

New therapeutic approaches to metastatic gastroenteropancreatic neuroendocrine tumors: A glimpse into the future

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Abstract

Neuroendocrine (NE) gastroenteropancreatic tumors are a heterogeneous group of neoplasias arising from neuroendocrine cells of the embryological gut. Their

incidence have increased significantly over the past 3 decades probably due to the improvements in imaging and diagnosis. The recent advances in molecular biology have translated into an expansion of therapeutic approaches to these patients. Somatostatin analogs, which initially were approved for control of hormonal syndromes, have recently been proven to inhibit tumor growth. Several new drugs such as antiangiogenics and others targeting mammalian target of rapamycin pathways have been approved to treat progressive pancreatic neuroendocrine tumors (NETs) although their role in non-pancreatic is still controversial. The treatment of NETs requires a coordinated multidisciplinary approach. The management of localized NETs primarily involves surgical resection followed by surveillance. However, the treatment of unresectable and/or metastatic disease may involve a combination of surgical resection, systemic therapy, and liver-directed therapies with the goal of alleviating symptoms of peptide release and controlling tumor growth. This article will review the current therapeutic strategies for metastatic gastroenteropancreatic NETs and will take a glimpse into the future approaches.

Key words: Gastroenteropancreatic neuroendocrine tumors; Peptide receptor radionuclide therapy; Somatostatin analogs; Octreotide; Transarterial chemoembolization; Carcinoid syndrome; Setotonin; Chromogranin

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Core tip: The management of localized NETs is straight forward, however, the treatment of advanced tumors involves several disciplines and requires a coordinated multidisciplinary approach. Recent advances in molecular biology have expanded the therapeutic arsenal. Somatostatin analogs, initially approved for control of hormonal syndromes, have recently proven to inhibit tumor growth. Several new drugs, antiangiogenics,

mTOR inhibitors have been tested with promising results and some of them have already been approved. Several trials are still under way but the future should focus on patient selection, predictive markers, and tolerability improvement as critical aspects to continue advancing.

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INTRODUCTION

Neuroendocrine (NE) gastroenteropancreatic tumors are a heterogeneous group of neoplasias arising from neuroendocrine cells of the embryological gut^[1]. Their incidence have increased significantly over the past 3 decades with a crude incidence of 5.25/100000 per year. This is probably due to the improvements in imaging and diagnosis^[1-4].

Usually, the primary lesion is located in the gastric mucosa, the small and large intestine, rectum and pancreas^[2,3]. These tumors can appear at all ages, but the highest incidence is after the fifth decade. The carcinoid of the appendix is an exception as its highest incidence is at around 40 years of age^[1]. Those patients with multiple endocrine neoplasia type 1 or von Hippel-Lindau's disease, may have a clinical onset 15-20 years earlier than patients with sporadic neuroendocrine tumors (NETs)^[5].

The recent advances in molecular biology have translated into an expansion of therapeutic approaches to these patients. Somatostatin analogs, which initially were approved for control of hormonal syndromes, have recently been proven to inhibit tumor growth^[6].

Several new drugs such as antiangiogenics and others targeting mammalian target of rapamycin (mTOR) pathways have been approved to treat progressive pancreatic NETs although their role in non-pancreatic is still controversial^[7].

The treatment of NETs requires a coordinated multi-disciplinary approach. The management of localized NETs primarily involves surgical resection followed by surveillance. However, the treatment of unresectable and/or metastatic disease may involve a combination of surgical resection, systemic therapy, and liver-directed therapies with the goal of alleviating symptoms of peptide release and controlling tumor growth^[7].

Several completed and ongoing studies are evaluating somatostatin analogs (SSAs), vascular endothelial growth factor (VEGF) pathway inhibitors, mTOR inhibitors, cytotoxic chemotherapy, and peptide receptor radionuclide therapy (PRRT)^[7].

This article will review the current therapeutic strategies for metastatic gastroenteropancreatic NETs

and will take a glimpse into the future approaches.

MANAGEMENT OF ADVANCED NETS

NETs present in up to 40% of cases with metastases at diagnosis (mainly in the liver). If metastatic disease is localized or if > 70% of tumor burden can be resected, cytoreductive surgery should be considered. This approach has shown to reduce local symptoms and also systemic endocrine symptoms^[8].

NETs can arise in different organs and from different cell types, and so present a clinical challenge due to their diversity and the variety of symptoms they can cause. Functioning NETs are characterized by the hormones they produce and/or the symptoms they cause; these tumors usually produce clinical symptoms following dissemination to the liver^[8,9].

Carcinoid syndrome

Many functioning NETs release vasoactive peptides and amines (such as serotonin and tachykinins), into the systemic circulation. These can cause a group of symptoms known as "carcinoid syndrome", which appear in 10% of cases of metastatic NETs. This syndrome is characterized by flushing, diarrhea, abdominal pain, telangiectasia and bronchoconstriction^[8,9]. Carcinoid crisis are believed to be caused by a massive release of bioactive products from the tumor and can occur spontaneously or more frequently after stress, chemotherapy, surgery or anesthesia. These episodes are life-threatening^[10]. The clinical picture represents an exacerbation of the usual symptoms of carcinoid syndrome, including severe flushing with/without bronchospasm, tachycardia and hypo/hypertension^[10].

This needs prompt and effective management to prevent any carcinoid heart disease, though 10%-20% of patients suffer from this issue at diagnosis^[11]. This is characterized by fibrous thickening of the endocardium (classically on the right heart)^[12], tricuspid and pulmonary valves^[12].

Other syndromes

Pancreatic NETs can cause several other syndromes, such as Zollinger-Ellison syndrome, which is characterized by peptic ulcers, diarrhea and abdominal pain and caused by gastrinomas. Glucagonomas which produce hyperglycemia, leading to diabetes mellitus and also a chronic necrolytic migratory erythema. Insulinomas cause hypoglycemia and VIPomas a Verner-Morrison syndrome with severe watery diarrhea (10-15 L/d) and flushing^[13].

Nonfunctioning NETs

These are not associated with hormonal syndromes, thus they become more difficult to diagnose and patients present with advanced disease. Anyway, these tumors may secrete bioactive hormones or amines at subclinical levels^[13].

Table 1 Systemic treatment

Ref.	Type of tumor	Treatment	RR %	PFS (mo)	OS (mo)
Moertel <i>et al</i> ^[41]	Pancreatic	STZ	42		16.5
		STZ + 5FU	42		26
Moertel <i>et al</i> ^[39]	Poorly differentiated	CIS + ETO	18		19
Chan <i>et al</i> ^[58]	Carcinoid	TMZ + beva	0		18.8
	Pancreatic		33		41.7
Yao <i>et al</i> ^[72]	Pancreatic	Everolimus		9.7	
		Everolimus + octreotide		16.7	
Yao <i>et al</i> ^[74]	Midgut carcinoid	Everolimus + octreotide		16.4	
		Octreotide		11.3	
Yao <i>et al</i> ^[78]	Pancreatic	Everolimus	34		
		Placebo	9		
Yao <i>et al</i> ^[80]	Lung/GI NETs	Everolimus		11	
		Placebo		3.9	
Ahn <i>et al</i> ^[84]	Carcinoid	Pazopanib	0		
	Pancreatic		21.9		
Kulke <i>et al</i> ^[81]	Pancreatic	Sunitinib		11.4	
		Placebo		5.5	

PFS: Progression-free survival; STZ: Streptozocin; CIS: Cisplatin; ETO: Etoposide; 5FU: 5-fluorouracil; TMZ: Temozolomide; beva: Bevacizumab.

SOMATOSTATINE ANALOGS: PAST, PRESENT AND FUTURE

Most NETs express G-protein-coupled transmembrane somatostatin receptors (SSTRs)^[14]. There are five subtypes of SSTRs, and different NETs have different proportions of receptors expression^[7] (Table 1).

Somatostatin analogs bind to G-protein-linked receptors on the cell surface and inhibits the release of NE hormones. However, somatostatin has a short half-life *in vivo* (< 3 min)^[7] and therefore, synthetic somatostatin analogs have been developed for NET symptom control. These analogues form the first-line medical step for well-differentiated NETs^[3,15,16].

They bind with high affinity to the five SSRT (sstr₁₋₅) on secretory NE cells^[3,16,17], which have different inhibitory effects in the body. Subtypes sstr₂ and sstr₅ are the most important in inhibiting hormonal secretions in functioning NETs, thus dual inhibition of both may have a higher inhibitory benefit^[3,16,17]. These two subtypes may also mediate antiproliferative effects^[7]. Octreotide and lanreotide bind to the SSTR and decreased hormonal secretion, growth and proliferation, increased apoptosis, inhibit protein synthesis and have a direct antiproliferative activity^[17,18].

There is evidence that octreotide controls severe diarrhea and flushing in carcinoid syndrome^[14,19].

It has long been suggested that somatostatin analogs may exert antitumor effects for NETs^[20,21]. Moreover, there may inhibit the release of growth factor and trophic hormones, angiogenesis and modulation of the immune system.

Octreotide is the first somatostatin analogue available commercially, and it is a sstr₂-preferring agonist, although it has also moderate affinity for sstr₃ and sstr₅^[22,23]. It has a much longer half-life than somatostatin (2 h).

Lanreotide was the second analogue available and

has a similar binding profile to octreotide.

Octreotide was introduced in clinical practice in the 1987 as it confirmed ability to palliate carcinoid syndrome, as well as other hormonal syndromes caused by metastatic gastroenteropancreatic NETs. Several clinical trials of SSAs tested their ability to inhibit the release of NE hormones such as serotonin, glucagon, insulin, gastrin and vasoactive intestinal peptide (VIP)^[14].

Survival rate at 5 years of 67% have been reported in patients receiving somatostatin analogues compared with 18% for historical controls^[3].

Several years after the approval of octreotide, evidence of its antineoplastic activity emerged. Although objective radiographic responses (ORR) were rare, many cases of prolonged stable disease (SD) were documented, leading to the hypothesis that SSAs exert an inhibitory effect on tumor growth^[24-27].

Recently, this has been tested in a phase III trial. Initial evidence demonstrating that octreotide can reduce symptoms of carcinoid syndrome and decrease 5-HIAA levels was shown with the subcutaneous formulation^[28].

The first controlled study of octreotide LAR for treating carcinoid syndrome was conducted in 93 patients with NETs over at least 20 wk^[29].

There was a significant decrease in the number of daily stools and incidence of flushing. Treatment success was obtained in 66% of patients receiving octreotide LAR 10-30 mg/mo. It also decreased 5-HIAA levels by 50%^[29].

This study demonstrated that monthly octreotide LAR was at least as effective as subcutaneous octreotide for symptom control. Its efficacy for the symptomatic and biochemical control in NETs have subsequently been demonstrated in other studies^[21,22].

The mechanism by which somatostatin analogues normalize bowel function is not clear, however, it is hypothesized that involves inhibition of gut hormone

secretion, lengthening of intestinal transit time, increased water and electrolyte absorption and reduced splanchnic blood flow^[23-26]. Treatment with octreotide improves survival in patients with carcinoid crisis^[27]. Therefore, its prophylactic use is mandatory to prevent the development of a crisis. It is generally well tolerated, being the most common side effects, abdominal discomfort and bloating, generally mild and resolve spontaneously within the first week^[27].

Gallstones can develop, although only a small proportion of patients develop clinical symptoms. Local pain at the injection site has also been reported^[27].

A second somatostatin analog, lanreotide, was licensed in Europe in 1998 for the treatment of symptoms associated with NETs (particularly carcinoid).

Lanreotide is less widely studied than octreotide for symptomatic and biochemical control and no directly comparative trials have been conducted. The effects of lanreotide on symptom relief are comparable with those of octreotide^[28].

Ruszniewski *et al*^[29] carried out a study with 71 patients who received lanreotide for 6 mo and reported that 65% of the patients documented a 50% or greater reduction in flushing episodes, and 18% had a 50% or greater reduction in diarrhea episodes. The biochemical response rate is similar to octreotide, with higher responses in patients naive to somatostatin analogue therapy^[30].

Somatostatin analogs have got minimal adverse effects and have demonstrated antiproliferative activity *in vitro*^[23].

These have been used for patients with metastatic disease when surgical cure is not possible and have been also indicated for the relief of symptoms in patients with functionally active NETs^[31].

It has been controversial if somatostatin analogs control the growth of well-differentiated metastatic NETs. Uncontrolled studies have shown tumor shrinkage in response to somatostatin analogs^[32] and their combination with interferon alfa^[18].

Later trials were only able to confirm tumor stabilization in up to 50% of patients, but these studies were not placebo controlled^[30-35].

In 2009, Panzuto *et al*^[36] carried out a prospective, phase IIIB, double-blind, placebo-controlled trial to check the effect of octreotide LAR in the control of tumor growth in patients with well-differentiated metastatic midgut NETs. Treatment-naive patients were randomly assigned to either placebo or octreotide LAR 30 mg intramuscularly in monthly intervals until tumor progression or death.

The primary end point was time to tumor progression. Most patients (75%) had evidence of somatostatin receptor expression as evidenced by radiotracer uptake on Octreoscan. Thirty-eight percent had carcinoid syndrome (flushing and/or diarrhea associated with elevation in urine 5-HIAA). Only patients with mild carcinoid syndrome who tolerated flushing without intervention or responded to treatment with loperamide

and/or cholestyramine in cases of diarrhea were included. The trial showed a median time to tumor progression of 14.3 mo in the octreotide LAR compared to 6 mo in the placebo arm (HR = 0.34; 95%CI: 0.20-0.59, $P = 0.00072$). Functionally active and inactive tumors responded similarly. Chromogranin A or age did not make any impact on the result either. At 6 mo, tumor progression was seen in 24% of patients on the octreotide LAR arm vs 66% of patients receiving placebo ($P = 0.0079$)^[36].

Serious adverse events were balanced (11 patients in the octreotide LAR 30 mg arm and 10 patients in the placebo arm).

The most favorable effect was observed in patients with low hepatic tumor load (10%) and resected primary tumor, however both of these subgroups contained the majority of study patients. Even patients with higher hepatic tumor burden (> 10%) experienced a near doubling in time to progression on the octreotide LAR arm^[36].

The small number of deaths in both treatment arms (seven in the octreotide LAR 30 mg arm; nine in the placebo arm) precluded any analysis of differences in survival.

Authors concluded that Octreotide LAR significantly increased the time to tumor progression in patients with functionally active and inactive metastatic midgut NETs.

This PROMID trial unfortunately does not clarify the appropriate timing for the treatment, either at initial diagnosis or at the moment of tumor progression or if these data can be extrapolated to patients with G2 NETs^[36].

No major differences in classical efficacy have been seen between octreotide and lanreotide^[36,37].

One study has evaluated the antiproliferative efficacy of lanreotide in 25 patients. They found partial tumor remission in one patient and stable disease in seven patients, whereas tumor progression occurred in 14.

The CLARINET study is a randomized, double-blind, placebo-controlled study of lanreotide in advanced, well or moderately differentiated, non-functioning, SSTR-positive NETs (Ki-67 < 10%)^[38]. Tumors could be in the pancreas, midgut, or hindgut or unknown origin. Patients were randomized to receive an lanreotide 120 mg or placebo every 28 d for 24 mo. The primary end point was progression-free survival (PFS). Secondary end-points were overall survival (OS), quality of life and safety. Thirty-three percent had liver tumor > 25%. Lanreotide significantly prolonged PFS (median not reached vs median of 18.0 mo, $P < 0.001$). The estimated rates of PFS at 24 mo were 65.1% and 33.0% for the lanreotide and the placebo group respectively.

There were no significant differences in quality of life or OS between-groups. The most common adverse effect was diarrhea (26% vs 9% for lanreotide and placebo respectively)^[36].

The somatostatin analog should be the first

approach for Grade 1 and 2 gastrointestinal NETs^[39].

Predictive factors for no-response to somatostatin analog are Ki67 > 5%^[39] and distant extra-hepatic metastasis. In these situations chemotherapy should be considered alternatively^[39].

SOM230 (Pasireotide) is a novel multireceptor ligand analogue that has high affinity for four of the five somatostatin receptor SSTR (sstr₁, 2, 3 and sstr₅); it has 40-fold higher affinity and 158-fold higher functional activity for sstr₅ than octreotide^[37,38].

CHEMOTHERAPY: PAST, PRESENT AND FUTURE

Responses to chemotherapeutics are extremely heterogeneous in gastroentero-pancreatic NETs. These responses are influenced by tumor differentiation/grade and primary site. Poorly differentiated gastroenteropancreatic NETs respond typically to platinum-based regimens, and the reported RR > 50%^[40].

Though recent data point to the relevance of proliferative rate (Ki-67) as higher proliferative levels (> 55%) are significantly linked to higher response to platinum/etoposide compared with high-grade tumors with lower rates of proliferative activity^[40].

Pancreatic NETs are sensitive to alkylating agents, including streptozocin, dacarbazine, and temozolomide, as well as fluoropyrimidines. Streptozocin showed response rates of 63% in combination with fluorouracil vs 36% in monotherapy^[41].

When combined with doxorubicin vs streptozocin + 5-FU, the response rates and time to progression benefited the first combination (69% and 20 mo vs 45% and 6.9 mo respectively)^[42]. However, radiographic assessment was not accurate and this fact makes difficult to draw final conclusions about the efficacy of streptozocin.

Unfortunately the use of streptozocin is limited due to its toxicity such as myelosuppression, nausea, and renal insufficiency.

But the role of chemotherapy in NETs has evolved in recent years. It represents a useful option mainly for symptomatic patients, progressive disease, G2 differentiation, and a more aggressive behavior. It also should be considered when the primary objective is tumor load reduction for bulky lesions.

Single agents such as fluorouracil, dacarbazine, doxorubicin and streptozotocin were initially assessed in midgut carcinoid tumors with little benefit^[43]. Therefore these monotherapies could be reserved to pretreated patients or for patients with a poor performance status. In fact midgut NETs are particularly chemoresistant, possibly due to their low proliferative activity as well as their high expression of methyl guanine methyl transferase (MGMT), which is a DNA repair enzyme^[44]. For many years there was no evidence that combination regimens were any more effective. None of the regimens demonstrated a response rate (RR) greater than

15%^[45]. Though recently this has changed. Combination of chemotherapy and IFN- α therapy does not appear to improve on the results of monotherapy^[46,47].

Pancreatic NETs RR of approximately 40% have been reported for streptozotocin in combination with other agents such as 5-fluorouracil, cisplatin or doxorubicin^[22,45]. Temozolomide has also demonstrated promising anti-tumor effects in pancreatic NETs^[48]. Kulke *et al*^[49] carried out a phase II trial of temozolomide and thalidomide in patients with metastatic NETs. This combination was associated with a biochemical (chromogranin A) response of 40%, and radiologic response of 25% (45% among pancreatic NETs, 33% among pheochromocytomas, and 7% among carcinoid tumors). Median duration of response was 13.5 mo, 1-year survival was 79%, and 2-year survival was 61%. The response rate seems to be related to the expression of 06-MGMT. Low expression gives a higher response rate (40%) vs high expression (0%).

Orally administered temozolomide and thalidomide seems to be an active regimen for the treatment of NETs. This regimen appeared more active in pancreatic NETs than in carcinoid tumors^[49].

Saif *et al*^[50] carried out a retrospective study of capecitabine and temozolomide (CAPTEM) in patients with metastatic pancreatic NETs who have failed prior therapies (long-acting release octreotide, chemotherapy and hepatic chemoembolization). Seven patients were treated, and authors reported a total response rate of 43%, and clinical benefit (responders and stable disease) 71%. The median duration of response was 8 mo and the most common toxicities were grade 1-2 neutropenia, fatigue and hand-foot syndrome.

Authors concluded that CAPTEM was well tolerated and further prospective studies are warranted to evaluate this regimen with targeted therapies in pNETs^[50].

Recently Ramirez *et al*^[51] reported the results of another study reviewing the CAPTEM regimen again but in a wide variety of metastatic NETs. Twenty nine patients were included, small bowel (31%), pancreas (52%), lung (10%), and rectum (7%)^[51].

Partial response was documented in 17% and stable disease in 48%. According to Ki-67 values, partial response (PR)/stable disease (SD) were noted in 13/63% if Ki-67 < 2%^[51]. Values 2%-20%, PR/SD 19%/50%. If Ki-67 > 20% PR/SD were 20% each. Authors reported a median PFS of 12 mo. They concluded that this regimen may prolong survival although prospective data are needed. Although adverse reactions were experienced, most patients tolerated this regimen, thus CAPTEM should be considered as a reasonable option for metastatic NET patients^[50].

A phase II study carried out by Claringbold *et al*^[52] assessed the role of the radiopeptide ¹⁷⁷Lu-octreotate and capecitabine as a treatment for progressive disseminated NETs. Thirty-three patients were included to receive four cycles of 7.8 GBq (¹⁷⁷Lu)-octreotate 8-weekly, with 14 d of capecitabine.

Twenty-four percent showed PR, 70% SD. Median PFS and median OS had not been reached at a median follow-up of 16 mo with the survival at 1 and 2 years 91% and 88% respectively. Minimal transient myelosuppression with one grade 3 thrombocytopenia but no neutropenia were seen and nephrotoxicity was absent.

The addition of capecitabine radiosensitizing chemotherapy did not increase the minimal toxicity of ¹⁷⁷Lu-octreotate and led to significant clinical benefit in terms of response and SD in patients with progressive metastatic NETs^[52].

A phase I-II study to assess the safety and efficacy of combining lutetium-177 octreotate with capecitabine/temozolomide in advanced low-grade NETs was published in 2012. Thirty-five patients received fixed activities of 7.8 GBq lutetium-177 octreotate each 8 wk, with capecitabine for 4 cycles^[53].

In phase I, successive cohorts of patients received escalating doses of temozolomide in the last 5 d of each capecitabine cycle^[54].

In phase II, patients were treated with 200 mg/m² temozolomide. Adverse events were mild to moderate. Complete response was achieved in 15%, PR 38%, SD 38%. Median PFS was 31 mo and median OS was not reached with 90% surviving at 24 mo. Response rates were higher in patients with gastropancreatic NETs than in those with bowel primaries. This study showed that lutetium-177 octreotate in combination with capecitabine and temozolomide was well tolerated in patients with advanced low-grade NETs with significant tumor control rates^[55].

Temozolomide, an oral analog of dacarbazine, has activity against NETs when administered alone or in combination with other agents.

A systematic review of temozolomide in advanced NETs has been published by Abdel-Rahman *et al*^[54] in 2015. These authors assessed 16 trials including 348 patients. Median PFS reported ranged from 6 to 31 mo. Disease control rate 65%-100%. They found that most frequent toxicities were leukopenia, lymphopenia and elevated transaminases.

The data suggested that temozolomide-based combinations with some antineoplastic agents (especially capecitabine) could be an effective treatment for advanced low-intermediate grade NETs^[54,55].

NEW AGENTS: PRESENT BUT LOOKING MORE INTO THE FUTURE

NETs are highly vascularised tumours that express high levels of the VEGF ligand together with its receptor VEGFR. These tumors may show 30%-40% RR to combination chemotherapies but the response to single-agents is only 10%^[55].

Bevacizumab

Tyrosine kinase inhibitors targeting the VEGF receptor

and bevacizumab, a monoclonal antibody targeting VEGF, have demonstrated activity in NETs.

Bevacizumab has been shown to induce objective tumour responses and improvement in median time to progression in advanced carcinoid tumours^[56,57].

Several studies have found that temozolomide had significant effect on NETs.

A previous report examining a variety of NETs suggested that the combination of bevacizumab and temozolomide can be safely administered and showed promising activity in patients who had progressed after prior treatments^[57].

A phase II study evaluating the same combination in advanced/metastatic NETs was carried out including 34 patients with carcinoid and pancreatic NETs. All patients received prophylaxis against *Pneumocystis carinii* and varicella zoster. The combination of temozolomide and bevacizumab was associated with grade 3-4 toxicities, including lymphopenia (53%) and thrombocytopenia (18%)^[58].

Although overall radiographic response rate was 15%, response rates were different between pancreatic NETs (33%) and carcinoids (0%). The median PFS was 11 mo (14.3 mo for pancreatic NETs vs 7.3 mo for carcinoid tumors). Median OS was 33.3 mo (41.7 mo for pancreatic NETs vs 18.8 mo for carcinoid tumors). Authors concluded that this combination could be safely administered and seemed to be promising in pancreatic NETs^[59].

Koumarianou *et al*^[60] had carried out a similar study where temozolomide was delivered continuously at 100 mg daily, a so-called metronomic schedule, together with bevacizumab 7.5 mg/kg once every 3 wk and somatostatin long-acting release 30 mg once every 4 wk. The number of patients with carcinoids was small but authors found occasional durable responses. In their comment published in JCO 2013, these authors suggested the the necessity of further studies with larger numbers of patients to be able to identify who those patients are.

This combination seems to be an important approach as it uses treatments with possibly direct antiangiogenic action on the endothelial cells together with an antibody that blocks the action of VEGF produced by the tumor cells. And therefore, this dual antiangiogenic activity may prove to be an efficacious therapy in NETs which are highly vascularized tumors^[11].

Several combinations with bevacizumab have been studied with different results^[61-66].

These approaches are mainly effective in G1 and G2 tumors, with a Ki-67 < 20%. However, it is relevant to identify the patients who will most probably benefit from this approach. Koumarianou *et al*^[60,67] proposed that this combination should be restricted to advanced NET G1/2 tumors, possibly with a Ki-67 < 20%.

mTOR inhibitors

mTOR is a key regulator of protein synthesis in cancer,

cell growth, proliferation, angiogenesis and cell metabolism. Abnormal PI3K-Akt/PKB-mTOR pathway signaling has been implicated in the pathogenesis of pancreatic NETs.

Everolimus, or RAD001 is an oral, once-daily mTOR inhibitor that blocks the mTOR pathway by binding to its intracellular receptor, FKBP-12. It has shown synergistic anti-tumor activity when combined with other anticancer therapies^[68,69].

In a phase III study, patients with low- and intermediate-grade advanced pancreatic NETs were randomized to receive everolimus 10 mg/d or placebo. Median PFS was significantly prolonged in the everolimus arm, 11 mo vs 4.6 mo^[70].

Everolimus may have a similar effect when used in combination with a somatostatin analogue. In the study by Grozinsky-Glasberg *et al*^[71], octreotide and everolimus showed significant anti-proliferative effects and they suggested that everolimus could interact with the same pathway at a site or sites similar to octreotide.

A study to assess the antiproliferative effect of combining everolimus with octreotide in patients with metastatic low to intermediate grade NETs was carried out. It enrolled 60 patients. Authors found promising activity in those receiving everolimus 10 mg daily^[72,73].

A Phase II trial of everolimus with or without octreotide LAR in patients with advanced pancreatic NETs following chemotherapy failure (RADIANT-1) found that in those receiving everolimus monotherapy, median PFS was 9.7 mo. PR 9.6%, 67.8% SD and 13.9% showed progressive disease. In the combination arm, median PFS was 16.7 mo, 4.4% PR, 80% SD, and no patients with progressive disease^[74]. Authors found that an early CgA or NSE response was associated with a longer PFS compared with those without an early response^[74]. Most adverse events were mild to moderate.

A Phase III trial, RADIANT-2, was carried out in advanced (unresectable locally advanced or distant metastatic and disease progression within the past 12 mo) midgut carcinoid tumors with low-grade or intermediate-grade NETs (carcinoid). It compared everolimus 10 mg/d plus octreotide LAR 30 mg every 28 d with placebo and octreotide LAR every 28 d. Four hundred and twenty-nine patients were randomly assigned to study groups. The combination arm showed a median PFS of 16.4 mo vs 11.3 mo for the control arm ($P = 0.026$). This did not meet a prespecified significance level by central review ($P = 0.024$)^[75].

However, by an investigator review the median PFS was 12.0 mo for the combination arm and 8.6 mo for the control arm ($P = 0.018$).

Authors concluded that everolimus plus octreotide LAR, compared with placebo plus octreotide LAR, improved PFS in advanced NETs associated with carcinoid syndrome^[76].

Both everolimus and temozolomide are associated with single-agent activity in patients with pancreatic NETs.

A phase I-II study was performed to evaluate the safety and efficacy of temozolomide in combination with everolimus in advanced pancreatic NET. Patients received temozolomide 150 mg/m² per day on days 1 through 7 and days 15 through 21 in combination with everolimus daily in each 28-d cycle.

In cohort 1, everolimus as administered at 5 mg daily. In cohort 2 it was increased to 10 mg daily. Temozolomide was administered for 6 mo^[77]. Forty-three patients were enrolled. No synergistic toxicities were reported. Forty percent had PR. The median PFS was 15.4 mo. Median OS was not reached. Authors concluded that this regimen could be safely given to advanced pancreatic NETs with significant antitumor activity^[77].

RADIANT-3 trial is another phase III prospective, double-blind, randomized, placebo-controlled study carried out in patients with advanced, low or intermediate grade pancreatic NETs. Patients were randomised to receive everolimus 10 mg daily or placebo. Four hundred and ten patients were included. The median PFS was 11.0 mo with everolimus and 4.6 mo with placebo ($P < 0.001$). Estimates of the proportion of patients who were alive and progression-free at 18 mo were 34% with everolimus as compared with 9% with placebo^[78].

Adverse events were mostly grade 1 or 2, mainly stomatitis rash, diarrhea, fatigue and infections primarily upper respiratory. Grade 3 or 4 included anemia and hyperglycemia.

Everolimus significantly prolonged PFS among patients with progressive advanced pancreatic NETs and was associated with a low rate of severe adverse events.

Mature data showed a median OS of 44.02 mo in the everolimus arm compared with 37.68 mo in the placebo; However, a high crossover of patients from placebo to everolimus (85%) may have contributed to the long median OS in the placebo arm and may have confounded the ability to detect a difference in the overall survival results^[79].

RADIANT-4 is another phase III study assessing the efficacy and safety of everolimus compared with placebo in patients with advanced, progressive, well-differentiated, non-functional NETs of the lung or gastrointestinal tract^[80]. Patients were randomised to receive everolimus 10 mg per day or placebo. Three hundred and two patients were enrolled. Median PFS was 11 mo in the everolimus group and 3.9 mo in the placebo arm. Everolimus was associated with a 52% reduction in the estimated risk of progression. In the first pre-planned interim OS analysis, the results of everolimus showed a reduction in the risk of death, although not statistically significant. The safety findings were consistent with the known side-effect profile of everolimus.

Authors concluded that everolimus is the first targeted agent to show robust anti-tumour activity with acceptable tolerability across a broad range of NETs (pancreas, lung, and gastrointestinal tract)^[80].

Sunitinib

NETs express VEGF and its receptor VEGFR. Sunitinib malate, an oral multi-targeted tyrosine kinase inhibitor targets VEGFR-1, -2, and -3; platelet-derived growth factor receptor; and c-KIT. Sunitinib is currently approved for treatment of pancreatic NETs. Its toxicity profile includes diarrhea, fatigue, cytopenias, nausea, hypertension, and palmar-plantar erythrodysesthesia. The efficacy of sunitinib was assessed in a two-cohort, phase II study of advanced carcinoid and pancreatic NETs. Patients were treated with repeated 6-wk cycles of oral sunitinib (50 mg/d for 4 wk, followed by 2 wk off treatment). The trial showed an overall response rate of 2.4% and 16.7% in patients with carcinoid tumors and pancreatic NETs, respectively. Median time to tumor progression was 7.7 mo in pancreatic NETs and 10.2 mo in carcinoid. The authors concluded that sunitinib has antitumor activity in pancreatic NETs whereas its activity against carcinoid tumors could not be definitively determined^[81].

A phase III randomized, double-blind trial in low and intermediate grade pancreatic NETs with sunitinib 37.5 mg/d orally or placebo showed. PFS of 11.4 mo vs 5.5 mo in the sunitinib and placebo arms respectively was statistically significant^[82].

A phase II study testing the efficacy and safety of everolimus and octreotide LAR or everolimus, bevacizumab, and octreotide LAR in advanced pancreatic NET with evidence of progression was presented at ASCO annual conference 2015. PFS was 16.7 mo on everolimus + bevacizumab + octreotide LAR vs 14 mo for everolimus + octreotide LAR. Response rate 31% in triplet arm vs 12% in doublet. Toxicity was significantly higher on the triplet with 81% grade 3-4 adverse events vs 49% on the doublet. Investigators commented on promising results but future trials to learn about patients selection are warranted^[82].

Pazopanib

Pazopanib is an orally bioavailable, multitargeted kinase inhibitor that inhibits VEGF receptors 1, 2, and 3. It has been evaluated in a nonrandomized phase II study of 37 patients with gastroenteropancreatic NETs. The overall response rate was 24% with a median PFS of 9.1 mo^[83].

The PAZONET study is another phase II which showed clinical activity of pazopanib in patients with advanced NETs regardless of previous treatments. Authors suggested that circulating tumor cell counts and soluble *VEGFR2* and *VEGFR3* gene polymorphisms could be potential biomarkers for selecting patients for pazopanib^[84].

Another phase II study in metastatic or locally advanced grade 1-2 carcinoid tumours or pancreatic NETs, using pazopanib 800 mg orally once per day and octreotide showed a response of 21.9% in pancreatic NETs whereas no responses in carcinoid tumours^[85].

Based on all these results, a randomized phase III trial

of pazopanib vs placebo for advanced carcinoid tumors is ongoing and other phase III trials are warranted^[86].

There are few effective therapies for pancreatic NETs. Recent placebo-controlled phase III trials of everolimus and sunitinib have reported improved PFS. Preclinical studies have suggested enhanced antitumor effects with combined mTOR and VEGF pathway-targeted therapy. A phase II trial was carried out with a combination of temsirolimus 25 mg intravenously (iv) once per week and bevacizumab 10 mg/kg iv once every 2 wk in well or moderately differentiated pancreatic NETs and progressive disease^[87]. Fifty-eight patients were enrolled, response rate was 41%, PFS at 6 mo was 79% with median PFS 13.2 mo. Median OS 34 mo. The investigators concluded that this combination had shown significant activity with acceptable toxicity in pancreatic NETs with progressive disease^[87].

Interferon

Interferon therapy is generally recommended as a second-line in patients with functioning NETs and low proliferation^[28-30]. The benefits of interferons on symptom control is similar to that of somatostatin analogues but they may have higher antiproliferative activity^[30]. Unfortunately their safety profile is not as favourable, with fever, fatigue, anorexia and weight loss among others^[29,30].

IFN- α has shown in a pooled analysis of trials in patients with NETs a 40% of biochemical responses (similar to octreotide and lanreotide) with 10% of objective tumor responses^[9,29,30,87,88].

Bondanelli *et al*^[89] have suggested that a combination of IFN- α with somatostatin analogues might have a synergistic effect. A phase II prospective trial randomized 44 patients to receive bevacizumab or pegylated IFN- α for 18 wk, followed by both agents in combination. At the end of the single-agent administration period, the rate of PFS was 95% in the bevacizumab arm vs 68% in the IFN- α arm. This study demonstrated activity with bevacizumab in patients with carcinoid tumor^[56].

A phase III trial comparing bevacizumab vs IFN- α showed that a combination with bevacizumab obtained longer time to failure compared to IFN- α arm. Responses were also higher with bevacizumab. However, it did not meet its primary endpoint of improvement in PFS.

Participants had advanced NETs with poor prognosis, as defined by one or more of the following criteria: Progressive disease, G2 with 6+ lesions, colorectal or gastric primaries.

Toxicity was higher on the interferon arm with 26% grade 3-4 fatigue. Based on these results, the investigators concluded that neither bevacizumab nor IFN- α -2b arm should be used as standard treatment^[90].

LIVER-DIRECTED THERAPIES

NETs present in up to 40% of cases with metastases at

diagnosis (liver mainly). Although radical surgery would be the treatment of choice, however, it is generally not possible. Liver resection is generally advocated in those cases with limited hepatic disease in which more than 90% of tumors can be successfully resected or ablated^[91].

Patients with liver metastases may experience symptoms such as pain, anorexia, and weight loss related to tumor burden. Additional symptoms include flushing and diarrhea caused by secretion of hormones directly into the systemic circulation. Medical treatments and locoregional therapies are palliative approaches in symptomatic patients or in cases of progressive disease. As the liver metastases from NET are hypervascular, endovascular treatments are interesting^[92,93] too as a cytoreductive technique.

Overall hepatic-directed therapies include liver resection or ablation, hepatic artery embolization (transarterial embolization, transarterial chemoembolization and radioembolization) and liver transplantation. These therapies are generally reserved for patients whose tumors are predominantly confined to the liver.

Ablation

Ablation techniques are generally reserved for unresectable metastases smaller than 5 to 7 cm in diameter. Several ablation techniques have been described. Those include cryoablation, alcohol ablation and radiofrequency ablation (RFA).

There are no randomized studies comparing surgical to nonsurgical treatments and though long survivals have been observed in surgically treated patients, these could be due to the fact those patients have got favourable prognosis as low tumour burden.

RFA has been used with good results and minimal morbidity for the treatment of patients with NET hepatic metastases^[94]. One disadvantage with this therapy has been the relatively small volume of tissue that can be coagulated and clinical trials with RFA have shown that complete responses are more likely to occur with tumours ≤ 4 cm^[95].

With the use of simultaneous multiple fiber laser induced thermotherapy or next generation bipolar RFA, some authors have reported ablation of tumours as large as 7 cm in diameter^[95,96].

Moreover, up to 7 lesions at one time may be ablated using specialized techniques to increase lesion size^[96,97].

The morbidity associated is 5%-10% and mortality rate is about 0.5%^[98,99].

Berber *et al*^[98] reported a total and significant symptom relief in 95% and 80% respectively in 34 patients with NET liver metastases. The median duration of the benefit was 10 mo. These benefits were seen even in patients with extrahepatic disease.

These techniques are suitable for repeated treatments in patients with local recurrence or new metastases.

Microwave ablation

Microwave ablation (MWA) is more appropriate than RFA to treat tumours next to major hepatic vasculature. In those areas the adjacent blood flow theoretically predisposes RFA to a heat sink effect^[100].

Although clinical experience with MWA has mostly involved hepatocellular carcinoma, though NETs have also been included in some series.

Martin *et al*^[101] reported NET patients undergoing MWA with a 90% success rate for complete ablation with no recurrences at the ablation sites. Most of these patients had MWA performed under ultrasound guidance during open surgery (concomitant hepatectomy and/or extrahepatic metastasectomy). Median overall survival reported was 41 mo. But these results need further studies to be confirmed as these authors only included 11 patients.

There is a lack of data comparing MWA (especially percutaneous) to RFA but geographic patterns of preference have been described. Whereas RFA is widely adopted in the United States, MWA is in Europe and Asia^[101].

Hepatic artery embolization

This technique is performed in patients with diffuse, unresectable liver metastases. The rationale for embolization is related to liver blood supply. Liver metastases get the majority of their blood supply from the hepatic artery, while the normal liver parenchyma gets blood supply primarily from the portal vein. In patients with bilobar hepatic metastases, staged lobar embolizations are typically performed at 4- to 6-wk intervals^[102-104]. Several techniques have been included such as TAE, TACE and drug eluting beads (DEB)-TACE.

TACE and DEB-TACE

TACE has been used several decades. It combines the benefits of embolization and locoregional chemotherapy and provides with a high rate of tumour and symptomatic response^[103].

TACE follows the same principles as TAE, but the intra-arterial administration of a chemotherapeutic agent is added at the time of embolization. With this technique intratumoral concentrations of the drug are over 20 times higher than those obtained by systemic administration of the same drug. Moreover, with this technique, it exists the further potential clinical benefit of tumour ischaemia as a result of embolization.

This technique is indicated in nonsurgical candidates with progressive or refractory disease despite medical treatment (SSAs) and no contraindication to TACE. The best results are obtained if liver involvement is $< 60\%$ and good ECOG (0-1).

Conventional TACE uses a mixture of doxorubicin, lipiodol and embolic agent. The symptoms response has been as high as 73% to 100%, objective response 55% to 80% and time to progression from 8 to 42 mo^[103,104].

Toxicity profile shows grade 2 alopecia, 2-3 nausea and vomiting, postembolization syndrome, acute meta-

bolic syndrome or infection^[91,104]. Some of these toxicities blamed the unfavorable pharmacokinetic profile of doxorubicin binding to lipiodol^[105].

DEB-TACE more recently has improved the pharmacokinetics of the delivered drug. However, a higher incidence of bile duct injury has made its indication controversial in NET metastasis in some institutions.

DEB is a new product which has been shown to achieve higher intratumoral drug concentration and less concentration in the bloodstream TACE in animal studies^[106].

De Baere *et al*^[107] carried out a study of 20 patients and showed 80% objective tumor response and disease control, with time to progression of 15 mo. Drug toxicity was very low with grade 2 alopecia around 1% and only a few cases of mild nausea and vomiting. They reported high rate of liver infarction and bile duct injuries although most cases were asymptomatic^[107].

In normal liver parenchyma, intrahepatic bile ducts do not have a dual blood supply and are fed only from the hepatic arterial branches that form a vascular plexus (peribiliary capillary plexus) around the bile ducts. Therefore, ischemia of the intrahepatic bile ducts can easily occur after TACE^[108].

Some authors have suggested that the incidence of DEB-TACE-related bile duct injury is the result of inadvertent retention at the capillary peribiliary network of DEB loaded with doxorubicin. This may occur as a consequence of over-embolization related to a very aggressive TACE resulting in a high DEB dose and/or complete vessel occlusion.

Experienced operators are aware that the technique is different from conventional TACE notably the embolization. In 35 consecutive patients with liver NET treated in a single institution with DEB-TACE, two different embolization endpoints were compared (complete vs limited embolization). The results showed lower rate of adverse events (14% vs 57%, $P < 0.05$) using the latter. No statistically significant difference in response comparing the two endpoints^[109].

It seems not to be definitively clear which technique should be used, although DEB-TACE has an excellent pharmacokinetic profile which results only in minimal drug toxicity, but it has shown to increase the risk of biliary tree injury, albeit asymptomatic in most cases.

Both techniques, conventional TACE and DEB-TACE offer a high objective response rate and disease control with satisfactory duration of the response. Some authors have suggested that there seems not to be rational in performing conventional TACE or DEB-TACE, because of doxorubicin has no proven effect in NETs. Moreover, the highest benefit from these techniques seems to be due to the embolization rather than the drug effect^[110].

The ablation techniques include cryoablation, alcohol ablation and radiofrequency ablation. These methods are reserved for unresectable oligometastases smaller than 5-7 cm. There are no randomized trials

comparing surgical vs nonsurgical approaches in the management of gastroenteropancreatic NETs with liver metastases^[96,111].

TAE

In targeted embolization of the hepatic artery (TAE) several occlusive materials have been used such lipiodol, gel foam particles, polyvinyl alcohol foam or bland microspheres. It produces tumoral ischemic necrosis while the surrounding liver is perfused by the portal vein. If bilobar metastases, staged lobar embolizations may be needed.

Contraindications to TAE include > 75% replacement of liver parenchyma by tumour, predominant extrahepatic tumour burden, indolent tumours, and hepatic dysfunction.

In cases of revascularization, TAE or TACE can often be repeated. Postembolization syndrome can occur after this technique. It consists of self-limiting pain, fever and nausea/vomiting. This syndrome occurred in most patients, with an 11% major complication rate. There are no completed randomized trials comparing TAE with TACE and the superiority of one technique to another has never been shown^[111].

Selective internal radiotherapy

A novel approach to liver metastases from gastroenteropancreatic NETs involves embolization of ⁹⁰Y embedded either in a resin microsphere (SIR-Sphere) or a glass microsphere (TheraSphere)^[112].

This technique also known as selective internal radiotherapy (SIRT) will produce tumor necrosis through direct delivery of radiation. Response rates in metastatic GEP-NETs have been encouraging. A retrospective multicenter study of 148 patients treated with SIR-Spheres showed overall response rate of 63%^[113].

SIRT has never been compared prospectively to other embolic therapies and long-term toxicities such as radiation fibrosis represent potential risks. Its cost is substantially higher than more traditional embolization therapies, therefore its widespread adoption should await prospective randomized trials.

HIGH-INTENSITY FOCUSED ULTRASOUND

High-intensity focused ultrasound (HIFU) has been recently introduced for the treatment of pancreatic cancer^[114]. HIFU is a non-invasive technique for the treatment of several primary tumors and metastases. Wu *et al*^[115] have reported large areas of coagulation necrosis with this technique in hepatocellular carcinoma. Zhang *et al*^[116] have documented complete tumour necrosis even in lesions adjacent to major hepatic blood vessels.

HIFU achieves ablation by focused ultrasound energy

from an external source that is targeted within the body and induces thermally necrosis. The acoustic intensity is high only within the focal region and therefore it minimizes the risk of injury to the surrounding tissues.

This technique can reach tumours in unfavourable locations for a needle placement and it has proved to offer better disease control and quality of life.

HIFU appears to be an alternative for pancreatic NETs when no indication for a different minimally invasive approach exists. It may be easily repeated and provides good local tumour control^[116].

Moreover, it could be used as a cytoreductive therapy aiming at improving the palliation of patients with locally advanced pancreatic malignancies. However, more studies are needed to evaluate its real impact on survival or quality of life.

Currently and until solid data become available in NETs, HIFU should be reserved for patients whose symptoms cannot be controlled by medical therapy and they are not candidates for surgery or a different minimally invasive therapy^[116].

THE FUTURE

Mutations in the PI3-kinase (PI3K) pathway occur in 16% of patients with pancreatic NETs. Therefore, these tumors are a potential setting for PI3K/AKT/mTOR pharmacological interventions^[117].

Everolimus, a mTOR inhibitor, is used to treat patients with advanced pancreatic NETs. However, resistance to mTOR targeted therapy is emerging partially due to the loss of mTOR-dependent feedback inhibition of AKT. In contrast, the response to PI3K inhibitors in pancreatic NETs is unknown^[118].

Soler *et al*^[118] carried out a study to assess the frequency of PI3K pathway activation in human pancreatic NETs and in RIP1-Tag2 mice, which is a preclinical tumor model of pancreatic NETs. They investigated the therapeutic efficacy of inhibiting PI3K in RIP1-Tag2 mice using a combination of pan (GDC-0941) and p110 α selective (GDC-0326) inhibitors and isoform specific PI3K kinase-dead mutant mice. They found that treatment of these mice with GDC-0941 reduced tumor growth without impact on vascular area and the selective inactivation of the p110 α PI3K isoform reduced tumor growth as well as vascular area.

The authors concluded that p110 α could have a role in pancreatic NETs and unravel a new function of this kinase in cancer biology through its role in promoting metastasis^[118].

Andersson *et al*^[119] carried out a study to define the transcriptome of small intestinal NETs to identify clinically relevant subgroups of tumors, prognostic markers and novel targets for treatment.

Genome-wide expression profiling was conducted on biopsies from 33 patients with well-differentiated metastatic NETs of the distal ileum. They identified three groups: The largest, characterized by longer patient survival and higher expression of NE markers,

including SSTR2. Then, tumors with higher grade (G2/3) or gain of chromosome 14 which were associated with shorter survival and increased expression of cell cycle-promoting genes^[118].

The prostaglandin E receptor 2 is the most significantly activated regulator in tumors of higher grade, whereas Forkhead box M1 was the most significantly activated regulator in tumors with gain of chromosome 14^[118].

Evaluation of candidate drug targets on NET cells (GOT1) showed significant inhibition of tumor cell growth after treatment with tyrosine kinase inhibitors or inhibitors of HDAC, HSP90 and AKT^[118].

Authors found specific gene expression patterns associated with tumor grade and chromosomal alterations^[118]. The results of several practice-changing phase III clinical trials have been presented at The North American Neuroendocrine Tumor Society symposium 2015: The TELESTAR randomized phase III trial of telotristat vs placebo in patients with carcinoid syndrome^[119,120].

Telotristat etiprate is an oral inhibitor of tryptophan hydroxylase (This enzyme triggers the excess serotonin production within metastatic NET cells that leads to carcinoid syndrome). It decreased significantly the mean of daily bowel movements by 35% among patient who received 500 mg of the drug three times a day and 29% among those who received 250 mg three times a day, compared with 17% for those who received placebo^[119,120].

Urinary 5-HIAA levels were significantly reduced as well, for patients receiving the active drug, suggesting effective inhibition of serotonin production.

Telotristat etiprate has received Fast Track and Orphan Drug designation from the United States Food and Drug Administration. Whereas current treatments for carcinoid syndrome reduce the release of serotonin outside tumor cells, telotristat etiprate works to reduce serotonin production within the tumor cells^[119,120].

Currently, there are limited therapeutic options for patients with advanced midgut neuroendocrine tumors progressing on first-line somatostatin analog therapy.

NETTER-1 randomized phase III trial of radiolabelled somatostatin analog 177-Lutetium-dotatate vs high dose octreotide (LAR) 60 mg in patients with progressive midgut NETs. Results showed that the median PFS, the trial's primary endpoint, improved by nearly 80%. The median PFS with high-dose octreotide was 8.4 mo and was not yet reached in the ¹⁷⁷Lu-Dotatate arm at a median follow-up of 18 mo but update data indicate that it will probably be in excess of three years. Although the OS data were not mature enough for a definitive analysis, the number of deaths was 13 in the Lutathera group and 22 in the Octreotide LAR 60 mg group at interim analysis which suggests an improvement in OS. The overall response rate was 18% vs 3%. Safety data confirmed favorable results of the preceding phase I/II studies^[121,122].

Serious adverse events related to treatment were 9%

for Lu-Dotatate and 1% for octreotide. Withdrawals due to adverse events were 5% for Lu-Dotatate and did not occur in patients treated with octreotide. Lu-Dotatate is the most advanced candidate in development of PRRTs, which target tumors with radiolabelled somatostatin analog peptides. In April 2015, the FDA granted a fast track designation to Lu-Dotatate for the treatment of inoperable progressive midgut NETs^[122,123].

Radiolabeled SSA therapy (also called peptide receptor radiotherapy or PRRT) has shown to be an effective treatment for gastroenteropancreatic NETs, as it allows targeted delivery of radionuclides to SSTR-expressing tumor cells. Selection criteria for PRRT include evidence of strong radiotracer uptake on somatostatin-receptor scintigraphy, ideally higher than in normal liver tissue.

The agents ⁹⁰Y-DOTATOC and ¹⁷⁷Lu-Dotatate are the latest generation of PRRT. ⁹⁰Y is a high-energy β -particle emitter. Strosberg *et al*^[123], Kwekkeboom *et al*^[124] and Valkema *et al*^[125] reported ORR > 25%. A later large multicenter trial of 90 patients with metastatic carcinoids showed a RR of 4%, and 70% of SD^[126].

¹⁷⁷Lu emits both β and γ rays. A large nonrandomized trial including 310 patients, has reported a 30% RR with gastroenteropancreatic NETs receiving ¹⁷⁷Lu-octreotate.

Responses were particularly high in patients with pancreatic NETs^[127]. PRRT toxicities include myelosuppression and renal insufficiency, with the latter generally ameliorated by concurrent amino acid infusion.

CONCLUSION

NE gastroenteropancreatic tumors are a heterogeneous group of neoplasias arising from NE cells of the embryological gut^[1] whose incidence have increased due probably to the improvements in diagnosis^[1-4]. Many recent advances in molecular biology have expanded the therapeutic arsenal and we have shifted from somatostatin analogs^[6] only, to a new scenario where antiangiogenics and mTOR inhibitors among others have started to take over^[7]. The treatment of NETs continues being a challenge and requires a coordinated multidisciplinary approach. Although the management of localized NETs involves surgical resection followed by surveillance, the treatment of unresectable and/or metastatic disease may involve several disciplines (surgical resection, systemic therapy, liver-directed therapies)^[7].

Several completed and ongoing studies are evaluating somatostatin analogs, VEGF pathway and mTOR inhibitors, cytotoxic chemotherapy, PRRT^[7], new liver-directed therapies, *etc.* but future trials should focus on patient selection, predictive markers, and tolerability improvement as these aspects are critical to continue advancing.

The circulating tumour cells (CTCs), which are detectable in the blood of 50% of patients with functioning midgut NETs, are usually related to poor prognosis. The CALM-NET, a phase IV, multicentre, open label, single

group exploratory study to assess the clinical value of enumeration of CTCs to predict clinical symptomatic response and PFS in patients receiving lanreotide to treat the symptoms of functioning midgut NETs is under way. The results of this trial could be valuable as if positive, CTCs could be used as predictive markers to help make therapeutic decisions.

Pancreatic NETs are heterogenous neoplasms still with limited therapeutic options but everolimus has recently been approved for the treatment of progressive, well-differentiated, non-functional, unresectable, locally advanced or metastatic NETs of gastrointestinal or lung origin. This is the first approved treatment for these rare cancers whose prognosis is poor and their options limited.

Alkylating cytotoxic agents, such as streptozocin and temozolomide, play an important role in the treatment of pancreatic NETs, although RR varies widely. Future studies of cytotoxics in gastroenteropancreatic NETs should stratify patients based on primary site and tumor grade. Over the next years, randomized clinical trials are expected to provide more data about role of radiolabeled somatostatin analogs. Predictive biomarkers that would allow for individualized selection of treatments are needed.

New findings have shed light on the biological processes of pancreatic NETs and have identified a tumorigenic cell population that suggest these cells can hide from immune surveillance.

These discoveries will hopefully open the door to new potential therapeutic targets^[128] which can lead to personalised treatments and optimize the results in this heterogeneous group of tumors.

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