Original Article

Assessing the effectiveness and safety of surufatinib versus everolimus or sunitinib in advanced neuroendocrine neoplasms: insights from a real-world, retrospective cohort study using propensity score and inverse probability treatment weighting analysis

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Background: While surufatinib, sunitinib, and everolimus have shown efficacy for advanced neuroendocrine neoplasms (NENs) in randomized controlled trials (RCTs), direct comparisons in a real-world setting remain unexplored. This gap highlights the clinical need to understand their comparative effectiveness and safety within the diverse Chinese population. Addressing this, our study provides insights into the real-world performance of these therapies, aiming to inform treatment selection and improve patient outcomes.

Methods: A retrospective, observational study was conducted at Fudan University Shanghai Cancer Center, including patients with advanced NENs treated with surufatinib, sunitinib, or everolimus between July 2020 and April 2023. Eligibility criteria focused on histologically confirmed, locally advanced, unresectable, or metastatic NENs, with patients having received at least one month of targeted therapy. We employed inverse probability weighting (IPW) with the propensity score (PS) matching to adjust for the bias of baseline characteristics. The assessment of covariates included age, sex, performance status, primary tumor site, functional status, genetic mutations, tumor differentiation, Ki67 index, tumor grade, metastasis site, and previous therapies. The primary outcome was progression-free survival (PFS), and secondary outcomes included objective response rate (ORR), disease control rate (DCR), and adverse events (AEs).

Results: The study enrolled 123, 56, and 68 locally advanced or metastatic NEN patients treated with surufatinib, sunitinib, and everolimus, respectively. Before adjusting for confounding factors, surufatinib was used less frequently as a first-line treatment compared to sunitinib and everolimus in pancreatic NENs (pNENs) (11.1% *vs.* 22.1%, P=0.057). Significant differences were noted in prior treatments and tumor characteristics between surufatinib and everolimus groups in extrapancreatic NENs (epNENs) (P<0.05). Post-IPW, these disparities were resolved (P>0.05). Surufatinib demonstrated superior median PFS (mPFS) in both pancreatic [8.30 *vs.* 6.33 months, hazard ratio (HR) 0.592, P<0.001] and epNENs (8.73 *vs.* 3.70 months, HR 0.608, P<0.001) compared to everolimus or sunitinib. Notably, male gender (HR 1.75, P=0.001), functional status (HR 2.09, P=0.01), Ki67 index >20% (HR 12.7, P=0.004), previous somatostatin analogue (SSA) treatment (HR 1.73, P=0.001), germline mutation (HR 5.62, P<0.001), poor differentiation

(HR 7.45, P<0.001), liver metastasis (HR 1.72, P=0.001) and multiple treatment lines (HR 1.62 for 2nd line, P=0.04; HR 1.88 for ≥3rd line, P=0.01) were identified as negative prognostic factors for PFS. Conversely, dose adjustment (HR 0.63, P=0.009) and treatment with surufatinib (HR 0.58 for pNEN, P<0.001; HR 0.62 for epNEN, P=0.002) were correlated with longer PFS.

Conclusions: In a real-world Chinese cohort, surufatinib significantly outperformed sunitinib and everolimus in prolonging PFS among advanced NEN patients, with identifiable clinical features impacting survival, and conclusions regarding superiority should be interpreted with caution due to the retrospective design. Our findings underscore the need for prospective studies to further validate these results and explore additional predictive biomarkers for personalized treatment strategies.

Keywords: Neuroendocrine neoplasms (NENs); real-world study; targeted therapy; inverse probability treatment weighting; surufatinib

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Introduction

Neuroendocrine neoplasms (NENs) represent a rare entity originating from neuroendocrine cells, accounting for about 0.5% of all newly diagnosed malignancies (1,2). In the last decades, the incidence of NENs has shown a significant upward trend worldwide (3,4), with a large-sample study (64,791 NEN cases) based on the Surveillance, Epidemiology, and End Results (SEER) database finding that the age-adjusted incidence in 2012 (6.98/100,000 people) increased 6.4 times from that in 1973 (1.09/100,000 people) (5). NENs are highly heterogeneous tumors which can be divided into well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) according to tumor differentiation, with significant differences in their natural course and prognosis (6).

In view of the high complexity, rapidly growing incidence, and relatively longer survival, extensive treatment demands occur in NEN patients, and long-term and personalized health management play a crucial role. Surgery is the cornerstone of NEN therapeutic strategies, but 13–44% of NEN patients are detected with metastatic diseases at the diagnosis (7,8). Systemic therapy remains vital in advanced/metastatic NEN patients to control tumor growth and alleviate symptoms, which have been continuously developed in the past few decades, including biotherapy, chemotherapy, targeted therapy, and radiopharmaceuticals (6,9). With the gradual exploration of molecular pathways in NEN, relatively less toxic and efficient targeted therapies have received promising attention. In this context, the National Comprehensive Cancer Network (NCCN), European Neuroendocrine Tumor Society (ENETS), and Chinese Society of Clinical Oncology (CSCO) guidelines recommended targeted drugs as suitable options for patients with advanced NENs (10-12). Currently, three targeted

Highlight box

Key findings

- In a real-world setting in China, surufatinib significantly prolongs progression free survival for locally advanced or metastatic pancreatic neuroendocrine neoplasms (NENs) and extrapancreatic NENs patients compared with other targeted therapies.

What is known and what is new?

- Surufatinib, sunitinib and everolimus, all of which have been approved as standard treatment for advanced NENs patients in China, showed outstanding efficacy and safety compared with placebo in randomized controlled trials, while a head-to-head comparison and real-world studies are still lacking.
- This study demonstrates that the effectiveness and safety of surufatinib appears to be better than sunitinib and everolimus in Chinese real-life clinical practice. Potential predictive factors (e.g., tumor differentiation, Ki67 index, liver metastases) and clinical treatment pattern on targeted therapies have been also investigated.

What is the implication, and what should change now?

- Effectiveness data and safety profile, together with predictive clinical features, may lead to implications for selection of targeted agents in Chinese advanced NEN patients. Furthermore, these results should be investigated and validated in well-designed prospective studies, in which more laboratory and molecular biomarkers should be explored to facilitate personalized treatments for advanced NEN.

drugs have been approved in Chinese clinical practice including surufatinib, sunitinib, and everolimus.

NENs are characterized by a highly vascularized microenvironment, in which multiple angiogenic factors drive tumorigenesis and progression (13-15). Surufatinib, developed independently in China, is a novel tyrosine kinase inhibitor (TKI) which simultaneously targets vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and colony stimulating factor-1 receptor (CSF1 receptor), and has been shown to prolong progression-free survival (PFS) in advanced pancreatic (pNEN) and extrapancreatic NEN (epNEN) through the SANET-p and SANET-ep phase III trials (16,17). At present, surufatinib covers nearly all site-originated NEN, whereas sunitinib has shown survival benefits for advanced pNEN (18) and everolimus, an oral mTOR inhibitor (mTORi), was reported to achieve a significantly longer PFS in advanced gastroenteropancreatic (GEP) or lung NENs through the RADIANT-3 and RADIANT-4 trials (19,20).

While surufatinib, sunitinib and everolimus have shown efficacy for advanced NENs in randomized controlled trials (RCTs), direct comparisons in a real-world setting remain unexplored. Due to the heterogeneity of NEN, the difficulty of diagnosis and treatment in real-world clinical practice appears significantly higher than in strictly-controlled clinical trial environments. The actual benefits of targeted drugs remain unclear, so this gap highlights the clinical need to understand their comparative effectiveness and safety within the diverse Chinese population. Therefore, we conducted an observational study and analyzed real-world data to evaluate the efficacy and safety of surufatinib compared with sunitinib and everolimus for advanced NEN patients in China, in order to provide insights, inform treatment selection and improve patient outcomes into the real-world performance. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-218/rc).

Methods

Study design and patients

This was a retrospective cohort study conducted at Fudan University Shanghai Cancer Center. Patients treated with surufatinib, sunitinib, or everolimus between July 2020 and April 2023 were identified, with the observation period lasting from first administration of targeted agents until disease progression/death, loss to follow-up, or the end of the study. The follow-up was until November 2023. Genomic profiles for pNEN were clearer than epNEN, in which more abundant evidences demonstrated that molecular circuits regulating angiogenesis exerts a critical role throughout the development of pNEN (14,21). Furthermore, considering the differences in disease characteristics and indications, the included patients were divided into pNEN and epNEN patients, among whom the study analysis were made on surufatinib treatment cohort *vs.* sunitinib or everolimus (sunitinib + everolimus) treatment cohort for pNEN patients and surufatinib treatment cohort *vs.* everolimus treatment cohort for epNEN patients.

The eligibility criteria were as follows: histological diagnosis of locally advanced unresectable or metastatic NEN (including pheochromocytoma/paraganglioma), having already received at least 1 month of targeted therapy. Patients with incomplete medical records were excluded. During baseline and follow-up period, clinical characteristics, treatment, efficacy and safety pertaining to included patients were collected through the electronic hospital information system (HIS) and telephone, based on International Agency for Research on Cancer (IARC)/World Health Organization (WHO) classification framework and consensus (22). The sample size of the study was determined by the number of patients that could be retrospectively collected from HIS of Fudan University Shanghai Cancer Center. Clinico-pathologic variables were collected and assessed for the propensity score (PS) calculation, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG-PS), primary tumor site, functional status, genetic mutations, tumor differentiation, Ki67 index, tumor grade, metastasis site, and previous therapies. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by institutional ethics committee of Fudan University Shanghai Cancer Center (No. 2205254-19) and individual consent for this retrospective analysis was waived.

Treatment

The standard doses were set at 300 mg for surufatinib, 37.5 mg for sunitinib, and 10 mg for everolimus, once daily continuously. Initial dose, dose modification, and dose interruption were made solely at the physician's discretion, according to disease severity and patient tolerance.

Moreover, we imposed no restrictions on treatment lines or combination therapies, leaving this to the judgement of the medical staff.

Evaluation and endpoints

The primary outcome was PFS, defined as the time from first targeted agent administration to disease progression or death. Tumor responses were evaluated routinely every 2–3 months as complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) (23). If disease progression or death had not occurred in a certain patient, the last follow-up time was censored. Secondary outcomes included objective response rate (ORR), defined as the proportion of patients achieving CR and PR; disease control rate (DCR), defined as the proportion of patients with CR, PR, and SD; adverse events (AEs), identified and graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) (24).

Statistics

Descriptive statistical methods were utilized to summarize data. The Pearson's chi-square test/Fisher's exact test and the Wilcoxon test/*t*-test were used to assess differences of categorical variables and continuous variables among groups.

Inverse probability weighting (IPW) with the PS was applied to account for the bias of baseline characteristics, which created a pseudo-population for the following analysis between targeted agent groups. IPW adjusts weights based on PSs to address confounding factors. Compared to PS matching, IPW method does not result in sample size loss and can fully utilize all case data to avoid sample selection bias. Unadjusted and IPW-adjusted Kaplan-Meier curves were drawn, and PFS was compared using Cox proportional hazards model with hazard ratio (HR) and 95% confidence interval (CI). ORR and DCR were compared with the Pearson's chi-square test method. Univariate and multivariate analyses were performed using Cox proportional hazards model to determine meaningful independent indicators on efficacy outcomes with HR and 95% CI estimation. In addition, exploratory subgroup analyses were performed for PFS between treatment groups.

Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA). A two-sided significance level of P<0.05 on all statistic tests was defined.

Results

Patient characteristics

Out of 267 assessed patients, those eligible were enrolled as follows: 123 in the surufatinib group, 56 in the sunitinib group, and 68 in the everolimus group (*Figure 1*). *Table 1* summarizes the patients' baseline characteristics. The inferior baseline profile of the surufatinib group, compared to others, created an imbalance between groups, hence all were incorporated into the PS calculation for IPW. Before IPW, for pNEN, the number of patients receiving surufatinib as first-line treatment was slightly less than that in the sunitinib + everolimus group (11.1% *vs.* 22.1%, P=0.057); for epNEN, there were significant differences in previous somatostatin analogues (SSA), primary tumor site, liver metastasis, treatment line, and treatment regimen between surufatinib and everolimus (P<0.05). After IPW adjustment, all baseline data of the two groups were balanced without significant differences (P>0.05).

Clinical treatment

In the IPW-adjusted cohort, nearly 80% of pNEN and epNEN patients received monotherapy in the two treatment groups, and the remaining patients were treated with combination therapy including SSAs, targeted agents, chemotherapy, and immune checkpoint inhibitors (ICIs).

Figure 2 shows the initial and final dose of the three targeted agents at IPW-adjusted cohort. Less patients received the standard dose initially and throughout the whole treatment course in the surufatinib group with 300 mg/day compared to that in sunitinib group with 37.5 mg/day and everolimus group with 10 mg/day (P<0.001). Through the treatment course, in the pNEN population, surufatinib's dose of 250 mg increased from 22.4% to 49.5%, whereas that of 200 mg decreased from 66.3% to 45.1%. Sunitinib's 25 mg dose rose from 19.5% to 34.8%, and that of 37.5 mg fell from 80.5% to 63.8%. Everolimus saw a rise in the 10 mg dose from 35.3% to 59.0%, and a drop in 5 mg from 59.3% to 16.4%. Through the treatment course, surufatinib's 250 mg dose increased from 2.5% to 9%, and 200 mg decreased from 86.3% to 76.2% in epNEN patients. Everolimus's 10 mg dose increased from 29.5% to 54.5%, and that of 5 mg decreased

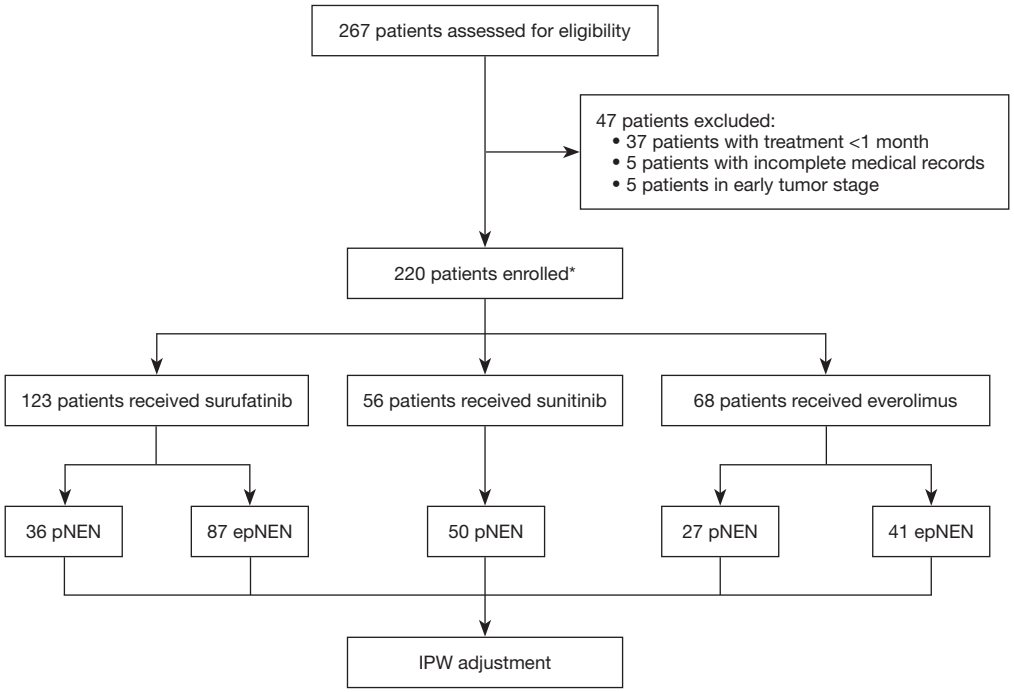

Figure 1 Flow chart of patient enrollment. pNEN, pancreatic neuroendocrine neoplasm; epNEN, extrapancreatic neuroendocrine neoplasm; IPW, inverse probability weighting.

from 52.7% to 18.8%.

Efficacy

In the unadjusted and IPW-adjusted cohort, surufatinib showed significantly longer median PFS (mPFS) than did sunitinib + everolimus in pNEN patients with the median follow-up time as 11 and 15 months, respectively (unadjusted cohort: 8.67 *vs.* 6.37 months, HR 0.587, 95% CI: 0.372–0.927, P=0.02; IPW-adjusted cohort: 8.30 *vs.* 6.33 months, HR 0.592, 95% CI: 0.436–0.804, P<0.001) (*Figure 3A,3B*). For epNEN patients, surufatinib showed significantly superior mPFS benefit over everolimus after IPW adjustment with the median follow-up time as 10 and 13 months, respectively (unadjusted cohort: 9.47 *vs.* 6.70 months, HR 0.728, 95% CI: 0.471–1.126, P=0.15; IPW-adjusted cohort: 8.73 *vs.* 3.70 months, HR 0.608, 95% CI: 0.456–0.810, P<0.001) (*Figure 3C,3D*). In addition, ORR and DCR were also found to have significant differences between targeted agent groups in pNEN and epNEN patients (*Table 2*).

Subgroup analysis of PFS in the IPW-adjusted cohort is shown in *Figure 4* and demonstrated surufatinib's notable survival benefits over controls. In pNEN, mPFS was 11.3 months with Ki67 3–20%, to 11.87 months for first-line, 12.63 months for initial full dose, and 13.13 months with dose adjustment. In epNEN, Ki67 3–20% had a mPFS of 10.4 months, first-line was 12.63 months, initial full dose was 9.47 months, dose adjustment was 11.1 months, and lung/thymus was 10.4 months.

To define whether certain clinical features impacted on PFS in NEN patients with targeted agents, univariate and multivariate analysis were performed (*Tables 3,4*). Multivariate Cox analysis revealed that male, functional status, Ki67 index >20%, previous SSA and germline mutation, poor differentiation at histopathology, liver metastasis, and multi treatment lines had a negative effect on PFS in pNEN and epNEN patients, respectively, whereas previous mTORi, dose adjustment, and surufatinib correlated with longer PFS.

Table 1 Patient baseline characteristics

Characteristics	Unadjusted cohort						IPW-adjusted cohort					
	pNEN			epNEN			pNEN			epNEN		
	Suru, N=36	Suni + Eve, N=77	P value	Suru, N=87	Eve, N=41	P value	Suru	Suni + Eve	P value	Suru	Eve	P value
Sex			0.72			0.43			0.72			0.91
Male	16 (44.4)	37 (48.1)		51 (58.6)	21 (51.2)		50.2%	52.6%		50.8%	51.5%	
Female	20 (55.6)	40 (51.9)		36 (41.4)	20 (48.8)		49.8%	47.4%		49.2%	48.5%	
Age, years	50.6±14.7	50.2±13.0	0.76	54.3±11.8	52.9±10.3	0.51	48.2±26.2	49.7±15.3	0.57	54.4±14.6	54.6±18.0	0.92
ECOG-PS			>0.99			0.59			0.34			0.47
0–1	36 (100.0)	76 (98.7)		85 (97.7)	39 (95.1)		100%	99.1%		96.7%	98.1%	
≥2	0	1 (1.3)		2 (2.3)	2 (4.9)		0%	0.9%		3.3%	1.9%	
Primary tumor site			–			0.005			–			0.32
Thymus/mediastinum	–	–		28 (32.2)	6 (14.6)		–	–		25.2%	20.3%	
Lung	–	–		16 (18.4)	8 (19.5)		–	–		24.1%	34.7%	
Colorectum	–	–		13 (14.9)	16 (39.0)		–	–		22.5%	22.2%	
Stomach	–	–		4 (4.6)	3 (7.3)		–	–		5%	4.2%	
Small intestine	–	–		0	3 (7.3)		–	–		0%	2.4%	
Other	–	–		13 (14.9)	3 (7.3)		–	–		11.8%	7.6%	
Multiple primary	–	–		7 (8.0)	1 (2.4)		–	–		6.1%	4.9%	
Unknown primary	–	–		6 (6.9)	1 (2.4)		–	–		5.3%	3.7%	
Functional status			0.38			>0.99			0.45			0.38
Functional	3 (8.3)	3 (3.9)		4 (4.6)	2 (4.9)		8.1%	5.5%		5%	2.9%	
Non-functional	33 (91.7)	74 (96.1)		83 (95.4)	39 (95.1)		91.9%	94.5%		95%	97.1%	
Genetic syndrome			0.55			0.14			0.10			0.68
Sporadic	36 (100.0)	74 (96.1)		74 (85.1)	39 (95.1)		100%	97.4%		88.4%	86.7%	
Germline mutated	0	3 (3.9)		13 (14.9)	2 (4.9)		0%	2.6%		11.6%	13.3%	
Differentiation			–			0.71			–			0.16
Well-differentiated	36 (100.0)	77 (100.0)		80 (92.0)	39 (95.1)		100%	100%		92.5%	87.2%	
Poorly-differentiated	0	0		7 (8.0)	2 (4.9)		0%	0%		7.5%	12.8%	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Unadjusted cohort						IPW-adjusted cohort					
	pNEN			epNEN			pNEN			epNEN		
	Suru, N=36	Suni + Eve, N=77	P value	Suru, N=87	Eve, N=41	P value	Suru	Suni + Eve	P value	Suru	Eve	P value
Ki67 index			0.44			0.17			0.88			0.93
<3%	1 (2.8)	1 (1.3)		7 (8.0)	5 (12.2)		1.4%	1.3%		7.1%	6.1%	
3–20%	32 (88.9)	64 (83.1)		57 (65.5)	31 (75.6)		82.5%	85%		71.3%	71.4%	
>20%	3 (8.3)	12 (15.6)		23 (26.4)	5 (12.2)		16%	13.7%		21.6%	22.5%	
Distant metastasis			>0.99			0.16			0.80			0.32
Locally advanced	1 (2.8)	2 (2.6)		9 (10.3)	1 (2.4)		3.6%	3%		7.8%	11.4%	
Distant metastatic	35 (97.2)	75 (97.4)		78 (89.7)	40 (97.6)		96.4%	97%		92.2%	88.6%	
Metastatic site number			0.54			0.80			0.44			0.82
0	33 (91.7)	66 (85.7)		64 (73.6)	31 (75.6)		90.3%	87%		75.6%	76.7%	
≥3	3 (8.3)	11 (14.3)		23 (26.4)	10 (24.4)		9.7%	13%		24.4%	23.3%	
Liver metastasis			0.67			0.02			0.80			0.48
Yes	33 (91.7)	73 (94.8)		39 (44.8)	27 (65.9)		93.9%	94.6%		50.1%	54.6%	
No	3 (8.3)	4 (5.2)		48 (55.2)	14 (34.1)		6.1%	5.4%		49.9%	45.4%	
Bone metastasis			0.88			0.54			0.19			0.41
Yes	6 (16.7)	12 (15.6)		46 (52.9)	24 (58.5)		19.6%	13.1%		48.4%	43.2%	
No	30 (83.3)	65 (84.4)		41 (47.1)	17 (41.5)		80.4%	86.9%		51.6%	56.8%	
Prior surgery			0.20			0.45			0.46			0.23
Yes	15 (41.7)	42 (54.5)		47 (54.0)	25 (61.0)		42.7%	47.7%		53.1%	60.5%	
No	21 (58.3)	35 (45.5)		40 (46.0)	16 (39.0)		57.3%	52.3%		46.9%	39.5%	
Prior radiotherapy			>0.99			0.51			0.30			0.28
Yes	0	1 (1.3)		26 (29.9)	10 (24.4)		0%	1%		32%	38.5%	
No	36 (100.0)	76 (98.7)		61 (70.1)	31 (75.6)		100%	99%		68%	61.5%	
Previous SSA			0.40			<0.001			0.42			0.59
Yes	24 (66.7)	45 (58.4)		26 (29.9)	26 (63.4)		65.7%	60.4%		41.9%	38.6%	
No	12 (33.3)	32 (41.6)		61 (70.1)	15 (36.6)		34.3%	39.6%		58.1%	61.4%	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Unadjusted cohort						IPW-adjusted cohort					
	pNEN			epNEN			pNEN			epNEN		
	Suru, N=36	Suni + Eve, N=77	P value	Suru, N=87	Eve, N=41	P value	Suru	Suni + Eve	P value	Suru	Eve	P value
Previous anti-ang agents			0.13			0.07			0.56			0.83
Yes	6 (16.7)	23 (29.9)		12 (13.8)	11 (26.8)		21.7%	25.1%		20.6%	21.7%	
No	30 (83.3)	54 (70.1)		75 (86.2)	30 (73.2)		78.3%	74.9%		79.4%	78.3%	
Previous mTORi			0.16			0.34			0.28			0.93
Yes	1 (2.8)	9 (11.7)		7 (8.0)	6 (14.6)		5%	8.8%		8.3%	8.6%	
No	35 (97.2)	68 (88.3)		80 (92.0)	35 (85.4)		95%	91.2%		91.7%	91.4%	
Previous chemotherapy			0.12			0.3			0.93			0.27
Yes	16 (44.4)	46 (59.7)		53 (60.9)	21 (51.2)		55.3%	55.8%		58.5%	65.2%	
No	20 (55.6)	31 (40.3)		34 (39.1)	20 (48.8)		44.7%	44.2%		41.5%	34.8%	
Treatment line			0.057			0.03			0.71			0.55
1	4 (11.1)	17 (22.1)		20 (23.0)	6 (14.6)		14.4%	18.5%		19.7%	15.2%	
2	20 (55.6)	25 (32.5)		43 (49.4)	14 (34.1)		41.6%	40.2%		40.3%	39.2%	
≥3	12 (33.4)	35 (45.4)		24 (27.6)	21 (51.2)		44%	41.3%		40.1%	45.5%	
Treatment regimen			0.40			<0.001			0.81			0.48
Monotherapy	27 (75.0)	63 (81.8)		79 (90.8)	26 (63.4)		77.4%	78.7%		79.6%	83%	
Combined therapy	9 (25.0)	14 (18.2)		8 (9.2)	15 (36.6)		22.6%	21.3%		20.4%	17%	

Data are presented as n (%), mean ± SD, or percentage. IPW, inverse probability weighting; pNEN, pancreatic neuroendocrine neoplasm; epNEN, extrapancreatic neuroendocrine neoplasm; Suru, surufatinib; Suni, sunitinib; Eve, everolimus; SD, standard deviation; ECOG-PS, Eastern Cooperative Oncology Group performance status; SSA, somatostatin analogues; anti-ang, anti-angiogenesis; mTORi, mTOR inhibitor.

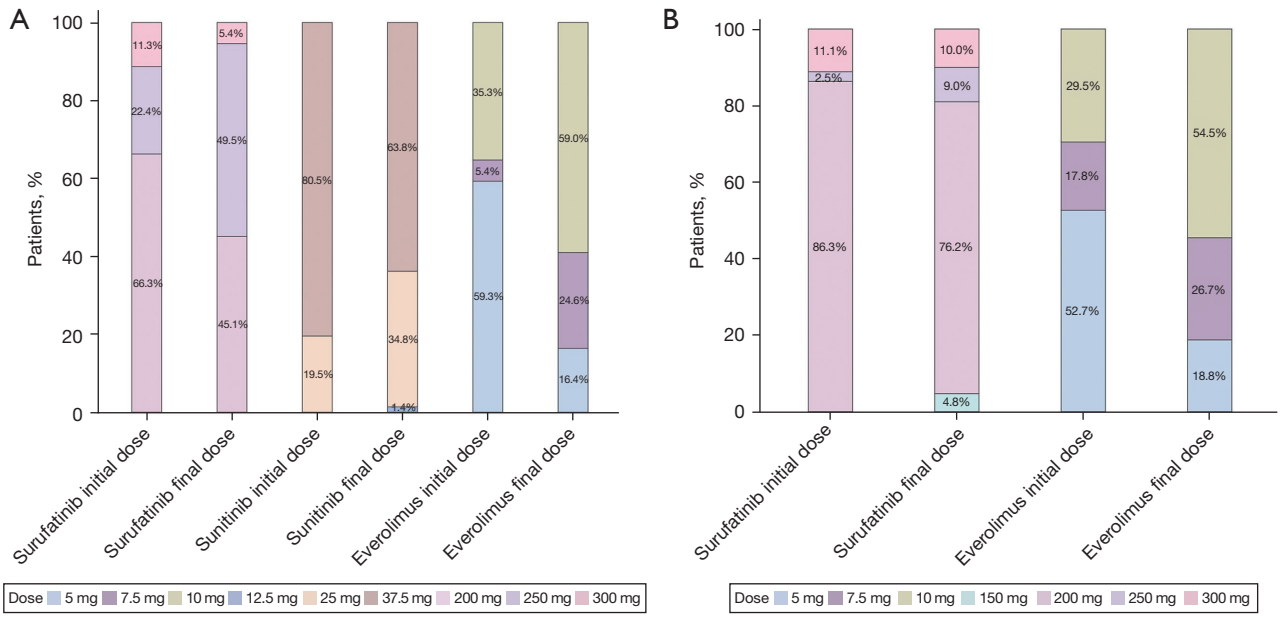

Figure 2 Initial and final dose of targeted agent during treatment course in (A) pNEN and (B) epNEN patients at IPW-adjusted cohort. pNEN, pancreatic neuroendocrine neoplasm; epNEN, extrapancreatic neuroendocrine neoplasm; IPW, inverse probability weighting.

Safety

Overall, no significant differences were found in the frequency of treatment-related AE with surufatinib, sunitinib, and everolimus in pNEN and epNEN patients (P=0.46 and 0.42) (*Tables 5*,*6*). In the pNEN cohort, the reported incidence of grade 3 or higher treatment-related AE were 26.0% for sunitinib, 25% for surufatinib, and 11.1% for everolimus (*Table 5*). Within the epNEN group, such AEs occurred in 31% of patients treated with surufatinib and 17.1% with everolimus (*Table 6*). The spectrum of AEs varied between targeted agents. The most frequent AEs were proteinuria, hypertension, increased blood thyroid-stimulating hormone, increased bilirubin, and hyperuricemia with surufatinib; hematologic toxicity (decreased platelet count, deceased white blood cell, decreased neutrophil count, and anemia) with sunitinib; anemia, hyperglycemia, hyperlipemia, stomatitis, and increased liver enzymes (γ-glutamyl transferase, aspartate aminotransferase) with everolimus. Moreover, the most common grade 3 or >3 AE that patients experienced was hypertension with surufatinib, which was typically controlled with medical management; decreased neutrophil count with sunitinib and anemia with everolimus were also effectively managed as per clinical guidelines. Apart from that, diarrhea (P=0.03), hypothyroidism (P=0.02), and occult blood positive (P=0.02) were found more commonly with surufatinib, whereas interstitial pneumonia (P=0.009) was more likely to appear with everolimus.

Discussion

NEN is a neoplasm with extremely high heterogeneity, which in some cases can be mixed with non-neuroendocrine components, resulting in significant differences in biological behavior, malignant potential and prognosis of NEN (25). NENs have been found in multiple organs, of which GEP-NENs are more common and thymic/lung NEN appear relatively rare (6,26). The development and advancement of targeted therapies have revolutionized the treatment landscape for advanced NENs, with endorsement by worldwide national treatment guidelines. To our knowledge, this is the first study to compare the efficacy and safety of surufatinib, sunitinib, and everolimus, all of which have been approved as standard treatment for advanced NENs patients in China. With high heterogeneity of NEN, it is critical to explore whether various clinical subtypes could benefit from current targeted agents in the real world.

Our study demonstrated that surufatinib (pNEN: 8.30 months, epNEN: 8.73 months) showed significantly superior mPFS benefit over sunitinib and everolimus in the overall population. Data on surufatinib, a targeted

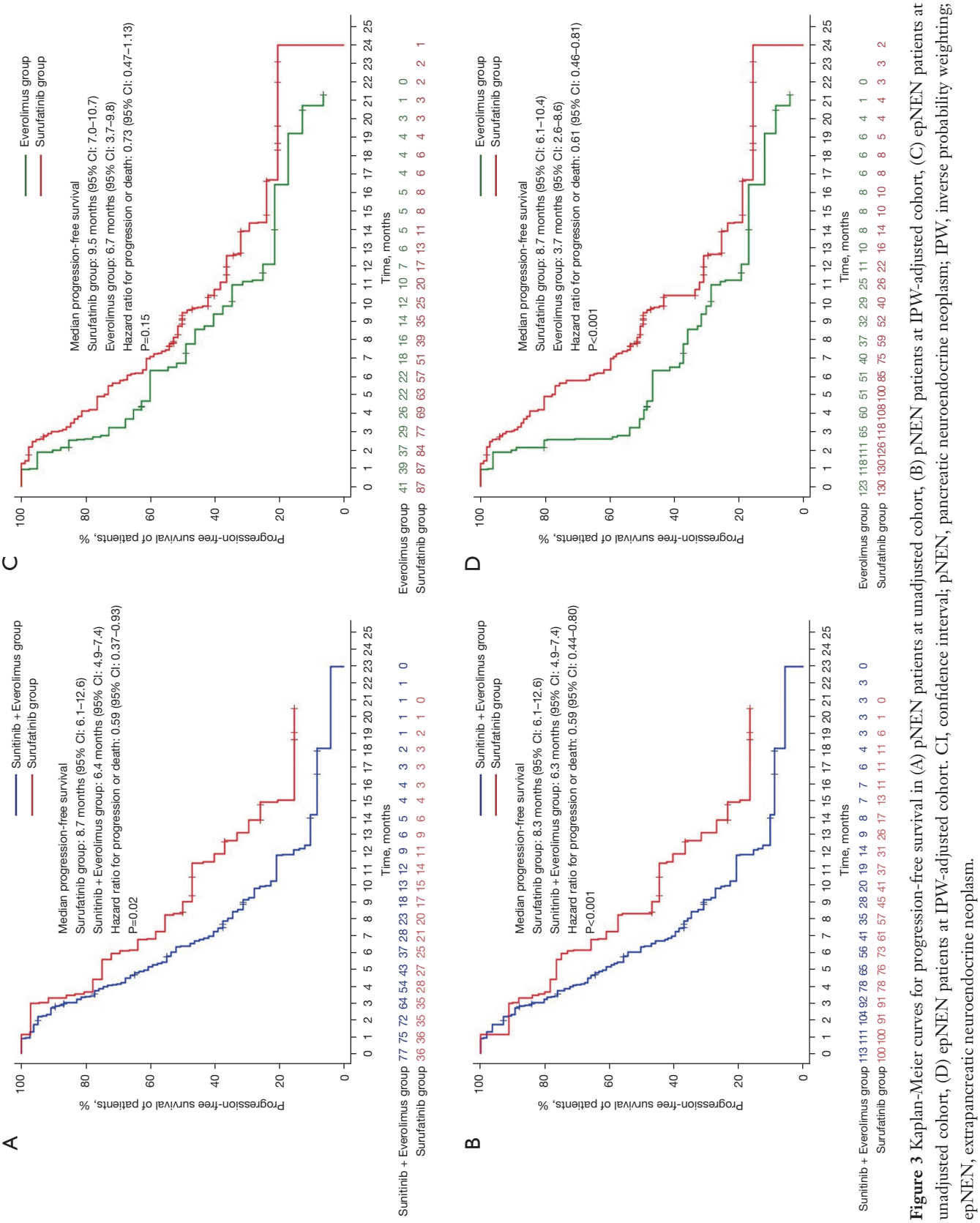

Figure 3 Kaplan-Meier curves for progression-free survival in (A) pNEN patients at unadjusted cohort, (B) pNEN patients at IPW-adjusted cohort, (C) epNEN patients at unadjusted cohort, (D) epNEN patients at IPW-adjusted cohort. CI, confidence interval; pNEN, pancreatic neuroendocrine neoplasm; IPW, inverse probability weighting; epNEN, extrapancreatic neuroendocrine neoplasm.

Table 2 Treatment response with targeted agents in IPW-adjusted cohort

Treatment response	pNEN (%)			epNEN (%)		
	Suru	Suni + Eve	P value	Suru	Eve	P value
Best response						<0.001
PR	21.0	9.9	0.004	6.2	5.6	
SD	70.2	65.7		79.7	58.4	
PD	8.8	24.3		14.1	36.0	
ORR	21.0	9.9	0.03	6.2	5.6	0.84
DCR	91.2	75.7	0.004	85.9	64.0	<0.001

IPW, inverse probability weighting; pNEN, pancreatic neuroendocrine neoplasm; epNEN, extrapancreatic neuroendocrine neoplasm; Suru, surufatinib; Suni, sunitinib; Eve, everolimus; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

agent originally researched and launched in China, warrant further explorations currently. In the SANET-p and SANET-ep trials, the mPFS was 10.9 months (95% CI: 7.5–13.8) and 9.2 months (95% CI: 7.4–11.1), respectively, for surufatinib, which were slightly longer than that in our study (16,17). Our approach, unlike clinical trials, did not impose strict entry criteria to better mirror real-world scenarios, accommodating patients with ECOG-PS ≥2, primarily ≥2 lines of treatment, Ki67% ≥20%, advanced pathological grades, poor differentiation, and uncommon/multiple primary tumor sites, potentially contributing to the shorter mPFS than that in previous studies comparing sunitinib and everolimus (27,28). In addition, we did not exclude patients receiving combination therapy with other agents, including SSAs, chemotherapy, and ICIs to meet practical treatment demands, although survival periods showed no statistical differences compared with monotherapy. Combination therapy has become a common medication pattern in the current tumor treatment area. Several RCTs had been developed to explore whether everolimus plus SSA could improve effectiveness in advanced NENs, but the desired results were not achieved with no adequate improvement on PFS and overall survival (OS). The RADIANT-2 trial demonstrated that everolimus plus octreotide long-acting repeatable (LAR) obtained mPFS (16.4 *vs.* 11.3 months, HR 0.77, 95% CI: 0.59–1.00, one-sided P=0.02) and OS (29.2 *vs.* 35.2 months, HR 1.17, 95% CI: 0.92–1.49) with no statistical significances in advanced NENs and carcinoid syndrome patients (29,30), whereas just in the colorectal NENs subgroup this combined treatment was associated with a 66% reduction in the estimated risk for disease progression (29.90 *vs.* 6.57 months, HR 0.34, 95% CI: 0.13–0.89, P=0.01) (31). The COOPERATE-2 trial showed that the addition of pasireotide to everolimus was not associated with the improvement in PFS compared with everolimus alone (16.8 *vs.* 16.6 months, HR 0.99, 95% CI: 0.64–1.54, P=0.48) (32). For sunitinib and surufatinib, evidences on combination therapy were limited. A single-arm phase I trial evaluated that the overall ORR and DCR were 23.8% and 76.2% in 21 NEN patients (more than half were NECs) receiving surufatinib combined with toripalimab (a programmed cell death protein-1inhibitor) (33), which provided a potential option for higher malignancy subtypes. With regard to targeted agents, further studies are warranted to confirm whether combination therapy can bring more benefits in advanced NENs.

In this study, some histopathological factors associated with tumor grading/classification/staging (differentiation, Ki67 index, liver metastasis, functional status, germline mutation) were identified as related with mPFS in advanced NEN patients, which had been also validated by numerous studies (34-37). Phase III trials of targeted therapy solely encompassed patients with G1/G2 NENs, while the effectiveness and safety of drugs for high-grade (G3 or Ki67 >20%) NENs and poorly-differentiation NECs remain unexplored. Two prospective phase 2 trials tried to verify everolimus and sunitinib activity in advanced G3/NEC patients and found that efficacy was limited with mPFS of 1.2 and 1.4 months (38,39), respectively, whereas surufatinib achieved a 23% ORR and 4.14 months mPFS in NEC (40). Hence, application of targeted agents needs careful consideration. Liver metastasis was considered a common influencing factor (5,41), while compared to the presence of

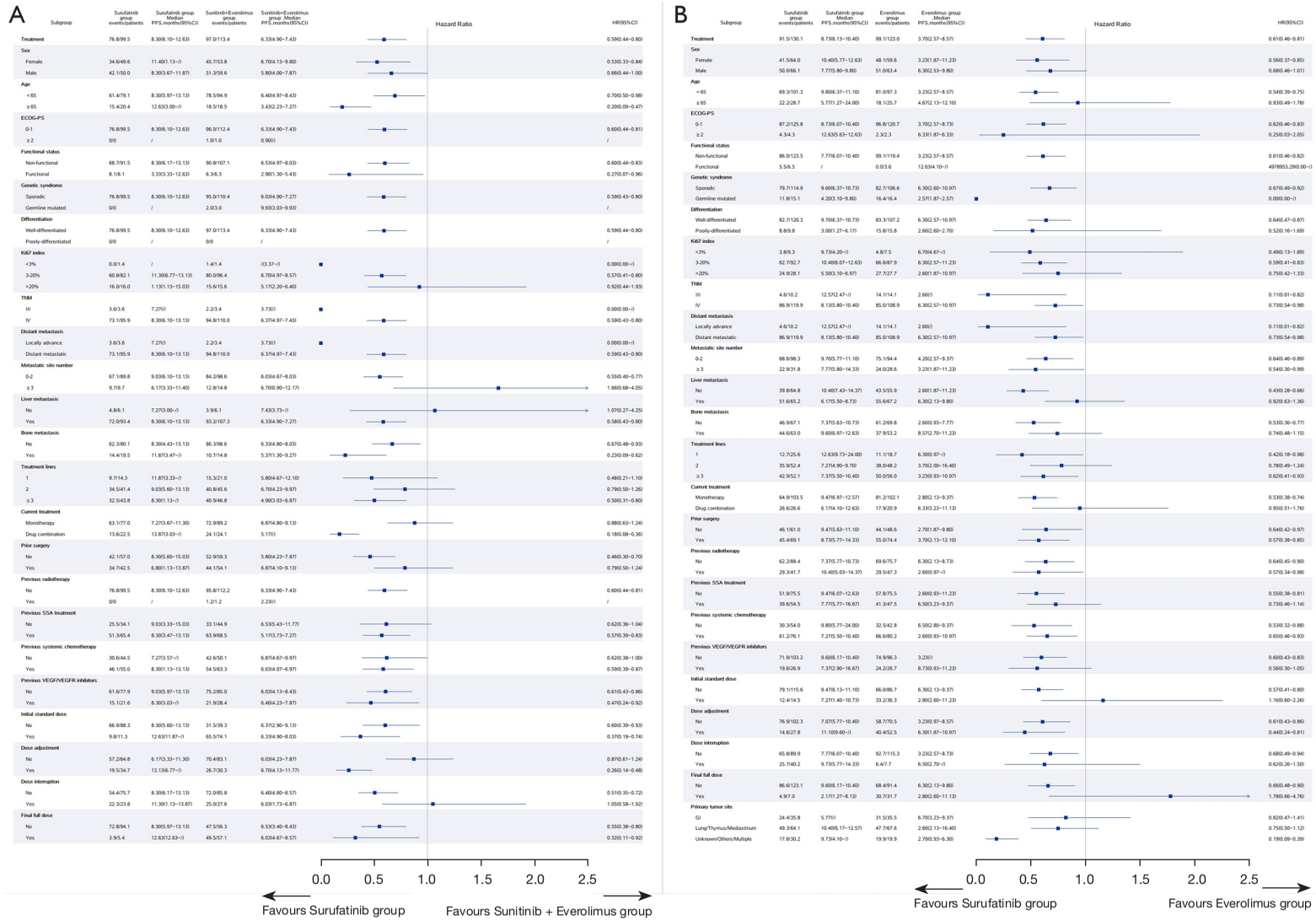

Figure 4 Forest plot of subgroup analysis for progression-free survival in (A) pNEN and (B) epNEN patients at IPW-adjusted cohort. PFS, progression-free survival; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; TNM, tumor, node, metastasis; SSA, somatostatin analogues; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; pNEN, pancreatic neuroendocrine neoplasm; epNEN, extrapancreatic neuroendocrine neoplasm; IPW, inverse probability weighting.

Table 3 Univariate and multivariate analysis on clinical features associated with PFS in pNEN patients at IPW-adjusted cohort

Clinical features (surufatinib *vs*. sunitinib + everolimus)	HR (95% CI)	P value
Univariate analysis		
Male *vs.* female	1.33 (0.98–1.80)	0.06
Age ≥65 *vs.* <65 years	1.02 (0.70–1.49)	0.90
ECOG-PS ≥2 *vs.* 0–1	NR (0.00–NR)	>0.99
Functional *vs.* non-functional	1.85 (1.07–3.19)	0.02
Germline mutated *vs.* sporadic	0.92 (0.23–3.74)	0.91
Ki67 index		
3–20% *vs.* <3%	2.07 (0.40–10.77)	0.38
>20% *vs.* <3%	6.20 (1.16–33.24)	0.03
Distant metastatic *vs.* locally advanced	0.57 (0.25–1.31)	0.18
Metastatic site number ≥3 *vs.* 0–2	1.68 (1.07–2.64)	0.02
Liver metastasis (yes *vs.* no)	0.87 (0.44–1.73)	0.69
Bone metastasis (yes *vs.* no)	0.80 (0.53–1.23)	0.31
Treatment line		
Second line *vs.* first line	1.17 (0.74–1.84)	0.50
≥3rd line *vs.* first line	1.32 (0.84–2.09)	0.22
Prior surgery (yes *vs.* no)	1.19 (0.88–1.60)	0.27
Previous SSA (yes *vs.* no)	1.35 (0.98–1.85)	0.06
Previous chemotherapy (yes *vs.* no)	1.26 (0.93–1.72)	0.13
Previous anti-angiogenesis agents (yes *vs.* no)	0.85 (0.59–1.22)	0.37
Previous mTORi (yes *vs.* no)	0.39 (0.19–0.81)	0.01
Surufatinib *vs.* sunitinib + everolimus	0.59 (0.44–0.80)	<0.001
Combination therapy *vs.* monotherapy	0.75 (0.52–1.09)	0.12
Initial standard dose (yes *vs.* no)	1.09 (0.80–1.47)	0.58
Dose adjustment (yes *vs.* no)	0.50 (0.35–0.70)	<0.001
Dose interruption (yes *vs.* no)	0.84 (0.60–1.19)	0.33
Multivariate analysis		
Male *vs.* female	1.75 (1.25–2.44)	0.001
Functional *vs.* non-functional	2.09 (1.16–3.74)	0.01
Ki67 index >20% *vs.* <3%	12.74 (2.26–71.95)	0.004
Surufatinib *vs.* sunitinib + everolimus	0.58 (0.42–0.79)	<0.001
Previous mTORi (yes *vs.* no)	0.48 (0.23–0.99)	0.04
Previous SSA (yes *vs.* no)	1.73 (1.24–2.40)	0.001
Dose adjustment (yes *vs.* no)	0.63 (0.45–0.89)	0.009

PFS, progression-free survival; pNEN, pancreatic neuroendocrine neoplasm; IPW, inverse probability weighting; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; NR, not reported; SSA, somatostatin analogues; mTORi, mTOR inhibitor.

Table 4 Univariate and multivariate analysis on clinical features associated with PFS in epNEN patients at IPW-adjusted cohort

Clinical features (surufatinib *vs.* sunitinib + everolimus)	HR (95% CI)	P value
Univariate analysis		
Male *vs.* female	1.00 (0.75–1.33)	0.99
Age ≥65 *vs.* <65 years	1.03 (0.72–1.47)	0.86
ECOG-PS ≥2 *vs.* 0–1	1.11 (0.51–2.42)	0.79
Primary tumor site		
Lung/thymus/mediastinum *vs.* GI	1.18 (0.78–1.79)	0.43
Others *vs.* GI	0.91 (0.65–1.27)	0.58
Functional *vs.* non-functional	0.55 (0.24–1.29)	0.17
Germline mutated *vs.* sporadic	2.62 (1.74–3.95)	<0.001
Poorly-differentiated *vs.* well-differentiated	5.04 (3.14–8.08)	<0.001
Ki67 index		
3–20% *vs.* <3%	1.55 (0.78–3.09)	0.20
>20% *vs.* <3%	3.42 (1.66–7.03)	<0.001
Distant metastatic *vs.* locally advanced	0.77 (0.48–1.25)	0.28
Metastatic site number ≥3 *vs.* 0–2	1.09 (0.78–1.52)	0.61
Liver metastasis (yes *vs.* no)	1.34 (1.00–1.79)	0.04
Bone metastasis (yes *vs.* no)	0.76 (0.57–1.02)	0.06
Treatment line		
Second line *vs.* first line	2.08 (1.29–3.35)	0.003
≥3rd line *vs.* first line	2.41 (1.51–3.84)	<0.001
Prior surgery (yes *vs.* no)	0.92 (0.69–1.22)	0.56
Previous SSA (yes *vs.* no)	1.02 (0.76–1.36)	0.90
Previous chemotherapy (yes *vs.* no)	1.68 (1.24–2.29)	<0.001
Previous anti-angiogenesis agents (yes *vs.* no)	1.08 (0.77–1.51)	0.67
Previous mTORi (yes *vs.* no)	0.77 (0.46–1.29)	0.31
Surufatinib *vs.* everolimus	0.61 (0.46–0.81)	<0.001
Combination therapy *vs.* monotherapy	1.24 (0.89–1.74)	0.21
Initial standard dose (yes *vs.* no)	1.38 (0.99–1.94)	0.058
Dose adjustment (yes *vs.* no)	0.78 (0.57–1.08)	0.13
Dose interruption (no *vs.* yes)	1.63 (1.11–2.39)	0.01
Multivariate analysis		
Germline mutated *vs.* sporadic	5.62 (3.49–9.04)	<0.001
Poorly-differentiated *vs.* well-differentiated	7.45 (4.40–12.61)	<0.001
Liver metastasis (yes *vs.* no)	1.72 (1.24–2.39)	0.001
Treatment line		
Second line *vs.* first line	1.62 (1.00–2.62)	0.04
≥3rd line *vs.* first line	1.88 (1.16–3.06)	0.01
Surufatinib *vs.* everolimus	0.62 (0.45–0.84)	0.002

PFS, progression-free survival; epNEN, extrapancreatic neuroendocrine neoplasm; IPW, inverse probability weighting; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; GI, gastro-intestinal neuroendocrine neoplasms; SSA, somatostatin analogues; mTORi, mTOR inhibitor.

Table 5 Adverse events with targeted agents in pNEN patients at unadjusted cohort

Adverse events	Surufatinib, n=36, n (%)		Sunitinib, n=50, n (%)		Everolimus, n=27, n (%)		P value (any grade)	P value (grade ≥3)
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3		
Any AE	31 (86.1)	9 (25.0)	39 (78.0)	13 (26.0)	20 (74.1)	3 (11.1)	0.46	0.28
Hypertension	6 (16.7)	1 (2.8)	9 (18.0)	3 (6.0)	0	0	0.03	0.56
Proteinuria	8 (22.2)	0	6 (12.0)	0	0	0	0.01	NA
WBC decreased	2 (5.6)	0	17 (34.0)	0	2 (7.4)	0	<0.001	NA
Neutrophil decreased	1 (2.8)	0	15 (30.0)	6 (12.0)	1 (3.7)	0	<0.001	0.01
Febrile neutropenia	0	0	1 (2.0)	1 (2.0)	0	0	>0.99	>0.99
LYM decreased	5 (13.9)	0	2 (4.0)	0	4 (14.8)	0	0.16	NA
Anemia	4 (11.1)	2 (5.6)	11 (22.0)	0	8 (29.6)	0	0.18	0.15
PLT decreased	4 (11.1)	0	19 (38.0)	1 (2.0)	2 (7.4)	0	0.001	>0.99
Hemorrhage	2 (5.6)	1 (2.8)	2 (4.0)	1 (2.0)	1 (3.7)	0	>0.99	>0.99
Occult blood positive	5 (13.9)	0	1 (2.0)	0	0	0	0.02	NA
AST increased	4 (11.1)	2 (5.6)	4 (8.0)	0	7 (25.9)	1 (3.7)	0.09	0.17
ALT increased	3 (8.3)	1 (2.8)	6 (12.0)	0	7 (25.9)	1 (3.7)	0.11	0.30
ALP increased	5 (13.9)	0	2 (4.0)	0	3 (11.1)	0	0.26	NA
GGT increased	3 (8.3)	0	1 (2.0)	0	7 (25.9)	2 (7.4)	0.003	0.055
LDH increased	4 (11.1)	0	3 (6.0)	0	4 (14.8)	0	0.36	NA
Bilirubin increased	11 (30.6)	2 (5.6)	3 (6.0)	0	2 (7.4)	0	0.003	0.15
Hypoalbuminemia	4 (11.1)	0	6 (12.0)	0	5 (18.5)	0	0.72	NA
Edema	0	0	5 (10.0)	0	1 (3.7)	0	0.08	NA
Creatinine increased	3 (8.3)	0	4 (8.0)	0	1 (3.7)	0	0.80	NA
Hyperuricemia	6 (16.7)	0	1 (2.0)	0	1 (3.7)	0	0.02	NA
Hyperlipemia	4 (11.1)	1 (2.8)	0	0	7 (25.9)	0	<0.001	0.55
Hyperglycemia	7 (19.4)	0	0	0	8 (29.6)	0	<0.001	NA
Hypoglycemia	1 (2.8)	0	1 (2.0)	0	0	0	>0.99	NA
TSH increased	6 (16.7)	0	1 (2.0)	0	0	0	0.006	NA
Hypothyroidism	3 (8.3)	0	0	0	0	0	0.03	NA
Nausea/vomiting	2 (5.6)	0	0	0	1 (3.7)	0	0.17	NA
Diarrhea	6 (16.7)	0	1 (2.0)	0	1 (3.7)	0	0.02	NA
Abdominal discomfort	1 (2.8)	0	1 (2.0)	0	0	0	>0.99	NA
Stomatitis	0	0	3 (6.0)	0	7 (25.9)	0	<0.001	NA
Muscle pain	0	0	0	0	0	0	NA	NA
Fatigue	0	0	2 (4.0)	0	0	0	0.50	NA
HFS reaction	1 (2.8)	0	5 (10.0)	2 (4.0)	0	0	0.16	0.50
Cough	0	0	0	0	1 (3.7)	0	0.23	NA
Interstitial pneumonia	0	0	0	0	1 (3.7)	0	0.23	NA
Infection	1 (2.8)	0	1 (2.0)	1 (2.0)	3 (11.1)	1 (3.7)	0.15	0.71
Cardiac toxicity	1 (2.8)	0	0	0	1 (3.7)	0	0.30	NA

AE, adverse event; pNEN, pancreatic neuroendocrine neoplasm; WBC, white blood cell; LYM, lymphocyte; PLT, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone; HFS, hand-foot skin syndrome; NA, not available.

Table 6 Adverse events with targeted agents in epNEN patients at unadjusted cohort

Adverse events	Surufatinib, n=87, n (%)		Everolimus, n=41, n (%)		P value (any grade)	P value (grade ≥3)
	Any grade	Grade ≥3	Any grade	Grade ≥3		
Any AE	73 (83.9)	27 (31.0)	32 (78.0)	7 (17.1)	0.42	0.09
Hypertension	30 (34.5)	14 (16.1)	0	0	<0.001	0.005
Proteinuria	33 (37.9)	2 (2.3)	1 (2.4)	0	<0.001	>0.99
WBC decreased	7 (8.0)	2 (2.3)	4 (9.8)	0	0.74	>0.99
Neutrophil decreased	3 (3.4)	1 (1.1)	3 (7.3)	2 (4.9)	0.38	0.24
Febrile neutropenia	0	0	1 (2.4)	1 (2.4)	0.32	0.32
LYM decreased	12 (13.8)	2 (2.3)	7 (17.1)	0	0.62	>0.99
Anemia	15 (17.2)	3 (3.4)	15 (36.6)	3 (7.3)	0.01	0.38
PLT decreased	6 (6.9)	3 (3.4)	4 (9.8)	0	0.72	0.55
Hemorrhage	6 (6.9)	1 (1.1)	1 (2.4)	0	0.42	>0.99
Occult blood positive	5 (5.7)	0	0	0	0.17	NA
AST increased	16 (18.4)	2 (2.3)	7 (17.1)	1 (2.4)	0.85	>0.99
ALT increased	9 (10.3)	2 (2.3)	4 (9.8)	0	>0.99	>0.99
ALP increased	4 (4.6)	1 (1.1)	5 (12.2)	0	0.14	>0.99
GGT increased	8 (9.2)	3 (3.4)	7 (17.1)	1 (2.4)	0.24	>0.99
LDH increased	18 (20.7)	0	9 (22.0)	0	0.87	NA
Bilirubin increased	17 (19.5)	3 (3.4)	1 (2.4)	0	0.009	0.55
Hypoalbuminemia	12 (13.8)	0	5 (12.2)	0	0.80	NA
Edema	1 (1.1)	0	0	0	>0.99	NA
Creatinine increased	9 (10.3)	0	2 (4.9)	1 (2.4)	0.50	0.32
Hyperuricemia	18 (20.7)	1 (1.1)	1 (2.4)	0	0.007	>0.99
Hyperlipemia	7 (8.0)	0	10 (24.4)	0	0.01	NA
Hyperglycemia	8 (9.2)	0	15 (36.6)	0	<0.001	NA
Hypoglycemia	3 (3.4)	0	0	0	0.55	NA
TSH increased	22 (25.3)	0	0	0	<0.001	NA
Hypothyroidism	3 (3.4)	0	0	0	0.55	NA
Nausea/vomiting	2 (2.3)	0	1 (2.4)	0	>0.99	NA
Diarrhea	13 (14.9)	0	2 (4.9)	0	0.14	NA
Abdominal discomfort	1 (1.1)	0	0	0	>0.99	NA
Stomatitis	0	0	9 (22.0)	1 (2.4)	<0.001	0.32
Muscle pain	1 (1.1)	0	0	0	>0.99	NA
Fatigue	6 (6.9)	0	2 (4.9)	0	>0.99	NA
HFS reaction	1 (1.1)	0	2 (4.9)	0	0.24	NA
Cough	0	0	1 (2.4)	0	0.32	NA
Interstitial pneumonia	0	0	4 (9.8)	0	0.009	NA
Infection	1 (1.1)	0	2 (4.9)	0	0.24	NA
Cardiac toxicity	1 (1.1)	0	2 (4.9)	0	0.24	NA

AE, adverse event; epNEN, extrapancreatic neuroendocrine neoplasm; WBC, white blood cell; LYM, lymphocyte; PLT, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone; HFS, hand-foot skin syndrome; NA, not available.

liver metastasis itself, the liver tumor burden may serve as a more instructive prognostic factor (42,43). A retrospective study found that liver tumor burden ≤25% (HR 0.27, 95% CI: 0.13–0.55, P<0.001) became the significant factors influencing OS in pNENs treated with everolimus (44), which could offer limited proof on availability of therapeutic effect prediction. Apart from that, we also found that functional and germline-mutated NENs, subgroups that clinical trials commonly excluded, were related with worse PFS. A small portion of NENs (approximately 10%) were related to genetic factors, namely those carrying germline gene mutations and occurring hereditary syndromes (45). Nuñez *et al.* found that everolimus achieved similar efficacy in multiple endocrine neoplasia type 1 (MEN1) and Von-Hippel-Lindau (VHL) compared with sporadic NENs (46). This differed from the conclusion we drew, but considering the small population, more evidences would be needed. Regarding treatment-related factors, previous SSA was considered to increase the risk of disease progression, whereas RADIANT-4 subgroup analysis indicated that everolimus had not significantly improved PFS in any previous SSA subgroup (47). NCCN, European Society for Medical Oncology (ESMO), and ENETS guidelines recommend SSAs as the first-line treatment of patients with somatostatin receptor (SSTR) positivity, G1/2 NENs with relatively low proliferative activity (Ki67 <10%), low tumor burden, and indolent behavior (11,12,48). In the absence of high-level evidences, systemic therapy selection and sequencing in advanced NENs are not fully elucidated, which mainly depends on the biological behavior and malignancy of the tumor, patient characteristics and treatment goals (49). Multiple prior treatment lines tended to be unfavorable factors on PFS in our study, in similarity with conclusions drawn in other investigations (27,28,50), which was probably due to the powerful invasiveness of an uncontrollable tumor.

A considerable portion of patients received surufatinib, sunitinib, and everolimus at reduced doses initially in this study. Although combination therapy possibly induced physicians to further take tolerance into account, more than 60% of patients with monotherapy did not accept standard dose initially. We analyzed that the initial recommended dose for treatment would not affect PFS and dose adjustment may play a positive role on PFS in pNEN patients. It is common that the strategy with lower tolerant initial dose and gradually increased dose is chosen to avoid AEs as far as possible in clinical practice. For small molecule kinase inhibitors, dose escalation is indeed one of the methods to optimize administration strategy. The DESIREE prospective trial reported that the use of a stepwise dose-escalation schedule of everolimus (2.5 mg week 1 increased by 2.5 mg per week to 10 mg) could significantly reduce the incidence of high-grade stomatitis in patients with hormone receptor $(HR)^+$/human epidermal growth factor receptor 2 $(HER2)^-$ metastatic breast cancer (51). Escalation of sunitinib dosing (12.5 mg steps) in patients with metastatic renal cell cancer, based on tolerable toxicity, has been shown to be safe and improve outcome (52). Despite lacking related evidences in advanced NENs, dose escalation of targeted agents can be a reasonable attempt in real-world practice. As a result, dose adjustment appeared in nearly one-third of patients in an effort to balance efficacy and tolerance. Berardi *et al.* reported that cumulative dose >3,000 mg and dose intensity >9 mg/day of everolimus played a prognostic role for patients with advanced pancreatic neuroendocrine tumors (pNETs) (53). Despite that a small sample-size study suggested that median daily dose reduction of sunitinib would probably not alter prognosis and safety for patients with advanced pNENs (54), Lee *et al.* demonstrated that severe AEs occurred in 63% of patients with sunitinib whose prolonged treatment period was significantly correlated with decreased relative dose intensity (55). Consequently, well-developed patient management with appropriate initial dose selection, dose adjustment, and interruption will provide guarantees for the long-term application of targeted agents.

In general, the safety profile of surufatinib, sunitinib, and everolimus was substantially similar to the reports of RCTs (16-20), which illustrated that under appropriate management, combination therapy would not increase the potential toxicity. Except adverse events of special interest (AESI) for the three drugs, there were differences in common AEs including hematologic toxicity and hepatotoxicity. Hematologic toxicity, which mainly manifested as myelocyte and megakaryocyte suppression, occurred more frequently with sunitinib, whereas everolimus and surufatinib were more likely to cause erythrocytes suppression and hemorrhage, respectively. Hepatotoxicity was also represented as different abnormal liver function indexes among the drugs. Considering that there is currently no clear evidence for position and sequence among targeted agents, it is recommended to match baseline characteristics of patients with drug toxicity for selection in clinical settings.

Our study had some limitations. Firstly, the most important constraint was the retrospective observational

design with inherent bias, although we applied statistical methods to balance heterogeneity as far as possible. The relatively small sample size probably expanded the negative impact, so that we collected substantial variables and conducted subgroup analysis in order to explore the outcomes under different clinical features. Moreover, clinical data capture based on medical records system, together with early approval of sunitinib and everolimus in China, may have resulted in patient loss of follow-up and biased survival outcome. What's more, surufatinib's approval period was much shorter than everolimus and sunitinib, which resulted in differences on patients' follow-up time and survival outcome acquiring. Under these circumstances, prospective research is required for further verification and OS data would be reported. Finally, we included NENs originating from any organ and tissue to reflect a real-world setting, yet the intrinsic heterogeneity possibly confused the results considering drug indication and histopathological difference.

Conclusions

This study explored the efficacy and safety of surufatinib, sunitinib, and everolimus in advanced NEN patients in real-world clinical practice in China. We demonstrated that surufatinib significantly prolonged PFS compared to sunitinib and everolimus in patients with advanced NEN treatments with different AE types to provide future perspective in patient management. This finding, together with identified clinical features affecting survival outcome, may lead to implications for selection of targeted agents in Chinese advanced NEN patients. These results should be further validated in well-designed prospective studies, in which specific molecular biomarkers should be explored to facilitate personalized treatment progress for advanced NEN.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-218/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by institutional ethics committee of Fudan University Shanghai Cancer Center (No. 2205254-19) and individual consent for this retrospective analysis was waived.

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