced NETs, including both islet cell tumors and carcinoids [45]. Patients were randomized to receive everolimus either 5 or 10 mg/day orally, combined with octreotide long-acting repeatable (LAR) 30 mg/28 days intramuscularly. The overall median progression-free survival (PFS) for patients treated with octreotide and everolimus was 60 weeks; according to patient stratification by tumor group, the PFS was 63 weeks for carcinoids and 50 weeks for pancreatic islet cell tumors [45]. In particular, the median PFS of patients treated with 5 and 10 mg of everolimus was 50 and 72 weeks, respectively, thus showing a better effect on PFS of the 10-mg dose of everolimus on both types of NETs [45]. Although used in combination with octreotide LAR, the results of this study showed that everolimus at 5–10 mg/day was well tolerated by patients and, therefore, provided the basis to further investigate its antitumor efficacy.

The RADIANT-1 study enrolled 160 patients with advanced well- and moderately differentiated pancreatic tumors after the failure of cytotoxic chemotherapy [46]. Patients who received everolimus at a daily dose of 10 mg and were randomized in two arms stratified according to previous octreotide therapy: the first arm received everolimus 10 mg daily (n = 115 patients) and the second arm received everolimus 10 mg daily plus octreotide LAR 30 mg/28 days (n = 45 patients). The tumor response to treatments was determined every 3 months according to the response evaluation criteria in solid tumors criteria [47,48]. The

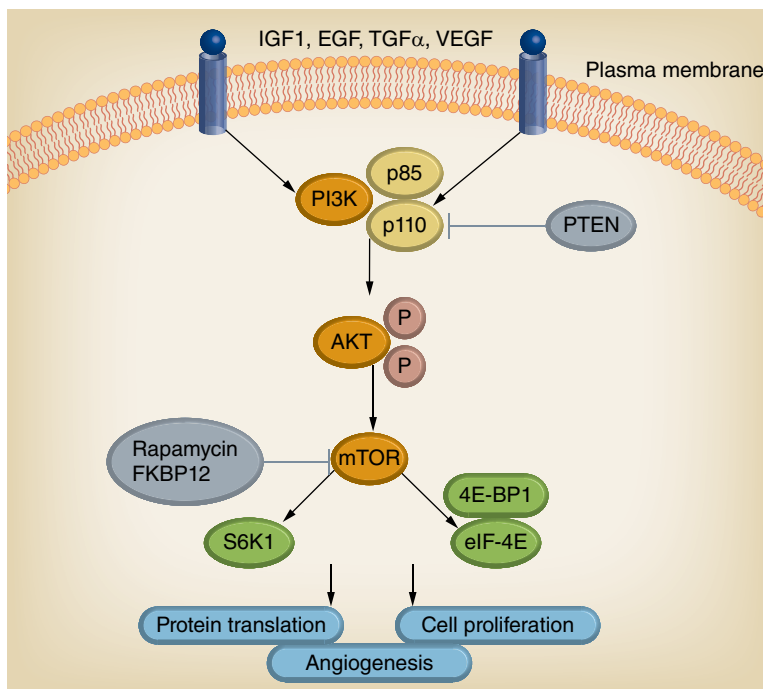


Figure 1. mTOR molecular pathway. The major molecular signaling involved in the PI3K/AKT cascade activated by a variety of growth factors (e.g., IGF1, EGF, TNF- α and VEGF). As a result, the consequent activation of the mTOR contributes to a number of effects, such as protein translation, cell proliferation and angiogenesis. In cell cancer, the mTOR deregulation, leading to an uncontrolled cellular proliferation, can be targeted by rapamycin and related analogs, that is, everolimus, by binding the immunophilin FK506 binding protein (FKBP12).

overall objective-response rate was about 10%, while a stable disease was achieved in 68% of patients. The median PFS was 16.7 months in the second arm and 9.7 months in the first arm, supporting the important antitumor activity of everolimus. Interestingly, in both arms of the RADIANT-1 study, patients who showed an early reduction of the chromogranin A and neuron specific enolase levels had a longer PFS compared with patients without such an effect [49]. Although interesting, this finding deserves further investigation to prove that changes in tumor markers may predict a better response to everolimus.

A subsequent Phase III randomized, double-blind, cross-over study, labeled as RADIANT-3, enrolled 410 patients with progressive advanced pNETs treated with everolimus (10 mg daily) or placebo in combination with best supportive care (i.e., somatostatin analogs in both arms). The overall objective response rate was approximately 5%, while a stable disease was achieved in 73% of patients. The median PFS associated with the everolimus treatment was 11 months compared with 4.6 months in the placebo group (hazard ratio for disease progression or death of any cause

with everolimus was 0.35; 95% CI: 0.27–0.45; $p < 0.001$ [50]. This study demonstrated that everolimus significantly prolonged PFS among patients with progressive advanced pNETs [50]. The prolonged PFS induced by everolimus was associated with a consistent stabilization of the disease or in a lower size of tumor mass, as well as a reduced incidence of tumor progression.

Similarly to the RADIANT-3, the RADIANT-2 trial was a randomized, placebo-controlled, double-blind, cross-over Phase III study comparing everolimus (10 mg daily) with placebo both in combination with octreotide LAR (30 mg intramuscularly/28 days) in advanced NETs associated with carcinoid syndrome. Of the 429 enrolled patients in both arms, 358 discontinued the treatment (one patient was lost in the follow up). Owing to the cross-over design, patients on the octreotide/placebo arm were switched to everolimus/placebo with disease progression. The median PFS was 16.4 and 11.3 months in the everolimus-plus-octreotide-LAR ($n = 216$) arm versus the placebo-plus-octreotide-LAR ($n = 213$) arm, respectively, which just missed the one-sided p value of ≤ 0.0246 [51]. The clinical benefit was a 5.1-month increase in median PFS in patients with progressive advanced functional NETs. Subset analysis also showed a tendency (i.e., not statistically proven) that the median PFS improved in patients who did not receive somatostatin analogs prior to enrollment [51]. These data suggest that everolimus may be considered a therapeutic option for patients with advanced NETs.

Combined targeting mTOR & other pathways

Research data indicate that mTOR activation is dependent on a variety of mediators, such as growth hormone and IGF1. The inhibition of these bioactive

substances is thought to reduce mTOR activity, thus providing a pharmacological basis to the combination of everolimus with somatostatin analogs, which has been evaluated in a number of studies discussed earlier. Furthermore, a recent Phase I study showed promising results in patients with advanced NETs treated with everolimus in association with pasireotide (SOM230), a novel somatostatin analog [52]. This combination is now under investigation in low to intermediate grade advanced pNETs [53]. Furthermore, in addition to somatostatin analogs, studies are currently underway to evaluate everolimus in combination with other agents in patients with advanced pNETs. Preliminary data showed that everolimus appears to have an additive effect in combination with the cytotoxic alkylating agent temozolomide (which shares similarities with streptozotocin and dacarbazine [1]) [54].

Safety

Although mTOR plays a central role in many biologic processes, rapalogs have generally been well tolerated. The safety of everolimus in NET patients has been confirmed by its three major trials (RADIANT-1, -2 and -3) [46,49,55].

Usually, adverse events reported by patients during everolimus treatment are of mild-to-moderate severity. The most common adverse events (grades 1 and 2) included stomatitis, rash, diarrhea, fatigue, nausea and infections. The immunosuppressive properties of everolimus predisposed patients to bacterial, fungal, viral or protozoan infections, including those with opportunistic pathogens. Localized and systemic infections, including pneumonia, have also been described. In addition, noninfectious pneumonitis is another known side effect of everolimus and it has

Table 4. The most common adverse events of everolimus expressed as range percentages from RADIANT-1, -2 and -3.

Adverse Event	All Grades (% of patients)	Grade III–IV (% of patients)
Stomatitis	45–64	2–7
Rash	37–49	1
Diarrhea	27–40	2–3
Fatigue	31–35	2–7
Nausea	20–33	1–2
Infections	20–23	2–5
Peripheral edema	13–20	<1
Anemia	13–17	1–4
Hyperglycemia	12–13	2–5
Asthenia	10–15	1–3
Thrombocytopenia	7–13	2–10
Lung event	7–17	1–3

been typically accompanied by non-specific symptoms such as dyspnea, fatigue, nonproductive cough and fever. In these cases, a chest CT scan revealed a 'ground-glass' or alveolar infiltrate. If necessary, interstitial pneumonitis can be treated with steroid therapy along with drug discontinuation. Caution is required for severe (grade 3) pneumonitis occurring in 1–3% of patients, leading to either dose reduction or temporary cessation of everolimus. Steroid treatment is mandatory in all cases characterized by everolimus-related interstitial pneumonitis. A thorough review of the different experience so far acquired (mainly in patients with metastatic renal cancer) has been covered by two recently published papers, to which the reader is referred [56,57]. A summary of the adverse events experienced by patients treated with everolimus in the three RADIANT trials is presented in Table 4.

Conclusion & future perspective

pNETs are a group of heterogeneous and uncommon tumors in which numerous pathophysiological and

therapeutic aspects remain unclear. As a result, management of pNET patients is still largely unsatisfactory. Surgery with curative intent represents the first-line strategy, although it is dependent on the stage of disease and most patients have metastatic disease at the time of diagnosis. Current treatment options for these advanced tumors include traditional chemotherapy (which shows limited efficacy and is associated with severe adverse events and toxic effects), long acting somatostatin analogs (which have a limited efficacy/still undefined effect on tumor growth in NETs and pNETs, respectively) and PRRT (not available in all centers and still considered an experimental option that requires further evaluation). In this context, a number of targeted therapies are currently emerging for treatment of pNETs. In particular, everolimus was efficacious in terms of tumor stabilization and significantly prolonged PFS. Overall, everolimus appears to be well tolerated and adverse events are generally mild. In addition to well- and moderately differentiated pNETs, it is plausible that everolimus may show efficacy also in poorly differentiated tumors with high

Executive summary

- Pancreatic neuroendocrine tumors are rare neoplasms with different biological behavior and clinical features, requiring individual management.
- Modern histopathological classification, grading pNETs, provides appropriate guidelines for improving treatment of these tumors.
- Current treatment options, including somatostatin analogs, cytotoxic agents, peptide receptor radionuclide therapy, show a number of limitations, for example, poor efficacy in terms of antiproliferative effects, major side effects, or little availability and supporting evidence.
- Recent data indicate that a novel therapeutic approach may involve targeting the molecular signaling pathways involved in tumor cell growth, proliferation and survival.
- In this respect, the mTOR pathway plays an important role as it could be targeted by a number of compounds such as rapamycin and its analogs.
- mTOR signaling has been shown to be deregulated in many type of cancers, including pNETs. Thus, mTOR inhibitors represent an important anticancer therapy.
- Everolimus, an oral mTOR inhibitor, has shown efficacy and safety for the treatment of patients with advanced pNETs.
- Recent trials (RADIANT-1, and -3) showed that patients treated with 5 or 10 mg/day of everolimus demonstrated an improvement in progression-free survival as compared with patients treated with placebo.
- Everolimus is generally well tolerated and adverse events are generally manageable with dose reduction, temporary interruption of therapy or both.
- The most common adverse events are stomatitis, rash, diarrhea, fatigue, nausea, infections, hyperglycemia and noninfectious pneumonitis.
- Everolimus and likely future targeted therapies may represent an important step forward in improving the treatment of patients with advanced pNETs.

expression rate of phosphorylated mTOR [58]. Another exciting area of pharmacological application is related to the development of new agents (e.g., BEZ235 and EX147) exerting selective inhibition of mTORC1 and mTORC2. This selectivity is expected to overcome the antitumor activity due to feedback upstream AKT

activation resulting from mTOR inhibition [35].

In conclusion, everolimus and likely other targeted therapies can be proposed as effective therapeutic options for the medical management of patients with advanced pNETs.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or

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