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SPECIAL ARTICLE

Future Directions in the Treatment of Neuroendocrine Tumors: Consensus Report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting

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ABSTRACT

Neuroendocrine tumors (NETs) arise from a variety of anatomic sites and share the capacity for production of hormones and vasoactive peptides. Because of their perceived rarity, NETs have not historically been a focus of rigorous clinical research. However, the diagnosed incidence of NETs has been increasing, and the estimated prevalence in the United States exceeds 100,000 individuals. The recent completion of several phase III studies, including those evaluating octreotide, sunitinib, and everolimus, has demonstrated that rigorous evaluation of novel agents in this disease is both feasible and can lead to practice-changing outcomes. The NET Task Force of the National Cancer Institute GI Steering Committee convened a clinical trials planning meeting to identify key unmet needs, develop appropriate study end points, standardize clinical trial inclusion criteria, and formulate priorities for future NET studies for the US cooperative group program. Emphasis was placed on the development of well-designed clinical trials with clearly defined efficacy criteria. Key recommendations include the evaluation of pancreatic NET separately from NETs of other sites and the exclusion of patients with poorly differentiated histologies from trials focused on low-grade histologies. Studies evaluating novel agents for the control of hormonal syndromes should avoid somatostatin analog washout periods when possible and should include quality-of-life end points. Because of the observed long survival after progression of many patients, progression-free survival is recommended as a feasible and relevant primary end point for both phase III studies and phase II studies where a delay in progression is expected in the absence of radiologic responses.

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INTRODUCTION

Neuroendocrine tumors (NETs) arise in diverse anatomic locations and are classically associated with symptoms resulting from the secretion of hormones or vasoactive peptides into the systemic circulation. Historically perceived as exceedingly rare, NETs have recently been shown to be more common than previously suspected. In an analysis of the Surveillance, Epidemiology, and End Results database, the estimated annual incidence of carcinoid tumors in 2004 was 5.25 per 100,000 population, and the 29-year limited duration prevalence in the United States was estimated to exceed 100,000 individuals.[1]

Surgical resection alone is often curative in patients with early-stage disease. However, patients with advanced disease may suffer from complications of uncontrolled hormone secretion and usually succumb to fatal complications caused by secreted hormones or tumor progression. The NET Task Force of the National Cancer Institute GI Steering Committee was created to encourage clinical and translational research in NETs and to facilitate the development and coordination of relevant clinical trials in this disease. As part of this effort, the task force convened a clinical trials planning meeting to identify key unmet needs and to formulate priorities for future NET studies for the US cooperative group program. Other key meeting objectives included the development of recommendations for appropriate study end points and imaging techniques and standardization of clinical trial inclusion criteria.

Participants in this day and a half meeting included clinical, translational, and laboratory-based investigators in neuroendocrine cancer as well as representatives from the patient advocacy community, pharmaceutical industry, and the National Cancer Institute. The meeting was structured to include brief didactic presentations during an initial half-day session, summarizing recent developments

and current questions in the field. Subsequently, participants participated in breakout sessions where they discussed clinical trial priorities in specific areas. Recommendations from the breakout sessions were then brought back to the larger group for consensus on the second day of the meeting. Ideas and concepts from the meeting were further developed and refined during subsequent meetings of the NET Task Force, leading to the key recommendations (Table 1) outlined in this article. This report is structured to address key issues for clinical trials in NETs by stating the key recommendations followed by a summary of the deliberations leading to the recommendation.

Table 1. Key Recommendations From the NET Clinical Trials Planning Meeting

Recommendation
Classification of neuroendocrine tumors
Carcinoid tumors and pancreatic NETs should be examined separately in clinical trials. Stratification of carcinoid tumors by primary site should be considered in larger, randomized studies.
The American Joint Committee on Cancer staging system for NETs should be used as the staging standard in clinical trials.
A formal assessment of grade or differentiation should be required for clinical trial enrollment; well-differentiated and poorly differentiated NETs should be studied separately.
Although large-scale, prospective studies specifically enrolling patients with specific molecular subtypes are not currently indicated, useful information regarding the activity of specific drugs in molecular subtypes can be gained from retrospective analyses of tumors and annotated clinical data.
Adjuvant trials in patients with resected NETs
Adjuvant therapy is not currently indicated in patients with completely resected NETs. Additional data regarding time to recurrence and overall survival of patients with resected NETs will be necessary to design adequately powered studies in this setting.
Evaluation of therapeutic agents for carcinoid syndrome
Refractory carcinoid syndrome is an unmet medical need. The successful clinical development of new agents for this indication has proven challenging because of difficulty in selecting appropriate entry criteria and clinical trial end points.
Use of a somatostatin washout in trials of novel agents for carcinoid syndrome should be avoided when possible.
A symptom severity index based on a composite score of flushing and diarrhea would provide an appropriate measure of patient-reported outcomes and could be used as an end point in trials of novel agents for carcinoid syndrome. Randomized, placebo-controlled studies incorporating such an index, in conjunction with more general quality-of-life measures, are recommended for the investigation of novel agents in this indication.
Hepatic-directed therapy
Because of the highly selected nature of patients undergoing either hepatic resection or orthotopic liver transplantation, randomized controlled trials evaluating patient outcomes with these treatment modalities would likely be difficult to perform.
Hepatic artery embolization is commonly performed in patients with unresectable, hepatic-predominant disease. A variety of techniques, including bland embolization, chemoembolization, and radioembolization, are currently used but have never been compared in a controlled setting. Randomized phase II trials exploring the relative efficacy and toxicity of these techniques are recommended.
Peptide receptor radiotherapy
Randomized phase III studies comparing peptide receptor radiotherapy to standard systemic therapy are warranted.
Clinical trials of novel systemic agents for advanced NET
Study design and end points
Overall survival is not a practical end point for most advanced NET studies. PFS is recommended as the primary end point for phase III studies, as well as for phase II studies where a delay in progression is expected in the absence of significant radiologically defined tumor responses.
Randomized phase II studies, requiring disease progression before study entry and using PFS as a primary end point, should be used to screen novel agents in NETs.
Randomized trials in NETs investigating novel therapies need to account for the potential antitumor activity of somatostatin analogs.
Imaging considerations
Cross-sectional anatomic imaging of the abdomen should be performed with either multiphasic CT or MRI.
Study baseline cross-sectional anatomic imaging should include chest, abdomen, pelvis, and any additional known sites of disease.
Somatostatin scintigraphy should not be used to assess tumor response in clinical trials.
Incorporation of biomarkers
Serial measurements of plasma chromogranin A should be incorporated into prospective clinical trials.
Assessment of tumoral O^6-methylguanine–DNA methyltransferase expression is warranted in future studies of alkylating agents.
Imaging with perfusion CT should be considered in future studies of antiangiogenic agents.
Specific recommendations for ongoing and future studies
Advanced carcinoid tumors
Successful completion of the ongoing phase III study of bevacizumab versus interferon in patients with advanced carcinoid tumors (SWOG S0518) may define the role of bevacizumab in patients with advanced carcinoid tumors.
The results of a phase III study of everolimus plus octreotide versus octreotide alone may define the role of everolimus in patients with advanced carcinoid tumors.
Randomized studies of tyrosine kinase inhibitors targeting VEGFR should be considered in patients with advanced carcinoid tumors.
Advanced pancreatic neuroendocrine tumors
Sunitinib and other tyrosine kinase inhibitors targeting VEGFR are active in patients with advanced pancreatic NETs.
Everolimus is active in patients with advanced pancreatic NETs. A randomized phase II study comparing everolimus alone with the combination of everolimus plus bevacizumab in patients with pancreatic NET will build on the recent observation of activity with everolimus alone and may help define the potential additive activity of bevacizumab in this setting.
In contrast to carcinoid tumors, there is now substantial evidence that pancreatic NETs are sensitive to alkylating agents. Randomized studies assessing the relative efficacy of streptozocin or temozolomide and assessing the efficacy of temozolomide alone or a temozolomide-based doublet are warranted.

Abbreviations: NET, neuroendocrine tumor; PFS, progression-free survival; CT, computed tomography; MRI, magnetic resonance imaging; SWOG, Southwest Oncology Group; VEGFR, vascular endothelial growth factor receptor.

CLASSIFICATION OF NET

Classification by Site of Origin

Carcinoid tumors and pancreatic NETs should be examined separately in clinical trials. Although carcinoid and pancreatic NETs often have nearly identical characteristics on routine histologic evaluation, it is increasingly clear that these two tumor subtypes have different biology, respond differently to therapeutic agents, and should be evaluated as separate entities in clinical trials. Carcinoid tumors themselves may differ in their response to treatment depending on their site of origin, most commonly the small bowel, appendix, rectum, stomach, and lungs.[1,2] Individual clinical trials targeting specific carcinoid anatomic subgroups may not be feasible as a result of limited patient numbers. However, stratification of carcinoid tumors by primary site should be considered in larger randomized studies.

Classification by Tumor Stage

The American Joint Committee on Cancer staging system for NETs should be used as the staging standard in clinical trials. Several organizations, including the European Neuroendocrine Tumor Society[3,4] and the American Joint Committee on Cancer (AJCC), have proposed staging systems for NETs using the commonly accepted TNM notation.[5] Although these two staging systems are similar for tumors arising in the luminal gut, they differ for earlier stage tumors arising in the pancreas or appendix. In pancreatic NETs, for example, the European Neuroendocrine Tumor Society system incorporates tumor diameter in its assessment of T stage, whereas the AJCC system incorporates factors determining tumor resectability. Both systems have been clinically validated and are nearly identical in their definitions of stage IV disease. Because the AJCC system has been widely adopted for other malignancies in North America, use of the AJCC system is also recommended for NETs to avoid confusion and to enhance consistency in clinical trials.

Histologic Classification

A formal assessment of grade or differentiation should be required for clinical trial enrollment; well-differentiated and poorly differentiated NETs should be studied separately. A number of often conflicting histologic and anatomic classification systems have been proposed to subclassify NETs (Table 2). These systems are inconsistent in their specific criteria for tumor grading, their reporting of mitotic count, and their requirements for measurement of proliferation index (Ki-67). Despite these differences, all commonly used classification systems reflect the basic observation that NETs comprise a spectrum of malignancies, ranging from more indolent, well-differentiated tumors to far more aggressive poorly differentiated ones. As a general rule, tumors with a high grade (grade 3), a mitotic count of more than 20 per 10 high-powered fields, or a Ki-67 proliferation index of more than 20% represent highly aggressive malignancies that should be evaluated apart from more classic carcinoid, islet cell, or well-differentiated (low- to intermediate-grade) NETs. In large multicenter studies, central pathology review or pathology auditing would enhance consistency in pathology reporting and ensure enrollment of patients with appropriate tumor histologies.

Molecular Classification

Although large-scale, prospective studies enrolling patients with specific molecular subtypes are not currently feasible, useful information regarding the activity of specific drugs in molecular subtypes can be gained from retrospective analyses of tumors and annotated clinical data. NETs are associated with a number of inherited syndromes associated with mutations in well-studied oncogenes and tumor suppressor genes. These syndromes include multiple endocrine neoplasia types 1 and 2, von Hippel-Lindau disease, and tuberous sclerosis.[7] Patients with NET with such syndromes may represent subgroups particularly responsive to novel therapies targeting the underlying genetic defect or pathway. Characteristic allelic imbalances have also been observed in sporadic carcinoid and pancreatic NETs. Loss of chromosome 18, for example, seems to be a characteristic feature of small bowel carcinoid tumors.[8-10] A more detailed understanding of the molecular aberrations in NETs will be increasingly relevant as additional molecularly targeted therapies are developed. The rigorous analysis of molecular aberrations and clinical outcomes in annotated biospecimens would

Table 2. Nomenclature and Classification of Neuroendocrine Tumors

Differentiation and Grade	Mitotic Count (/10 HPF)*	Ki-67 Index (%)†	Traditional Classification	ENETS/WHO Classification	Moran et al[6]
Well differentiated					
Low grade (grade 1)	< 2	≤ 2	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, grade 1	Neuroendocrine carcinoma, grade 1
Intermediate grade (grade 2)	2-20	3-20	Carcinoid, atypical carcinoid,‡ islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, grade 2	Neuroendocrine carcinoma, grade 2
Poorly differentiated					
High grade (grade 3)	> 20	> 20	Small-cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell	Neuroendocrine carcinoma, grade 3, small cell
			Large-cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell	Neuroendocrine carcinoma, grade 3, large cell

Abbreviations: HPF, high-power field; ENETS, European Neuroendocrine Tumor Society.
*HPF = 2 mm^2; at least 40 fields (at ×40 magnification) were evaluated in areas of highest mitotic density. Cutoff values were taken from American Joint Committee on Cancer staging system (seventh edition).[5]
†MIB1 antibody; percentage of 2,000 tumor cells in areas of highest nuclear labeling. Cutoff values were taken from American Joint Committee on Cancer staging system (seventh edition).[5]
‡The term atypical carcinoid only applies to intermediate-grade neuroendocrine tumor of the lung.

represent a useful and feasible first step in defining clinically relevant molecular subgroups of carcinoid and pancreatic NETs.

ADJUVANT TRIALS IN PATIENTS WITH RESECTED NET

Adjuvant therapy is not currently indicated in patients with completely resected NETs. Additional data regarding time to recurrence and overall survival (OS) of patients with resected NETs will be necessary to design adequately powered studies in this setting. Whenever possible, complete surgical resection with curative intent of the primary tumor should be performed; however, many patients may nevertheless develop disease recurrence. The probability of recurrence may vary depending on the site and the biologic aggressiveness of the tumor. However, the design and completion of definitive studies evaluating adjuvant regimens in patients with fully resected NETs is challenging, and no adequately controlled studies have been performed. A lack of data regarding recurrence rates and median time to tumor recurrence after resection of carcinoid or pancreatic NETs presents a major obstacle to designing studies of appropriate power and duration. The ongoing development of tumor registries and databases should help provide such data, facilitating the development of future adjuvant studies. Analysis of such data should also help identify patient subgroups at particularly high risk of recurrence, for example, patients who have undergone complete resection of hepatic metastases.

EVALUATION OF THERAPEUTIC AGENTS FOR CARCINOID SYNDROME

Refractory carcinoid syndrome is an unmet medical need. Carcinoid syndrome is caused by the secretion of serotonin and other bioactive amines into the systemic circulation and is clinically manifested by flushing, diarrhea, and fibrosis of the right-sided heart valves and intestinal mesentery. Currently available somatostatin analogs including octreotide and lanreotide (the latter approved only for acromegaly in the United States) ameliorate symptoms of carcinoid syndrome.[11,12] Over time, however, patients with carcinoid syndrome may become refractory to somatostatin analogs. A number of novel somatostatin analogs and serotonin synthesis inhibitors are currently undergoing clinical evaluation in patients with refractory carcinoid syndrome. However, the successful clinical development of these agents has proven challenging, in large part because of difficulty in selecting appropriate entry criteria and clinical trial end points for this indication.[13]

Use of a somatostatin washout in trials of novel agents for carcinoid syndrome should be avoided when possible. Prior studies of novel agents for the treatment of carcinoid syndrome have required a somatostatin analog washout period to establish baseline levels of flushing and diarrhea. A requirement for washout periods is a clear deterrent to enrollment for patients and may pose an ethical dilemma for physicians. Such a washout may not be necessary to establish efficacy if study end points are measured at predefined time points (eg, two to three half-lives after the last dose of prestudy medication) after initiation of investigational therapy.

A symptom severity index based on a composite score of flushing and diarrhea would provide an appropriate measure of patient-reported outcomes and could be used as an end point in trials of novel agents for carcinoid syndrome. Randomized, placebo-controlled studies incorporating such an index, in conjunction with more general quality-of-life measures, are recommended for the investigation of novel agents in this indication. The evaluation of flushing and diarrhea as separate end points requires multiple parallel analyses (eg, flushing only, diarrhea only, flushing and diarrhea) and necessitates a greater number of patients because many patients may not have both components of the classic syndrome. Use of a validated symptom severity index based on a composite score of flushing and diarrhea would simplify end point analyses. Additionally, preliminary studies suggest that quality-of-life measures correlate closely with both flushing and diarrhea frequency in patients with carcinoid syndrome.[14] The European Organisation for Research and Treatment of Cancer has recently developed a quality-of-life instrument specifically designed for patients with carcinoid tumors and NETs (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire GI.NET21) that incorporates questions on disease-specific symptoms.[15] Used together with a more general quality-of-life questionnaire, this may be a useful tool in future trials. Randomized, controlled studies of novel agents in patients with hormonal syndrome refractory to somatostatin analogs, using patient-reported outcome measures, are appropriate and should be feasible. Although some agents, including somatostatin analogs, may have effects on both symptom and tumor control, studies focused on symptom relief should in general be clearly differentiated from studies focused primarily on tumor control (discussed later) in light of the different end points and different requirements for trial design.

HEPATIC-DIRECTED THERAPY

Hepatic-directed therapies include hepatic resection, orthotopic liver transplantation (OLT), and hepatic arterial embolization. These techniques are most often used in patients with hepatic-predominant disease to improve symptoms.[16] OLT has been attempted in patients with NET who are not candidates for hepatic resection. Although associated with encouraging 5-year survival rates, OLT has also been associated with relatively high rates of tumor recurrence, and it has no clear role in the routine treatment of patients with NET.[17] Because of the highly selected nature of patients undergoing either hepatic resection or OLT, randomized controlled trials evaluating patient outcomes with these treatment modalities would likely be difficult to perform.

Hepatic artery embolization is commonly performed in patients with unresectable, hepatic-predominant disease. A variety of techniques, including bland embolization, chemoembolization, and radioembolization, are currently used but have never been compared in a controlled setting. Randomized phase II trials exploring the relative efficacy and toxicity of these techniques are recommended. Hepatic artery embolization has been routinely reported to result in both tumor responses and improvement in symptoms. Although the addition of intra-arterial cytotoxic chemotherapy (chemoembolization), as opposed to bland embolization, has been reported to improve outcome for patients with pancreatic NETs, the relative benefit of adding intra-arterial chemotherapy has not been as clearly established in patients with carcinoid tumors.[18] More recent studies have suggested that radioembolization is an effective and potentially less toxic approach in the short term, although this technique has not been

formally compared with either chemoembolization or bland embolization in a prospective fashion.[19,20] Given the logistical challenges of performing randomized studies of these modalities, definitive large-scale randomized phase III studies may not be feasible. However, randomized phase II studies are warranted to shed light on the relative cost, toxicity, and efficacy of newer embolization techniques compared with more standard bland embolization.

PEPTIDE RECEPTOR RADIOTHERAPY

A high prevalence of somatostatin receptor expression among NETs provides the rationale for peptide receptor–targeted therapy as a treatment modality in patients with inoperable or metastatic disease. The most frequently used radionuclides for targeted radiotherapy in NETs are indium (^{111}In), yttrium (^{90}Y), and lutetium (^{177}Lu), which differ from one another in terms of emitted particles, particle energy, and tissue penetration.[21,22] Both the yttrium- and the lutetium-labeled compounds have demonstrated promising activity in patients with NET.[23-25] However, many reported studies have had suboptimal methodology, lacked intent-to-treat analyses, and used nonstandard end point definitions. Furthermore, no studies have compared the relative efficacy and toxicity of ^{177}Lu-DOTA-Tyr^3-octreotate and ^{90}Y-DOTA-Tyr^3-octreotide.

Randomized phase III studies comparing peptide receptor radiotherapy with standard systemic therapy are warranted. Patients enrolling onto such studies should be selected based on somatostatin expression. Recent data suggesting that octreotide alone has antitumor efficacy in midgut carcinoid tumors make it both feasible and relevant to randomly assign patients prospectively to either radiopeptide therapy or treatment with unlabeled octreotide in midgut tumors and perhaps also in other carcinoid tumors.[26] In pancreatic NETs, appropriate control groups could include unlabeled octreotide or potentially also everolimus, sunitinib, or streptozocin-based chemotherapy.[27-30]

CLINICAL TRIALS OF NOVEL SYSTEMIC AGENTS FOR ADVANCED NET

The unique clinical characteristics of NETs present specific challenges to the design and successful completion of clinical trials. Among these challenges are the selection of appropriate end points, use of reproducible imaging modalities, and incorporation of biomarkers. A number of systemic agents have recently been evaluated for the treatment of advanced NETs. Among the most promising of these therapies are somatostatin analogs, temozolomide, vascular endothelial growth factor (VEGF) pathway inhibitors, and mammalian target of rapamycin (mTOR) inhibitors. The continued rigorous evaluation of these and other promising agents in future trials is encouraged and is likely to lead to significant advances in the treatment of patients with NETs.

Study Design and End Points

OS is not a practical end point for most advanced NET studies. Improving OS is clearly a primary goal in developing novel agents. In selected patients with NETs, particularly those with highly refractory disease or for whom survival duration is otherwise expected to be limited, trials using OS as a primary end point may be feasible. However, the long survival after progression and the wide variability of salvage regimens in many patients with NETs preclude the use of OS as a practical end point in most studies. For example, in the Placebo-Controlled Prospective Randomized Study on the Antiproliferative Efficacy of Octreotide LAR in Patients With Metastatic Neuroendocrine Midgut Tumors (PROMID), where octreotide was studied in the first-line setting among patients with midgut carcinoid tumors, median survival after progression was estimated to be more than 60 months.[31] In an everolimus study enrolling patients with progressive carcinoid tumors, survival after progression was estimated to be more than 12 months.[32] Similarly, in recently reported studies of sunitinib and everolimus among patients with progressive pancreatic NETs, median survival times after progression were also both greater than 12 months.[27,28] In this situation, use of OS as a primary end point may be complicated by treatment after progression. Postprogression treatment (either from a planned cross-over design using the investigational therapy or with investigator-selected treatment) poses no significant scientific challenges in studies using progression-free survival (PFS) as a primary end point and is attractive from both an ethical and feasibility standpoint. In contrast, if OS is used as a primary end point, the incorporation of cross over may significantly reduce the probability of observing a treatment benefit. OS also tends to require a larger sample size. For example, when the hazard ratio is assumed to be the same for both end points, the time to observe the same number of OS events as PFS events is much longer, requiring either much longer study follow-up or an increased sample size to reach a study conclusion in a shorter time period. Moreover, if the same absolute improvement in PFS is propagated into improvement in OS, the relative effect size in a disease with longer baseline OS would be smaller, translating into a need for a greater number of patients.[33,34]

In general, PFS is recommended as the primary end point for phase III studies, as well as for phase II studies where a delay in progression is expected in the absence of significant radiologically defined tumor responses. Many recent phase II studies of novel agents in NETs have reported low tumor response rates, resulting in a perception that the evaluated agents had little or no antitumor activity in this setting. However, recent randomized studies of octreotide,[31] sunitinib,[28] and everolimus[27] suggest that tumor response rate may not be an optimal marker for antitumor activity in NETs. Although associated with only modest radiologic tumor response rates, treatment with these agents resulted in significant improvements in PFS when compared with placebo or best supportive care in controlled studies.

Using PFS as an end point in NET trials may present its own challenges. Investigator bias is a potential concern, particularly when cross-over designs are used. Blinded trial designs or central review for progression determination can be used to mitigate this concern.[35] Each of these options, however, has its own limitations. Blinded trials may be difficult to conduct when adverse event profiles differ dramatically between the treatment arms. Central review may be logistically difficult and can be particularly challenging in NETs, where imaging characteristics are often highly variable. Significant discrepancies between local and central review have recently been reported in a large randomized trial of everolimus in carcinoid tumors (RAD001 in Advanced Neuroendocrine Tumors [RADIANT] -2). Such discrepancies can contribute to the phenomenon of informative censoring, which

may significantly reduce the power of a study.[36] Use of real-time central review in trials using PFS as a primary end point may help overcome the obstacles caused by discrepancies between local and central review. Pilot studies using real-time central review in NET trials are encouraged. The incorporation of end points beyond radiologic progression, such as quality-of-life end points, is also encouraged to provide further information on the potential clinical benefit of novel agents in NETs.

Randomized phase II studies, requiring disease progression before study entry and using PFS as a primary end point, should be used to screen novel agents in NETs when the primary benefit is expected to be delay in progression. Because of the lack of reliable historical control data for patients with NETs, single-arm trials are not likely to provide sufficient evidence of activity to guide the design of phase III trials. Disease heterogeneity and selection bias in existing studies suggest that randomized designs should be prioritized in NET studies. A particularly vexing issue in prior phase II studies has been the wide variability in the requirement (or lack thereof) for disease progression before study entry. When PFS is the primary end point, a general requirement for clinical evidence of disease progression within 12 months before study entry, as has been required in recently completed phase III studies, is highly encouraged in future phase II studies; this requirement should also facilitate cross-study comparisons. When feasible, randomized phase II studies using a PFS end point should be performed to more accurately explore efficacy among novel therapeutic agents.

Randomized trials in NETs should either include somatostatin analogs in all arms or stratify for the concurrent administration of somatostatin analogs. In a recent study, 85 patients with advanced midgut NETs and predominantly low-volume disease were randomly assigned to receive treatment with octreotide long-acting release or placebo (Table 3). Patients randomly assigned to the octreotide arm had a significantly longer median time to progression than patients assigned to the placebo arm (14.3 *v* 6 months, respectively; $P < .01$) at a planned interim analysis, leading to early termination of the study.[31] Given the evidence of antitumor activity associated with somatostatin analogs in this study, concurrent use of somatostatin analogs should be formally taken into account in NET studies. Randomized studies examining whether other somatostatin analogs also improve PFS are of potential future interest, particularly in patients with pancreatic NETs or carcinoid tumors not of midgut origin. A randomized trial evaluating the effect of lanreotide versus placebo on PFS in patients with nonfunctioning NETs is currently ongoing.

Table 3. Randomized Phase III Trials in Advanced NETs

Study and Regimen	Total No. of Patients	ORR (%)	Median PFS (months)	Median TTP (months)	Criteria	*P*
Pancreatic NETs						
Moertel et al[30]	105					
Streptozocin + doxorubicin		69		20.0	Nonstandard*	.001
Streptozocin + fluorouracil		45		6.9		
Raymond et al[28]	171					
Sunitinib		9		11.4	RECIST	< .001
Placebo		0		5.5		
Yao et al[27]	410					
Everolimus			11.0		RECIST	< .001
Placebo			4.6			
Carcinoid tumors						
Rinke et al[31]	90					
Octreotide LAR		2		14.3	WHO	< .001
Placebo		2		6.0		
Pavel et al[32]	429					
Everolimus + octreotide LAR			16.4		RECIST	.026
Placebo + octreotide LAR			11.3			
Recruiting	200					
Lanreotide						
Placebo						
Recruiting	283					
Bevacizumab + octreotide LAR					RECIST	
Interferon alfa + octreotide LAR						
Carcinoid syndrome						
Recruiting	202					
Octreotide LAR						
Pasireotide LAR						
Recruiting	100					
Lanreotide						
Placebo						

Abbreviations: NETs, neuroendocrine tumors; ORR, overall response rate; PFS, progression-free survival; TTP, time to progression; RECIST, Response Evaluation Criteria in Solid Tumors; LAR, long-acting release.
*Nonstandard includes computed tomography scan, radioisotope scan, physical exam, or hormonal response.

Imaging Considerations

Cross-sectional anatomic imaging of the abdomen should be performed with either multiphasic computed tomography or magnetic resonance imaging. NETs are highly vascular and enhance intensely with intravenous contrast during the early arterial phases of imaging, with washout during the delayed portal venous phase. In other phases, however, tumor metastases may appear isodense with liver and, as a consequence, may be poorly visualized. The dramatic variation in the appearance of NET metastases with different contrast phases can create significant challenges in evaluating tumor response or progression during clinical trials. Multiphasic computed tomography (CT), which includes both arterial and portal venous phase images, often provides a more consistent assessment of tumor burden in patients with NETs and is encouraged for clinical trials. Magnetic resonance imaging (MRI) is a reasonable alternative for imaging NETs because lesions can be visualized without contrast in T1 and T2 sequences, reducing the variability sometimes seen with CT-based imaging results.[37,38] One limitation of MRI scanning is that it may be less sensitive than CT scan for imaging extrahepatic disease.

Baseline cross-sectional anatomic imaging for clinical trials should include chest, abdomen, pelvis, and any additional known sites of disease. Although the liver is often the predominant site of metastases in patients with NETs, disease may occur in the chest and other sites. Therefore, baseline imaging for clinical trials should include imaging of the chest, abdomen, and pelvis, with the choice of follow-up imaging individualized by patient.

Somatostatin scintigraphy should not be used to assess tumor response in clinical trials. [^{111}In-DTPA^{0}]octreotide was developed for nuclear scintigraphy of NETs expressing somatostatin receptors 2 and 5. Whole-body nuclear imaging using this approach may establish the presence or absence of somatostatin receptors in the tumor, identify occult sites of metastases, and help characterize otherwise indeterminate lesions found on anatomic imaging. However, because [^{111}In-DTPA^{0}]octreotide uptake is a function of both somatostatin receptor status and tumor bulk, changes in intensity of uptake should not be used as a standard to assess tumor response to therapeutic agents.

Incorporation of Biomarkers

Serial measurements of plasma chromogranin A should be incorporated into prospective clinical trials. Both plasma chromogranin A and 24-hour urinary 5-hydroxyindoleacetic acid levels have been evaluated in prior NET studies as surrogate markers of response. Although 5-hydroxyindoleacetic acid levels are generally elevated in patients with metastatic midgut carcinoid tumors, they are not as useful in patients with foregut (bronchial, gastric) or hindgut (rectal) carcinoid tumors or in most patients with pancreatic NETs, which do not secrete serotonin. Chromogranin A (CgA) is a 49-kDa protein that is contained in the neurosecretory vesicles of NET cells and is commonly detected in the plasma of patients with endocrine neoplasms.[39,40] Elevated plasma CgA levels have been associated with poor overall prognosis in patients with NETs.[40] Additionally, early decreases in CgA have been associated with favorable treatment outcomes in some studies.[29,41] However, the prognostic value and predictive value of CgA have not been widely validated and may also be therapy dependent. Validation of CgA as a prognostic and potentially predictive biomarker in future studies is warranted.

Assessment of tumoral O^6-methylguanine–DNA methyltransferase expression is warranted in future studies of alkylating agents. The sensitivity of tumor cells to alkylating agents, including temozolomide, has been associated with decreased levels of the DNA repair enzyme O_6-methylguanine-DNA methyltransferase (MGMT), which, through its ability to restore DNA to its normal form, can prevent chemotherapy-induced cell death.[42] MGMT deficiency seems to be more common in pancreatic NETs than in carcinoid tumors, potentially explaining the greater sensitivity of pancreatic NETs to treatment with the alkylating agents streptozocin or temozolomide and raising the possibility of using MGMT expression as a predictive marker in future studies of these tumors.[43]

Imaging with perfusion CT should be considered in future studies of antiangiogenic agents. Recent studies evaluating VEGF pathway inhibitors in NET have shown treatment-associated decreases in tumor blood flow as measured by dynamic contrast-enhanced MRI and perfusion CT. Moreover, in recent phase II studies of bevacizumab or bevacizumab and everolimus in carcinoid tumors, early decreases in tumoral blood flow were associated with improved clinical outcomes.[44,45] Assessment of tumor blood flow as a potential predictive marker of response is warranted in future studies evaluating angiogenesis inhibitors in NET.

SPECIFIC RECOMMENDATIONS FOR ONGOING AND FUTURE STUDIES OF SYSTEMIC THERAPY IN ADVANCED NET

Advanced Carcinoid Tumors

Successful completion of the ongoing phase III study of bevacizumab versus interferon in patients with advanced carcinoid tumors (Southwest Oncology Group trial S0518) may define the role of bevacizumab in patients with advanced carcinoid tumors. In an initial randomized, run-in, phase II trial, patients with advanced carcinoid tumors were randomly assigned to treatment with bevacizumab or pegylated interferon alfa-2b.[44] Clinical activity of bevacizumab was evidenced by a response rate of 18% and an improved PFS rate at week 18 (95% *v* 68% with interferon). These encouraging results led to the development of a randomized phase III study led by the Southwest Oncology group (S0518), in which patients are randomly assigned to receive either interferon alfa-2b or bevacizumab in addition to octreotide, with a primary end point of PFS (Table 3). The results of this study may strongly influence whether bevacizumab is incorporated into future trials of advanced carcinoid tumors.

The results of a phase III study of everolimus plus octreotide versus octreotide alone may define the role of everolimus in patients with advanced carcinoid tumors. mTOR is a serine-threonine kinase implicated in the regulation of cell growth, proliferation, and apoptosis through modulation of the cell cycle. A promising response rate of 17% in patients with advanced carcinoid tumors was observed in a single-center study evaluating the mTOR inhibitor everolimus in combination with depot octreotide.[46] Everolimus, in combination with octreotide, was subsequently taken forward in a randomized phase III study and compared with placebo plus octreotide (RADIANT-2). The complete results of this study, when available, may help further define the potential role of everolimus in patients with advanced carcinoid tumors.

Randomized studies of tyrosine kinase inhibitors targeting VEGF receptor should be considered in patients with advanced carcinoid tumors. Three tyrosine kinase inhibitors (sunitinib, sorafenib, and pazopanib), all with demonstrated inhibitory activity for the VEGF

receptor tyrosine kinases, have been evaluated in patients in advanced carcinoid tumors in prospective phase II studies.[47-49] Although these agents have consistently been associated with higher Response Evaluation Criteria in Solid Tumors (RECIST) –defined tumor response rates in advanced pancreatic NETs than in carcinoid tumors, PFS duration in the carcinoid cohorts has been encouraging, supporting the evaluation of these or similar tyrosine kinase inhibitors in the randomized setting in patients with advanced carcinoid tumors.

Advanced Pancreatic NETs

Sunitinib and other tyrosine kinase inhibitors targeting VEGF receptors are active in patients with advanced pancreatic NETs. Consistent, if relatively modest, tumor responses have been reported in prospective phase II trials evaluating sunitinib, sorafenib, or pazopanib in patients with advanced pancreatic NETs.[47-49] The activity of sunitinib in advanced pancreatic NETs has been further evaluated in an international placebo-controlled study. This study was discontinued before the first planned interim analysis after the enrollment of 170 patients and the observation of 85 PFS events. Among patients evaluable for investigator-based response or progression, treatment with sunitinib was associated with a median PFS of 11.4 months, as compared with a PFS of 5.5 months in the placebo arm (hazard ratio, 0.41; 95% CI, 0.19 to 0.89; $P < .01$).[28]

Everolimus is active in patients with advanced pancreatic NETs. In a multinational phase II study (RADIANT-1) enrolling 160 patients with advanced pancreatic NETs and evidence of RECIST-defined progression after chemotherapy, treatment with everolimus was associated with an overall response rate of 9% and a disease control rate of 72%.[41] A subsequent randomized phase III study in 410 patients with progressive advanced pancreatic NETs (RADIANT-3) demonstrated a significant improvement in PFS associated with everolimus compared with placebo (11 *v* 4.6 months, respectively; hazard ratio, 0.35; 95% CI, 0.27 to 0.45; $P < .01$).[27]

A randomized phase II study comparing everolimus alone with the combination of everolimus and bevacizumab in patients with pancreatic NETs will build on the recent observation of activity with everolimus alone and may help define the potential additive activity of bevacizumab in pancreatic NETs. mTOR is a downstream mediator of VEGF signaling. In a recently completed phase II study, the combination of everolimus and bevacizumab was shown to be well tolerated and associated with an overall tumor response rate of 26% in patients with advanced NETs. On the basis of these results, the Cancer and Leukemia Group B 80701 trial will evaluate everolimus or everolimus plus bevacizumab in patients with advanced pancreatic NETs, using a randomized phase II design. A similar design could be also be considered in patients with advanced carcinoid tumors, depending on the results of RADIANT-2, which randomly assigned patients with advanced carcinoid tumors to receive either everolimus and octreotide or octreotide alone.

Randomized studies assessing the relative efficacy of streptozocin or temozolomide and assessing the efficacy of temozolomide alone or a temozolomide-based doublet are warranted in patients with pancreatic NETs. In contrast to carcinoid tumors, there is now substantial evidence that pancreatic NETs are sensitive to alkylating agents. Although cytotoxic chemotherapy is associated with only modest activity in patients with advanced carcinoid tumors, a randomized trial comparing streptozocin/doxorubicin to streptozocin/fluorouracil demonstrated improved survival associated with streptozocin/doxorubicin in patients with pancreatic NETs. Streptozocin is the only US Food and Drug Administration–approved therapy for patients with advanced pancreatic NETs.[30] Traditional streptozocin-based regimens used for pancreatic NETs include streptozocin/fluorouracil, streptozocin/doxorubicin, and a three-drug combination of streptozocin/doxorubicin/fluorouracil.[29] However, the widespread acceptance of streptozocin for this indication has been limited by concerns regarding toxicity.

Recent prospective and retrospective studies have suggested that regimens incorporating the oral alkylating agent temozolomide may be similar in efficacy to streptozocin-based regimens in pancreatic NETs.[19-21] In one retrospective series, for example, temozolomide-based therapy was associated with an overall response rate of 34% in patients with pancreatic NETs.[43] An adequately powered study comparing streptozocin and temozolomide-based therapy may not be feasible. However, a randomized phase II study would be beneficial to estimate both the activity and relative toxicities of these regimens. Additional uncertainty surrounds the relative activity of temozolomide as a single agent or in combination with other therapeutic agents. An assessment of the antitumor activity and toxicity of temozolomide alone or a temozolomide-based doublet should be incorporated into such a study.

SUMMARY

Despite early concerns regarding the ability to accrue patients and complete large randomized trials, ongoing or recently completed studies of bevacizumab, sunitinib, octreotide, lanreotide, and everolimus have demonstrated the feasibility of rigorous evaluations of novel antitumor therapies in patients with NETs. Therapies targeting hormonal symptoms are of equal importance given their potential effects on patient quality of life, and well-designed clinical trials with clearly defined efficacy criteria will be critical in accelerating the development of such agents. The development of standardized histologic and staging criteria should enhance the selection of appropriate patients for clinical studies. Randomized phase II trial designs, using PFS end points, are encouraged to more rapidly identify promising new agents to bring forward for definitive evaluation in this disease.

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