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REVIEW

Association between time to disease progression end points and overall survival in patients with neuroendocrine tumors

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Abstract: Overall survival can be difficult to determine for slowly progressing malignancies, such as neuroendocrine tumors. We investigated whether time to disease progression is positively associated with overall survival in patients with such tumors. A literature review identified 22 clinical trials in patients with neuroendocrine tumors that reported survival probabilities for both time to disease progression (progression-free survival and time to progression) and overall survival. Associations between median time to disease progression and median overall survival and between treatment effects on time to disease progression and treatment effects on overall survival were analyzed using weighted least-squares regression. Median time to disease progression was significantly associated with median overall survival (coefficient 0.595; P=0.022). In the seven randomized studies identified, the risk reduction for time to disease progression was positively associated with the risk reduction for overall survival (coefficient on −ln[HR] 0.151; 95% confidence interval −0.843, 1.145; P=0.713). The significant association between median time to disease progression and median overall survival supports the assertion that time to disease progression is an alternative end point to overall survival in patients with neuroendocrine tumors. An apparent albeit not significant trend correlates treatment effects on time to disease progression and treatment effects on overall survival. Informal surveys of physicians' perceptions are consistent with these concepts, although additional randomized trials are needed.

Keywords: neuroendocrine tumors, progression-free survival, disease progression, mortality

Introduction

Overall survival (OS) remains the gold standard end point for randomized controlled clinical trials in patients with cancer.[1] Health technology assessments and cost-effectiveness analyses of cancer therapies also typically require estimates of treatment effects on OS. Clinical trial design assessing OS as a primary end point can be particularly challenging in rare tumor types because of increased requirements for patient recruitment and follow-up.[2,3] Time to disease progression (TDP) end points such as progression-free survival (PFS) and time to tumor progression (TTP), evaluated using prespecified criteria, are often accepted by regulatory authorities as alternative or surrogate end points to OS, particularly in situations in which it may not be feasible to use OS as a primary end point.[1] This may be particularly relevant when it is not feasible to determine the OS benefit irrespective of antitumor activity, such as in trials that have crossover designs or populations in whom survival would be expected to be prolonged beyond 12 months despite disease progression.[1,3–5]

Use of PFS as a primary end point in cancer clinical trials has some important advantages and disadvantages.[3] For instance, compared with OS, measurement of

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PFS benefit derived from a particular therapeutic agent or regimen in a clinical trial is less confounded by other variables, such as crossover to active agents or subsequent active therapies.[3] Moreover, statistically significant differences in PFS compared with OS can be measured in smaller patient populations in shorter time frames; however, there are risks for potential measurement errors or statistical biases in smaller patient populations.[3] Other possible limitations are the difficulty validating PFS as a surrogate for survival in certain treatment settings; the definition of PFS varies among trials and does not typically account for factors such as quality of life, pain, and performance status, which may be important in the patient population with neuroendocrine tumors (NET) because of the indolent nature of the disease, the requirement for frequent radiologic or other assessments to determine disease status, and the requirement for balanced timing of assessment among treatment arms.

NET represent a tumor type in which OS is particularly difficult to evaluate because of disease heterogeneity (resulting in difficult patient recruitment in large Phase III trials), low numbers of eligible patients (ie, those with proper diagnoses), and variable survival times for patients with distal or regional NET (median OS, 33 or 111 months, respectively).[6] Survival times are even shorter among patients with specific subtypes of NET. For example, patients with metastatic pancreatic NET have a median OS time of 17 months, whereas those with regionally advanced pancreatic NET have a median OS time of 69 months.[7]

In rare tumors such as NET, for which treatment options are limited, crossover to the active agent is often included in the trial study design, thus confounding the impact of the specific therapy on OS. Although statistical methods such as inverse probability of censoring weights and rank-preserving structural failure time can be used to account for crossover in the estimation of OS, the impact of a specific drug on survival is often unclear in most crossover clinical trial designs.

Although overall response rate (complete response + partial response) remains an important end point in NET, results from recent prospective Phase II and III trials in NET have demonstrated low overall response rates with different therapeutic agents (including everolimus, octreotide long-acting repeatable, and sunitinib) in spite of observed benefits in PFS and TTP.[8–14] It may be that a morphologic response to treatment in patients with NET is not demonstrated as clearly and obviously on radiologic imaging as it is in patients with other tumors. This has certainly been the case in gastrointestinal stromal tumors, for which Response Evaluation Criteria In Solid Tumors (RECIST) did not capture clinical response to treatment in clinical trials.[15]

It should also be noted that although PFS has already been recognized as a valuable primary end point for several solid tumors (colorectal, breast, ovarian, and kidney),[3] discussions continue as to whether PFS may be regarded as a clinically meaningful end point if an OS benefit is not ultimately achieved.[2,16] Recently, a consensus report from the US National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting recommended PFS as a feasible and relevant primary end point for Phase III NET clinical trials.[17] In many diseases, PFS may be an important clinical outcome for treating physicians as well. A 2009 survey of physicians showed that PFS had the most influence on their treatment decisions for patients with advanced NET.[18]

Clearly, clinical trials in NET must be designed using end points that enable safe and efficacious agents to be identified and that ultimately offer improved outcomes to patients. Using OS as the sole threshold for the adoption of new drugs in a rare cancer such as NET would likely discourage the development of new, much needed agents in uncommon tumors.

One approach is to project these effects on the basis of estimates of the association between treatment effects on TDP and those on OS. In addition, PFS used as a disease end point and its use to estimate the OS benefit of a particular therapeutic agent or regimen yield important information for clinicians. We discuss here the evidence (based on a thorough review of the literature and a weighted least-squares regression analysis) that supports the use of TDP end points (including PFS and TTP) in the design of clinical trials in NET.

Materials and methods

Data identification

A thorough review of the literature was conducted to identify published or presented clinical trials of medical therapies in patients with NET. Our approach differs from a comprehensive systematic review in that the literature review and analysis of the relationship between PFS and OS conducted herein involved only major studies (not all possible studies available) and did not include all possible arms within each study. Trials published in the English language after January 1, 2000, were identified from the PubMed/MEDLINE database. Additional trials were identified by reviewing the reference lists of a previous technology assessment[19] and retrieved articles and by searching the 2007–2010 conference proceedings of the American Society of Clinical Oncology, the European

CanCer Organisation, the North American Neuroendocrine Tumor Society, and the European Neuroendocrine Tumour Society. To be included in the analysis, the study had to be a clinical trial (single-arm clinical trial or randomized clinical trial; Phase I, II, or III); be conducted in patients with NET; assess somatostatin analogs, targeted therapies (ie, inhibitors of endothelial growth factor receptors, vascular endothelial growth factor receptors, mammalian target of rapamycin [mTOR], and tyrosine kinases), immunotherapies, cytotoxic chemotherapy, or peptide receptor radionuclide therapy; and report survival probabilities for both TDP and OS. Any trials not meeting these criteria were excluded from the analysis. For each of the studies selected for inclusion, data on study design, treatments, patient characteristics, and outcomes measurements were extracted.

Analyses

Associations between median TDP and median OS (unit of observation: study arm) and between treatment effects on TDP and treatment effects on OS (unit of observation: comparison of study arms) were analyzed using weighted least-squares regression. The intercept of the regression equations was not forced to zero. The negative log of the hazard ratio (HR) for TDP and OS (ie, −ln[HR]) was used as a measure of treatment effects on TDP and OS.[20] For small treatment effects, −ln(HR) is approximately equal to 1−HR; therefore, −ln(HR) is approximately equal to the relative risk reduction with treatment. If necessary, HRs of the observed treatment effect between treatment groups were estimated on the basis of reported survival probabilities.[21] Prediction intervals were calculated for each regression line using the mean number of subjects per arm or comparison as a weight.

Results

Association between TDP end points and OS

A total of 1,343 potential studies were identified from the PubMed/MEDLINE database, conference proceedings, and reference lists of health technology assessments and retrieved articles; 1,213 were excluded because they did not meet the inclusion criteria (controlled or uncontrolled clinical trial; conducted in patients with NET; assessed somatostatin analogs, targeted therapies, immunotherapies, cytotoxic chemotherapy, or peptide receptor radionuclide therapy; or reported survival probabilities for both TDP and OS). After a detailed review of the remaining 130 articles and abstracts, 22 were identified as meeting all inclusion criteria and were included in the analysis (Figure 1). These 22 studies included seven controlled and 15 uncontrolled trials, representing 29 unique treatment arms and 2,584 patients (Table 1).[8,9,11–14,22–37]

The trials covered a broad range of therapeutics, including octreotide,[8,11,37] everolimus,[13,14,37] interferon-α,[8,34] sunitinib,[9,12] and streptozocin plus 5-fluorouracil.[26,34,36] Four of the controlled studies included placebo arms.[11,12,14,37] Eight of the single-arm studies investigated chemotherapies,[22–24,27–29,31] and the others studied peptide receptor radionuclide therapy, imatinib, or interferon-γ.

Although tumor grade is not consistently reported, most patients had well-differentiated or moderately differentiated disease; patients with poorly differentiated tumors were included in some of the uncontrolled trials. Similarly, although the subtype of NET is not consistently reported, most patients had gastroenteropancreatic NET. Most of these patients had carcinoid syndrome. Overall, 24 of the 29 treatment arms reported both median TDP and OS (Table 1). Across available treatment arms, median TDP and OS averaged 9.6 and 30.1 months, respectively. In 14 studies, the TDP measure was PFS; in the remaining eight studies, the TDP measure was TTP. Of these 24 treatment arms, three used somatostatin analogs as the experimental therapy, three used targeted therapies, two used immunotherapies, eleven used cytotoxic chemotherapy, and two used peptide receptor radionuclide therapy; one trial had a placebo arm, and two trials used somatostatin analogs in combination with agents of different modalities (one immunotherapy, one targeted therapy). Of the seven randomized trials, four reported median TDP and OS for both treatment arms (Table 1).

Association between median TDP and median OS

Based on linear regression of the 24 eligible treatment arms, median TDP was significantly associated with median OS (coefficient on median TDP 0.595; 95% confidence interval [CI] 0.094–1.097; P=0.022, Figure 2A). The low R^2 of 0.216 suggests that median TDP explains a relatively small proportion of the variability in median OS. When the extreme outlier values of TDP =6 and OS =75 (obtained from the placebo arm of the PROMID study of octreotide, ClinicalTrials.gov identifier NCT00171873[11]) were excluded, the coefficient on median TDP increased to 0.698 (95% CI 0.311–1.086). Results were also similar if the RADIANT-2[37] and RADIANT-3[14] controlled trials of everolimus (ClinicalTrials.gov identifiers NCT00412061 and

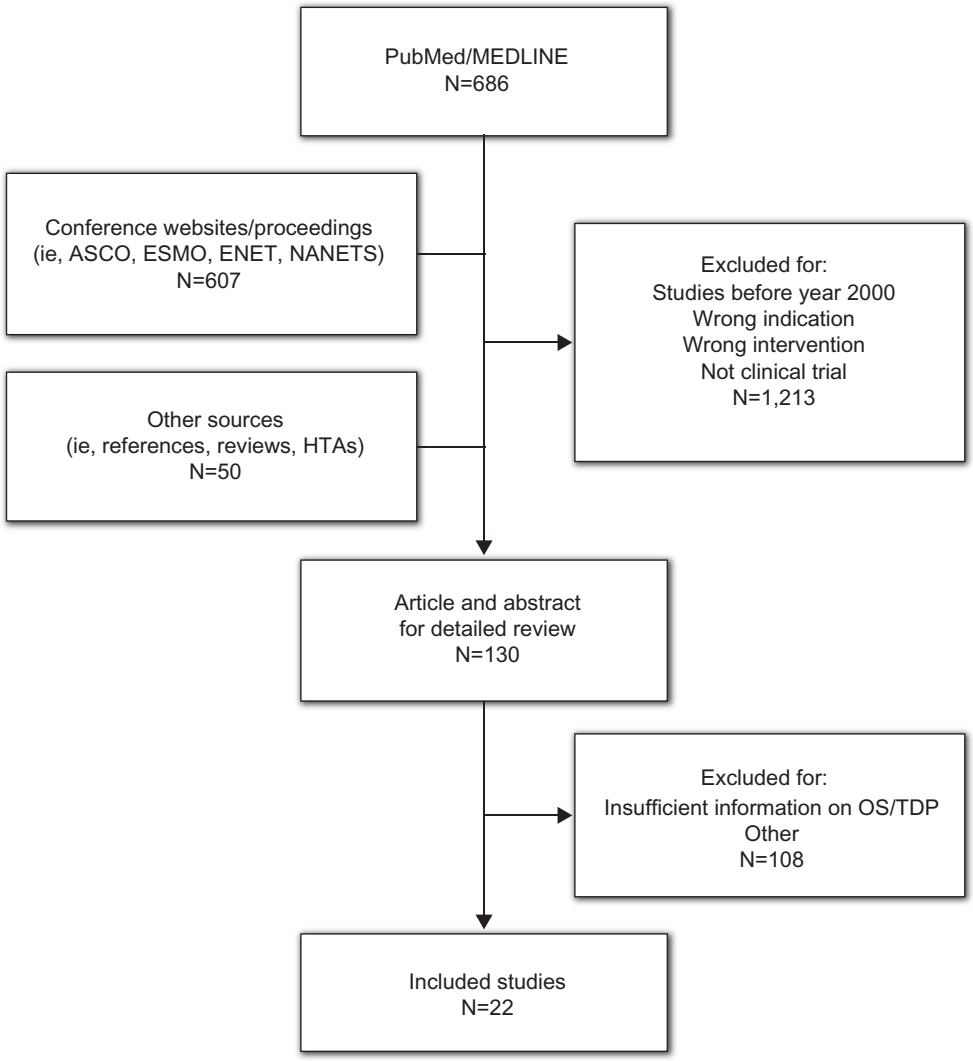

Figure 1 Results of the search strategy.
Abbreviations: ASCO, American Society of Clinical Oncology; ENET, European Neuroendocrine Tumor Society; ESMO, European Society for Medical Oncology; HTA, health technology assessment; NANETS, North American NeuroEndocrine Tumor Society; OS, overall survival; TDP, time to disease progression.

NCT00510068, respectively), each of which included a high proportion of crossover from control to active therapy after progression, were excluded from the analysis (coefficient on median TDP 0.625; 95% CI 0.110–1.139; P=0.020).

Association between risk reduction for PFS and risk reduction for OS in controlled trials

Seven comparisons were available for the analysis of the association between treatment effects on TDP and treatment effects on OS, including six randomized trials[8,11,12,14,34,37] that reported HRs for both TDP and OS and one randomized trial[26] for which the HRs could be estimated on the basis of reported survival probabilities. Based on linear regression of these seven randomized studies, the risk reduction for TDP was positively associated with the risk reduction for OS (coefficient on −ln[HR] 0.151; 95% CI −0.843, 1.145; P=0.713, Figure 2B). Similar to the analysis of the association between median TDP and median OS, the low R^2 of 0.030 suggests that the HR for TDP explains a relatively small proportion of the variability in the HR for OS. If the RADIANT-2 and RADIANT-3 studies[13,37] were excluded from the linear regression because of the high degree of crossover, the coefficient increased to 0.413 and the R^2 increased nearly 10-fold to 0.273; however, the relationship between risk reduction for median TDP and risk reduction for median OS remained statistically insignificant (P=0.366).

Publication bias (eg, if studies with small and/or nonsignificant findings remain unpublished) was assessed using the funnel plot method (Figure 3). Egger's regression test was conducted to test for funnel plot asymmetry. Neither the plot nor the test (P=0.2828) suggests publication bias.

Table 1 Summary characteristics and results of included studies

Number	Reference number	Type of NET	Grade	Arm 1				Arm 2				Δ Median		HR	
				Intervention	n	Median TDP[a]	Median OS[a]	Intervention	n	Median TDP[a]	Median OS[a]	Median TDP[a]	Median OS[a]	TDP	OS
Randomized trials															
1	8	GEP-NET	WD	Octreotide + IFN-α	54	5.8[b]	54.0	Octreotide	51	6.0[b]	32.0	–0.2[b]	22.0	0.89	0.82
2	26	Carcinoid	NR	Streptozocin + 5-FU	88	5.3	24.3	Doxorubicin + 5-FU	88	4.5	15.7	0.8	8.6	0.85	0.68
3	34	Carcinoid	WD	IFN-α	32	14.1	44.3	5-FU + streptozocin	32	5.5	30.4	8.6	13.9	0.75	0.92
4	11 (PROMID)	NET midgut	WD	Octreotide LAR	42	14.3[c]	NR	Placebo	43	6.0	73.7[d]	8.3	–	0.34	0.81
5	12	pNET	WD	Sunitinib	86	11.4	NR	Placebo	85	5.5	NR	5.9	–	0.42	0.41
6	37 (RADIANT-2)	Carcinoid	WD, MD	Everolimus + octreotide LAR	216	16.4	DOF	Placebo + octreotide LAR	213	11.3	DOF	5.1	DOF	0.77	1.22
7	14 (RADIANT-3)	pNET	WD, MD	Everolimus + BSC	207	11.0	NR	Placebo + BSC	203	4.6	NR	6.4	–	0.35	1.05
Single-arm trials															
8	22	GEP-NET	Extensive	Paclitaxel	24	3.2[c]	18.0	–	–	–	–	–	–	–	–
9	23	NET	NR	5-FU + dacarbazine + epirubicin	82	21.0[c]	38.0	–	–	–	–	–	–	–	–
10	24	NET	WD, PD	Gemcitabine	18	8.3	11.5	–	–	–	–	–	–	–	–
11	25	Carcinoid	NR	IFN-γ	48	5.5[c]	42.0	–	–	–	–	–	–	–	–
12	27	GEP-NET	WD	Irinotecan + 5-FU + leucovorin	20	5.0	15.0	–	–	–	–	–	–	–	–
13	28	NET	PD	Paclitaxel + carboplatin + etoposide	78	7.5	14.5	–	–	–	–	–	–	–	–
14	29	NET	WD, PD	Irinotecan + cisplatin	15	4.5[c]	11.4	–	–	–	–	–	–	–	–
15	30	GEP-NET	NR	Radiolabeled octreotide	58	14.3	36.7	–	–	–	–	–	–	–	–
16	31	NET	MD, PD	Cisplatinum + etoposide + lanreotide long-acting release	27	9.0[c]	24.0	–	–	–	–	–	–	–	–
17	32	Carcinoid	NR	Imatinib	27	5.9	36.0	–	–	–	–	–	–	–	–
18	9	Carcinoid	NR	Sunitinib	41	10.2[c]	25.3	–	–	–	–	–	–	–	–
		pNET	NR	Sunitinib	66	7.7[c]	NR	–	–	–	–	–	–	–	–
19	33	GEP-NET	NR	Radiolabeled octreotate	310	33.0	46.0	–	–	–	–	–	–	–	–
20	35	Carcinoid	NR	Radiolabeled edotreotide	90	16.3	26.9	–	–	–	–	–	–	–	–
21	36	NET	WD, PD	5-FU + cisplatin + streptozocin	79	9.1[c]	31.5	–	–	–	–	–	–	–	–
22	13 (RADIANT-1)	pNET, no octreotide LAR	WD, MD	Everolimus	115	9.7	24.9	–	–	–	–	–	–	–	–
		pNET, on octreotide LAR	WD, MD	Everolimus	45	16.7	NR	–	–	–	–	–	–	–	–

Notes: [a]Median TDP and median OS are presented as months; [b]TDP was extrapolated from a figure in the reference; [c]TDP measurement is PFS unless marked with superscript c, which indicates that it is TTP; [d]the estimation of OS of 73.7 months in the placebo group may not be robust because of the low number of deaths in this trial.

Abbreviations: –, not reported; 5-FU, 5-fluorouracil; BSC, best supportive care; DOF, data on file (Novartis Oncology, Florham Park, New Jersey, USA); GEP-NET, gastroenteropancreatic neuroendocrine tumor; HR, hazard ratio; IFN-α, interferon-alpha; IFN-γ, interferon-gamma; LAR, long-acting repeatable; MD, moderately differentiated; n, number of patients considered; NET, neuroendocrine tumor or endocrine carcinoma or endocrine tumor; NR, not reported; OS, overall survival; PD, poorly differentiated; pNET, pancreatic neuroendocrine tumor or pancreatic islet cell tumor; PFS, progression-free survival; TDP, time to disease progression; TTP, time to progression; WD, well differentiated; RADIANT-2 and RADIANT-3, ClinicalTrials.gov identifiers NCT00412061 and NCT00510068, respectively; PROMID, ClinicalTrials.gov identifier NCT00171873.

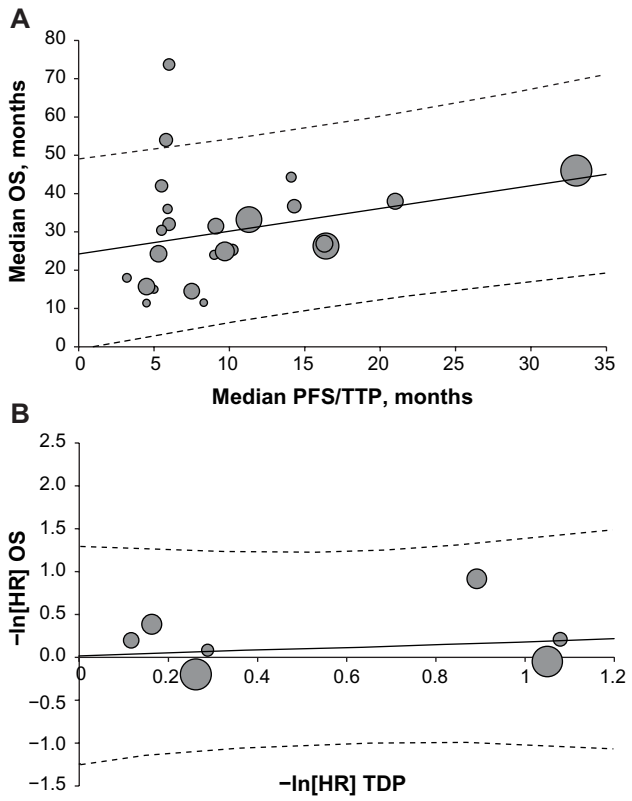

Figure 2 Linear regression and treatment effects comparison.
Notes: (**A**) Association between median TDP and median OS. (**B**) Association between risk reduction for median PFS and risk reduction for median OS in controlled trials. Solid line, linear trend line. Dashed lines, 95% prediction interval. Bubble areas are proportional to sample sizes.
Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TDP, time to disease progression; TTP, time to tumor progression.

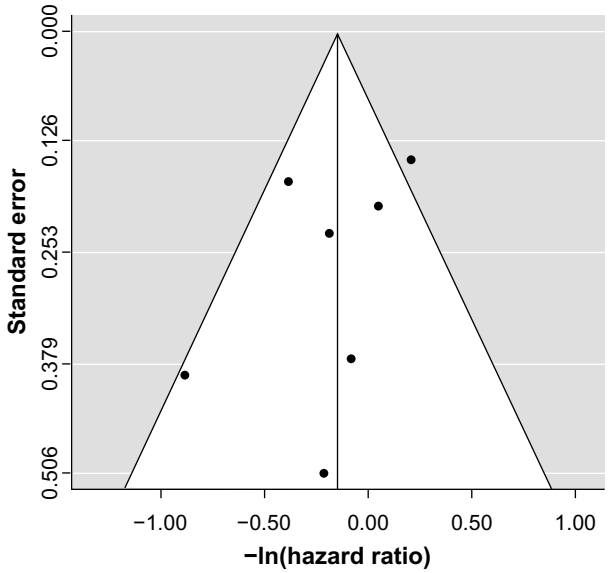

Figure 3 Funnel plot for –ln(hazard ratio) for overall survival.
Notes: Egger's regression test was conducted to test for funnel plot asymmetry (P=0.2828). Neither the plot nor the test result suggests publication bias.

Discussion

Based on this analysis of 22 controlled and uncontrolled studies representing 29 unique treatment arms and 2,584 patients, median TDP is positively and significantly associated with median OS in clinical trials of medical treatments for NET. When only randomized controlled trials were considered, the treatment effects on TDP appeared to show a trend for association with the treatment effects on OS, although the association was not statistically significant because of the small number of randomized trials. The small number of trials also limited the analysis to a pooled analysis rather than one by response criteria (World Health Organization versus RECIST). Regardless, these associations are consistent with findings in other cancers in which the surrogacy of TDP for OS has been well established, but they clearly underscore the need for a larger number of randomized trials in NET to generate sufficient data to meet the consensus-defined significance threshold for survival measures.[20,38–44] For example, in an analysis of the relationship between TTP and OS in 146 trials of first-line chemotherapy for metastatic colorectal cancer, the treatment effect on TTP was positively and significantly correlated with the treatment effect on OS (R^2=0.33; P<0.0001).[42] An analysis of 67 studies of therapy for metastatic breast cancer revealed that a treatment effect on TDP was positively and significantly associated with a treatment effect on OS (R^2=0.30; P<0.001).[44] Analyses of metastatic colorectal and breast cancer showed that the treatment effect on OS was less than the treatment effect on TDP. A likely explanation for this difference is the susceptibility of OS to differences between treatment groups in post-progression therapies, which typically are not controlled and are subject to the discretion of the investigator. Trials in which the study design dictates that patients in the control group who experience disease progression be allowed to cross over to receive active treatment are particularly sensitive to the confounding effects of post-study treatment on OS, perhaps because another effective treatment may not be available for these patients. The confounding effects of selective crossover were illustrated in the present analysis of advanced NET by the larger correlation between the treatment effect on TDP and the treatment effect on OS when the RADIANT-2[37] and RADIANT-3[14] studies of everolimus were excluded (R^2=0.030 with the RADIANT studies; R^2=0.273 without the RADIANT studies). Aside from the exclusion of RADIANT-2 and RADIANT-3, we did not attempt to control for the crossover effect or for the potential correlation of arms within trials. These observations seem to support the hypothesis that TDP is a truer measure than OS of the study therapy effect, especially when a crossover design is used.

In clinical practice, physicians with experience treating patients with advanced NET have their own definitions and perceptions about disease progression. In 2009, 502 practicing physicians, either oncologists (n=398) or gastroenterologists/endocrinologists (n=104), from six countries (USA, 250; UK, 51; Spain, 51; France, 50; Germany, 50; Italy, 50) participated in a brief, online, third-party survey sponsored by Novartis Pharmaceuticals Corporation concerning their opinions about the definition of disease progression in patients with NET (data on file). The specific ratio of oncology to gastroenterology/endocrinology specialties in each country was set deliberately to try to replicate the approximate mix of specialists who treat advanced NET; thus, no weighting of the data by specialty was necessary. All qualified physicians met specific screening criteria, including the following: in practice between 2 and 30 years, >50% of professional time spent in direct patient care, and currently treating a minimum of three patients with advanced NET (minimum of one patient in Japan). Information regarding clinician perceptions of disease progression was extracted from the survey and presented at the 35th Congress of the European Society for Medical Oncology, held October 8–12, 2010, in Milan, Italy.[18] Among the surveyed physicians, the effect on PFS was the attribute most likely to affect clinical therapeutic decisions (Figure 4).[18] Increased tumor size (albeit not necessarily per RECIST) and the development of clinical symptoms associated with NET were the top considerations for defining and measuring disease progression (Table 2). Additional criteria mentioned frequently included changes in biomarkers and increased metastases (Table 2). This survey provides needed insight regarding physicians' perceptions of disease progression at a clinical level.

Given the usefulness of TDP end points and physicians' perceptions of disease progression as presented here, the way in which progression is assessed becomes a pivotal issue. Traditionally, both PFS and overall response rate end points have been based on RECIST; however, PFS also takes disease stabilization into consideration, whereas overall response rate addresses only changes in tumor size. In fact, the updated RECIST (version 1.1) does not require confirmation of tumor response in studies for which PFS is the primary end point, particularly in Phase III trials.[45] Because of the broader inclusion of patients who derive treatment benefit on the basis of delayed disease progression, the US Food and Drug Administration issued specific guidance in 2007 on clinical trial end points that confirmed the acceptability of PFS as a primary end point for drug approval.[4]

Although RECIST has been adopted as the standard for assessment of imaging-related end points in clinical trials in populations with solid tumors,[46,47] this set of rules has

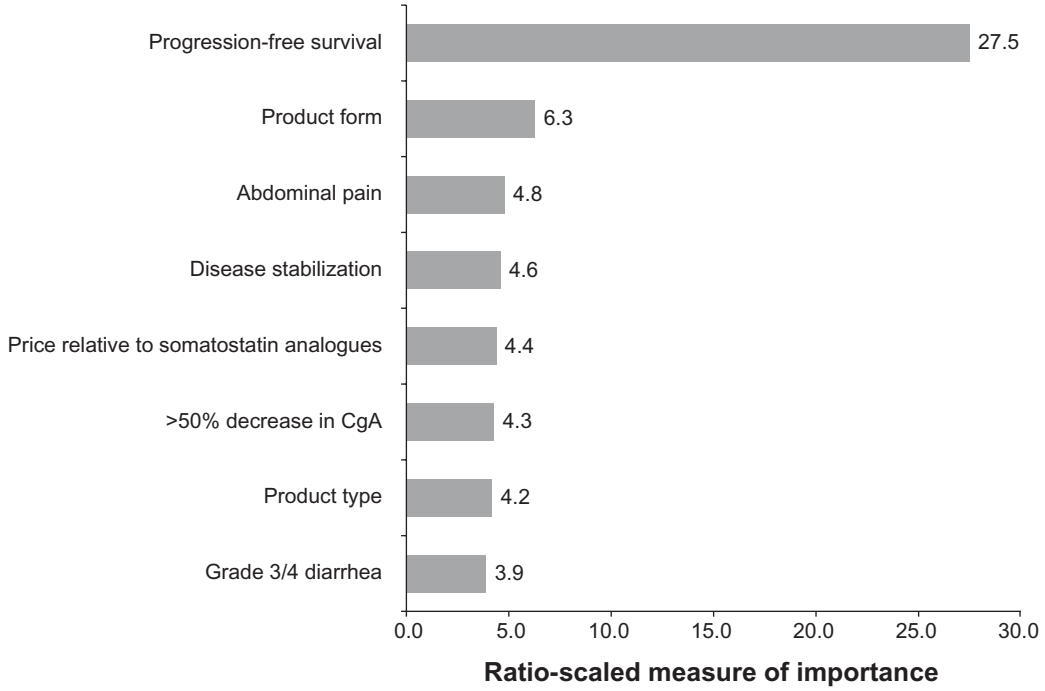

Figure 4 Importance of advanced therapy attributes (n=397).
Note: Data were based on choice-based conjoint methods. Data from Singh and Law.[18]
Abbreviation: CgA, chromogranin A.

Table 2 Physicians' definitions of disease progression in patients with NET

How do you define progression when it comes to:	GI/Lung NET (carcinoid), %			Pancreatic NET, %		
	Total (n=502)	USA (n=250)	European Union (n=252)	Total (n=502)	USA (n=250)	European Union (n=252)
Increased tumor size	79	84	75	82	83	81
Development of symptoms	52	54	51	33	36	31
Biomarkers	27	30	25	20	20	19
Increased metastases	30	27	33	18	14	21
Miscellaneous	6	3	9	7	3	10

Note: Only mentions greater than 5% are displayed. Data from Singh and Law.[18]
Abbreviations: GI, gastrointestinal; NET, neuroendocrine tumor.

recognized limitations in the current era of evolving assessments and may not fully measure or quantify disease control in patients with tumors such as NET and gastrointestinal stromal tumors, which are slow growing or present radiologic challenges, and in patients with widely disseminated disease.[47] Moreover, newer targeted cytostatic agents may work by mechanisms unlikely to cause radiologically measurable tumor regression.[45] For example, RECIST has been shown to underestimate the effect of imatinib in patients with gastrointestinal stromal tumors, an observation that may be related to the occurrence of drug-induced cystic changes early in the course of treatment.[48] Such a response may be better measured by tumor density rather than size, which is not measured according to RECIST. This is especially true in cancers such as NET, which are often associated with functional hormonal secretion causing patient symptoms and decreased quality of life. Meaningful clinical response in such cancers may include decreased hormonal secretion with or without obvious radiologic changes according to RECIST. Another measurement of response may include imaging with ^{68}Ga-labeled analogs of octreotide, such as DOTATOC, DOTANOC, and DOTA-TATE.[49]

Improved methods of assessing tumor response have been developed. RECIST was updated (version 1.1) in 2009 to incorporate advances in imaging technology and issues arising from recent clinical trials.[49] Both computed tomography (CT) and magnetic resonance imaging (MRI) are used for localizing and staging NET, and although CT and MRI have similar sensitivities,[50] MRI has been shown to equal or exceed CT in some applications.[51] Combined functional/morphologic positron emission tomography (PET)/CT imaging has been demonstrated to detect tumor response more accurately than either modality alone.[52] Fluorine-18 2-fluoro-2-deoxy-D-glucose/PET has limited usefulness compared with CT/MRI, especially in patients with well-differentiated NET. Another type of tumor response assessment, ie, the Choi criteria, developed in 2007,[15] involves tumor size reduction ≥10% or tumor density reduction ≥15%, particularly in tumors that have indistinct boundaries or are diffuse. The Choi criteria have been positively correlated with TTP and disease-specific survival in patients with gastrointestinal stromal tumors.[15,53]

The literature search was not conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Our evaluation differs from a systematic review in that our analysis of the relationship between PFS and OS did not include all possible studies; thus, there may be gaps in the available data that were analyzed. Other limitations of this study include the following: we could not look at the potential confounding effects of individual factors such as age, gender, histologic stage, and therapies because these data were not available for all patients in all studies; we could not control for the potential correlation of arms within trials (although randomization would assist with independence); we could not control for the confounding effects of selective crossover of patients from placebo to active treatment arms because of tumor progression on OS; the overall sample size was small (including a small number of trials and a small number of participants within each trial), and this could have contributed to the lack of statistical significance for the relationship between risk reduction for median TDP and risk reduction for median OS; the small number of trials limited our analysis to a pooled analysis rather than one by response criteria (World Health Organization versus RECIST); and the inclusion of patients with poorly differentiated NET might have introduced bias. The number of studies in patients with poorly differentiated tumors was very small, and the number of patients in each of those studies was small. Thus, any potential impact of bias is expected to be minimal. Further, we cannot predict how tumor differentiation and grade might have affected our analysis because these data were not consistently reported across studies, nor were the effects of these factors evaluated on PFS

Table 3 Practice guidelines for imaging and biomarkers in NET

	Follow-up recommendations	Imaging	Biomarkers
ESMO[55,59]	Every 3 months in patients receiving chemotherapy or biological therapy or every 3–6 months after surgery with curative intent for >5 years	CT or MRI every 6 months	Biochemical markers specific to the associated clinical syndrome, if present, tested every 3 months
NCCN[60]	Follow-up recommended 3–12 months after resection and annually thereafter	CT or MRI as clinically indicated	Biochemical marker evaluation
UKNET[54]	As clinically indicated	Spiral CT, MRI, and ultrasound are useful for monitoring lesions	CgA potential correlation with response and relapse; rapid elevation suggests poor prognosis
Canadian guidelines[58]	Close follow-up tailored to patient's clinical presentation stratified to risk	Triphasic CT or MRI as needed; ^{111}In-pentetreotide as needed	CgA every 3–6 months; include 5-HIAA for tumors with secretory symptoms
NANETS guidelines[56,57]	Routine surveillance visits on annual basis[56]	CT or MRI every 6–12 months as clinically indicated; ^{111}In-pentetreotide as needed[57]	CgA, 5-HIAA, NSE, or other markers for follow-up[57]

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; CgA, chromogranin A; CT, computed tomography; ESMO, European Society for Medical Oncology; MRI, magnetic resonance imaging; NANETS, North American Neuroendocrine Tumor Society; NCCN, National Comprehensive Cancer Network; NET, neuroendocrine tumor; NSE, neuron-specific enolase; UKNET, United Kingdom Neuroendocrine Tumour Group.

and OS in the studies included in our analysis. Collection of these data (tumor grade and differentiation) is important for survival analysis in future clinical trials in NET.

A wide variety of clinical practice guidelines for NET recommend regular follow-up, including MRI, CT, and biomarker assessment, especially for chromogranin A, to aid in determination of disease progression (Table 3).[54–60]

Conclusion

In summary, median TDP is significantly associated with median OS in clinical trials of therapies for NET. Associations between median TDP and median OS and HR for TDP and OS observed in NET trials are consistent with those in other cancers for which surrogacy has been established. Although the small number of studies conducted to date in patients with NET did not enable significance to be achieved, a positive association was noted between treatment-related effects on TDP and treatment-related effects on OS. Thus, TDP appears to be an appropriate alternative end point to OS in patients with NET. Informal surveys of physicians' perceptions are consistent with these concepts. Preliminary PFS results from three recent Phase III trials have been reported for patients with advanced NET, but long-term follow-up is required for validation of PFS as a valuable end point in this patient population. The key implication from the results of our study is that choice of an appropriate end point for NET clinical trials is imperative to provide both accurate evaluation of therapies and clinically meaningful extension of patient life span. Because of the short time frames of the studies included in our analysis and patient crossover from the placebo arm to the treatment arm on disease progression, we acknowledge that an end point such as OS will likely not be met, whereas determination of PFS may be a feasible surrogate for OS. Contemporary clinical trials of treatments for patients with advanced NET are incorporating investigation of these hypotheses and have the potential to affect how disease progression and PFS in the NET population are defined in the future.

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Author contributions

SS developed the concept, assisted in analyzing the results from the clinician survey, wrote the manuscript, reviewed the drafts, and approved the final draft for submission. XW analyzed the results, wrote the manuscript, reviewed the drafts, and approved the final draft for submission. CL developed the concept, assisted in analyzing the results from the clinician survey, wrote the manuscript, reviewed the drafts, and approved the final draft for submission.

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SS has received research grants from Novartis and consulting fees and honoraria from Novartis and Pfizer. XW is an employee of and a stockholder in Novartis Oncology. CL has received research grants from Novartis Oncology and consulting fees from Pfizer Oncology and Novartis Oncology, and serves on the speakers bureau for Novartis Oncology. Financial support for writing and editorial assistance was provided by Novartis Pharmaceuticals, Inc., in compliance with international guidelines on Good Publication Practice.

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