

# Systemic Therapy for Advanced Carcinoid Tumors: Where Do We Go From Here?

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## Abstract

Carcinoid tumors are relatively indolent, but the treatment of advanced disease remains a challenge. Liver-directed therapies are a consideration in patients with liver-dominant disease. Somatostatin analogs (SSTa) are routinely used to control hormone-mediated symptoms (carcinoid syndrome), but the identification of systemic agents with antitumor efficacy has proven difficult. Aside from octreotide for small bowel carcinoid (which is associated with delayed progression), no treatment has proven antitumor activity. Chemotherapy seems to be of limited value. The role of interferon is also controversial; it is typically used after failure of octreotide. Peptide receptor radionuclide therapy may have activity in patients with SST receptor-expressing tumors, but randomized controlled trials are lacking. Advances in the understanding of the mechanisms underlying tumor progression have led to the identification of several potential therapeutic targets (including the vascular endothelial growth factor [VEGF] and mammalian target of rapamycin [mTOR] signaling pathways), but none has been definitively validated in carcinoid. Everolimus is associated with a trend toward improved progression-free survival in patients with progressive carcinoid, but is not approved for this indication. Therefore, a serious unmet need remains for additional therapeutic strategies for patients with advanced disease. Several avenues are under study, including the use of novel SSTa; VEGF and mTOR inhibitors; and agents that interfere with insulin growth factor 1 receptor and AKT signaling. Moving forward, optimizing patient selection based on clinical features or biomarkers holds promise for identifying individuals most likely to benefit from therapy. (*JNCCN* 2012;10:785–793)

Neuroendocrine tumors (NETs) encompass a heterogeneous group of neoplasms arising nearly anywhere in the body. Importantly, the nomenclature and staging of NETs have evolved considerably, with progressively more attention paid to grade and site of origin. According to the 2010 WHO classification scheme, NETs are divided into well-differentiated (low- and intermediate-grade) NETs and poorly differentiated (high-grade) neuroendocrine carcinomas.<sup>1–3</sup> The distinction between poorly differentiated and well-differentiated tumors is based on tumor grade (high vs. low/intermediate), mitotic count (> 20 per 10 high-powered field), and Ki-67 proliferation index (> 20%). Given their high predilection for metastases, high-grade tumors are typically treated with platinum-based systemic chemotherapy.<sup>4</sup>

Among well-differentiated tumors, distinguishing between carcinoid and pancreatic NETs (pancNETs) has become increasingly important, given accumulating evidence suggesting a differential response to therapy.<sup>1,2</sup> Although histologically similar, pancNETs are thought to be more responsive to chemotherapy.<sup>5</sup> In addition, sunitinib and everolimus were both recently approved specifically for pancNETs; neither agent has received FDA approval for carcinoid.<sup>6–9</sup> In contrast, the antitumor activity of octreotide has only been definitively shown in carcinoid.<sup>5,10</sup> Although somewhat archaic, the term *carcinoid* will be used throughout this article to encompass well-differentiated NETs arising from the foregut (lungs, thymus, stomach, duodenum), midgut (small bowel, cecum, appendix), or hindgut (descending colon, rectum).

Carcinoid tumors are relatively indolent, but the treatment of advanced disease remains a serious challenge.<sup>11,12</sup> Surgical resection of both primary and metastatic lesions remains the mainstay of treatment, but patients frequently present with advanced, unresectable disease. In these patients, management of hormone-mediated symptoms and/or tumor bulk eventually be-

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comes necessary. Importantly, the potentially indolent nature of carcinoids is a serious consideration. Although tumor grade, stage, and primary site influence overall survival, most patients can expect to experience slow progression over many years. For example, patients with metastatic tumors arising in the small bowel (jejunum and ileum) have a median overall survival longer than 5 years (65 months), a 5-year overall survival of 54%, and a 10-year overall survival of 30%.<sup>13</sup> As a result, the type and timing of therapy must be carefully considered in the context of the expected disease course (weighing risks and benefits). In the absence of syndrome-associated symptoms or resectable disease, many advocate for waiting until evidence for radiographic progression or progressive symptoms before initiating antitumor therapy.<sup>11,14</sup> For liver-dominant disease, liver-directed treatment such as resection, ablation, and embolization are often used.<sup>15</sup> Octreotide is routinely used to control hormone-mediated symptoms, but also has proven antitumor activity in tumors arising in the small bowel.<sup>10</sup> Beyond octreotide, no standard therapy exists. Additional systemic treatment options are desperately needed. Recent data suggest that vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) may be valid therapeutic targets, but definitive proof is lacking.

## Chemotherapy

On average, carcinoid tumors seem to be less sensitive to chemotherapy than panNETs.<sup>5</sup> Single-agent capecitabine showed modest activity in a recent phase II study, with 13 of 19 patients experiencing stable disease (lasting > 1 year in 4 patients).<sup>16</sup> Streptozocin-based combinations have been studied extensively, with response rates ranging from 16% to 33%. In a rare phase III trial, streptozocin/5-FU was compared with doxorubicin/5-FU. The response rate was 16% in both arms, but a statistically significant improvement in overall survival (24.3 vs. 15.7 months) was noted in the streptozocin-containing arm. Importantly, 35% of patients on the streptozocin-containing arm developed mild to moderate renal toxicity, suggesting that the risk/benefit ratio of this regimen is not particularly favorable.<sup>17</sup>

Temozolomide-based regimens have also been studied in carcinoid. Limited data suggest a possible benefit in bronchial carcinoids (4 of 13 patients with partial

responses)<sup>18</sup>; however, other retrospective data suggest limited activity in carcinoid overall (1 of 44 patients with partial response).<sup>19</sup> Oxaliplatin-based chemotherapy regimens have also been studied, but randomized data are lacking and the radiographic response rate seems to be relatively low in carcinoid.<sup>20</sup>

Collectively, the data suggest that traditional chemotherapy is of limited value in carcinoid. Radiographic responses (e.g., according to Response Evaluation Criteria in Solid Tumors [RECIST]) are rare, and the value of stable disease is questionable in a disease that often progresses slowly even without treatment. No standard chemotherapy exists, and generally its use is restricted to patients with progressive, octreotide-refractory disease and no other treatment options.

## Somatostatin Analogs

Somatostatin (SST) inhibits multiple glandular and exocrine secretions, particularly gastrointestinal secretions, such as serotonin, gastrin, and insulin. In addition to this effect on hormonal release, preclinical studies of its proapoptotic and antiproliferative functions suggest potential as a targeted therapeutic for NETs.<sup>21</sup> Five G-coupled SST receptors have been identified (sstr<sub>1-5</sub>), each with varying tissue- and receptor-specific activity. They are highly expressed on NETs regardless of functionality, although the subtype expression patterns vary widely.<sup>21</sup>

Somatostatin analogs (SSTa) have a proven role in the treatment of carcinoid syndrome because of their ability to bind these receptors and block the release of bioactive peptides and amines.<sup>22,23</sup> In the United States, octreotide is the only SSTa approved for this indication, with 2 preparations available: immediate and long-acting release (LAR). Octreotide bindssstr<sub>2</sub> andsstr<sub>5</sub> with high affinity (showing significantly less affinity for the remaining 3 receptors). The depot (LAR) form of octreotide allows for monthly, rather than daily, injections. It is currently FDA-approved for the control of symptoms related to carcinoid syndrome. Notably, lanreotide autogel, an analog with a similar receptor binding profile, is used worldwide for a similar indication but is not approved for use in the United States.

In addition to its role in symptom management, octreotide has been shown to have antitumor activity. The PROMID study was a double-blind, prospective, randomized trial of octreotide LAR

versus placebo in previously untreated NETs of midgut origin.<sup>10</sup> Interim results showed that octreotide LAR extended time to progression compared with placebo (14.3 vs. 6 months, respectively;  $P = .000072$ ). Notably, 95% of patients had tumors with Ki-67 values of 2% or less; 75% had a hepatic tumor burden of 10% or less. No differences in overall survival were identified at analysis (33 of 43 placebo patients received octreotide LAR in the post-study setting), and the radiographic response rate (according to WHO criteria) was less than 3% in both arms.

The results indicate that octreotide LAR shows antitumor activity in advanced, well-differentiated midgut tumors (especially in the absence of bulky hepatic disease). The PROMID study is important because it provides proof-of-principle, showing that octreotide does, in fact, have cytostatic activity in midgut NETs. In the absence of an overall survival benefit, however, the results do not provide insight into the optimal timing of therapy (at diagnosis or after evidence for progression). Furthermore, the efficacy of octreotide in patients with bulky hepatic disease or NETs originating outside the midgut remains unclear.

Recognizing these limitations, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Neuroendocrine Tumors include octreotide LAR as a treatment option for patients with progressive metastatic carcinoid of any primary site, well- to moderately differentiated NETs of unknown primary, and pancNETs (available in this issue; to view the most recent version of these guidelines, visit [NCCN.org](http://NCCN.org)).<sup>14</sup> Importantly, lanreotide autogel is currently under investigation in a phase III study (CLARINET) assessing antitumor activity in patients with nonfunctioning NETs of the pancreas, hindgut, and midgut (ClinicalTrials.gov identifier: NCT00353496). The results of this study should complement the PROMID data, allowing a deeper understanding of the antitumor activity of SSTa in NETs as a whole. For now, considering the available data and the cost and the relative inconvenience of monthly octreotide LAR injections, deferring initiation of therapy until disease progression is a reasonable option in an asymptomatic patient (as per NCCN Guidelines for Neuroendocrine Tumors; in this issue and at [NCCN.org](http://NCCN.org)).

Beyond octreotide and lanreotide, SSTa with varying receptor binding profiles are currently in development. Hybrid somatostatin/dopamine compounds and nonpeptide analogs are also being investigated.<sup>22</sup> Pasireotide (SOM230) is an SSTa with high affinity for  $sstr_{1-3}$  and  $sstr_5$ . Relative to octreotide, it has slightly less affinity for  $sstr_2$  but greater affinity for the remaining receptors. Phase II data suggest that 27% of patients for whom standard therapy fails experience symptom control on pasireotide.<sup>24</sup> A phase III trial to assess symptom relief in patients with octreotide-refractory carcinoid is ongoing, as are studies to assess antitumor activity (Table 1).

### Peptide Receptor Radionuclide Therapy

Radiolabeled octreotide has been used for years as a diagnostic tool (<sup>1131</sup>octreotide scintigraphy). More recently, peptide receptor radionuclide therapy with radiolabeled SSTa has been developed for therapeutic use. In patients with SST receptor-expressing tumors, this strategy can target radiation directly to advanced NETs. Clinical trials with radionuclide therapy for carcinoid have primarily focused on 2 radiolabeled SSTa: [<sup>177</sup>Lu-DOTA<sup>0</sup>,Tyr<sup>3</sup>]octreotate (<sup>177</sup>Lu-DOTATATE) and [<sup>90</sup>Y-DOTA]-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-octreotide (<sup>90</sup>Y-DOTATOC).<sup>11,25,26</sup> Radiographic response rates as high as 30% have been observed in phase II trials. Notable adverse events include cytopenias and renal toxicity. Although encouraging, the results must be interpreted with caution, because prospective, randomized, controlled studies are lacking. Importantly, the development of this therapeutic strategy has been limited by issues related to drug availability.<sup>27</sup> Therefore, the use of this modality is currently limited to selected centers with the expertise to generate and administer the radiolabeled SSTa.<sup>5,27</sup> Additional studies are needed to definitely establish the safety and efficacy of radiolabeled SSTa. Accessibility also must be improved for this treatment to become routine in the United States.

### Interferon

Interferon is another targeted therapy that has activity in carcinoid tumors. Interferon alpha-2a and -2b act directly on NET cells through binding to interferon receptors on their surfaces, result-

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**Table 1 Selected Ongoing Trials of Somatostatin Analogs in Carcinoid Tumors**

Regimen	Phase	Category	Primary End Point	Secondary End Points
Lanreotide autogel vs. placebo (CLARINET)	III	Somatostatin analog	TTP	Safety, quality of life, OS, PFS
Pasireotide	II	Somatostatin analog	PFS	OS, ORR, safety
Pasireotide vs. octreotide LAR	III	Somatostatin analog	Symptom control	Safety, ORR, biochemical response
Pasireotide + RAD001	I	Somatostatin analog, mTOR inhibitor	Maximum tolerated dose	Toxicity profile
<sup>90</sup> Y-DOTATOC	II	Radiolabeled somatostatin analog	Response	Safety
<sup>177</sup> Lu-DOTATATE	II	Radiolabeled somatostatin analog	PFS	Dose-limiting toxicity

Abbreviations: LAR, long-acting release; mTOR, mammalian target of rapamycin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

ing in altered gene expression and secretory function.<sup>28</sup> Several studies suggest that interferon can provide significant relief of symptoms, with biochemical response rates as high as 30% to 35%.<sup>11,28</sup> The data also suggest the potential for synergy when used in combination with an SSTa.<sup>29</sup> However, use in the first-line setting is limited by its side effects (including myelosuppression, depression, and fatigue) relative to octreotide alone.<sup>30</sup> Interferon is approved for the treatment of carcinoid syndrome in Europe but not in the United States.<sup>12</sup>

In addition to its effects on hormone-mediated symptoms, interferon is believed to carry some degree of antitumor activity, through direct action on tumor cells and immunomodulation.<sup>28</sup> Small studies have shown trends towards improved time to progression.<sup>29</sup> However, a randomized trial of octreotide with or without interferon alpha in patients with progressive, metastatic NETs showed no significant differences in time to treatment failure or survival. Although several patients experienced stable disease, radiographic responses were infrequent (2%–5%).<sup>31</sup> Therefore, use of interferon as an antitumor strategy remains controversial, and is typically reserved for patients with SSTa-resistant disease.<sup>11,14,29</sup> Notably, treatment with interferon is the control arm for an ongoing randomized phase III study exploring the use of bevacizumab in patients on octreotide (SWOG 0518 [ClinicalTrials.gov identifier: NCT00569127]; Table 2).

## VEGF Pathway

In well-differentiated NETs, increased VEGF, a key regulator of angiogenesis, and VEGF receptor expression have been linked to metastases, angiogenesis, and decreased progression-free survival.<sup>32</sup> Preclinical models provide support for the notion that VEGF is a valid target for therapy in NETs.<sup>33</sup> Numerous inhibitors have been approved for other indications, including the anti-VEGF antibody, bevacizumab, and the oral VEGF receptor tyrosine kinase inhibitors (TKIs), sunitinib, sorafenib, and pazopanib. Sunitinib, an oral inhibitor of c-KIT, VEGFR-, and PDGFR-signaling, was recently approved for use in progressive pancNETs based on improved progression-free survival.<sup>6</sup> The results in pancNETs are encouraging, and underscore the potential value of the VEGF pathway as a therapeutic target in carcinoid.

In a randomized phase II study by Yao et al.,<sup>34</sup> 44 patients with advanced carcinoid received 18 weeks of bevacizumab or pegylated interferon alpha-2b. All patients were on a stable dose of octreotide. Up-front bevacizumab was associated with a higher response rate (18% vs. 0%), reduction of tumor blood flow by functional CT, and improved progression-free survival at 18 weeks compared with the interferon arm. These results prompted an ongoing phase III trial in patients with high-risk/poor-prognosis carcinoid (SWOG 0518; Table 2). Pilot studies of bevacizumab combined with chemotherapy, RAD001, or other agents have been performed, but no combination regimen has proven efficacy in NETs.<sup>35,36</sup>

The activity of several different TKIs in NETs has also been evaluated in phase II trials (Table 3),

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with results consistently showing low radiographic response rates ( $\leq 10\%$ ) in patients with carcinoid tumors.<sup>7,37</sup> Despite the lack of significant tumor shrinkage, the fact that disease stabilization is observed (6-month progression-free survival ranging from 40%–73% across studies) suggests a potential cytostatic effect. Enrollment to the carcinoid stratum of a phase II trial of sunitinib was stopped because of insufficient evidence of radiographic response after the first stage.<sup>7</sup> In retrospect, 82.9% of patients with carcinoid tumors experienced stable disease and 43.9% of patients showed at least some degree of tumor shrinkage (median time to progression, 10.2 months). The results hint at underlying antitumor activity, despite the fact that the prespecified radiographic response rate was not met.

Collectively, the data suggest that disease stabilization (e.g., progression-free survival) may be a better end point than radiographic response when evaluating VEGF inhibitors in carcinoid. However, because the disease has the potential to progress slowly (e.g., median progression-free survival of 6–9 months in untreated patients),<sup>10</sup> progression-free survival data should be interpreted with caution in the absence of adequate controls. The use of a control arm and the requirement for radiographic progression at baseline may improve one's ability to assess antitumor activity when progression-free survival is the primary end point.<sup>5</sup> At a minimum, stable disease ( $< 20\%$  growth according to RECIST criteria) will be a more convincing indicator of drug activity in carcinoid if the study population is experiencing progression at baseline.

**Table 2 Selected Current Trials of Novel Agents/Combinations in Carcinoid Tumors**

Regimen	Phase	Planned Enrollment	Target	Primary End Point
Octreotide LAR + bevacizumab or IFN (SWOG S0518)	III	400	VEGF, SST receptor, IFN	PFS
Everolimus vs. placebo (RADIANT-4 <sup>a</sup> )	III	279	mTOR	PFS
Bevacizumab + everolimus	II	41	VEGF, mTOR	Change in tumor blood flow on CT
Capecitabine and streptozocin +/- cisplatin	II	84	Chemotherapy	ORR
LX1606	II	16	Tryptophan hydroxylase inhibitor	Symptom control
AMG 479	II	60	IGF-1R	Objective response rate
Panitumumab	II	20	EGFR	Objective response rate, symptom control
Cabozantinib	II	70	Met, VEGFR-2	ORR
Axitinib	II	30	VEGFR-1, -2, -3; PDGFR; cKIT	PFS
AMG 706 + octreotide LAR	II	44	VEGFR-1, -2, -3; PDGFR; cKIT; SST receptor	TTP, PFS
MK-0646	II	25	IGF-1R	ORR
Pazopanib	II	60	VEGFR-1, -2, -3; PDGFR; cKIT	ORR
Everolimus + erlotinib	II	44	mTOR, EGFR	ORR
MK-2206	II	8	AKT	ORR
Cixutumumab, everolimus, octreotide	I	27	IGF-1R, SST, mTOR	Safety profile, dose limiting toxicity

Abbreviations: EGFR, epidermal growth factor receptor; IFN, interferon; IGF-1R, insulin-like growth factor 1 receptor; LAR, long-acting release; mTOR, mammalian target of rapamycin; ORR, overall response rate; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; SST, somatostatin; TTP, time to progression; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

<sup>a</sup>Not yet open for participant recruitment (ClinicalTrials.gov identifier: NCT01524783).

Source: ClinicalTrials.gov

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**Table 3 Summary of Results of Clinical Trials With VEGF/mTOR Pathway Inhibitors in Carcinoid Tumors**

Regimen	Target(s)	Subjects	Radiographic Response Rate (%)	Median TTP or PFS	Reference
<i>VEGF Pathway Inhibitors</i>					
Bevacizumab (vs. IFN)	VEGF	22	18 (0 in IFN arm)	66 wk (PFS)	Yao et al., <sup>34</sup> 2008
Sunitinib	VEGFR-1, -2, -3; PDGFR- $\alpha$ and - $\beta$ ; KIT; RET; CSF-1R; FLT3	41	2	10.2 mo (TTP)	Kulke et al., <sup>7</sup> 2008
Sorafenib	VEGFR, PDGFR, Braf	50	10	7.8 mo (PFS)	Hobday et al., <sup>50</sup> 2007
Pazopanib	VEGFR-1, -2, -3; PDGF- $\alpha$ and - $\beta$ ; and c-kit	22	0	12.7 mo (PFS)	Phan et al., <sup>37</sup> 2010
<i>mTOR Inhibitors</i>					
Everolimus (with octreotide LAR)	mTOR	30	22	60 wk (PFS)	Yao et al., <sup>8</sup> 2011
Temsirolimus	mTOR	21	5	6.0 mo (TTP)	Duran et al., <sup>51</sup> 2006
Everolimus + octreotide LAR vs. placebo + octreotide LAR (RADIANT-2)	mTOR, SST receptor	429	2.4 (everolimus) vs. 1.9 (placebo)	16.4 vs. 11.3 mo (PFS)	Pavel et al., <sup>9</sup> 2011

Abbreviations: IFN, interferon; LAR, long-acting release; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; SST, somatostatin; TTP, time to progression; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

### mTOR Pathway Inhibitors

The results of several recent studies suggest that mTOR is also an attractive target in NETs and may be important in carcinoid (Table 3).<sup>38</sup> The mTOR pathway lies at the center of a complex network of growth factor pathways active in NETs, including the VEGF and insulin-like growth factor 1 (IGF-1) signaling pathways.<sup>39</sup> An analysis of primary pancNETs by Misigaglia et al.<sup>40</sup> revealed downregulation of phosphatase and tensin homolog (PTEN) and tuberous sclerosis-2 (TSC2) products, both of which are key inhibitors of the mTOR pathway. The precise mechanisms underlying the alterations of PTEN and TSC2 activity are unclear, but inactivating mutations have been identified in a subset of patients.<sup>40</sup> In well-differentiated carcinoid tumors, mTOR pathway components are frequently activated via hyperphosphorylation; similar activation profiles were not identified in poorly differentiated tumors.<sup>41,42</sup> Interestingly, activation of the mTOR pathway was strongly correlated with SST receptor expression in one such study.<sup>41</sup>

Similar to sunitinib, treatment with everolimus (an oral inhibitor of mTOR/TORC1, also known as RAD001) improves progression-free survival in patients with progressive pancNET (4.6 months with placebo vs. 11.0 months with RAD001; hazard ratio [HR], 0.35; log-rank  $P < .0001$ ).<sup>8</sup> However, the benefits of everolimus in carcinoid are less clear. In the RADIANT-2 trial, 429 patients with a history of symptoms attributed to carcinoid syndrome and evidence for radiographic progression within 12 months were randomized to receive either everolimus plus octreotide LAR or placebo plus octreotide LAR.<sup>7</sup> The primary end point of the study was progression-free survival through adjudicated central review (which was not performed in real-time). Although a progression-free survival benefit in favor of everolimus was seen (HR, 0.77;  $P = .026$ ), the predefined statistical boundary ( $P = .0246$ ) was not met.<sup>5,9</sup> Importantly, the discordance between the central and investigator (local) review resulted in several patients being censored for the final analy-

sis, leading to a loss of events and loss of statistical power for the primary end point. No impact on overall survival was noted (crossover from placebo to everolimus was allowed).

Everolimus is not approved for use in carcinoid, although additional trials with everolimus and related agents are ongoing and/or planned (including trials with everolimus combinations and TORC1/2 inhibitors). RADIANT-4 is slated to assess the activity of single-agent everolimus in nonfunctional tumors of gastrointestinal or lung origin in the context of a randomized phase III placebo-controlled study (ClinicalTrials.gov identifier: NCT01524783). Importantly, the current NCCN Guidelines for Neuroendocrine Tumors include everolimus as a category 3 recommendation, recognizing the lack of available therapies in this disease (available in this issue; to view the most recent version, visit NCCN.org).

### Future Targets/Trials

Numerous new targets have been identified in carcinoid, which could lead to novel single-agent or combination regimens (e.g., with SSTa, VEGF- and/or mTOR-pathway inhibitors).<sup>43,44</sup> Although still in the pilot stages, several agents targeting components of growth factor signaling pathways are under investigation, including AKT, TORC1/2, and IGF-1R (Table 2).<sup>45</sup> In many cases, a rationale for combining agents can be readily identified (e.g., use of an AKT inhibitor to abrogate the feedback activation of the pathway that occurs with an isolated TORC1 inhibitor). Importantly, novel targets are also being explored in the context of symptom management. For example, blocking tryptophan 5-hydroxylase has emerged as a potential means for decreasing serotonin production in patients with carcinoid syndrome.<sup>46</sup> Preliminary results are encouraging, suggesting that future trials are warranted.

### Challenges Related to Therapy Development in Carcinoid

Several barriers exist to identifying novel therapies for carcinoid tumors. Their rarity alone makes studying large numbers of agents and/or combinations difficult. The inherent biologic heterogeneity (e.g., presence or absence of carcinoid syndrome, site of the primary tumor, proliferative index, grade) augments this prob-

lem. Furthermore, although the prevalence of carcinoid tumors is relatively high, not all patients with the disease are appropriate for therapy. With a disease course measured in years, if not decades, attention must be paid to the appropriate timing of intervention. Recent trials have tried to address this problem through restricting eligible patients to those with evidence of radiographic progression.<sup>6,8,9</sup> Additional considerations should include the use of appropriate end points for trials (e.g., considering progression-free survival over response rate) and the incorporation of proper controls (e.g., randomized phase II trials). Studies are also needed to clarify the relationship between site of origin and underlying genetic changes, because this information could lead to the identification of novel targets and further refinements to the selection of patients for systemic therapy.<sup>47,48</sup> Moving forward, advances in molecular classification of carcinoid tumors may enhance the ability to identify patients most likely to benefit from therapy.

Concurrent or prior octreotide use is another potential confounder in carcinoid trials. Having established the fact that octreotide has antitumor activity, investigators must account for SSTa treatment in clinical trials. Common practices include stratification for concurrent octreotide, stratification for prior octreotide, or the requirement of an SSTa in all treatment arms. Octreotide LAR was required in both arms of the RADIANT-2 trial, and 80% of patients had received prior treatment with an SSTa.<sup>9</sup> A subsequent exploratory analysis indicated that octreotide-naïve patients experienced better outcomes than those who had been previously treated, underscoring the need to account for SSTa use in the design of future trials.

A final barrier to identifying agents with antitumor activity stems from the fact that carcinoid tumors can be inherently difficult to image with standard cross-sectional imaging.<sup>49</sup> They can also grow extremely slowly, so that changes in tumor size may only be evident over many months (not weeks).<sup>5,39</sup> Even in the absence of dedicated antitumor therapy, many patients remain without evidence of overt radiographic progression for months. The discordance between the central and investigator reviewer interpretations in the RADIANT-2 study highlighted these challenges and called attention to the problem of informative censoring. In the future, real-time central review or identification of more reliable cri-

teria for assessing response (compared with RECIST 1.1) may help eliminate this issue when evaluating cytostatic agents in carcinoid.<sup>5</sup>

## Summary

Carcinoid tumors are generally slow-growing, and prolonged survival can be expected in most patients with optimal surgical management and symptom control. Octreotide is indicated for the treatment of hormone-related symptoms and delays progression in advanced small bowel carcinoid. Therefore, octreotide LAR is an obvious first choice when considering systemic treatment options for patients with advanced disease.<sup>14</sup> Although often used in other well-differentiated NETs, its therapeutic value outside the setting of small bowel carcinoid has not been established. Cytotoxic chemotherapy and interferon are typically reserved for selected patients with progressive tumors given their limited efficacy and relatively unfavorable side effect profiles. The mTOR inhibitor everolimus is approved for use in pancNETs and showed a trend toward improved progression-free survival in a recent phase III trial in patients with a history of carcinoid syndrome (but is not approved for this indication). As such, there is a serious unmet need for approved systemic treatment options. Additional studies with everolimus (alone and in combination with other agents) are planned or ongoing, as are trials with VEGF inhibitors and other novel agents. Moving forward, trials should be undertaken with careful consideration of efficacy end points, criteria for response assessment, SSTA use, and patient selection (recognizing that carcinoid has the potential to be indolent even in the absence of treatment).

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