Targeted Therapies in Neuroendocrine Tumors (NET): Clinical Trial Challenges and Lessons Learned

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Targeted Therapies in Neuroendocrine Tumors (NET): Clinical Trial Challenges and Lessons Learned

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ABSTRACT

In the past 3 years, we have witnessed the completion of four randomized phase III studies in neuroendocrine tumors and the approval of two new drugs, everolimus and sunitinib, for the treatment of patients with well-differentiated pancreatic neuroendocrine tumors. These studies demonstrate a shift from case series and single-arm studies toward prospective, randomized controlled clinical trials and evidence-based therapy in the neuroendocrine tumor field. However, the clinical development of these agents also highlights the potential challenges awaiting other new drugs in this area. Herein, we discuss the strengths and weaknesses of the most recent phase II and phase III neuroendocrine tumor studies and discuss how limitations inherent in current trial design can lead to potential pitfalls. We also discuss how trial design can be improved, with the hope of increasing the number of drugs successfully developed to treat patients with neuroendocrine tumors. ***The Oncologist*** 2013;18:000–000

Implications for Practice: With the approval of two new drugs, everolimus and sunitinib, for the treatment of patients with well-differentiated pancreatic neuroendocrine tumors, we are witnessing a shift from case series and single-arm studies toward prospective, randomized controlled clinical trials and evidence-based therapy in the neuroendocrine tumor field. However, the clinical development of these agents highlights the potential challenges awaiting other new drugs in this area. Focusing on the strengths, weaknesses, and limitations inherent in trial design can help identify pitfalls and potentially hasten the approval of drugs successfully developed to treat patients with neuroendocrine tumors.

INTRODUCTION

Although the incidence and prevalence of other types of cancer are decreasing in many countries [1, 2], diagnoses of neuroendocrine tumors (NET) appear to be increasing [3, 4]. Recent analysis of surveillance, epidemiology, and end results data from the United States has shown that the age-adjusted incidence of NET has increased almost fivefold over the past three decades, from 1.09 per 100,000 in 1973, to 5.25 per 100,000 in 2004 [3].

Early in the course of the disease, most patients with NET lack specific symptoms, resulting in frequent delays in diagnosis [5]. More than 50% of patients with NET have regional or distant metastatic disease at diagnosis. Prognosis varies widely, depending on grade (proliferative rate), stage, and primary tumor site. Clinical trial design and disease management pose a significant challenge because of the heterogeneous clinical presentations and the varying degrees of aggressiveness. For example, patients with large-volume functional tumors may require medical therapies for symptom control in addition to antitumor treatments. In contrast, patients with low-volume nonfunctional tumors are often completely asymptomatic and can be monitored expectantly for months and sometimes years.

For patients with diagnoses of localized NET, surgical resection is the treatment of choice; for patients with advanced disease, on the other hand, therapeutic options are limited [6, 7]. First-line therapy in patients with advanced, functioning tumors usually involves a somatostatin analog, most commonly octreotide or lanreotide (not approved for carcinoid syndrome in the United States) [6, 7]. Recent data suggest that octreotide long-acting repeatable (LAR) may also delay disease progression among patients with advanced midgut NET [8]. Until recently, additional effective systemic therapies for oncologic control were lacking. Before 2011, streptozocin was the only approved therapeutic agent for unresectable pancreatic NET. Its efficacy, however, was questionable, especially for nonpancreatic NET, and its toxicity was evident [9–11]. Although many agents had been studied in small phase II trials [12], no new agents had been approved in the past quarter century.

Better understanding of the mechanisms driving tumor growth has led to the development of several targeted anti-

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cancer agents [10, 13]. Two agents inhibiting relevant molecular targets have now been approved by the U.S. Food and Drug Administration for the treatment of patients with progressive, well-differentiated pancreatic NET: the vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) sunitinib, and the mammalian target of rapamycin (mTOR) inhibitor everolimus [9, 14, 15]. In phase III trials, both agents were associated with improved progression-free survival (PFS) compared with placebo [16, 17]. Both agents are now recommended in the most recently updated NET treatment guidelines [7, 18, 19]. Here we discuss what we have learned in the past decade, and how clinical trial design could and should be improved to increase the number of drugs successfully developed to treat patients with NET.

Phase II Clinical Trials in NET

Challenges in Past NET Trials

Although low success rates are common in phase II studies, failure is even more likely to occur with NET, given the tumor heterogeneity and rarity. A recent review [20] of clinical trials carried out between 2000 and 2011 in patients with NET indicates significant intertrial variability and lack of easily comparable data to aid interpretation. Of 46 articles evaluated, 39 involved phase II trials; of those, 36 (92%) were single-arm studies, and three (8%) were randomized studies. These 39 studies varied widely in size, ranging from just 17 patients to more than 150 [21, 22]. Although sample sizes in some studies were driven by statistical considerations [23, 24], others seemed to be based purely on feasibility [25]. Study populations were also extremely variable, with less than 25% of trials specifying a single tumor type and the remainder enrolling various combinations of carcinoid tumors or pancreatic NET. Some trials even allowed the inclusion of other endocrine tumor types [20–22].

The selection and reporting of NET trial endpoints also left much to be desired. Only 72% of trials carried out between 2000 and 2011 clearly defined their primary endpoint; moreover, endpoints differed according to the agent under assessment [20]. Intent-to-treat (ITT) analyses were often missing. Older studies frequently used objective response rate (ORR) as the primary outcome measure, potentially missing effects on PFS, which now is commonly used to assess efficacy, particularly for newer targeted agents. Of particular note, because many phase II studies did not meet their prespecified outcomes, many reports reveal a discordance between the interpretation of study results based on prespecified study design parameters and the interpretation provided by the authors of the publication [20].

Variability in past phase II clinical studies in NET is the result of multiple factors. Some studies were clearly suboptimally designed or conducted. At the same time, recent years have seen a clear evolution in thinking about NET trial design. Only recently has it become clear that different types of NET respond differently to therapeutic agents, that PFS is a supportable endpoint, and that large, randomized trials in this patient population are feasible.

Recent Phase II Studies in NET

Everolimus and sunitinib provide two examples of targeted agents that progressed from phase II trials to further development in patients with pancreatic NET on the basis of single-arm, open-label studies [23, 24]. Evidence of their activity in NET was provided by several prospective phase II studies. Everolimus was evaluated in combination with octreotide LAR in a phase II open-label study in 60 patients [26]. On the basis of the ITT analysis method, the overall response rate was 20%. Of 30 patients with carcinoid, five (17%) had partial response and 24 (80%) had stable disease. Median PFS was 63 weeks (approximately 14.7 months). Of 30 patients with pancreatic NET, eight (27%) had partial response and 18 (60%) had stable disease. Median PFS was 50 weeks (approximately 11.6 months). The larger phase II RADIANT-1 study of everolimus enrolled only pancreatic NET patients with Response Evaluation Criteria In Solid Tumors (RECIST) progression after cytotoxic chemotherapy. The study was stratified by ongoing octreotide therapy at study entry, with those receiving octreotide required to show evidence of disease progression while taking octreotide [24]. Patients in stratum 1 received everolimus 10 mg/day, and those in stratum 2 received everolimus 10 mg/day plus octreotide LAR intramuscularly at the prestudy dose ($\leq$30 mg). A two-stage Simon design with response rate was used. By central review, the ORR was 9.6% in stratum 1 and 4.4% in stratum 2, with median PFS of 9.7 and 16.7 months, respectively, in this refractory population [24]. Differences in response in these two trials despite the same drug and tumor type likely reflect the heterogeneity of the patient population and illustrate the importance of consistent entry eligibility.

The phase II study of sunitinib enrolled patients with carcinoid tumors and pancreatic NET in separate strata and used an open-label, Simon two-stage design to evaluate efficacy on the basis of ORR [23]. In patients with pancreatic NET, ORR was 16.7% and median PFS was 7.7 months. However, lack of confirmed responses in carcinoid patients during the first enrollment stage led to early termination of the carcinoid cohort for presumed futility [23].

Recommendations for Future Phase II Studies

Interpretation of results from single-arm phase II studies can be challenging. Evidence of tumor response in the phase II setting is generally interpreted as evidence of activity [27, 28]; indeed, the fact that both sunitinib and everolimus were associated with responses in phase II led to phase III studies that proved successful. However, if a drug is associated with an improvement only in PFS in the absence of tumor regression, this will not be picked up in a single-arm phase II study unless it is a dramatic improvement over historical controls. Such cross-study comparisons are extremely difficult in NET, given the heterogeneous clinical characteristics of this patient population. Analysis of single-arm trials has in fact indicated that random and systematic variation in historical control data could increase type 1 (false-positive) error rates by twofold to fourfold [27]. One way to try to limit this variability and to improve the ability to use historical controls is to use uniform entry criteria. In more recent neuroendocrine studies, this has increasingly been accomplished by separating carcinoid NET from pancreatic NET and by requiring evidence of progression within a fixed time period before study entry.

Novel agents may also be tested in patient populations defined by diagnostic tests or biomarkers. Prognostic biomarkers can be used to select patients with more aggressive course for treatment and can be used as stratification factors in ran-

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domized studies to balance arms. Predictive biomarkers can be used to select patients likely to benefit from specific treatments. Numerous studies have recognized the prognostic significance of chromogranin A [28]. Biomarker analyses of the RADIANT-1 data recently demonstrated the prognostic significance of neuron-specific enolase in pancreatic NET [29]. However, the interpretation of studies using diagnostic tests or biomarkers to select patients requires caution. Single-arm studies generally cannot differentiate the prognostic effect of such tests or biomarkers from the treatment effect, making subsequent comparison with historical controls impossible [30]. For example, studies with peptide receptor radiotherapy (PRRT) select patients with positive ^{111}In-DTPA0-octreotide scintigraphy results. However, it is also known that positive ^{111}In-DTPA0-octreotide scintigraphy results portend a more indolent course; patients selected for these studies will inherently have better outcomes than most historical controls [31]. Interpretation of PFS and overall survival (OS) results from such studies in particular requires randomization.

Although the problems inherent in the single-arm trial design can be overcome by using a randomized trial design [30, 32], the role of randomization in the phase II setting remains controversial [27]. Accrual may also be an issue because randomized trials require a greater number of patients [33]; for rare tumor types, such as some NET subtypes, recruitment to a randomized study from an already limited patient population may become problematic. The sample size for randomized phase II trials can be reduced by liberalizing the statistical parameters for type 1 and type 2 errors [27, 34]. Calculations indicate that even with such liberalization, the rate of false positives, and thus the phase III failure rate, may be better than that seen with the current system [27]. Another major concern is that a randomized phase II study, although substantially underpowered, may be judged as being as informative as a phase III study [32]. The high type 1 error rate and the low power inherent in randomized phase II designs, however, allow for only hypothesis generation and estimation of treatment effect; the results of randomized phase II studies should not be used to guide standard therapy.

Efficacy endpoints traditionally used in phase II oncology trials are imperfect predictors of benefit in phase III. The RECIST criteria for measuring tumor burden [35, 36] were designed primarily for cytotoxic agents and have clear limitations for anticancer treatments that may provide clinical benefit for patients without causing marked tumor shrinkage [37–39]. Moreover, the assumption that improvement in response rate will lead to improvement in clinical outcomes for patients has not always been borne out in subsequent phase III studies [40]. PFS has become the preferred endpoint for most phase II studies of targeted agents. However, it should generally be assessed using a randomized phase II design. In such studies, continuous measure of tumor size using waterfall and spider plots may provide additional information [41]. Unfortunately, these methods are used only for qualitative assessment.

Phase III Trials in NET

The completion of phase III studies in recent years has been a landmark achievement. Recent studies have provided rigorous, prospective evidence supporting the use of octreotide for tumor control in patients with advanced carcinoid, as well as the use of everolimus or sunitinib in patients with advanced pancreatic NET. At the same time, these studies have highlighted unanticipated issues and challenges that may be more common in NET trials than in trials evaluating other malignancies.

Octreotide and the PROMID Study

For almost 30 years, octreotide has been used to treat the symptoms of NET (e.g., flushing, diarrhea) with considerable success [42, 43]. However, PROMID (placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors) was the first and, thus far, the only phase III trial to show an antiproliferative effect with a somatostatin analog. The PROMID study (Fig. 1A) was a placebo-controlled, randomized, phase III study ($N = 85$) that demonstrated the antitumor efficacy of octreotide LAR in patients with advanced midgut NET [8]. The primary outcome measure was time to progression (TTP), and tumor response was judged by a blinded, central reader, according to World Health Organization criteria. Secondary endpoints included OS, quality of life, and biochemical response. In this study, median TTP was 14.3 months in the octreotide LAR arm and 6.0 months in the placebo arm (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.20–0.59; $p = .00007$) [8]. Stable disease was observed in 67% of octreotide LAR–treated patients compared with 37% of placebo patients, with no complete responses observed in either treatment group.

Although the PROMID study undoubtedly provides interesting and suggestive information, the results of this small, prospective trial should be interpreted with caution. PROMID enrolled just 85 carcinoid patients in a single country, all of whom were treatment naive, making it difficult to extrapolate the results to other NET populations. The original plan was to enroll 162 patients, but the trial was terminated early at a preplanned interim analysis [8]. It is possible that the early termination of PROMID led to overestimation of the treatment effect; although the study group intended to perform yearly follow-ups, no further data have been published. PROMID was intended to provide robust results by including a statistically significant TTP endpoint plus specification of an HR of 0.60 to detect a clinically meaningful difference [8]. In addition, imbalances in the two arms occurred despite the randomized trial design. For example, the median time since diagnosis was 7.5 months in the experimental arm versus 3.3 months in the placebo arm ($p < .01$). Patients had to have had stable disease to enroll in this trial, and the longer time since diagnosis in the experimental arm could suggest that those patients might have had more indolent disease. Also, more patients in the placebo arm had greater than 50% liver involvement (4.8% vs. 11.6%).

Overall, however, PROMID did support a long-held feeling by clinicians that octreotide may lead to antitumor effects in addition to symptomatic responses in some NET patients; and in response to PROMID, several guidelines for treatment of NET were updated to recommend 20–30 mg of octreotide LAR in patients with recurrent or unresectable gastrointestinal NET [44–47]. A recent review summarizes 27 additional studies that have reported the antitumor efficacy of the somatostatin analogs octreotide (16 studies) and lanreotide (11 studies) in gastroenteropancreatic NET [48]. There are two additional randomized, placebo-controlled, phase III trials of somatostatin analogs in patients with nonfunctioning in-

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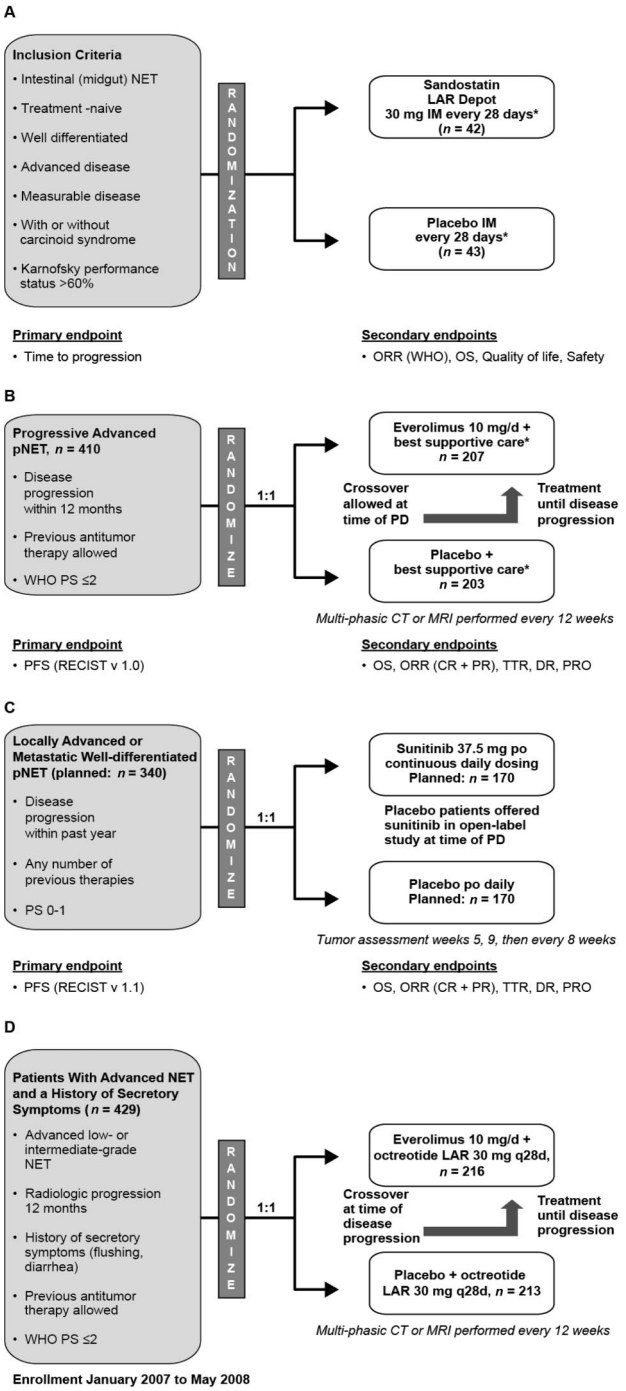

Figure 1. Study design in phase III trials in NET. **(A)** The PROMID trial of octreotide LAR [8]. **(B)** The RADIANT-3 study of everolimus [12]. **(C)** Study A6181111 of sunitinib [12]. **(D)** The RADIANT-2 study of everolimus plus octreotide LAR [58]. (**B** and **C** are reprinted from *Cancer Treatment Reviews* ©2012 with permission from Elsevier, Ltd. [12]).

testinal and pancreatic NETs that may also provide evidence of antitumor efficacy of somatostatin analogs. The multicenter, randomized, blinded efficacy and safety trial of the investigational somatostatin analog pasireotide LAR versus octreotide LAR in patients with metastatic NET and disease-related symptoms not controlled by currently available somatostatin analogs has recently been completed (NCT00690430). The CLARINET trial (NCT00353496), an international, randomized, placebo-controlled, phase III trial of 204 patients with nonfunctioning intestinal and pancreatic NETs, with the majority of patients (43%) having pancreatic NET, will be completed in 2013 [49]. In addition, a randomized phase II study, COOPERATE-2 (NCT01374451), evaluating the addition of pasireotide to everolimus, has completed accrual. These studies will provide invaluable insight regarding the role that somatostatin analogs may have as antitumor agents in NET.

Phase III Study of Sunitinib in Pancreatic NET

The VEGFr-TKI sunitinib (37.5 mg/day) was evaluated in a phase III prospective, multicenter, international, double-blind, placebo-controlled study of patients ($N = 171$) with well-differentiated pancreatic NET that were advanced, metastatic, or both (Fig. 1C). The primary study endpoint was PFS [17]. Although only one interim analysis had been planned, the Data Safety Monitoring Committee (DSMC) recommended termination after a third unplanned interim analysis, after observation of more deaths and serious adverse events in the placebo arm of the study [17]. At the final analysis, PFS favored sunitinib (median, 11.4 months vs. 5.5 months with placebo; HR, 0.42; 95% CI, 0.26–0.66; $p < .001$). Although sunitinib appeared to be associated with improved OS in a preliminary report based on 30 survival events [17], subsequent analyses did not demonstrate a survival advantage [42, 43]. The lack of a survival advantage may have been related, in part, to the fact that most patients in the placebo arm subsequently received sunitinib as part of a second study [42, 43].

Positive results of this study led to approval of sunitinib for patients with advanced pancreatic NET. Although there is little disagreement that the study demonstrated that sunitinib has activity in this setting, several aspects of the study limit interpretation of the actual effect size [50]. First, the performance of unplanned efficacy analyses led to an uncontrolled type 1 error rate [42]. When adjusted for the number of interim analyses actually taken, the observed PFS difference failed to cross the Lan-Demets and O'Brien-Fleming efficacy boundary for statistical significance. Second, the early interim efficacy analyses may have led to an overestimation of treatment effect because of the fact that large, random fluctuations of estimated treatment effect may occur early in the progress of randomized studies [42]. In one large analysis of randomized, controlled trials, the authors estimated that studies that terminate early may overestimate treatment effect by a factor of 0.71 [51]. In fact, subsequent OS reanalyses of the sunitinib data at a 43% event rate estimate nearly equal OS in the sunitinib and placebo arms (40% and 46%, respectively; HR, 0.74; 95% CI, 0.47–1.17) [50]. As in the PROMID study, early termination and the consequent smaller sample size increased the probability that imbalance in the arms could have contributed to the results [50]. Indeed, in this study, imbalances in randomization were seen with regard to Eastern Cooperative Oncology Group (ECOG) performance status (PS), extent of disease, and the presence of extrahepatic metastases [17].

Everolimus in the RADIANT-3 Study

Everolimus, the oral inhibitor of mTOR [52], has demonstrated antitumor efficacy in patients with advanced NET in phase III clinical studies [53]. In the large, prospective, international, multicenter, randomized, double-blind, placebo-controlled, phase III RADIANT-3 trial (Fig. 1B), involving 410 patients with

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progressing low- or intermediate-grade advanced pancreatic NET, everolimus 10 mg/day plus best supportive care (BSC) compared with placebo plus BSC demonstrated a 6.4-month prolongation of median PFS as assessed by the local investigator (11.0 months vs. 4.6 months; HR, 0.35; 95% CI, 0.27–0.45; $p < .0001$) [16]. Results from central assessment were consistent with those of the investigator analysis, recording median PFS of 11.4 months with everolimus compared with 5.4 months with placebo. Analyses of hormonal markers also demonstrated significant reductions in tumor-secreted hormones such as gastrin and glucagon among those with elevated markers at baseline [47].

Although the results of this study are robust with regard to the progression-free survival endpoint, as in the sunitinib study, no differences in overall survival were observed between the two arms. Although such a trend could have been obscured because of the inclusion of a crossover arm in the study design, improvements in PFS in studies with other malignancies nevertheless have often translated into trends favoring OS. In patients with neuroendocrine tumors, however, an OS endpoint is problematic, in large part because of the sometimes prolonged overall survival times in such patients. Estimation of OS, especially after disease progression, can be challenging if it is long in duration and if patients with rare diseases are treated. For example, a phase III study with 90% power to detect a 6-month improvement in OS (from 24 to 30 months) in pancreatic NET would require more than 1,400 patients—a number that far exceeds the total number of patients with newly diagnosed advanced disease in the United States. A similar carcinoid study conducted to detect a 6-month improvement in OS (from 4 to 4.5 years) would require more than 7,000 patients. Taking into account these considerations, an expert group that convened for a NET clinical trial planning meeting sponsored by the National Cancer Institute concluded that PFS, rather than OS, is the appropriate primary endpoint for most phase III studies in NET.

However, the inclusion of PFS as a primary endpoint in phase III studies is not without controversy, with some arguing that extending PFS does not provide any discernible clinical benefit to patients unless it is combined with other quantity- or quality-of-life advantages [54–56]. PFS estimates can be subjected to bias because of differences in evaluation times between treatment arms, making establishment of appropriate time points for measuring disease progression of critical importance [57]. In addition, given that missing data can complicate the analysis of PFS, the method for analyzing incomplete data and any censoring methods used should be clearly specified in the trial protocol, along with preplanned sensitivity analyses, to evaluate the robustness of the results [58]. PFS is also subject to potential investigator bias in reporting results, resulting in a recommendation for central, independent, blinded review or auditing to be used in pivotal phase III studies when true blinding is not possible [57].

Everolimus Plus Octreotide LAR in the RADIANT-2 Study

RADIANT-2 was a large, randomized, double-blind, placebo-controlled phase III trial of everolimus plus octreotide LAR in 429 patients with advanced, progressive NET with carcinoid symptoms (Fig. 1D) [59]. Patients were randomly assigned to receive everolimus + octreotide LAR or placebo + octreotide LAR. The primary endpoint was PFS assessed by central radiology review. Patients on placebo were allowed to cross over to everolimus on disease progression. As assessed by central review, median PFS was 16.4 months for the combination compared with 11.3 months for octreotide LAR alone (HR, 0.77; 95% CI, 0.59–1.00; one-sided log-rank test, $p = .026$; prespecified boundary for significance, $p \leq .0246$); the study therefore did not meet its prespecified endpoint [59].

A unique issue in this study, and one that may be more prevalent in NET studies than in studies of other malignancies, was the possible effect of informative censoring (i.e., determining whether patients who were taken off therapy early because of investigator-assessed radiologic progression and then were censored by central review could have affected the results). More PFS events were observed in both the everolimus arm and the placebo arm by local investigator review than by central review, suggesting an impact of informative censoring. The radiological assessment discrepancies between local investigator and central review resulted in a loss of events. Informative censoring likely occurred because patient treatment was based on local investigator review, whereas endpoint assessment was based on central review. When the local investigator determined that progression had occurred, patients receiving placebo were allowed to cross over to everolimus. If subsequent central review failed to confirm that the progression threshold had been crossed, these patients were then censored, and the central radiologist was effectively prevented from seeing the progression event, which may have come during the subsequent interval. This likely resulted in inflated PFS values in the placebo arm and reduced study power. An additional issue in the RADIANT-2 study was the heterogeneity of the patient population. Patient populations enrolled in RADIANT-3, PROMID, and the sunitinib trial were precisely defined and were relatively homogeneous. In contrast, the patient population enrolled in RADIANT-2 was heterogeneous, including patients with carcinoid tumors that arose in diverse locations and likely had different clinical behaviors. This diversity resulted in baseline imbalances that might have affected outcomes [59].

Appropriate Design and Implementation of Future Phase III Trials in NET

As observed in the previous examples, several aspects of phase III trials require particular attention when applied to patients with neuroendocrine tumors. One such issue is patient heterogeneity. Although patient populations enrolled in RADIANT-3, PROMID, and the sunitinib trial were carefully selected and were relatively homogeneous, patient populations enrolled in RADIANT-2 were heterogeneous, resulting in baseline imbalances that might have adversely influenced outcomes. These same studies, however, also provide an opportunity for a detailed, prospective analysis of prognostic as well as potential predictive markers that could be included as stratification factors in future studies. One such example is baseline chromogranin A [28], which appears to be a strong prognostic factor and is already currently included as a stratification factor in ongoing neuroendocrine tumor studies.

In part because of the heterogeneity of neuroendocrine tumors, early discontinuation of study accrual in neuroendocrine tumor trials may lead to a significant risk of imbalance in

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the treatment and control arms, as noted in the PROMID and sunitinib randomized trials. Early discontinuation is particularly problematic when it is based on unplanned interim analyses [50]. Particularly with a PFS endpoint, the decision to subsequently use the drug depends on weighing the magnitude of the benefit against its potential toxicity. Early interim analyses and early stopping limit the ability to estimate the magnitude of the PFS benefit [50].

Several other questions highlighted in recent NET randomized studies relate to the use of crossover designs, in which patients in the standard treatment arm receive the investigational agent at the time of tumor progression. Crossover has also recently become an area of controversy for randomized, controlled studies. Health authorities and some statisticians have cautioned against crossover. One major source of concern, best illustrated in the RADIANT-2 study, which based its primary endpoint on central radiology review, is that crossover of the control arm to the investigational therapy based on investigator-determined progression can lead to an imbalance in censoring. Such informative censoring has the potential to generate bias and inflate PFS in the control arm. The effect of crossover on censoring and on PFS estimates can be addressed by the use of investigator review data when true blinding is possible. Alternatively, real-time central review could be used to minimize informative censoring, or sponsors could decide to not censor patients for the start of new anticancer therapy. Although the latter approach would minimize informative censoring-induced bias, it could lead to inflated PFS estimates in both arms.

Another reason cited for avoiding crossover is that crossover tends to confound analyses of OS. The use of a formal crossover in RADIANT-3, as well as what was effectively a crossover in the randomized sunitinib study, may have contributed to the lack of survival benefit observed in these studies. However, these concerns must be balanced against ethical concerns about providing access to experimental therapy for patients who may have no other options and about the practicalities of accrual. If survival after disease progression is long in patients with NET, most studies designed for the PFS endpoint will have little power to detect an OS benefit. Longer survival means that any absolute benefits in PFS propagated into OS can be expected to result in a smaller relative change. In addition, heterogeneity in salvage therapy, whether crossover or off-protocol therapy, will further confound OS analyses. Thus, ethically, it would be difficult to deny the possibility of crossover when subsequent OS is likely underpowered and contaminated by chance.

Conclusions

The recent approval of two new therapeutic agents brings new hope for patients with NET after decades of treatment stagnation. However, it is clear that the drug development process in oncology leaves much to be desired, and particular challenges remain to be overcome in the attempt to have future agents for NET reach the market.

Although recent phase II and phase III trials in patients with NET have established the efficacy and safety of octreotide, everolimus, and sunitinib for treating patients with advanced NET, several important lessons have been learned from these studies that should be considered when future clinical studies are designed and conducted. Some of these lessons reveal limitations inherent in evaluating patients with NET, such as the inability to use OS as a primary endpoint because of the small patient population available and the often longer survival postprogression. Other lessons are based on the implications of study design and implementation, including the need to balance baseline prognostic factors and the consequences of early termination, informative censoring, and effect of crossover on OS analysis. The immediate future looks brighter for NET patients than it has for the past 25 years. It is hoped that investigators and sponsors will take steps to modify and focus future NET trials so that patients do not have to wait another 25 years for the next generation of therapeutic agents to arrive.

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Disclosures

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