A Shining Light in the Darkness for the Treatment of Pancreatic Neuroendocrine Tumors

Jaume Capdevila and Josep Tabernero

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Gastroenteropancreatic neuroendocrine tumors (GEPNET) constitute a heterogenic group of neoplasms derived from the Kulchitzky cells of the diffuse neuroendocrine system located in the gastrointestinal tract (origin of carcinoid tumors) and pancreatic islet cells (origin of pancreatic endocrine tumors). Although GEPNETs represent less than 2% of all gastrointestinal cancers, they constitute the second most prevalent advanced tumor of the gastrointestinal tract after colorectal cancer (1). The biological behavior of well-differentiated pancreatic neuroendocrine tumors (PNET) depends mainly on their histologic characteristics, such as differentiation grade, Ki67 expression, or angiovasculature, and the proportion of malignant tumors developing metastases varies widely between tumor types (from 10% of insulinomas to 90% of glucagonomas).

The medical treatment of advanced PNETs has included somatostatin analogs, interferon, and cytotoxic agents. This latter group of drugs has limited activity in PNETs for many reasons, including the fact that they usually have a low mitosis rate and also because of their particular biological properties, such as the presence of biologic markers related to chemoresistance (i.e., Akt expression) (2). The lack of effectiveness of conventional cytotoxic agents has prompted exploration of new targeted drugs exploiting phenotypical features of PNETs. Nevertheless, the development of targeted therapies in this field has been limited by a number of factors. First, PNETs are extremely heterogeneous with very different characteristics in highly and poorly differentiated tumors. Second, the preclinical development of drugs directed against these tumors is limited because very few in vitro and in vivo models exist. And last, but not least, the frequent shortage of resources has impacted strongly on rare neoplasms that require international efforts to design and implement scientifically valid studies. In-depth characterization of molecular features and pathways of cell growth, apoptosis, angiogenesis, and invasion are still lacking in this group of tumors, particularly concerning genetic mutations or epigenetic alterations that generate oncogenic dependency or even addiction. This is the concept behind an ideal target; unfortunately, however, the majority of new developments are based only on phenotypic overexpression of pathways with
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MANAGEMENT OF PNET

• Management of advanced PNETs is based on a multidisciplinary approach that includes surgery, liver-directed treatments, radionuclide and biological therapies, chemotherapy, and targeted agents.

• Strong molecular rationale supports antiangiogenic and mTOR-directed therapies for the treatment of PNETs, with a favorable toxicity profile compared with standard chemotherapy.

• After decades of slight improvement, sunitinib and everolimus have demonstrated a significant benefit in progression-free survival and response rate in the largest ever completed phase III studies in PNETs.

• No predictive biomarkers have been characterized so far for better patient selection. PTEN and TSC1/2 downregulation have been suggested to be prognostic factors in PNETs and their potential predictive value in the treatment with PI3K-pathway inhibitors is being evaluated.

• Gene expression profiling and tumor sequencing studies have confirmed the relevance of the PI3K-AKT-mTOR pathway in the pathogenesis of PNETs, and have highlighted other significant pathways less known in the PNET molecular profile, but with enough preclinical data to be assessed in the future, such as Wnt/β-catenin, Hedgehog, Notch, or TGF-β.

• The prolonged survival of patients with PNETs requires that they sequentially receive all the available treatment options. It is anticipated that ongoing and next-generation studies will clarify whether the best approach is to combine some active cytotoxic drugs with targeted agents or to sequentially administer all available treatment options. In this regard, predictive and prognostic biomarkers will likely be useful to better define the most appropriate sequence.

MODERATE SIGNALING REPERCUSSIONS IN PNETs

The (over)expression of some factors has been associated with poor prognosis and decreased progression-free survival (PFS), as well as with tumor growth, aggressiveness, and disease extent in patients with PNETs (4).

Currently, the medical management of functional PNETs almost invariably involves the use of somatostatin analogs to control the symptoms related to hormone secretion. Interferon-α is added when patients develop resistance. Although both treatments provide up to 70% to 80% of hormone syndrome control and relief of induced symptoms, antiproliferative effects are far from impressive, ranging from 5% to 10% at best. Cytotoxic chemotherapy is a treatment option in patients with PNETs, given that these tumors typically have intermediate cell proliferation rates (2% to 20% measured by Ki67 immunohistochemistry index). Combination regimens containing streptozocin, dacarbazine, epirubicin, lomustine, cisplatin, doxorubicin, etoposide, and 5-fluorouracil have shown the best efficacy, with overall response rates (ORR) of 20% to 60%, and a median overall survival (mOS) ranging from 15 to 26 months (5).

Surgery, the mainstay of treatment for localized tumors, can be considered in patients with metastatic disease, to reduce tumor mass, before or concomitantly with systemic therapy, and to palliate symptoms. Other approaches to reduce tumor burden or to contribute to hormone syndrome control include hepatic artery (chemo)embolization, radiofrequency ablation, and somatostatin receptor-targeted radionuclide therapy (6).

Several targeted agents have been studied in the treatment of GEPNETs including antiangiogenic compounds (e.g., bevacizumab), inhibitors of multiple receptors with kinase activity (e.g., sunitinib), and inhibitors of intracellular downstream effector proteins such as mTOR (e.g., everolimus). Two phase III studies with everolimus and sunitinib were recently conducted in patients with PNETs and demonstrated significant clinical activity increasing PFS, and results were published in the New England Journal of Medicine. The last publication of a chemotherapy combination in this disease in this prestigious journal was two decades ago, and that treatment became the standard of care of patients with advanced well-differentiated PNETs (7).

ANTIANGIOGENESIS TREATMENT IN ADVANCED PNETs

PNETs are some of the most vascularized tumors identified to date. Currently, a number of antiangiogenic compounds are being evaluated in the clinic, and can be divided into 3 groups: (i) drugs targeting VEGF, such as the VEGF-directed monoclonal antibody bevacizumab; (ii) small molecules that inhibit the receptor tyrosine kinase domains of VEGFR and other related receptors, such as sunitinib, sorafenib, and pazopanib; and (iii) other compounds with different antiangiogenic mechanisms, such as thalidomide or endostatin (Table 1).

The first evidence of activity of bevacizumab in GEPNETs was reported by Yao and colleagues (8) in a phase II study with 44 patients randomly assigned to receive bevacizumab (15 mg/kg every 3 weeks) or weekly pegylated interferon α-2b
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Table 1. Main antiangiogenic compounds in clinical development for advanced neuroendocrine tumors

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Target(s)</th>
<th>Phase</th>
<th>Tumor</th>
<th>ORR</th>
<th>PFS (m)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Phase II</td>
<td>Carcinoid</td>
<td>18%</td>
<td>16.5</td>
<td>Ongoing phase III</td>
<td>8</td>
</tr>
<tr>
<td>BV + CHT</td>
<td>FOLFOX</td>
<td></td>
<td>PNETs</td>
<td>20%–33%</td>
<td></td>
<td>Ongoing</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>XELOX</td>
<td></td>
<td>PNETs</td>
<td>31%</td>
<td></td>
<td>Ongoing</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Temozolomide</td>
<td></td>
<td>GEPNET</td>
<td>0%–24%</td>
<td></td>
<td>Ongoing</td>
<td>33</td>
</tr>
<tr>
<td>BV + everolimus</td>
<td>VEGF + mTOR</td>
<td>Phase III</td>
<td>GEPNET</td>
<td>21%</td>
<td>14</td>
<td>Ongoing</td>
<td>41</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR1-3, PDGFR, RET, FLT3, KIT</td>
<td>Phase II</td>
<td>Carcinoid</td>
<td>2%</td>
<td>10.5</td>
<td></td>
<td>10</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>PNETs</td>
<td>17%</td>
<td>7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GEPNET</td>
<td>9%</td>
<td>11.4</td>
<td>Positive phase III</td>
<td>11</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR2-3, PDGFR, Raf, KIT, RET</td>
<td>Phase II</td>
<td>Carcinoid</td>
<td>7%</td>
<td>7.8</td>
<td>Completed</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PNETs</td>
<td>17%</td>
<td>11.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GETNET</td>
<td>10%</td>
<td>12.4</td>
<td>Completed</td>
<td>35</td>
</tr>
<tr>
<td>Vatalanib</td>
<td>VEGFR1-3, PDGFR, KIT</td>
<td>Phase II</td>
<td>GEPNET</td>
<td>0%</td>
<td>NR</td>
<td>Withdrawn</td>
<td>—</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR1-3, PDGFR,</td>
<td>Phase II</td>
<td>Carcinoid</td>
<td>0%</td>
<td>12</td>
<td>Ongoing</td>
<td>36</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PNETs</td>
<td>19%</td>
<td>14.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motesanib</td>
<td>VEGFR1-3, PDGFR, RET</td>
<td>Phase II</td>
<td>GEPNET</td>
<td>—</td>
<td>—</td>
<td>Ongoing</td>
<td>—</td>
</tr>
<tr>
<td>Atiprimod</td>
<td>Inhibits VEGF secretion Deactivates Akt and STAT3</td>
<td>Phase II</td>
<td>GEPNET</td>
<td>0%</td>
<td>76% at 6 m</td>
<td>Ongoing</td>
<td>37</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>VEGF and bFGF</td>
<td>Phase II</td>
<td>GEPNET</td>
<td>0%</td>
<td>—</td>
<td>80% SD</td>
<td>38</td>
</tr>
<tr>
<td>Thalidomide + CHT</td>
<td>Temozolomide + VEGF and bFGF</td>
<td>Phase II</td>
<td>GEPNET</td>
<td>7%–45%</td>
<td>—</td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>rH-Endostatin</td>
<td>Endogenous endothelial inhibition</td>
<td>Phase II</td>
<td>Carcinoids</td>
<td>0%</td>
<td>5.8</td>
<td>80% SD</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PNETs</td>
<td>0%</td>
<td>7.6</td>
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</tr>
</tbody>
</table>

Abbreviations: BV, bevacizumab; CHT, chemotherapy; NR, not reached; PFS, progression-free survival; STAT, signal transducers and activators of transcription; rH, recombinant human; m, months.

(PIF; 0.5 μg/kg, for 18 weeks). After 18 weeks of treatment or in the event of disease progression, patients could receive the combination of the 2 drugs. The bevacizumab arm showed a higher ORR (18% vs. 0%), a lower progression rate (5% vs. 27%), and therefore a better PFS rate after 18 weeks of treatment (95% vs. 68%). Bevacizumab treatment was also associated with a significant tumor blood decrease measured by functional computed tomography (CT) scans compared with PIF (P < 0.01). The toxicity profile was manageable with hypertension as the main adverse event. A larger phase III study (SWOG S0518) is currently recruiting patients to confirm these promising results. Bevacizumab is being evaluated in combination with cytotoxic chemotherapy and also with other targeted therapies, including sorafenib and everolimus (Table 1).

Sunitinib malate (SU-11248) is a highly potent, ATP-competitive binding small molecule capable of inhibiting several tyrosine kinase membrane receptor proteins involved in the main angiogenic and proliferative pathways, such as VEGFR-1 to 3, PDGFR, FLT-3, c-KIT, and RET. The first evidence of activity of sunitinib in advanced GEPNETs was reported in a first-in-man phase I study (9), which was followed by a phase II trial with 107 patients (41 with carcinoid tumors and 66 with PNETs) with documented disease progression. The authors reported an ORR of 16.7% in PNETs with 68% of patients presenting stable disease (SD). In patients with carcinoid tumors, the ORR and SD rates were 2.4% and 83%, respectively. A pharmacodynamic study of potential soluble surrogate biomarkers was also done and identified sVEGFR-3 as a potential biomarker of the biological effect of sunitinib and interleukin-8 as a potential predictor of response (10). These results led to the design of a double-blind, placebo-controlled phase III study in advanced PNETs (11). The initial design planned to recruit 340 patients with disease progression documented by Response Evaluation Criteria in Solid Tumors (RECIST) in the 12 months prior to trial enrollment. The study was prematurely stopped following a recommendation of the Data Monitoring Committee due to significant differences in disease progression and deaths in the placebo arm. A total of 171 patients were enrolled in the trial, 86 receiving sunitinib (37.5 mg daily) and 85 receiving placebo. The results of the study regarding ORR, median PFS (mPFS), and estimated mOS significantly favored the sunitinib arm. Patients treated with sunitinib achieved mPFS of 11.4 months compared with 5.5 months in the placebo arm.

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INHIBITION OF mTOR IN PNETs

mTOR is an intracellular serine-threonine kinase downstream of the phosphatidylinositol 3′ kinase (PI3K)-AKT signaling pathway. Under physiologic conditions the PI3K-AKT-mTOR signaling pathway plays a major role in regulating cell growth, proliferation, motility, and survival, and cellular nutrient and energy levels, protein synthesis, autophagy, transcription, and redox status. mTOR integrates multiple upstream signals, including growth factors (e.g., EGF and IGF-1/2), and mitogens. Interestingly, mTOR is also involved in angiogenesis, regulating the translation and activity of hypoxia-inducible factor 1α (HIF1α), which is related to VEGF expression under hypoxic conditions.

Hyperactive mTOR signaling is a key participant in development, growth, and proliferation in about 50% of all human tumors. mTOR acts as the catalytic subunit of 2 distinct complexes, mTOR complex 1 (mTORC1) consists of mTOR, the target of the rapamycin complex subunit LST8 (LST8, also known as GBL), the proline-rich Akt substrate 1 (AKT1S1, also named PRAS40), and its main partner, the regulatory associated protein of mTOR (RAPTOR). mTOR complex 2 (mTORC2) is composed of mTOR, LST8, the target of rapamycin complex 2 subunit MAPKAP1 (SIN1), the proline-rich protein 5 (PRR5, or PROTOR1), and its most important partner, rapamycin-insensitive companion of mTOR (RICTOR). mTORC1 is characterized by the classic features of mTOR, functioning as a nutrient-energy-redox sensor and controlling protein synthesis. The activity of this complex is stimulated by several growth factors, hormones, nutrients (amino acids, glucose), cellular energy status, and stress conditions. mTORC2 functions as an important regulator of the cytoskeleton and also phosphorylates the serine-threonine protein kinase AKT when mTOR is blocked, through the use of an mTOR inhibitor. Activation of mTORC1 by positive regulators induces the phosphorylation of 2 of the main downstream effectors, the eukaryotic translation initiation factor 4E–binding protein-1 (4E-BP1) and the ribosomal protein S6 kinase β-1 (S6K1). The activation of these effectors leads to the enhancing of the translation of essential mRNAs involved in the cell cycle progression through G1 to S phase (12). Several targets of the PI3K-AKT-mTOR signaling pathway have been identified in PNETs, and several genetic disorders that have constitutive activation of this pathway along with increased incidence of neuroendocrine tumors have been well defined, such as the tuberous sclerosis complex (TSC), neurofibromatosis type I, Von Hippel-Lindau (VHL) disease, or multiple endocrine neoplasia type I (MEN1) (13).

Two rapamycin inhibitors have been evaluated in neuroendocrine tumors: temsirolimus and everolimus. Temsirolimus was only studied in a multicenter phase II trial with 37 advanced GEPNETs; although the therapy was generally well tolerated, the drug showed modest antitumor activity with only 2 confirmed responses (5.6%). The activity was similar between carcinoid and PNETs: mPFS was 6 months and OS at 1 year was 71.5%. The authors considered the activity was not sufficiently clinically meaningful for further development.

Everolimus has been intensively developed in GEPNETs. The first study in this disease, conducted at the MD Anderson Cancer Center, included 30 patients with carcinoid tumors and 30 patients with PNETs in 2 consecutive cohorts (14). The first cohort treated 30 patients with the combination of depot octreotide (30 mg intramuscularly every 28 days) plus everolimus (5 mg daily). The second cohort included 30 patients treated with octreotide at the same doses and everolimus (10 mg daily). The authors reported encouraging antitumor activity with an ORR of 17% in carcinoid tumors and 27% in islet cell carcinomas, with mPFS of 63 and 50 weeks, respectively. Moreover, patients included in the cohort receiving everolimus (10 mg) obtained a higher ORR (30% vs. 13%) and prolonged mPFS (72 vs. 50 weeks). Overall, everolimus showed an acceptable toxicity profile, the most frequent grade 3-4 adverse events being aphthous ulcers, fatigue, diarrhea, hyperglycemia, and hypophosphatemia.

After these encouraging results, the RAD001 in Advanced Neuroendocrine Tumors (RADIANT) trials were designed to explore the efficacy of everolimus in neuroendocrine tumors of different origins. The RADIANT-1 study was a confirmatory international phase II trial in progressive chemotherapy-refractory islet cell carcinomas divided into 2 strata: the first included 115 patients with advanced PNETs treated with everolimus (10 mg daily) and the second had 45 patients with the combination of depot octreotide (30 mg intramuscularly every 28 days) plus everolimus (10 mg daily) (15). The ORR was 7.8% in stratum 1 and 4.4% in stratum 2, with SD rates of 68.7% and 77.8%, respectively. The mPFS was 9.3 months in stratum 1 and 12.9 months in stratum 2. Additionally, 49% and 56% of patients with...
increased chromogranin A levels in stratum 1 and 2, respectively, achieved either normalization or a reduction greater than 50%. Moreover, the authors reported a statistically significant relationship between the decrease in chromogranin A levels and mPFS (decrease ≥30%, mPFS 13.3 months vs. nonresponders, 7.5 months). The treatment was generally well tolerated with few grade 3-4 adverse events, mainly fatigue, diarrhea, and stomatitis.

RADIANT-2 and RADIANT-3 studies are 2 international, double-blind, placebo-controlled phase III trials in advanced clinically functional extrapancreatic neuroendocrine tumors and advanced PNETs, respectively. The initial report of the RADIANT-2 trial was presented at the 35th European Society for Medical Oncology (ESMO) Congress (Milan, Italy, October 8–12, 2010). In this trial, the efficacy and safety of everolimus (10 mg/d) plus octreotide LAR (30 mg every 28 days) was compared to that of placebo plus octreotide LAR (30 mg every 28 days) in 429 patients with advanced carcinoid tumors and a history of hormone-related symptoms. Although the study did not meet its primary endpoint based on central radiologic review of data, the results showed that everolimus plus octreotide LAR significantly improved mPFS by 5.1 months (HR: 0.77; 95% CI, 0.59–1.00; P = 0.026) when compared with placebo. After adjusting for imbalances in baseline characteristics between the 2 treatment arms, and inconsistencies between radiology scans to assess disease progression, the results also showed that everolimus plus octreotide LAR significantly reduced the risk of disease progression by 40% (HR: 0.60; 95% CI, 0.44–0.84; P = 0.0014) when compared to octreotide LAR alone (16).

The results of the RADIANT-3 study were recently published, showing the efficacy of everolimus in advanced PNETs (17). A total of 410 patients with disease progression documented prior to inclusion were randomly assigned to receive either daily oral everolimus (10 mg/d) or placebo (1:1). Treatment with everolimus demonstrated a significant increase in mPFS by central radiological review, more than double that of placebo, from 4.6 to 11.0 months (HR: 0.35; 95% CI, 0.27–0.45; P < 0.0001) fulfilling the primary endpoint. At 18 months, PFS in the everolimus arm was 34%, with a subgroup of patients who obtained prolonged clinical benefit of everolimus treatment with an acceptable safety profile. The benefit in PFS was observed in all subgroups of patients regardless of previous therapies, ECOG PS, age, tumor burden, time since diagnosis, treatment with somatostatin analogs, and tumor grade. Although the response rate was relatively low—but significantly higher in the everolimus arm (5% vs. 2%, P = 0.001)–64.4% of patients had decreases of between 1% and 29% in target lesion size. Thus, the main benefit of everolimus in PFS was seen due to minor responses and tumor stabilizations. No differences in OS were observed due to the preplanned crossover at disease progression defined in the protocol (73% of patients in the placebo arm received open-label everolimus at progression). The most common grade 3-4 adverse events were stomatitis (observed in 7% of patients), anemia (6%), and hyperglycemia (5%). Infections (23%), pneumonitis (12%), and interstitial lung disease (2%), which often represent the main clinical concerns with everolimus therapy, were typically grade 1-2 and generally managed with antibiotics and steroids. Results of further secondary analyses of the RADIANT-3 study are expected in the near future, such as possible predictive biomarkers that may guide clinicians in the selection of patients who are more likely to respond to everolimus therapy. In summary, the RADIANT trials are the largest studies in advanced neuroendocrine tumors ever conducted and, as a result, everolimus will become a new standard of care in advanced well-differentiated PNETs and probably a new therapy option in advanced carcinoid tumors in combination with somatostatin analogs.

**KEY UNMET NEEDS AND FUTURE DIRECTIONS**

Almost half a century has elapsed since the most widely used neuroendocrine tumor classification, which was developed according to embryologic origin, was proposed by Williams and Sandler. Since then, various systems of nomenclature based on site of origin, tumor stage, histologic, or functionality classifications have been introduced, causing much confusion. These terminology issues have jeopardized not only the creation of a worldwide prognostic classification of neuroendocrine tumors but also the development of well-designed clinical trials, where the inclusion of tumors with different behavior has compromised interpretation of the results, such as happened in the RADIANT-2 study.

Fortunately, in recent years, gene expression profiling and surface sequencing have shown promising potential in the molecular features of neuroendocrine tumors. The key role of the PI3K-Akt-mTOR pathway in the pathogenesis of PNETs was known from phenotypes of hereditary syndromes, such as TSC, neurofibromatosis, VHL disease, or MEN1 syndromes, where constitutive activation of the PI3K-Akt-mTOR pathway leads to an increased incidence of PNETs (18–20). Data from tumor expression profiling in PNETs has also shown that the downregulation of PTEN and TSC2 correlates with poorer prognosis (3), but also microRNA expression profiling has demonstrated that the expression level of miR-21 is strongly associated with liver metastases, and a high Ki67 index and miR21 levels are inversely proportional to PNET levels (Fig. 1) (21, 22). The significance of HIF/p53 pathway in the development and progression of PNETs has also been highlighted and the protein encoded by the *MEN1* gene, Menin, has altered distribution and intensity in 80% of PNETs, leading to the inhibition of AKT activation by regulating its cellular location (23, 24). Moreover, activation of the PI3K-Akt-mTOR pathway in PNETs is also led by the (over)expression of membrane tyrosine kinase receptors that trigger this pathway, such as IGF-1R, fibroblast growth factor receptor 3 (FGFR3), or in the companion vasculature with mutations in the FLT1 gene, which encodes VEGFR1 (25). Furthermore, expression of EGFR has been widely described in PNETs, but no meaningful activity has been observed with EGFR inhibitors. Preclinical data with the most used transgenic mouse model, RIP-Tag2, have demonstrated that
The next step after this characterization is the design of molecularly guided clinical studies that could help to determine the best treatment combinations for PNETs. In order to counter escape mechanisms along with primary EGFR inhibition with erlotinib is able to abrogate the potential resistance mediated by Akt upregulation after mTORC1 inhibition (26).

Deep sequencing of the entire neuroendocrine tumor genome could be expected to provide not only instrumental knowledge for prognostic classification but also a “biotype” characterization that would allow assessment of potential drug pathways for individual patients. Currently, within the International Cancer Genome Consortium, there is a task force to perform deep sequencing of GEPNETs. Recent data based on deep sequencing have confirmed the key role of MEN1 and the PI3K-Akt-mTOR pathways, but has also highlighted the importance of several transcription factors, such as DAXX (death domain-associated protein), ATRX (X-linked mental retardation and α-thalassemia syndrome protein), or ATM (ataxia telangiectasia mutated), which may open new target opportunities for the treatment of PNETs (13).

The next step after this characterization is the design of molecularly guided clinical studies that could help to determine the best treatment combinations for PNETs. In order to counter escape mechanisms along with primary
and secondary resistance to mTOR inhibition, several combined approaches are being evaluated, including mTOR and IGF-1R inhibition, mTOR inhibition plus pan-analog of somatostatin receptors (SOM230), mTOR and EGFR inhibition, and dual mTORC1 and mTORC2 and dual PI3K and mTORC1/2 inhibition. Some studies are already in early recruitment (Table 2; also see clinicaltrials.gov). Nonetheless, despite the strong molecular rationale for this approach, it seems very unlikely that combination of targeted agents will displace the use of cytotoxic agents. We should keep in mind that PNETs are not completely resistant to chemotherapy. Moreover, recent data suggest that temozolamide, a cytotoxic agent approved for the treatment of glioblastoma, may be active in patients with PNETs. Encouragingly, the patients most sensitive to this treatment may be characterized by O6-methylguanine DNA methyltransferase (MGMT) expression using immunohistochemistry (27).

Another approach uses the abrogation of other signaling pathways such as Wnt/β-catenin, Hedgehog, Notch, or TGF-β, known to be critical in processes of epithelial-mesenchymal transition, and regulation of neuroendocrine differentiation and cancer stem cell proliferation and survival. Limited preclinical data support the evaluation of drugs targeting these pathways in patients with advanced PNETs (28–30).

**CONCLUSIONS**

The future management of advanced neuroendocrine tumors finally appears to be changing after decades of generally ineffective chemotherapy and limited usefulness of somatostatin analogs in hormone-related syndromes. Better knowledge of molecular mechanisms related to carcinogenesis, angiogenesis, and tumor progression have led to the development of specific targeted therapies that will change the armamentarium of treatment of neuroendocrine tumors. In April 2011, everolimus and sunitinib were presented to the Food and Drug Administration for approval in the treatment of advanced PNETs, and everolimus for tumors of gastrointestinal and lung origin, based on the RADIANT-2 results. Selection of one of these drugs for the treatment of advanced PNETs will be based mainly on their toxicity profiles because both drugs are able to double mPFS. Only the sunitinib study has assessed the QoL profile of these patients. Nonetheless, QoL is an important objective in this particular group of tumors because most are pauci- or asymptomatic and therefore drug side effects could jeopardize compliance with long-term treatment. Tumor response does not facilitate the choice between these new drugs because both give less than 10% ORR. Moreover, ORR with these drugs compares unfavorably with those of older studies of cytotoxic therapies in PNETs, which achieved rates of up to 60%. In this regard, it is suggested that these new targeted therapies are reserved for slow-growing tumors and that we should continue using traditional chemotherapy in those patients for whom reduction of tumor burden is the main objective. The vast population that achieves SD in these studies constitutes the main objective of prolonging mPFS, and the real benefit of these stabilizations can only be assessed in placebo-controlled phase III studies with documented disease progression before therapy begins. Furthermore, no relationship has been established between mPFS increase and prolongation of OS. The crossover design in placebo-controlled studies, although ethically mandatory, increases the difficulty of survival interpretation. Despite this, the sunitinib study showed OS gain reflecting the value of stabilizations in heavily pretreated PNET patients. With this scenario, sunitinib and everolimus will become new treatment options for PNETs but are far from becoming the new standard of care for all patients, in whom medical therapy, surgery, and locoregional ablations will continue to play the main role. The development of

Table 2. Main planned/ongoing clinical trials with targeted therapies in advanced pancreatic neuroendocrine tumors

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Target(s)</th>
<th>Phase</th>
<th>Protocol ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus + erlotinib</td>
<td>mTOR + EGFR</td>
<td>Phase II</td>
<td>NCT00843531</td>
</tr>
<tr>
<td>AMG479</td>
<td>IGFR</td>
<td>Phase II</td>
<td>NCT01024387</td>
</tr>
<tr>
<td>Bevacizumab + pertuzumab + octreotide LAR</td>
<td>VEGF + HER1/HER2 + SSRT</td>
<td>Phase II</td>
<td>NCT01121939</td>
</tr>
<tr>
<td>Everolimus + bevacizumab</td>
<td>mTOR + VEGF</td>
<td>Phase II</td>
<td>NCT1229943</td>
</tr>
<tr>
<td>LY284702 + everolimus</td>
<td>p70 S6 Kinase + mTOR</td>
<td>Phase Ib</td>
<td>NCT01115803</td>
</tr>
<tr>
<td>Cixutumumab + everolimus + octreotide LAR</td>
<td>IGF + mTOR + SSRT</td>
<td>Phase Ib</td>
<td>NCT1204476</td>
</tr>
<tr>
<td>Everolimus + pasireotide</td>
<td>mTOR + SSRT</td>
<td>Phase Ib</td>
<td>NCT1263353</td>
</tr>
<tr>
<td>Everolimus + sorafenib</td>
<td>mTOR + VEGFR2-3, PDGF, Raf, KIT, RET</td>
<td>Phase Ib</td>
<td>NCT00942682</td>
</tr>
<tr>
<td>FR901228</td>
<td>Histone deacetylase</td>
<td>Phase II</td>
<td>NCT00084461</td>
</tr>
<tr>
<td>MK-2206</td>
<td>Akt</td>
<td>Phase II</td>
<td>NCT1169649</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome</td>
<td>Phase II</td>
<td>NCT00017199</td>
</tr>
</tbody>
</table>

Abbreviations: HER, human epithelial growth factor receptor; SSRT, somatostatin receptors.
predictive biomarkers, such as reduced expression of PTEN or TSC1/2 for mTOR inhibition, should be run in parallel for better patient selection and consequently a better balance of clinical benefit, side effects, and resources limitation. New studies are combining everolimus and sunitinib with other targeted agents and cytotoxic drugs to evaluate if combination treatment translates into an increase in survival of patients with advanced PNets. In this regard, a phase III study is being designed in association with the European Neuroendocrine Tumor Society (ENETS) to assess the importance of sequentiality of everolimus and chemotherapy in this setting.

Disclosure of Potential Conflicts of Interest

J. Tabernero disclosed consulting and participation in advisory boards for Novartis and Pfizer; J. Capdevila disclosed consulting and participation in advisory boards for Novartis and Pfizer.

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