# Systemic Treatment in Unresectable Metastatic Well-Differentiated Carcinoid Tumors

## *Consensus Results From a Modified Delphi Process*

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**Objectives:** This study aimed to develop expert consensus for the use of systemic treatments for unresectable metastatic well-differentiated (grade 1–2) carcinoid tumors using the RAND/UCLA modified Delphi process.

**Methods:** After a comprehensive literature review, 404 patient scenarios addressing the use of systemic treatments for carcinoid tumors were constructed. A multidisciplinary panel of 10 physicians assessed the scenarios as appropriate, inappropriate, or uncertain (on a 1–9 scale) or as an area of disagreement before and after an extended discussion of the evidence.

**Results:** Experts were medical and surgical oncologists, interventional radiologists, and gastroenterologists. Among rated scenarios, disagreement decreased from 14% before the meeting to 4% after. Consensus statements about midgut carcinoids included the following: (1) Somatostatin analogs are appropriate as first-line therapy for all patients; (2) In patients with uncontrolled secretory symptoms, it is appropriate to increase the dose/frequency of octreotide long-acting repeatable up to 60 mg every 4 weeks or up to 40 mg every 3 weeks as second-line therapy for refractory carcinoid syndrome. Other options may also be appropriate. Consensus was similar for non–midgut carcinoids.

**Conclusions:** The Delphi process provided a structured methodological approach to assist clinician experts in reaching consensus on the appropriateness of specific medical therapies for the treatment of advanced carcinoid tumors.

**Key Words:** well differentiated, low-grade tumors, intermediate-grade tumors, neuroendocrine carcinomas, neuroendocrine tumors, carcinoid tumors

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Gastrointestinal and pancreatic neuroendocrine tumors (NETs) are rare neoplasms that originate from the secretory cells of the neuroendocrine system and produce peptides and neuroamines causing characteristic hormonal syndromes, including carcinoid syndrome.[1,2] Carcinoid tumors are defined as neuroendocrine neoplasms arising from the aerodigestive tract, whereas pancreatic NETs are thought to originate in the islets of Langerhans. The incidence of NETs in the United States was 5.25 cases per 100,000 people in 2004.[3] Recent analyses have suggested that the diagnosed incidence of NETs is increasing and that the prevalence of individuals with NETs in the United States may exceed 100,000.[3,4]

Carcinoid syndrome is associated with elevated serotonin levels and is characterized by episodic flushing, diarrhea, and right-sided valvular heart disease.[5] Although NETs at any site can produce hormone(s), well-differentiated NETs of the ileum and cecum are most closely associated with classic carcinoid syndrome. Because of their common embryologic origin, these NETs are often described as midgut carcinoids.[5,6]

Neuroendocrine tumors are often classified as well differentiated or poorly differentiated and as low or high grade. Well-differentiated NETs are characterized by organoid arrangements of the tumor cells, with nesting, trabecular, or gyriform patterns.[7] Tumor grade refers to the proliferative capacity of the tumor, and although low-grade NETs are typically indolent, high-grade tumors are aggressive and associated with short survival durations. Generally, well-differentiated NETs can be classified as either low or intermediate grade.[8]

Neuroendocrine tumors can be hormone producing (ie, "functioning") or hormonally silent (ie, "nonfunctioning").[9] Initial symptoms are usually nonspecific, which leads to delayed diagnosis and the frequent presence of metastases at the time of diagnosis.[10] With early diagnosis, surgical resection is often curative, representing traditional first-line therapy.[9,11] However, many patients with NETs are diagnosed with metastatic disease and require medical management to alleviate symptoms and suppress tumor growth.[9]

First-line systemic therapy for NETs often consists of somatostatin analogs (SSAs) such as octreotide or lanreotide. These drugs have an inhibitory effect on secretion of gastrointestinal

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Complete information of the co-authors in the GEPNET Treatment Consensus Panel appears in the Appendix of this article.

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hormones (such as serotonin) and were initially developed to palliate the symptoms of carcinoid syndrome.[12] Accumulating data indicate that SSAs are also capable of inhibiting NET growth.[13–15] The PROMID study, a randomized phase 3 trial, compared octreotide long-acting release (LAR) 30 mg versus placebo in patients with advanced well-differentiated midgut carcinoid tumors. The PROMID study reported a statistically significant improvement in median time to tumor progression from 6 to 14.3 months.[16] It is unclear whether SSAs can inhibit growth of other (non-midgut) NETs. The ongoing CLARINET trial, a randomized study of lanreotide depot versus placebo in nonfunctioning NETs, is designed to address this question.

As yet, there are no standard second-line systemic therapies. Interferon α (IFN-α) is known to be an inhibitor of serotonin secretion.[17,18] Several studies have demonstrated its efficacy in combination with SSAs for palliation of refractory carcinoid syndrome.[19,20] Subsequent randomized clinical studies have investigated whether IFN-α combined with an SSA can prolong overall survival as well as progression-free survival (PFS) compared with SSA monotherapy.[21–23] Two of these relatively underpowered studies demonstrated a trend toward improved overall survival, but the results were not statistically significant. Enthusiasm for IFN-α is tempered by its adverse effect profile, which includes fatigue, myalgia, and depression. Consequently, there continue to be doubts regarding the risk-benefit ratio of IFN-α in patients with progressive carcinoid tumors.

Novel targeted agents have emerged in recent years to provide a number of new treatment options for patients with NETs. Among the most promising biological drugs are inhibitors of mammalian target of rapamycin (mTOR). Somatic mutations in enzymes associated with the mTOR pathway are known to occur in approximately 15% of patients with pancreatic NETs[24]; the frequency of mutations in carcinoid tumors is unknown. In a randomized phase 3 trial, everolimus, an oral mTOR inhibitor, significantly improved PFS among patients with pancreatic NETs.[25] A similar trial in patients with functioning carcinoid tumors (RADIANT 2) met its secondary end point of improved PFS on local investigator assessment.[26] On central radiologic review, however, the statistical significance of this trial was borderline, after adjustment for 2 interim analyses ($P = 0.026$). As a result, the role of everolimus in the management of advanced carcinoid tumors has not been established.

Tumor angiogenesis is also proving to be a promising treatment target in patients with advanced NETs. Sunitinib, an oral tyrosine kinase inhibitor of the vascular endothelial growth factor receptor (among other targets), has been demonstrated to prolong PFS in patients with metastatic pancreatic NETs.[27] Sunitinib has not yet been studied in a randomized clinical trial in patients with metastatic carcinoid tumors. Bevacizumab, a humanized antibody to the vascular endothelial growth factor receptor ligand, was shown to improve the rate of PFS at 18 weeks compared with pegylated IFN-α in a randomized phase 2 study.[28] An ongoing phase 3 study led by the Southwest Oncology Group is comparing bevacizumab to IFN-α in patients with metastatic carcinoid tumors.

Liver-directed therapy is often recommended for patients with progressive hepatic tumors. Cytoreductive surgery is primarily indicated for patients with oligometastases where at least 90% of tumors can be successfully resected or ablated.[29–32] For patients with more diffuse hepatic metastases, transarterial hepatic embolization or transarterial chemoembolization is often performed.[33–36] A newer approach involves embolization of $^{90}$Yttrium embedded in either a resin microsphere (SIR-Spheres; Sirtex Medical Ltd, North Sydney, New South Wales, Australia) or a glass microsphere (TheraSphere; MDS Nordion, Ottawa, Ontario, Canada).[37,38] However, in the absence of prospective randomized trials, it is difficult to compare the relative efficacies and toxicities of various intra-arterial hepatic therapies.[39]

The emergence of new therapies has improved the options available to patients with NETs. However, clinicians are faced with having to make treatment recommendations in the absence of high-quality data comparing the effectiveness of the various treatment options; hence, many management decisions are based on experience and expert recommendations.[39] Several treatment guidelines for NETs have been previously published[10,40–44]; however, sometimes they lack specific guidance that help inform the choice and sequencing of the growing number of treatment options. Systematic methods for group decision making such as the RAND/UCLA modified Delphi process[45–48] have been used successfully in many areas to develop consensus recommendations regarding for treatments when high-quality comparative effectiveness data is not available.

The RAND/UCLA modified Delphi process has demonstrated validity and reliability for assessing the appropriateness, referring to the relative weight of the benefits versus risks, of a wide variety of medical procedures that lack a large evidence base.[45]

Our objective was to use the RAND/UCLA modified Delphi panel process to develop consensus on the use of systemic treatments for unresectable, metastatic, well-differentiated (grade 1–2) carcinoid tumors.

## MATERIALS AND METHODS

### Role of the Funder

Novartis' role was limited to selecting the research company that organized the meeting and determining the topic of the Delphi panel. A steering committee consisting of 3 medical oncologists with experience in NETs (J.R.S., G.A.F., A.B.B.), all of whom were blinded to the funding source. Neither the committee nor the moderator knew the source of the funding. A key feature of the Delphi process is the diversity of the panel with panelists representing different geographic regions and a variety of clinical specialties. The committee selected panelists to achieve this balance. Potential panelists' views on the use of drugs marketed by the funder were not queried, and they were not told of the funding source. The final list of panelists was shared with Novartis, but the steering committee made the selections. An independent moderator, experienced in the Delphi method and also blinded to the funding source (J.L.M.), was selected. The funder paid travel and honoraria for panel members and an independent moderator. The funder did not engage in any discussion about the panel with panelists or the moderator before, during, or after the panel. Novartis had no representatives at the panel meeting. The panel results were quantitatively summarized and shared with the panelists and Novartis, but Novartis did not direct or change these analyses. None of the panelists, steering committee, or the moderator learned the funding source until the present article was completely drafted. Novartis reviewed the article before submission.

### Panelists

The steering committee developed an a priori list of panelist attributes designed to achieve balance. The goal was to include experts on NETs from a diversity of geographic locations, practice settings, and specialties. The specialties considered important were medical and surgical oncology, interventional radiology, gastroenterology, endocrinology, and palliative care. A list of

potential panelists meeting the various criteria was contributed by the steering committee. From this list, the steering committee identified a diverse group of physician experts, who, along with 2 of the steering committee members (J.R.S. and G.A.F.) served as the Delphi panel (panel members listed in Appendix). It was understood that most, but not all, of the desired attributes would be represented on the panel. Ultimately, the single endocrinologist selected was unable to make it to the meeting.

## RAND/UCLA Delphi Panel Method

Cardinal features of the method are as follows[45,48]: (1) anonymity where each panelist rates the appropriateness of a given therapy in a particular scenario anonymously, limiting the ability of a single individual to dominate the meeting; (2) controlled feedback where after the first round of ratings are completed by the panel, panelists review the ratings from the entire group in a face-to-face meeting and discuss areas of disagreement; (3) iteration where multiple rounds of ratings are conducted, allowing panelists to change their minds after discussion; (4) statistical group response where all rated scenarios are analyzed to determine the extent of agreement.

## Developing Patient Scenarios

Researchers trained in the Delphi method (M.S.B. and D.C.), in conjunction with the moderator and steering committee, collected a summary of published evidence on NETs, which was distributed to the experts for review. The initial goal was to address both medical and liver directed therapies, but the group believed there would be inadequate time to address both topics in a single day-long session (the time allocated for the in-person meeting). Therefore, the decision was made to focus exclusively on medical therapy, with the comment that after each line of therapy, surgical or locoregional treatment should be considered. The group developed a list of variables to reflect the range of patient presentations in clinical practice (eg, anatomic site, line of treatment, as well as presence or absence of secretory symptoms) (Table 1). Using this information, 394 patient scenarios were developed. Each scenario describes a set of clinical circumstances in which a physician would need to choose a medical treatment of a NET. These scenarios were reviewed with the steering committee and refined iteratively. (All scenarios are described in Supplemental Digital Content, http://links.lww.com/MPA/A200.)

## Rating of Patient Scenarios and Development of Consensus Statements

For each patient scenario, panelists were asked to rate (on a 1–9 scale) the appropriateness of a given treatment option. An appropriate procedure is one in which the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing, without consideration of cost.[45] A rating of 1 implied that the expected harms greatly outweighed the expected benefits, a rating of 9 indicated that the expected benefits greatly outweighed the expected harms, and a 5 indicated either that the harms and benefits were equal or that the rater was unable to rate the degree of appropriateness for the patient described in the scenario.[45]

Panelists completed a first round of ratings in early October 2011 and subsequently convened on October 18, 2011, in a face-to-face meeting in Minneapolis, MN. At this meeting, the initial survey results were presented to the panelists, and a moderated discussion of areas of agreement and disagreement followed. At the end of the discussion, panelists again rated the appropriateness of clinical management options for each patient scenario. During the discussion, panelists decided to include 10 additional unique patient scenarios in the second round of ratings (ie, appropriateness of treatment with cytotoxic chemotherapy as third-line therapy). The results of this second round of ratings were summarized in the same manner as the first, and these data were summarized by the steering committee into consensus statements about systemic treatments for patients with carcinoid NETs. Panelists and the moderator were blinded to the funding source during the entire Delphi panel process and during the writing of this article. The funder reviewed but did not modify the manuscript.

## Analyses

For every patient scenario, we calculated the median of the 10 panelists' ratings and the absolute deviation from each panelist's rating to the median. Using previously established standards, each scenario was categorized as follows: a median rating of 7 to 9 with no disagreement was classified as

**TABLE 1.** Variables Used to Construct Clinical Patient Scenarios in Carcinoid Tumor Regions

| Variable | Range of Values |
|---|---|
| Anatomic sites of carcinoid tumors | Midgut; non-midgut |
| Line of treatment | Observation; first-line treatment; second-line treatment; third-line treatment |
| Patient's primary problem | Uncontrolled secretary symptoms; uncontrolled tumor-related symptoms, (rapid) radiographic progression; nonrapid radiographic progression; no symptoms and no radiographic progression; no symptoms |
| Postmarker and postscan testing status | No progression from previous marker and scan, progression after previous marker and scan |
| Frequency of testing a patient with markers and scans | Every 3 mo, every 6 mo, every 9 mo, every 12 mo |
| Cytoreductive surgery | Optimal cytoreductive surgery, suboptimal cytoreductive surgery, not a candidate for surgery |
| Systemic therapy | Somatostatin analog, everolimus, sunitinib, cytotoxic chemotherapy, IFN-α, temozolomide-containing regimen, streptozotocin-containing regimen |
| Response to lower octreotide LAR dose | Previously responded to a lower dose or frequency, previously did not respond to a lower dose or frequency |
| Octreotide LAR frequency | Every 2 wk, every 3 wk, every 4 wk |
| Octreotide LAR dosing | 30 mg, 40 mg, 60 mg, 90 mg, 120 mg |

**TABLE 2.** Number of Indications Scored as ''Inappropriate,'' ''Uncertain,'' ''Appropriate,'' or as ''Disagreement'' by Carcinoid Tumor Region

| | First Round Results | | | | Second Round Results | | | |
|---|---|---|---|---|---|---|---|---|
| Agreement | Frequency | Percentage | Cumulative Frequency | Cumulative Percentage | Frequency | Percentage | Cumulative Frequency | Cumulative Percentage |
| Unresectable metastatic well-differentiated carcinoid tumor indications | | | | | | | | |
| Inappropriate | 147 | 37.3 | 147 | 37.3 | 184 | 45.5 | 184 | 45.5 |
| Uncertain | 119 | 30.2 | 266 | 67.5 | 129 | 31.9 | 313 | 77.5 |
| Appropriate | 73 | 18.5 | 339 | 86.0 | 76 | 18.8 | 389 | 96.3 |
| Disagreement | 55 | 14.0 | 394 | 100 | 15 | 3.7 | 404 | 100 |
| Unresectable metastatic well-differentiated midgut carcinoid tumor indications | | | | | | | | |
| Inappropriate | 78 | 39.6 | 78 | 39.6 | 99 | 49.0 | 99 | 49.0 |
| Uncertain | 64 | 32.5 | 142 | 72.1 | 60 | 29.7 | 159 | 78.7 |
| Appropriate | 32 | 16.2 | 174 | 88.3 | 34 | 16.8 | 193 | 95.5 |
| Disagreement | 23 | 11.7 | 197 | 100 | 9 | 4.5 | 202 | 100 |
| Unresectable metastatic well-differentiated non–midgut carcinoid tumor indications | | | | | | | | |
| Inappropriate | 69 | 35.0 | 69 | 35.0 | 85 | 42.1 | 85 | 42.1 |
| Uncertain | 55 | 27.9 | 124 | 62.9 | 69 | 34.2 | 154 | 76.2 |
| Appropriate | 41 | 20.8 | 165 | 83.8 | 42 | 20.8 | 196 | 97.0 |
| Disagreement | 32 | 16.2 | 197 | 100 | 6 | 3.0 | 202 | 100 |

appropriate; a median rating of 1 to 3 with no disagreement was classified as inappropriate; and a median rating of 4 to 6 with no disagreement was classified as uncertain. Disagreement was defined as more than 2 responses of 1 to 3 and more than 2 of 7 to 9. The appropriateness classifications (eg, inappropriate, uncertain, appropriate, and disagreement) and summary statistics (ie, medians and absolute deviations) were summarized for both the first and second rounds of survey responses. All data and statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

## RESULTS

### Panelist Demographics

The 10 panelists had a mean age of 50.4 years and included members from the Northeast, Midwest, South, and West regions of the United States. Specialties represented included medical and surgical oncology, interventional radiology, and gastroenterology. Panelists had practiced for a mean of 15.5 years (range, 6–33 years), and an average of 49% of their time was spent seeing patients (range, 15%–60%), with 30% to 100% of that time spent caring for NET patients. All panelists were part of academic practices. Five of the panelists were previously involved with the development of other NET treatment guidelines (eg, North America Neuroendocrine Tumor Society and National Comprehensive Cancer Network [NCCN]).

### Consensus Results

Panelists rated 394 scenarios in the first round and 404 scenarios in the second round; the scenarios in each round were divided into 2 sections based on anatomic site: unresectable midgut and non–midgut carcinoid tumors.

In the first round of ratings (Table 2), 37% (147 scenarios) were rated inappropriate, 30% (119) uncertain, and 19% (73) appropriate. After extensive face-to-face discussion of areas of agreement and disagreement, in the second round of ratings, 46% (184 scenarios) were rated inappropriate, 32% (129) uncertain, and 19% (76) appropriate. The proportion on which there was disagreement decreased from 14% (55 scenarios) before the meeting to 4% (15) after the meeting. Average median rating was 3.6 for midgut and 3.9 for non-midgut, and the average distance from median was 1.0 for midgut and 0.9 for non-midgut NETs (Table 3).

### Unresectable Midgut NETs

Panelists rated 202 scenarios in unresectable midgut NETs. The proportion for which there was disagreement decreased

**TABLE 3.** Average Panel Median Rating and Absolute Deviation (ie, Distance) From Every Panelist's Rating to the Median for the Particular Scenario by Carcinoid Tumor Region

| | First Round Results | | | | | Second Round Results | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | n | Mean | SD | Minimum | Maximum | n | Mean | SD | Minimum | Maximum |
| Unresectable metastatic well-differentiated midgut carcinoid tumor indications | | | | | | | | | | |
| Median | 197 | 4.0 | 2.4 | 1.0 | 9.0 | 202 | 3.6 | 2.5 | 1.0 | 9.0 |
| Absolute deviation | 197 | 1.5 | 0.6 | 0.0 | 3.1 | 202 | 1.0 | 0.6 | 0.0 | 2.5 |
| Unresectable metastatic well-differentiated non–midgut carcinoid tumor indications | | | | | | | | | | |
| Median | 197 | 4.1 | 2.4 | 1.0 | 9.0 | 202 | 3.9 | 2.5 | 1.0 | 9.0 |
| Absolute deviation | 197 | 1.5 | 0.6 | 0.0 | 3.0 | 202 | 0.9 | 0.5 | 0.0 | 2.1 |

from 12% (23 scenarios) before the meeting to 5% (9) after. In the second round, 49% (99 scenarios) were rated inappropriate, 30% (60) were uncertain, and 17% (34) were appropriate (Table 2). If a particular systemic treatment was considered appropriate for an earlier line of therapy, it was assumed to be appropriate for the next line of therapy if it had not been used before. A summary of interventions rated "appropriate" in the management of midgut NETs is as follows:

1. Observation without therapy

Observation may be appropriate for patients with no symptoms and low-volume radiographically stable disease (median rating, 7.5). For patients with no progression from previous tests, markers and scans may be obtained every 6 to 9 months (median rating for 6 months, 7; for 9 months, 5); for patients with progression after previous tests, an appropriate interval is 3 to 6 months (median rating for 3 months, 8.5; for 6 months, 5.5).

2. First-line systemic therapy

Somatostatin analogs are appropriate as first-line therapy for patients with uncontrolled secretory symptoms (functional tumors) (median rating, 9) and uncontrolled tumor-related symptoms (nonfunctional tumors) (median rating, 8.5–9.0). Everolimus may be considered for patients who are symptomatic because of large tumor burden (median rating, 4–5).

3. Second-line systemic therapy

In patients with uncontrolled secretory symptoms, increasing the dose/frequency of an SSA is appropriate, particularly among patients who had previously responded to a lower dose/frequency (median rating, 9). The panel considered dose escalations of octreotide LAR up to 60 mg every 4 weeks or up to 40 mg every 3 weeks to be reasonable adjustments for refractory carcinoid syndrome (median rating, 7). Increasing the dose/frequency of SSA may be considered for patients with radiographic progression, particularly those whose disease was previously stabilized at a lower dose. The panel considered an increase in dose/frequency up to 40 mg every 3 or 4 weeks to be reasonable (median rating, 6–7). There is a lack of evidence that increasing the dose/frequency of SSAs slows radiographic progression.

Everolimus or IFN-α can be considered as second-line agent in patients who had rapid radiographic progression (median rating, 7) or had uncontrolled tumor-related symptoms (median rating, 7) while receiving an SSA. In patients with carcinoid syndrome, SSA treatment should be continued beyond the first line.

Although ratings indicated uncertainty, cytotoxic chemotherapy can be considered in cases of unusually rapid radiographic progression (median rating, 5) or uncontrolled tumor-related symptoms (median rating, 4) (consider also confirming the pathologic diagnosis, including mitotic index). The panel did not endorse any particular cytotoxic drug or regimen.

4. Third-line systemic therapy

Although randomized data are lacking, accumulating evidence suggests that antiangiogenic therapy may be active in midgut carcinoid tumors. At this time, no particular agent can be specifically recommended.

5. Surgical treatment

Scenarios for surgical treatment were not rated; however, there was consensus that at each stage, surgery or locoregional therapy should be considered in addition to, or instead of, medical treatment.

### Unresectable Non–Midgut NETs (Excluding Pancreatic NETs)

Among 202 rated scenarios in these non–midgut NETs, disagreement decreased from 16% (32 scenarios) before the meeting to 3% (6) after. In the second round, 42% (85 scenarios) were rated inappropriate, 34% (69) were uncertain, and 21% (42) were appropriate (Table 2). If a particular systemic treatment was considered appropriate for an earlier line of therapy, it was assumed to be appropriate for the next line of therapy if it had not been used before. A summary of interventions deemed "appropriate" in the management of non–midgut NETs is as follows:

1. Observation without therapy

Observation may be appropriate for patients with no symptoms and low-volume radiographically stable disease (median rating, 8). For patients with no progression from previous tests, markers and scans may be obtained every 3 to 12 months (median rating for 3 months, 5; for 12 months, 4.5); for patients with progression after previous tests, an appropriate interval is 3 to 6 months (median rating for 3 months, 9; for 6 months, 6).

2. First-line systemic therapy

Treatment with SSAs may be appropriate for patients with secretory symptoms (median rating, 9). Everolimus can be considered for patients with progressive, symptomatic, or high-volume disease (median rating, 5–7). Somatostatin analogs may also be appropriate for patients with nonfunctional tumors who have tumor-related symptoms (median rating, 7–8); however, there are limited data to support their use as antiproliferative agents in non–midgut NETs.

3. Second-line systemic therapy

In patients with uncontrolled secretory symptoms, increasing the dose/frequency of SSAs is appropriate (median rating, 8), particularly among patients who had previously responded to a lower dose. The panel considered dose escalations of octreotide LAR up to 60 mg every 4 weeks (median rating, 7) or up to 40 mg every 3 weeks (median rating, 7) to be reasonable adjustments for refractory carcinoid syndrome. Increasing the dose/frequency of SSAs may be considered in patients with radiographic progression, particularly those whose disease was previously stabilized at a lower dose. The panel considered an increase in dose/frequency up to 40 mg every 3 or 4 weeks to be reasonable (median rating, 4–5.5). There is a lack of evidence that increasing the dose/frequency of SSAs slows radiographic progression.

Everolimus or IFN-α can be considered as second-line agent in patients who progressed radiographically or symptomatically while receiving an SSA. In patients with carcinoid syndrome, treatment with an SSA should be continued beyond the first line.

Cytotoxic chemotherapy can be considered in cases of uncontrolled tumor-related symptoms or radiographic progression (median rating, 7–7.5) consider also confirming the pathologic diagnosis, including mitotic index. The panel did not endorse any particular cytotoxic drug or regimen.

4. Third-line systemic therapy

Although randomized data are lacking, accumulating evidence suggests that antiangiogenic therapy may be active in non–midgut carcinoid tumors. At this time, no particular agent can be specifically recommended.

5. Surgical treatment

Scenarios for surgical treatment were not rated; however, there was consensus that at each stage of therapy, when considering the next line of treatment, surgery or locoregional therapy should be considered.

## DISCUSSION

Providing patients with treatment options that are well grounded in the highest-quality evidence available requires a

synthesis of data. When high-quality comparative data on the effectiveness of treatment are available, formal quantitative approaches can be undertaken. When such data are lacking, expert opinion can be useful. In this study, we used the RAND/UCLA modified Delphi process to systematically derive expert opinion–based consensus statements for the medical management of unresectable metastatic carcinoid tumors.

The National Comprehensive Cancer Institute (NCCN) recently updated guidelines for treatment of NETs (NCCN 2012) and our consensus statements have both differences and similarities with this document. Our process focused solely on medical management, although general recommendations were made to consider surgical or locoregional therapy if appropriate after each phase of medical treatment, whereas the NCCN Guidelines address all areas of management. We used the Delphi method, which uses literature review; expert panelist discussions; and iterative, quantitative, anonymous ratings of specific clinical scenarios to provide a statistical summary of the resultant body of evidence.[46,47] The NCCN uses literature review, multiple rounds of unstructured discussion among expert panelists, and NCCN staff review to develop treatment algorithms (http://www.nccn.org/clinical.asp accessed June 27, 2012). There is substantial overlap between the recommendations from this panel and the NCCN guidelines. Both recommend observation alone or SSA as appropriate first-line management, with observation reserved for patients without symptoms and low disease burden. As second-line medical treatment, the Delphi panel recommends increasing SSA beyond the initial dose, with everolimus and IFN-α as alternatives. As third line, the panel suggests an emerging role for antiangiogenic chemotherapy. In contrast, the NCCN recommends everolimus (and cytotoxic chemotherapy if no other options are available) as medical treatment beyond first line and gives no specific direction about the sequence of further therapies.

The Delphi process allowed us to evaluate the appropriateness of a range of medical therapies for 404 distinct patient scenarios. The consensus statements produced in this study address specific scenarios not covered in other guidelines.[10,40–44] For example, the consensus statement on the appropriateness of frequency of testing was based on previous progression, whereas the recommendation for testing interval in the NCCN guidelines does not distinguish patients based on tumor behavior. Similarly, the panel developed consensus statements on higher and more frequent doses of SSA, depending on the results of previous treatment, whereas the NCCN guidelines are silent on this topic.

The treatment consensus statements described in this article were obtained using a well-established and systematic methodology that has been shown to capture group decision making in a valid, reproducible, and reliable way.[46,47] The panel experts represented a variety of multidisciplinary physician specialists across the United States who typically treat patients with carcinoid tumors and have contributed to the development of other treatment guidelines in NETs. Despite the paucity of evidence in some areas, we were able to obtain consensus statements with relatively low levels of disagreement.[49–54] The result is a detailed consensus statement that can inform the development of treatment guidelines and may also guide clinicians in their clinical care decision making.

The statements reflect the panelists' expert assessment of the medical literature and clinical judgment and, as such, do not necessarily follow the Food and Drug Administration–approved indication for the medications discussed. For example, everolimus is approved for adults with unresectable, locally advanced, or metastatic pancreatic NETs rather than the treatment of midgut or non–midgut carcinoids. Panelists considered evidence such as that presented in the RADIANT 2 trial in their deliberations.[26] Similarly, the recommendation for higher or more frequent doses of SSA is consistent with published evidence that dose escalation of long-acting octreotide acetate is well tolerated and can delay or spare potentially toxic systematic therapies, as compared with conventional dosing, in gastroenteropancreatic NETs.[55] Because cancer treatment evolves rapidly, many guidelines, including those developed by the NCCN, do not limit themselves to recommending treatments for the Food and Drug Administration–approved indication or limited to the approved dose.[10,40–44]

The study used experts to integrate all available evidence. A limitation is that the evidence derives from data beyond randomized, controlled trials. Although randomized, controlled trials are the criterion standard for evidence-based medicine, they cannot provide evidence at a level of detail that can be applied to the wide range of patients seen in everyday clinical practice.[45] Thus, this type of aggregation of evidence across trials is often required and can be valuable when combined with expert clinician review and incorporating real-world practice experience.

## CONCLUSIONS

The RAND/UCLA modified Delphi process is a useful methodology to inform physician decision making and assist in the development of treatment guidelines. The process permitted us to systematically combine and quantify available scientific evidence with the collective judgment of experts to produce consensus statements on the appropriateness of systemic therapies for the treatment of carcinoid tumors.[45] It is not surprising that statements derived using this approach are quite similar to those in the NCCN guidelines, given that both derive from the same body of evidence. However, the increased specificity of the panel-based statements may provide additional value to clinicians engaged in the daily challenge of applying existing evidence to clinical situations. As additional therapies for carcinoid tumors emerge, the Delphi methodology may be useful for evaluating these therapies and for extending the specificity of clinical treatment guidelines.

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## APPENDIX

Gastroenteropancreatic Neuroendocrine Tumors (GEPNET) Treatment Consensus Panel: Author Name, Specialty, and Affiliations (in Alphabetical Order)

| Name, Degrees | Specialty | Affiliations |
|---|---|---|
| Lowell B. Anthony, MD, FACP | Medical oncology | Department of Internal Medicine, Division of Medical Oncology, University of Kentucky Markey Cancer Center, Lexington, KY |
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| George A. Fisher, MD, PhD | Medical oncology | Department of Medicine, Division of Oncology, Stanford University Medical Center, Stanford, CA |
| John F. Gibbs, MD | Surgical oncology | Department of Surgery, State University of New York at Buffalo, Buffalo, NY |
| Edward Greeno, MD | Medical oncology | Department of Medicine, Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN |
| Renuka V. Iyer, MD | Medical oncology | Department of Medical Oncology, Roswell Park Cancer Institute, Buffalo, NY |
| Michelle K. Kim, MD, MSc | Gastroenterology | Department of Medicine, Gastroenterology Mount Sinai School of Medicine, New York, NY |
| William J. Maples, MD | Medical oncology | Mission Health System, Asheville, NC |
| Philip. A. Philip, MD, PhD, FRCP | Medical oncology | Department of Oncology, Karmanos Cancer Institute, Detroit, MI |
| Jonathan R. Strosberg, MD | Medical oncology | Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL |
| Edward M. Wolin, MD | Medical oncology | Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA |