Progression-free survival as a surrogate endpoint in advanced neuroendocrine neoplasms

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Abstract

In oncology clinical trials, overall survival (OS) is considered the gold standard outcome measure. In phase III trials for neuroendocrine neoplasms (NENs), however, progression-free survival (PFS) is more frequently used, as NENs are relatively rare and indolent neoplasms. But this surrogacy of PFS for OS has never been systematically validated. We, therefore, performed a literature-based analysis of phase II and III trials for NENs to evaluate the correlation between PFS and OS in NENs treated with medical treatment. We identified phase II and III clinical trials of medical treatment for advanced NENs based on a systematic electronic search using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. A total of 20 trials were identified, and 2530 patients and 30 treatment arms were included in the analysis. There was a statistically significant relationship between PFS and OS (r_s, 0.587; 95% confidence interval, 0.249–0.925). Conversely, the objective response rate was not significantly correlated with OS. The results of subgroup analyses indicated that the correlation between PFS and OS was higher for study arms that prohibited concomitant therapy with somatostatin analogues than for those that permitted it. The results of the present analysis indicate that PFS is significantly correlated with OS, and suggest that PFS is an acceptable surrogate for OS in clinical trials for NENs.

Key Words
- neuroendocrine neoplasms
- neuroendocrine tumor
- surrogate endpoint
- progression-free survival
- clinical trial

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Introduction

Neuroendocrine neoplasms (NENs) are epithelial neoplasms that exhibit neuroendocrine differentiation, and they can arise from neuroendocrine cells, which are distributed widely throughout the body. NENs are relatively rare, with an estimated incidence of approximately 3.65 patients per 10,000 person-years (Lawrence *et al.* 2011). However, the incidence of this neoplasm has been increasing over time (Yao *et al.* 2008).

NENs are typically indolent neoplasms, but their patterns of growth and progression are variable. Yao and coworkers reported that the incidence of localized, regional, and distant NENs were 40, 19 and 21%, respectively (Yao *et al.* 2008). Furthermore, NEN prognosis is highly dependent on extension behavior. Although surgical resection can sometimes result in long-term survival and even cure, (Landerholm *et al.* 2011, Norton *et al.* 2012) its indication is limited. Metastatic disease is associated

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with poorer prognosis, and median overall survival (OS) of metastatic NENs has been reported to be 12 months (Dasari *et al*. 2017). In the setting of metastatic NEN, systemic therapy is indicated for control of tumor growth and disease symptoms.

Somatostatin analogues (SSAs) have long been used to control clinical symptoms caused by functioning NENs. Additionally, SSAs have been shown to prolong progression-free survival (PFS) in NEN patients (Rinke *et al*. 2009, Caplin *et al*. 2014). The molecular targeted drugs, sunitinib and everolimus, have also been shown to prolong PFS in NENs patients, (Pavel *et al*. 2011, Raymond *et al*. 2011, Yao *et al*. 2011, 2016*a*) and are widely used to control tumor growth. The survival benefit of such systemic therapeutic agents for NENs is still unclear, however, and though PFS is the most frequently used primary endpoint in phase III trials for NENs, its surrogacy for OS has never been systematically validated.

Therefore, we performed a literature-based study of prospective trials of NEN treatments to assess the validity of PFS as a surrogate for the gold standard outcome measure, OS. The primary endpoint of this study was to evaluate the correlation between PFS and OS in subjects enrolled in medical treatment clinical trials for NENs. The secondary endpoint was to explore potential correlations between other possible surrogate markers (objective response rate (ORR) and disease control ratio (DCR)) and OS.

Materials and methods

Literature search

We identified phase II and III clinical trials of medical treatment for advanced NENs published between January 1996 and December 2016, based on a systematic electronic search using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The authors (H I and M S) independently screened each record for eligibility by examining the titles, abstracts and keywords. The search terms included 'neuroendocrine tumor', 'neuroendocrine neoplasm', 'neuroendocrine cancer', 'neuroendocrine carcinoma', or 'carcinoid'; 'drug therapy' or 'chemotherapy'; and 'clinical trial', 'controlled clinical trial', or 'randomized controlled trial'. The bibliographies of the identified articles were then screened for additional eligible articles. Among the identified articles, reports on trials including ≥20 patients per-arm were analyzed if they reported median OS and at least one surrogate endpoint. Excluded were: studies in which any arm received chemoradiotherapy, arterial infusion chemotherapy, or peptide receptor radionuclide therapy; phase I clinical trials with dose escalation design as a protocol; studies that included patients with neuroendocrine cancer defined by the WHO classification 2017. The search was limited to articles published in English.

Data collection

For each trial, the following data were extracted: first author's name; year of publication or report; trial design; medical treatment regimen; number of patients in each arm; potential surrogate markers (ORR, DCR, OS, PFS, time to progression (TTP), 6-month PFS rate, 12-month PFS rate, 12-month OS rate and biochemical response rate defined as normalization or ≥50% reduction in elevated serum chromogranin A level). In cases for which OS data were not described, data from updated reports, if available, were abstracted to complete them.

Statistical analysis

The nonparametric Spearman's rank correlation coefficient (r_s) or Pearson correlation coefficient (rp) were used to evaluate the correlations between potential surrogate markers and OS (per-arm correlation), and between treatment effects on surrogate endpoints and on OS (per-trial correlation). Furthermore, we used linear regression analysis to predict the effect of a treatment on OS based on its effect on PFS. The treatment effects on PFS and on OS were measured in terms of the differences in PFS (ΔPFS), OS (ΔOS), and log-transformed HRs (log HRPFS, and log HROS). Accounting for the variability of the number of trials included in each model, adjusted R^2 values were used to compare the goodness-of-fit of regression models. Values of r_s and rp closer to 1 indicated a strong positive correlation between the endpoints, and those of R^2 closer to 1 indicated that the variability of OS was predominantly explained by the surrogate endpoints.

To investigate possible reasons for heterogeneity of correlation, subgroup analyses were conducted according to publication year (before 2011 vs 2011 or later), origin of the tumor (pancreas only vs extrapancreatic organs included), study design (randomized trial vs non-randomized trial), progressive disease requirement as a protocol (required vs not required), crossover treatment (permitted vs not permitted), concomitant therapy with SSAs (allowed vs not allowed), and treatment drug type (molecular targeted drugs only vs drugs other than molecular targeted).

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Bootstrap methods with 1000 replications were applied to estimate confidence intervals (CIs) for the correlation parameters. P values <0.05 were considered statistically significant and all P values were two-sided. Data were analyzed using STATA version 14.2 statistical software (StataCorp, College Station, TX, USA).

Results

Selection of studies

A total of 20 trials (Ramanathan *et al*. 2001, Kulke *et al*. 2004, 2008, 2015, Stuart *et al*. 2004, Arnold *et al*. 2005, Sun *et al*. 2005, Yao *et al*. 2007, 2010, 2011, 2015, Dahan *et al*. 2009, Rinke *et al*. 2009, Pavel *et al*. 2011, Raymond *et al*. 2011, Chan *et al*. 2012, Meyer *et al*. 2014, Hobday *et al*. 2015, Bendell *et al*. 2016, Strosberg *et al*. 2016) with ≥20 patients per-arm were identified (10 randomized trials and 10 non-randomized trials), as well as four update reports (Yao *et al*. 2013, 2016*b*, Faivre *et al*. 2016, Rinke *et al*. 2017) (Fig. 1 and Table 1). The primary endpoint of 11 trials (55%) was ORR, and that of seven trials (35%) was PFS. Fifteen trials (75%) included pancreatic neuroendocrine tumor (PNET): nine of these also included gastrointestinal neuroendocrine tumor (GINET), but six included PNET only. A total of 2530 patients and 30 treatment arms were included in the analysis. The medians of the reported median OS and PFS were 34.5 months (range, 15.7–84.7 months) and 11.0 months (range, 4.5–26.7 months), respectively. Objective RR, DCR, PFS, TTP, 12-month PFS rate and biochemical response rate were reported in 30 (100.0%), 27 (90.0%), 23 (76.7%), 8 (26.7%), 7 (23.3%) and 9 treatment arms (30.0%), respectively.

Correlation between PFS and OS (per-arm analysis)

There was a significant relationship between PFS and OS (P=0.001). The r_s value for PFS and OS was 0.587 (Fig. 2), which corresponds to a moderate association. Results of subgroup analyses are summarized in Table 2. The correlation between PFS and OS was higher for study arms that prohibited concomitant therapy with SSAs (r_s=0.821; P=0.013) than for those that permitted it (r_s=0.423; P=0.053). Moreover, analyses according to crossover treatment showed that the correlation was higher for studies that prohibited concomitant SSA therapy (r_s=0.566; P=0.016). Correlations tended to be higher for study arms that: were in randomized trials; included

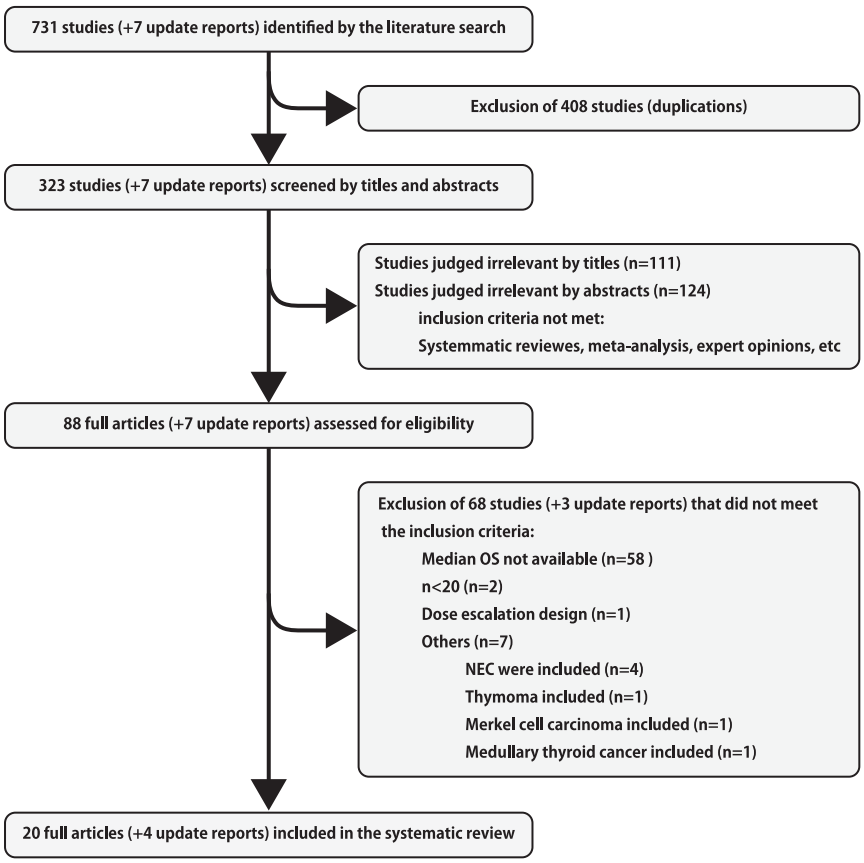

Figure 1
Flow chart of studies included in the systematic review of the literature. NEC, neuroendocrine carcinoma; OS, overall survival.

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Table 1 Characteristics of the trials included in the analysis.

Trials	Publication year	Phase	Primary endpoint	Treatment arm	No. of patients	PFS (months)	OS (months)
Randomized trial							
Sun *et al.* (2005)	2005	Phase 2/3	objective RR/PFS	Doxorubicin/FU vs STZ/FU	85 vs 78	4.5 vs 5.3	15.7 vs 24.3
Arnold *et al.* (2005)	2005	Phase 3	TTF	Octreotide/IFNα vs Octreotide	54 vs 51		54 vs 32
Dahan *et al.* (2009)	2009	Phase 3	1 year-PFS rate	IFNα vs STZ/FU	32 vs 32	14.1 vs 7.3	44.3 vs 30.4
Rinke *et al.* (2009)	2009	Phase 3	TTP	Octoreotide LAR vs Placebo	42 vs 43		84.7 vs 83.7 (Rinke *et al.* 2017)
Pavel *et al.* (2011)	2011	Phase 3	PFS	Everolimus/Octoretide LAR vs Placebo/Octoretide LAR	216 vs 213	16.4 vs 11.3	35.2 (Yao *et al.* 2013) vs 29.2
Yao *et al.* (2011)	2011	Phase 3	PFS	Everolimus vs Placebo	207 vs 203	11 vs 4.6	44 vs 37.7 (Yao *et al.* 2016*b*)
Raymond *et al.* (2011)	2011	Phase 3	PFS	Sunitinib vs Placebo	86 vs 85	11.4 vs 5.5	38.6 vs 29.1 (Faivre *et al.* 2016)
Meyer *et al.* (2014)	2014	Randomized Phase 2	objective RR	STZ/capecitabine/CDDP vs STZ/capecitabine	42 vs 42	9.7 vs 10.2	27.5 vs 26.7
Kulke *et al.* (2015)	2015	Randomized Phase 2	PFS	Everolimus/Bevacizumab vs Everolimus	75 vs 75	16.7 vs 14	36.7 vs 35
Yao *et al.* (2015)	2015	Phase 3	PFS	Bevacizumab/Octreotide LAR vs IFNα/Octreotide LAR	200 vs 202	16.6 vs 15.4	35.2 vs 47.3
Single-arm trial							
Ramanathan *et al.* (2001)	2001	Phase 2	Objective RR	Dacarbazine	50		19.3
Stuart *et al.* (2004)	2004	Phase 2	Objective RR	IFNγ	48		42
Kulke *et al.* (2004)	2004	Phase 2	Objective RR	Docetaxel	21	10	24
Yao *et al.* (2007)	2007	Phase 2	Objective RR	Imatinib	27	5.9	36
Kulke *et al.* (2008)	2008	Phase 2	Objective RR	Sunitinib	41		25.3
Yao *et al.* (2010)	2010	Phase 2	Objective RR	Everolimus	115	9.7	24.9
Chan *et al.* (2012)	2012	Phase 2	Objective RR	Temozolomide/Bevacizumab	34	11	33.3
Hobday *et al.* (2015)	2015	Phase 2	Objective RR/6 months-PFS rate	Temsirolimus/Bevacizumab	56	13.2	34
Bendell *et al.* (2016)	2016	Phase 2	Objective RR	Bevacizumab/Pertuzumab/ Octoreotide LAR	43	6.5	26.4
Strosberg *et al.* (2016)	2016	Phase 2	PFS	Axitinib	30	26.7	45.3

CDDP, cisplatin; FU, fluorouracil; IFN, interferon; OS, overall survival; PFS, progression-free survival; RR, response rate; STZ, storeptozocin; TTF, time to failure; TTP, time to progression.

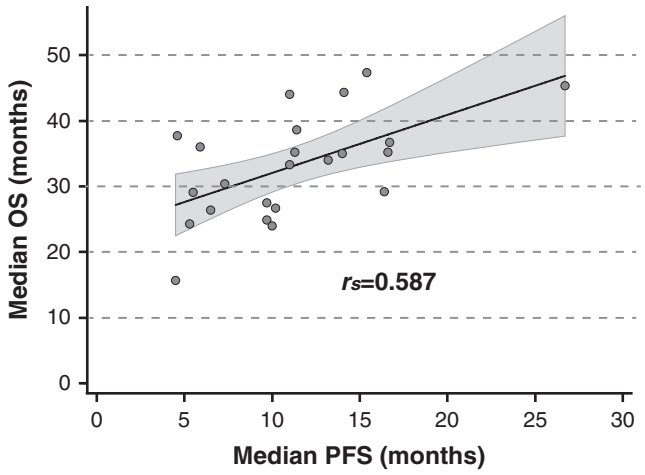

Figure 2
Correlation between PFS and OS. The gray area indicates the 95% confidence interval. r_s denotes Spearman's rank correlation coefficient. OS, overall survival; PFS, progression-free survival.

disease originating in extrapancreatic organs (e.g., GINET); not required progressive disease as a protocol; and included drugs other than molecular targeted drugs (e.g., cytotoxic drugs).

Correlation between the effects of treatment on PFS and OS (per-trial analysis)

For the analysis of correlations between the effects of treatment on PFS and OS, pair-wise treatment comparisons from the 10 randomized trials were analyzed as a unit. A total of eight pairs of ΔPFS/ΔOS were compared, and the correlation indicated a strong association between ΔPFS and ΔOS (r_s=0.810; 95% CI, 0.411–1.208; Fig. 3). The regression equation was ΔOS=−7.671 (95% CI, −16.551 to 1.210)+2.348 (95% CI, 0.347–4.348)×ΔPFS, and the adjusted R^2 was 0.509. Thus, per this model, differences in median PFS of 3, 6, 9, and 12 months corresponded to differences in median OS of −0.6, 6.4, 13.5, and 20.5 months, respectively. However, the large CI indicated the potential uncertainty due to small sample size. A total of six pairs of HRsPFS/OS were compared, but correlation between the HRPFS and HROS in each arm was negligible (rp=0.174; 95% CI −0.865 to 1.213).

Correlation between potential surrogate markers and OS (per-arm analysis)

Correlation between potential surrogate markers and OS are summarized in Table 3. The 12-month PFS rate showed a moderate correlation with OS (r_s=0.679; P=0.035); ORR and DCR were not significantly correlated with OS.

Discussion

The present study shows that PFS is significantly correlated with OS for subjects in NEN medical treatment clinical trials. The PFS-related surrogate marker, 12-month PFS

Table 2 Correlation analyses between PFS and OS according to each subgroup.

Subgroup	No. of treatment arms	r_s	95% CI	*P*-Value
Publication year				
≤2010	7	0.500	−0.407–1.407	0.280
≥2011	16	0.486	0.057–0.915	0.026
Origin of tumor				
Pancreas only	8	0.095	−0.676–0.866	0.809
Extrapancreatic organs included	15	0.665	0.268–1.062	0.001
Study design				
Randomized trial	16	0.533	0.110–0.955	0.013
Non-randomized trial	7	0.321	−0.658–1.301	0.520
Progressive disease requirement as a protocol				
Required	14	0.455	−0.059–0.969	0.083
Not required	9	0.617	0.044–1.190	0.035
Crossover treatment				
Permitted	5	−0.100	−1.398–1.198	0.880
Prohibited	18	0.566	0.104–1.028	0.016
Concomitant therapy with SSAs				
Allowed	18	0.423	−0.006–0.851	0.053
Not allowed	5	0.821	0.173–1.469	0.013
Study treatment				
Molecular targeted drugs only	11	0.373	−0.245–0.990	0.237
Drugs other than molecular targeted*	12	0.594	0.031–1.158	0.039

Drugs other than molecular targeted: cytotoxic drugs, SSAs, interferon, placebo. r_s denotes Spearman's rank correlation coefficient. CI, confident interval; SSA, somatostatin analog.

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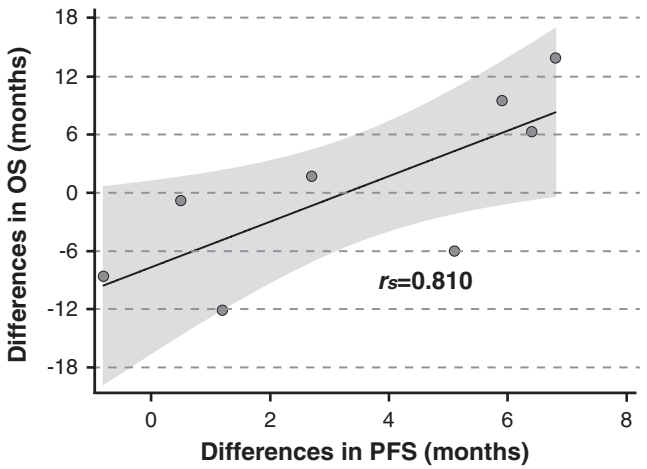

Figure 3
Correlation between the trial-level difference of PFS and that of OS. The gray area indicates the 95% confidence interval. r_s denotes Spearman's rank correlation coefficient. OS, overall survival; PFS, progression-free survival.

rate, is also correlated with OS. These findings support the legitimacy of using PFS as a surrogate for OS in clinical trials for NEN therapies. We also found that ORR, which most phase II trials employ as a primary endpoint, has no correlation with OS. Use of ORR as a primary endpoint in a preliminary phase II trial could result in a potentially effective therapy being missed.

Endpoints are measurable clinical and biological findings that are used for development and assessment of treatments. In oncology clinical trials, OS is considered the gold standard and it is the most commonly used primary endpoint. OS, generally defined as the span of time from study registration or randomization until death by any cause, is clinically meaningful and objectively measurable. To be informative, however, it requires long follow-up periods and a large trial population, elements that render a clinical trial both time-consuming and costly. Reliance on OS alone also delays the introduction of potentially effective therapies into clinical practice. PFS, generally defined as the time from study registration or randomization to the first of either disease progression or death from any cause, requires shorter follow-up periods and smaller sample sizes. Thus, PFS is frequently used as a surrogate endpoint for OS in oncology clinical trials. It has some important limitations, though: PFS can be affected by measurement timing, resulting in overestimation, and it may be biased by subjective assessment. Whether PFS can be accepted as a primary endpoint depends on its value as a surrogate endpoint for OS.

Surrogacy of PFS for OS has already been validated in certain types of tumors: in metastatic colorectal cancer and renal cell carcinoma, it has been shown that the effect of treatments on PFS is strongly associated with that on OS (Buyse *et al*. 2007, Delea *et al*. 2012). PFS has therefore been accepted as a primary endpoint in phase III trials for these cancers, (Douillard *et al*. 2010, Choueiri *et al*. 2015) accelerating development of new chemotherapeutic agents via rapid study completion. NENs are relatively rare, and tend to exhibit indolent progression, both of which factors could complicate recruiting for, and completion of clinical trials. Thus, in clinical trials for NENs, PFS is the most commonly used endpoint. Although Ter-Minassian *et al*. reported the correlation between PFS and OS in patients treated with SSAs or everolimus in their single institutional retrospective study, (Ter-Minassian *et al*. 2017) the surrogacy of PFS for OS has never been systematically validated. Therefore, we performed this literature-based study of prospective trials for NENs to assess the surrogacy of PFS for OS.

Although we found the correlation between PFS and OS to be significant, the degree of correlation was modest. This could be due to various kinds of correlation heterogeneity exhibited by the clinical trials that we analyzed. To characterize and clarify this heterogeneity, we performed subgroup analyses based on several clinical perspectives. The correlation between PFS and OS was higher in subgroups that prohibited concomitant

Table 3 Correlation analyses between potential surrogate markers and OS.

Endpoint	No. of treatment arms	r_s	95% CI	*P*-Value
ORR	30	−0.264	−0.636–0.108	0.164
DCR	27	−0.144	−0.556–0.269	0.495
PFS	23	0.587	0.249–0.925	0.001
TTP	8	0.048	−0.743–0.839	0.906
6-month PFS rate	5	0.600	−0.297–1.497	0.190
12-month PFS rate	7	0.679	0.047–1.310	0.035
12-month OS rate	13	0.517	−0.052–1.087	0.075
Biochemical response rate (Chromogranin A)	9	−0.350	−1.063–0.363	0.336

r_s denotes Spearman's rank correlation coefficient.
CI, confidence interval; DCR, disease control ratio; ORR, response rate; PFS, progression-free survival; TTP, time to progression.

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therapy with SSAs than in subgroup that allowed it. Because SSAs improve symptoms caused by excess hormone secretion by some NENs, many studies allowed concomitant SSA therapy. Recently, SSAs have also been shown to control tumor growth in patients with NENs. Thus, SSAs obviously affect apparent NEN prognosis: concomitant therapy with SSAs may bias the estimation of treatment effect on survival. Our subgroup analysis also showed that the correlation was higher in subgroups that (1) not required progressive disease as a protocol and (2) included NENs that originated in extrapancreatic organs. The prognoses and natural histories of NENs are highly variable and several trials required documentation of disease progression as an eligibility criterion because well-differentiated NENs sometimes remain symptom-free for years, even if untreated. The prognoses of NENs may also vary depending on site of origin; Panzuto and coworkers for example, reported that PNET has a more aggressive course than GINET (Panzuto *et al.* 2005). Thus, both treatment factors (concomitant therapy with SSAs) and disease factors (requirements regarding disease progression and site of origin) may contribute to heterogeneity of correlations in clinical trials for NENs.

This study had some limitations. First, we relied on summary data from published trials to assess the validity of a surrogate endpoint, so individual patient data were unavailable for analysis. It has already been reported that trial-level surrogacy is not necessarily reflective of individual-level outcomes, (Berlin *et al.* 2002) so our data cannot be used to predict an individual's chance of survival on the basis of their response to treatment. The second limitation is the small number of prospective studies—especially randomized trials—available for NENs, a factor that likely contributes to the heterogeneity of the clinical trials. Finally, the study lacked optimal statistical power and should therefore be considered only as an exploratory investigation. Given that clinical trials for NEN treatments frequently face recruitment and completion difficulties, however, the use of PFS instead of OS in clinical trials would allow for faster development and earlier implementation of new therapeutic agents via rapid study completion.

In conclusion, the results of the present analysis indicate that PFS is significantly correlated with OS. In clinical trials for NEN therapies, the surrogacy of PFS for OS in NENs is acceptable, and PFS can be used to support development of new therapeutic agents via rapid study completion.

Declaration of interest

M I has received research funding from Novartis Pharma K.K. and honoraria from Novartis Pharma K.K.; and is a member of advisory board for Norvartis Pharma K.K., Teijin Pharma and Nobel Pharma. The other authors have no conflicts of interest.

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Author contribution statement

The corresponding author was involved in the study design, interpretation and writing the manuscript. Data were analyzed by Mitsuhito Sasaki. The corresponding author and Mitsuhito Sasaki independently screened each record for eligibility. All authors had the opportunity to review the analysis plan and outcome, participated in the preparation of this report and provided final approval. The corresponding author had full access to the data and final responsibility for the decision to submit for publication.

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The corresponding author was involved in the study design, interpretation and manuscript composition. All authors reviewed the analysis plan and outcome, participated in the preparation of this report and provided final approval. The corresponding author had full access to the data and carries final responsibility for the decision to submit for publication.

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