European ENETS Neuroendocrine Tumor Society

Title: **Safety Profile and Adverse Events of Special Interest for Surufatinib in Chinese Patients with Advanced Extra-Pancreatic Neuroendocrine Tumors: Analysis of the Phase 3 SANET-ep Trial**

Authors: Jie Li[1], Jianming Xu[2], Zhiwei Zhou[3], Chunmei Bai[4], Yihebali Chi[5], Zhiping Li[6], Nong Xu[7], Enxiao Li[8], Tianshu Liu[9], Yuxian Bai[10], Sha Guan[11], Lin Shen[1]

Institution: please see at the bottom of the poster

Institution's Location: China

Safety Profile and Adverse Events of Special Interest for Surufatinib in Chinese Patients with Advanced Extra-Pancreatic Neuroendocrine Tumors: Analysis of the Phase 3 SANET-ep Trial

Introduction

- Surufatinib is a novel, small-molecule inhibitor that simultaneously targets vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, fibroblast growth factor receptor 1 (FGFR1), and colony stimulating factor-1 receptor (CSF-1R).
- In phase 1-2 studies, surufatinib showed encouraging antitumor activity and manageable toxicities in patients with advanced neuroendocrine tumors (NETs) (ORR of 19% in pancreatic NETs and 15% in extra-pancreatic NETs), irrespective of primary origin, possibly due to its unique angio-immuno kinase mechanism of action [1, 2].
- The previously reported phase 3 SANET-ep trial (NCT02588170) demonstrated surufatinib significantly improves progression-free survival (PFS) in patients with advanced extra-pancreatic NETs compared to placebo; median PFS (9.2 vs. 3.8 months; HR = 0.334, 95% CI 0.223 to 0.499, p<0.0001) [3]. It was also the first study of advanced NETs including tumors originating from any extra-pancreatic location.
- A parallel phase 3 study of surufatinib treating patients with advanced pancreatic NETs has also demonstrated significantly improved PFS in a pre-planned interim analysis (SANET-p trial, NCT02589821), which will be presented in future.

Keywords: extra-pancreatic, neuroendocrine tumors, safety

Aims

The present analysis evaluates the safety profile and adverse events (AEs) of special interest (AESIs) of surufatinib from SANET-ep data.

Patients and Methods

Eligible patients ≥ 18 years with unresectable or metastatic well-differentiated extra-pancreatic NETs of pathologic grade 1 or 2, as per the World Health Organization classification. Patients were randomized (2:1) to receive surufatinib (300 mg once daily continuously) or placebo (Figure 1).

Treatment-emergent adverse events (TEAEs) were those occurred between the first dose of surufatinib and ≤37 days after the last dose, which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), 4.03.

Safety data including TEAEs, AESIs and time-to-first occurrence of AESIs were summarized. Predefined AESIs included hepatic failure (hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions), proteinuria, hypertension, haemorrhage, and acute renal failure, which were searched with narrow MedDRA Standardized MedDRA Query (SMQ v22.0).

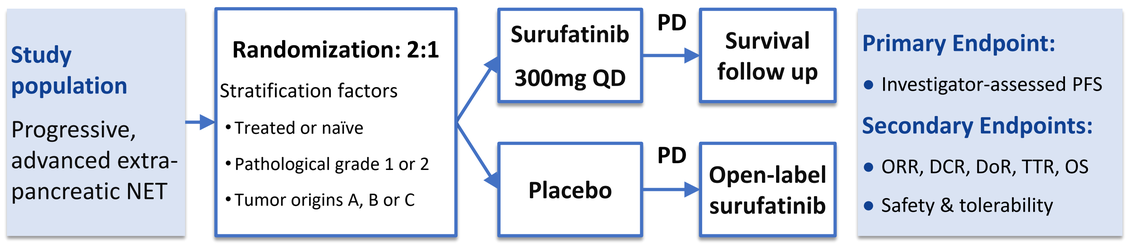

Figure 1. Study design. [a]Tumor origin A: jejunum, ileum, duodenum, thymus, cecum; B: lung, stomach, liver, appendix, colon, rectum; C: others or unknown origin. PD, disease progression. QD, once daily. ORR, objective response rate. DCR, disease control rate. DoR, duration of response. TTR, time to response. OS, overall survival

Results

Patients and Exposure

- As of 31 March 2019, 198 eligible patients were randomized at 23 sites across China (129 in the surufatinib group and 69 in placebo group). Baseline characteristics were well-balanced between the two groups (Table 1). One patient in placebo group failed to start the treatment by the cutoff date and was not included in the analysis of exposure and safety.
- The mean relative dose intensity (the ratio of actual to planned dose intensity) was presented (Table 2).

Table 1. Demographics and baseline characteristics

	Surufatinib (N=129)	Placebo (N=69)
Age, median (range), years	52.0 (19.0, 72.0)	54.0 (25.0, 79.0)
Male	56.6%	50.7%
ECOG PS 0/1	55.8% / 44.2%	66.7% / 33.3%
Pathological grade 1/2	16.3% / 83.7%	15.9% / 84.1%
Non-functional tumors	94.6%	97.1%
Primary tumor origins		
Gastrointestinal tract *(rectum / stomach / small intestine* / others)*	47.3% *(29.5% / 7.8% / 7.8% / 2.4%)*	46.4% *(21.7% / 13.0% / 8.7% / 2.9%)*
Lung	9.3%	15.9%
Unknown	14.0%	13.0%
Others	29.4%	24.7%
Liver metastasis	75.2%	76.8%
Previous systemic anti-tumor treatment for advanced disease	69.0%	63.8%
Chemotherapy	40.3%	39.1%
Somatostatin analogue	34.1%	27.5%
Everolimus	7.8%	11.6%

*Small intestine included the tumor origin reported as jejunum, ileum, duodenum, or small intestine.

Table 2. Drug exposure

	Surufatinib (N=129)	Placebo (N=68)
Exposure median (range), days	217 (4.0, 1032.0)	146 (6.0, 844.0)
Dose intensity mean (std), mg/day	259.25 (39.460)	290.34 (26.920)
Relative dose intensity mean (std), %	86.42 (13.153)	96.78 (8.973)

Common Treatment Emergent Adverse Events (TEAEs)

Almost all patients experienced at least one TEAEs (98.4% in the surufatinib group and 95.6% in the placebo group). Common TEAEs are presented in Table 3.

Table 3. Most common (≥20%) TEAEs by preferred term (PT)

TEAEs	Surufatinib (N=129) n（%）		Placebo (N=68) n（%）	
	Any grade	≥ grade 3	Any grade	≥ grade 3
Proteinuria	91 (70.5)	25 (19.4)	36 (52.9)	0
Hypertension	83 (64.3)	47 (36.4)	18 (26.5)	9 (13.2)
Diarrhea	60 (46.5)	2 (1.6)	14 (20.6)	0
Blood thyroid stimulating hormone increased	51 (39.5)	0	5 (7.4)	0
Blood bilirubin increased	50 (38.8)	3 (2.3)	12 (17.6)	0
Aspartate aminotransferase increased	47 (36.4)	5 (3.9)	17 (25.0)	2 (2.9)
Fecal occult blood positive	46 (35.7)	0	12 (17.6)	0
Hypertriglyceridaemia	41 (31.8)	3 (2.3)	6 (8.8)	0
Hypoalbuminaemia	37 (28.7)	0	4 (5.9)	0
Alanine aminotransferase increased	32 (24.8)	4 (3.1)	19 (27.9)	0
Hyperbilirubinaemia	29 (22.5)	5 (3.9)	8 (11.8)	0
Abdominal pain upper	29 (22.5)	1 (0.8)	9 (13.2)	0
Anemia	27 (20.9)	9 (7.0)	11 (16.2)	2 (2.9)

Adverse Events of Special Interest (AESIs)

- A total of 121/129 (93.8%) patients in the surufatinib group and 50/68 (73.5%) in the placebo group had ≥ 1 treatment-emergent AESI. The most commonly reported (>10% of patients) AESIs by SMQ term were as below:
  - Proteinuria (84.5% in surufatinib group vs 57.4% in placebo group), the most common PT of which were proteinuria, protein urine present and albumin urine present;
  - Hypertension (68.2% vs 30.9%), the most common PT of which were blood pressure increased and hypertension;
  - Haemorrhage (55.8% vs 27.9%), the most common PT of which were occult blood positive, blood urine present and gingival bleeding.
- The grade ≥3 AESIs by SMQ term were hypertension (40.3% vs 16.2%), proteinuria (23.3% vs 0) and haemorrhage (3.1% vs 2.9%), hepatic failure (2.4% vs 1.5%) and acute renal failure (0.8% vs 0) (Table 4). Two patients had fatal AESIs: one was due to disseminated intravascular coagulation and hepatic encephalopathy, and the other was due to liver injury; disseminated intravascular coagulation and liver injury were assessed as possibly related to surufatinib by investigators.
- The median time-to-onset of AESIs by SMQ term in the surufatinib group were 13.5 days for hypertension, 28 days for proteinuria, 32 days for haemorrhage, 79 days for acute renal failure and 110.5 days for hepatic failure (Table 5).
- AESIs (≥1% of patients in either group) leading to dose discontinuation were proteinuria (3.9% vs 0), haemorrhage (1.6% vs 1.5%), and hepatic failure (0.8% vs 1.5%) (Table 6).

Table 4. The incidence of AESI by SMQ term and by PT (≥1% PT presented)

	Surufatinib (N=129) n(%)		Placebo (N=68) n(%)	
	Any grade	≥ grade 3	Any grade	≥ grade 3
Subjects with Any TEAE of Special Interest	121 (93.8)	69 (53.5)	50 (73.5)	14 (20.6)
Proteinuria	109 (84.5)	30 (23.3)	39 (57.4)	0
Proteinuria	91 (70.5)	25 (19.4)	36 (52.9)	0
Protein urine present	20 (15.5)	5 (3.9)	4 (5.9)	0
Albumin urine present	2 (1.6)	0	2 (2.9)	0
Hypertension	88 (68.2)	52 (40.3)	21 (30.9)	11 (16.2)
Hypertension	83 (64.3)	47 (36.4)	18 (26.5)	9 (13.2)
Blood pressure increased	6 (4.7)	5 (3.9)	4 (5.9)	2 (2.9)
Haemorrhage	72 (55.8)	4 (3.1)	19 (27.9)	2 (2.9)
Occult blood positive	46 (35.7)	0	12 (17.6)	0
Blood urine present	21 (16.3)	0	5 (7.4)	0
Gingival bleeding	9 (7.0)	0	0	0
Haematuria	5 (3.9)	0	2 (2.9)	0
Gastrointestinal haemorrhage	4 (3.1)	2 (1.6)	0	0
Epistaxis	4 (3.1)	0	1 (1.5)	0
Vaginal haemorrhage	4 (3.1)	0	0	0
Haematochezia	3 (2.3)	0	3 (4.4)	0
Haemoptysis	2 (1.6)	0	3 (4.4)	1 (1.5)
Menorrhagia	2 (1.6)	0	0	0
Hepatic failure	8 (6.2)	3 (2.4)	1 (1.5)	1 (1.5)
Ascites	6 (4.7)	1 (0.8)	0	0
Hepatic steatosis	3 (2.3)	0	0	0
Acute renal failure	1 (0.8)	1 (0.8)	0	0

Table 5. Time to Onset by SMQ term

SMQ term	Surufatinib (N=129)	Placebo (N=68)
Subjects with Hypertension, n (%)	88 (68.2)	21 (30.9)
Median Time to Onset, days	13.50	42.00
Min, Max	1.0, 286.0	1.0, 449.0
Subjects with Proteinuria, n (%)	109 (84.5)	39 (57.4)
Median Time to Onset, days	28.00	29.00
Min, Max	5.0, 282.0	7.0, 516.0
Subjects with Haemorrhage n (%)	72 (55.8)	19 (27.9)
Median Time to Onset, days	32.00	57.00
Min, Max	5.0, 310.0	8.0, 419.0
Subjects with Hepatic failure, n (%)	8 (6.2)	1 (1.5)
Median Time to Onset, days	110.50	17.00
Min, Max	54.0, 273.0	17.0, 17.0
Subjects with Acute renal failure, n (%)	1 (0.8)	0
Median Time to Onset, days	79.00	0
Min, Max	79.0, 79.0	0

Table 6. AESIs leading to dose modifications

	Surufatinib (N=129)		Placebo (N=68)	
AESIs-SMQ term	Total n (%)	≥ grade 3 n (%)	Total n (%)	≥ grade 3 n (%)
Hypertension				
Dose interruption	11 (8.5)	10 (7.8)	0	0
Dose reduction	15 (11.6)	15 (11.6)	2 (2.9)	2 (2.9)
Dose discontinuation	1 (0.8)	1 (0.8)	0	0
Proteinuria				
Dose interruption	21 (16.3)	5 (3.9)	1 (1.5)	0
Dose reduction	27 (20.9)	19 (14.7)	0	0
Dose discontinuation	5 (3.9)	4 (3.1)	0	0
Haemorrhage				
Dose interruption	5 (3.9)	1 (0.8)	2 (2.9)	0
Dose reduction	4 (3.1)	0	1 (1.5)	0
Dose discontinuation	2 (1.6)	2 (1.6)	1 (1.5)	1 (1.5)
Hepatic failure				
Dose interruption	1 (0.8)	1 (0.8)	0	0
Dose reduction	0	0	0	0
Dose discontinuation	1 (0.8)	1 (0.8)	1 (1.5)	1 (1.5)
Acute renal failure				
Dose interruption	1 (0.8)	0	0	0
Dose reduction	0	0	0	0
Dose discontinuation	0	0	0	0

Conclusions

- The AE profile of surufatinib was consistent with the observations of prior studies [1-2], and no new safety signal was identified.
- Hypertension, proteinuria and haemorrhage were the most common AESIs by SMQ term, while hepatic failure by SMQ term was less common and acute renal failure was uncommon.
- Grade 3 or higher haemorrhage, hepatic failure and acute renal failure by SMQ term with surufatinib treatment was comparable to placebo arm.
- Proteinuria was the most reported reason for surufatinib discontinuation (3.9 % vs 0%), while other AESI leading to treatment discontinuation were uncommon.
- Surufatinib has a manageable safety profile in patients with advanced extra-pancreatic NETs.

References

1. Xu JM, et al. Oncotarget 2017;8:42076-86.
2. Xu JM, et al. Clin Cancer Res 2019;25:3486-94.
3. Xu JM, et al. Presented at ESMO. Barcelona, Spain, 27 September – 1 October 2019; Abstract #4979.

Institutions

[1]Department of Gastrointestinal Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing 100142, China
[2]Department of Gastrointestinal Oncology, The Fifth Medical Center, General Hospital of the People's Liberation Army, Beijing 100071, China
[3]Department of Gastric Surgery, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou 510060, China
[4]Department of Oncology, Peking Union Medical College Hospital, Beijing 100032, China.
[5]National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China.
[6]Department of Abdominal Oncology, West China Hospital, Sichuan University, Chengdu 610041, China.
[7]Department of Medical Oncology, The First Affiliated Hospital of Zhejiang University, Hangzhou 310003, China.
[8]Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China.
[9]Department of Oncology, Zhongshan Hospital of Fudan University, Shanghai 200032, China.
[10]Department of Gastrointestinal Oncology, Harbin Medical University Cancer Hospital, Harbin 150081, China.
[11]Industry-sponsored