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ORIGINAL RESEARCH

Treatment-related adverse events as predictive biomarkers of efficacy in patients with advanced neuroendocrine tumors treated with surufatinib: results from two phase III studies

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Background: No validated biomarkers currently exist for predicting the efficacy outcomes in patients with neuroendocrine tumors (NETs) treated with antiangiogenic therapy. We aimed to evaluate the association between treatment-related adverse events (TRAEs) and efficacy outcomes of surufatinib in patients with advanced NET.

Patients and methods: We included patients with NET treated with surufatinib in two multicenter, randomized, double-blind, placebo-controlled, phase III trials (SANET-p and SANET-ep) in this study. The main exposure was the presence of any of the TRAEs including hypertension, proteinuria, and hemorrhage in the first 4 weeks of surufatinib treatment. The primary outcome of the study was investigator-assessed progression-free survival (PFS). PFS outcomes were estimated using the Kaplan—Meier method with the log-rank test. Hazard ratios (HRs) were calculated by using univariable and multivariable Cox proportional hazard regression models. Blinded independent image review committee (BIIRC) assessments and 4-week landmark analysis were also performed as supportive evaluations.

Results: During the study period, a total of 242 patients treated with surufatinib were included in the analysis, and 164 (68%) patients had at least one of hypertension, proteinuria, and hemorrhage in the first 4 weeks of treatment. The presence of TRAEs in the first 4 weeks was associated with prolonged median PFS [11.1 versus 9.2 months; HR 0.67, 95% confidence interval (CI) 0.47-0.97; $P = 0.036$]. In multivariable Cox regression analysis, the presence of TRAEs was also significantly associated with longer PFS (HR 0.65, 95% CI 0.44-0.97; $P = 0.035$). Similar results were obtained in the BIIRC assessments and 4-week landmark analysis.

Conclusions: Treatment-related hypertension, proteinuria, and hemorrhage could be potential biomarkers to predict antitumor efficacy of surufatinib in patients with advanced NET. Future prospective studies are needed to validate the findings.

Trial registration: ClinicalTrials.gov NCT02589821; https://clinicaltrials.gov/ct2/show/NCT02589821 and ClinicalTrials.gov NCT02588170; https://clinicaltrials.gov/ct2/show/NCT02588170

Key words: neuroendocrine tumor, surufatinib, SANET, biomarker, adverse event

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INTRODUCTION

Neuroendocrine tumors (NETs) are relatively rare malignancies but have a rising incidence. In the United States, the annual incidence of NETs was 1.09 per 1 00 000 population in 1973 and increased to 6.98 per 1 00 000 population in 2012.[1] Although surgical excision is the primary treatment choice for locoregional NETs, ∼50% of patients with NET are diagnosed at an advanced or metastatic stage due to initial absence of specific symptoms.[2] Therefore, systemic treatment for NETs is essential.

NETs are highly vascularized tumors and have high expression of vascular endothelial growth factor (VEGF), which indicates potential clinical application of angiogenesis inhibitors.[3,4] In a randomized, double-blind, phase III study, sunitinib, a multiple receptor tyrosine kinases inhibitor (TKI) including vascular endothelial growth factor receptor (VEGFR), demonstrated a significantly higher objective response rate (ORR) and longer progression-free survival (PFS) than placebo in patients who had advanced pancreatic NETs, which led to US Food and Drug Administration (FDA) approval of sunitinib for advanced pancreatic NETs in 2011.[5] However, NETs can originate from different organs throughout the body with highly heterogeneous biological behaviors and respond to antiangiogenesis treatment differently. No treatment is approved by the FDA for NETs originating from both the pancreas and outside of the pancreas.[6]

Surufatinib is a novel small-molecule TKI that targets VEGFR-1, VEGFR-2, VEGFR-3, fibroblast growth factor receptor 1 (FGFR1), and colony-stimulating factor-1 receptor (CSF-1R) simultaneously.[7] In two randomized, double-blind, placebo-controlled, phase III trials named SANET-p and SANET-ep, surufatinib provided a significantly prolonged median PFS than placebo in both pancreatic [10.9 versus 3.7 months; hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.32-0.76; $P = 0.001$] and extrapancreatic (9.2 versus 3.8 months; HR 0.33, 95% CI 0.22-0.50; $P < 0.001$) patients with NET.[8,9] Based on the positive results of the two trials, the China National Medical Products Administration approved surufatinib in advanced extrapancreatic NET in 2020 and advanced pancreatic NET in 2021. Despite this, ∼30% of patients who received surufatinib still experienced disease progression within 6 months.[8,9] In addition, >60% of patients remained with stable disease and only 10%-20% of patients had complete response or partial response. Thus, exploring reliable biomarkers for predicting the response of surufatinib is essential.

Several retrospective studies of bevacizumab, axitinib, apatinib, and sunitinib suggested that antiangiogenesis-related adverse events (AEs) during the treatment period could predict clinical outcomes in multiple cancers.[10-12] However, treatment-related adverse events (TRAEs) have never been reported as predictive factors in patients with NET receiving surufatinib or any other similar antiangiogenic agents. In the SANET-p and SANET-ep trials, the most common TRAEs of surufatinib included hypertension, proteinuria, hemorrhage, and diarrhea, which are known AEs of angiogenesis inhibitors. Based on these observations, we conducted this study to investigate the relationship between TRAEs and efficacy outcomes in patients with advanced NET treated with surufatinib.

METHODS

Participants and study design

In this study, we included patients who had advanced, well-differentiated pancreatic or extrapancreatic NETs who received surufatinib from two multicenter, randomized, double-blind, placebo-controlled, phase III trials (SANET-p and SANET-ep). The detailed study design of the two trials have been previously reported.[8,9] The two trials were registered at ClinicalTrials.gov (NCT02589821 and NCT02588170, respectively). The inclusion criteria included patients who were >18 years old; had histologically proven advanced grade G1 or G2 NET; received at least one dose of surufatinib treatment; had at least one measurable lesion defined by RECIST version 1.1; and acceptable blood, liver, and renal functions. Patients received oral surufatinib 300 mg once daily in 4-week treatment cycles until disease progression or intolerable toxicity. Dose interruption and reduction (first to 250 mg and then 200 mg) were permitted to manage TRAEs during the study period.

All TRAEs verbatim descriptions were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or the most updated version. The grade of TRAEs was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The safety committee identified six TRAEs of special interest after reviewing safety data. The incidence of six prespecified categories of TRAEs in SANET-p and SANET-ep trials is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100453. The majority of TRAEs of surufatinib occurred before the initial 4 weeks of treatment. In addition, hypertension, proteinuria, and hemorrhage (any location of bleeding) were the most frequently reported TRAEs in first 4 weeks. Therefore, we defined the main exposure as the presence of any of these three TRAEs (i.e. hypertension, proteinuria, and hemorrhage) in the first 4 weeks of surufatinib treatment. Vital signs, laboratory tests, and Eastern Cooperative Oncology Group (ECOG) performance status were assessed at screening, day 1 of every cycle, and the end of treatment. Blood pressure measure, urinalysis, and chemistry tests were performed on days 8 and 22 of cycles 1 and 2; day 15 of cycle 2; and day 15 of subsequent cycles. TRAEs were collected throughout treatment and up to 30 days after the last dose.

Outcome measures

The primary outcome was investigator-assessed PFS, defined as the time from randomization to tumor progression or death. Secondary outcomes included investigator-assessed ORR, defined as the proportion of patients achieving complete or partial response as per RECIST version 1.1; and investigator-assessed disease control rate

(DCR), defined as the proportion of patients achieving complete response, partial response, or stable disease. Blinded independent image review committee (BIIRC)-assessed PFS, ORR, and DCR were supportive outcomes. Considering that patients with longer PFS may have a higher probability of developing TRAEs, landmark analyses were also performed by excluding patients who had disease progression or died before the landmark (4 weeks after the start of surufatinib treatment) as supportive analyses.

Statistical analysis

Characteristics of surufatinib-treated patients with NET with and without TRAEs were compared using a *t*-test for normally distributed continuous variables and chi-square test for categorical variables. Kaplan—Meier method was used to evaluate the endpoint of event arrival time, and log-rank test was applied to compare the survival differences between patients with and without TRAEs. The chi-square test was applied to compare ORR and DCR among groups. HR and 95% CI were calculated by the Cox proportional hazard regression model for PFS. Odds ratio (OR) and 95% Wald CI were calculated by the logistic regression model for ORR and DCR. Confounding factors were adjusted in multivariate regression models. Baseline covariates used for adjustment were selected using stepwise selection method from covariates with a *P*-value <0.2 in univariate analysis (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100453). Sex and age group were included based on subject matter knowledge. A *P*-value <0.05 (two-sided test) was considered to be statistically significant. The statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

Between 9 December 2015 and 11 November 2019, all patients ($n = 242$) treated with surufatinib in the SANET-p and SANET-ep trials were included in the analysis, and 164 (68%) patients had at least one of either hypertension, proteinuria, or hemorrhage in the first 4 weeks of treatment, of whom 116 (48%) patients had hypertension, 95 (39%) had proteinuria, and 47 (19%) had hemorrhage. The median follow-up time was 13.9 and 11.2 months in patients with and without TRAEs, respectively.

The baseline characteristics of patients who received surufatinib treatment are presented in Table 1. There was no significant difference in baseline characteristics between patients with TRAEs and without TRAEs except for age and sex. Compared with patients without TRAEs, patients who had at least one of the three AEs had an older median age at the time of diagnosis (53.0 versus 48.5 years; $P = 0.011$) and there was a higher percentage of females in this group (49% versus 36%; $P = 0.049$). Compared with patients without TRAEs, patients with TRAEs had statistically significant lower relative dose intensity (85.1% versus 93.0%; $P < 0.001$) and higher dose interruption or reduction rate (78.1% versus 62.8%; $P = 0.013$) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100453).

Table 1. Baseline characteristics of the patients with NET ($n = 242$) who received surufatinib treatment in the SANET-p and SANET-ep trials

Characteristics	With adverse events ($n = 164$)	Without adverse events ($n = 78$)	*P* value
Age, median (range)	53.0 (19-75)	48.5 (27-70)	0.011
Sex, *n* (%)			0.049
Male	83 (51)	50 (64)	
Female	81 (49)	28 (36)	
Primary tumor location, *n* (%)			0.104
Pancreas	69 (41)	44 (56)	
Gastrointestinal tract	47 (29)	14 (18)	
Lung and mediastinum	24 (15)	7 (9)	
Other/Unknown	24 (15)	14 (17)	
ECOG, *n* (%)			0.231
0	94 (57)	51 (65)	
1	70 (43)	27 (35)	
Pathological grade, *n* (%)			0.372
G1	26 (16)	9 (12)	
G2	138 (84)	69 (88)	
Ki-67, *n* (%)			0.512
<3%	27 (16)	9 (12)	
3%-10%	108 (66)	52 (66)	
>10%	29 (18)	17 (22)	
Functional status, *n* (%)			0.308
Functioning	9 (6)	7 (9)	
Nonfunctioning	155 (94)	71 (91)	
Number of organs involved, *n* (%)			0.352
≤2	67 (41)	27 (35)	
>2	97 (59)	51 (65)	
Received any previous systemic antitumor drug, *n* (%)			0.892
Yes	110 (67)	53 (68)	
No	54 (33)	25 (32)	
Received any prior somatostatin analogs treatment, *n* (%)			0.853
Yes	63 (38)	29 (37)	
No	101 (62)	49 (63)	

ECOG, Eastern Cooperative Oncology Group; NET, neuroendocrine tumor.

Association between TRAEs and antitumor efficacy

The presence of TRAEs in the first 4 weeks was statistically associated with longer median PFS (11.1 versus 9.2 months; HR 0.67, 95% CI 0.47-0.97; $P = 0.036$; Figure 1 and Table 2). The results remained consistent after adjusting for potential confounders, including age, sex, ECOG PS, prior somatostatin analogs treatment, and primary tumor location (Table 2). Patients with TRAEs also had numerically higher ORR (14.6% versus 11.5%; OR 1.31, 95% CI 0.58-2.98; $P = 0.512$) and DCR (82.3% versus 74.4%; OR 1.61, 95% CI 0.84-3.07; $P = 0.150$) than patients without TRAEs, but the differences were not statistically significant even after multiadjustment (Table 2). Additionally, we performed a complementary 4-week landmark analysis, and the results confirmed that the occurrence of TRAEs was significantly associated with prolonged median PFS (11.1 versus 9.2 months; HR 0.66, 95% CI 0.46-0.96; $P = 0.030$) (Supplementary Figure S2, available at

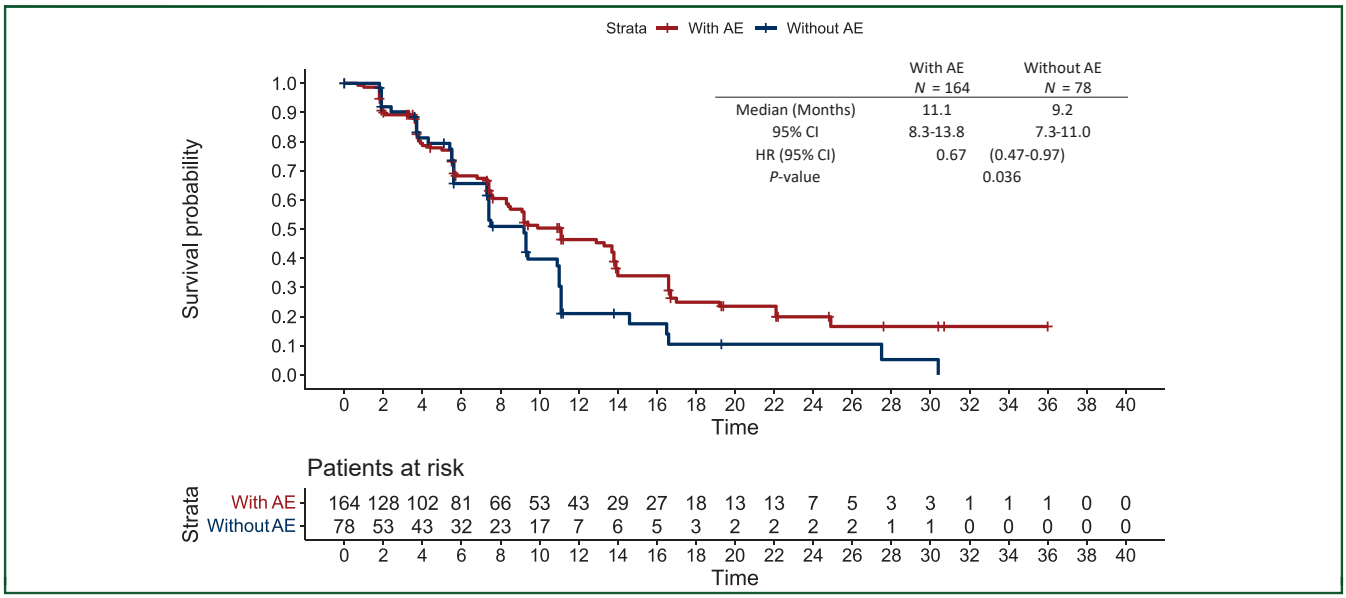

Figure 1. Kaplan–Meier curve of investigator-assessed progression-free survival by presence of treatment-related adverse events in the first 4 weeks of surufatinib treatment.
AEs, adverse events; CI, confidence interval.

https://doi.org/10.1016/j.esmoop.2022.100453). We did not find any significant differences in PFS between different grades of the TRAEs (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100453).

In the supportive analysis of BIIRC-assessed PFS, patients with TRAEs had numerically longer median PFS (9.4 versus 7.5 months; HR 0.75, 95% CI 0.51-1.10; $P = 0.132$), ORR (12.2% versus 6.4%; OR 2.03, 95% CI 0.73-5.62; $P = 0.167$) and DCR (78.7% versus 73.1%; OR 1.36, 95% CI 0.73-2.54; $P = 0.336$) than patients without TRAEs, and the differences in PFS (HR 0.63, 95% CI 0.41-0.95; $P = 0.027$) were statistically significant after multiadjustment (Table 2 and Supplementary Figure S4A, available at https://doi.org/10.1016/j.esmoop.2022.100453). The 4-week landmark analysis did not exclude any patients and thus obtained the same results (Supplementary Figure S4B, available at https://doi.org/10.1016/j.esmoop.2022.100453).

Compared with patients who received placebo, those who had TRAEs (11.1 versus 3.7 months; HR 0.43, 95% CI 0.32-0.58) and no TRAEs (9.2 versus 3.7 months; HR 0.61, 95% CI 0.43-0.88) had a statistically significant longer investigator-assessed median PFS (Supplementary Figure S5A, available at https://doi.org/10.1016/j.esmoop.2022.100453). Similar results were obtained in BIIRC assessment (Supplementary Figure S5B, available at https://doi.org/10.1016/j.esmoop.2022.100453).

DISCUSSION

In this study, treatment-related hypertension, proteinuria, and hemorrhage during the first 4 weeks of surufatinib treatment were associated with statistically significant longer PFS. These findings suggested that the TRAEs could be biomarkers to predict the antitumor efficacy of surufatinib in patients who had advanced NETs, which

Table 2. Correlation between the presence of at least one TRAE of surufatinib in the first 4 weeks and antitumor efficacy

Clinical outcomes	With TRAEs[a] ($n = 164$)	Without TRAEs[a] ($n = 78$)	Univariate analysis		Multivariate analysis[b]	
			HR/OR[c] (95% CI)	*P* value	HR/OR[c] (95% CI)	*P* value
Investigator assessment						
PFS, median (95% CI)	11.1 (8.3-13.8)	9.2 (7.3-11.0)	0.67 (0.47-0.97)	0.036	0.65 (0.44-0.97)	0.035
ORR, *n* (%)	24 (14.6)	9 (11.5)	1.31 (0.58-2.98)	0.512	1.55 (0.66-3.62)	0.315
DCR, *n* (%)	135 (82.3)	58 (74.4)	1.61 (0.84-3.07)	0.150	1.85 (0.91-3.77)	0.091
BIIRC assessment						
PFS, median (95% CI)	9.4 (9.2-13.9)	7.5 (7.3-11.0)	0.75 (0.51-1.10)	0.132	0.62 (0.40-0.94)	0.024
ORR, *n* (%)	20 (12.2)	5 (6.4)	2.03 (0.73-5.62)	0.167	2.26 (0.79-6.46)	0.130
DCR, *n* (%)	129 (78.7)	57 (73.1)	1.36 (0.73-2.54)	0.336	1.71 (0.88-3.37)	0.113

BIIRC, blinded independent image review committee; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; DCR, disease control rate; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse event.
[a]TRAEs are defined as hypertension, proteinuria, and hemorrhage.
[b]Adjusted for age, sex, ECOG, prior somatostatin analogs treatment and primary tumor location.
[c]HR for PFS; OR for ORR and DCR.

encouraged oncologists to pay attention to TRAEs that presented soon after starting surufatinib treatment.

In the SANET-p and SANET-ep trials, hypertension, proteinuria, and hemorrhage were the common TRAEs of surufatinib.[8,9] Although the incidence of the three TRAEs occurred in more than half of the patients (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100453) and there were three fatal bleeding events, most of these TRAEs could be managed through dose interruption and modification with an acceptable treatment discontinuation rate in the population. In addition, the safety profile of surufatinib was consistent with that of other angiogenesis inhibitors reported in previous clinical trials, but the spectrum of toxicities was a little different from those associated with other target treatment drugs in NET. For example, surufatinib had a much lower incidence of skin reactions (e.g. hand—foot syndrome) than the TKI sunitinib.[5] While a similar association between anti-angiogenesis related AEs of other TKIs and efficacy outcomes have been reported in other tumors, our findings are important because of the distinct tumor growth pattern of NETs and the unique antitumor mechanism of surufatinib.[7,10-12]

The mechanisms of antiangiogenic agent—induced AEs have not been fully elucidated, but several studies have suggested that the inhibition of VEGF pathway in tumor vasculature (rather than the tumors themselves) may play a role.[13] Inhibition of VEGFR on the surface of vascular endothelial cells can disrupt the cells' function and decrease the production of nitric oxide and prostacyclin, which could cause increased blood pressure and high susceptibility to hemorrhage.[14] The mechanism underlying proteinuria is complex, but it is suspected to involve treatment-induced hypertension and inhibition of podocyte-endothelial VEGF axis signalling.[15] It is hypothesized that angiogenesis inhibitor—induced AEs reflect the inherent susceptibility of blood vessels to VEGF blockade, and thus serve as a biomarker of VEGF pathway inhibition efficacy.[16]

The ideal biomarker should be simple, low-cost, testable, and easily manageable. Despite substantial efforts, identification of such a reliable biomarker for antiangiogenic agents remains elusive currently.[17] It has been previously reported that high expression of plasma-soluble VEGFR-2 and low expression of plasma basic fibroblast growth factor at baseline are prognostic biomarkers for prolonged PFS in advanced NETs treated with surufatinib.[18] Compared with biomarkers from tumor or blood sample, TRAEs cannot present before treatment, but they still occur quite early after initiation of therapy with advantages in measurement and cost. In addition, considering the dosage and schedule of drug administration can be adjusted case by case in patients experiencing TRAEs, TRAEs can help clinicians to optimize surufatinib treatment and move toward an individualized therapeutic approach. In conventional clinical practice, it is recommended to establish early close follow-up after treatment initiation and give patients easy access to unscheduled visits and consultations for detecting TRAEs and managing them promptly. It should also be noted that patients who received surufatinib but had no TRAEs still had a statistically significant longer PFS than patients who received placebo, so patients without early presence of TRAEs are still likely to benefit from remaining on surufatinib treatment.

Some limitations exist in this study. First, although the data were collected prospectively, the results were drawn retrospectively from published clinical trials. Second, pharmacokinetic data were not recorded. Although our study identified that patients with TRAEs had lower relative dose intensity than patients without TRAEs (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100453), we still cannot definitively exclude the possibility that association between clinical outcomes and TRAEs may result from increased drug exposure. In a meta-analysis that pooled pharmacokinetic and pharmacodynamic data of sunitinib from six clinical studies, sunitinib dose intensity and cumulative weekly dose were correlated with both higher blood pressure and improved clinical outcomes.[19] Third, the overall survival outcome was not mature at the cut-off date.

Conclusion

In conclusion, treatment-related hypertension, proteinuria, and hemorrhage in the first 4 weeks of surufatinib treatment could be viable predictive biomarkers of efficacy outcomes in patients with advanced NET. This simple, inexpensive, and testable biomarker deserves further investigation in future well-designed prospective studies.

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DISCLOSURE

The authors declare no competing interests.

DATA SHARING

The data of patients used in this study are available from the corresponding author upon reasonable request.

CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol, amendments, and informed consent forms were approved by the institutional review board or ethics committee of each participating center.

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