Subgroup analysis by Ki-67 and primary tumor origins of the randomized, placebo-controlled phase 3 study of surufatinib in advanced well-differentiated extrapancreatic neuroendocrine tumors (SANET-ep)

Abstract #4261

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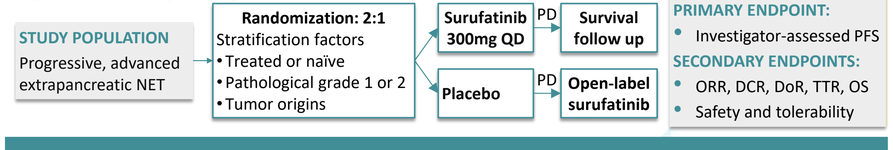
BACKGROUND

- **Surufatinib is a tyrosine kinase inhibitor** targeting vascular endothelial growth factor receptors (1-3), fibroblast growth factor receptor 1 and colony stimulating factor 1 receptor.
- **Surufatinib significantly prolonged progression-free survival with a tolerable safety profile** in patients with extrapancreatic neuroendocrine tumors (NETs) in a phase 3 study (SANET-ep, ESMO 2019 Abs. LBA76).
- **The proliferation marker Ki-67 and primary tumor origins are the major prognostic factors in NETs**. Here we present the post-hoc subgroup efficacy analysis according to these factors from SANET-ep study.

METHODS

- **SANET-ep was a multicenter, placebo-controlled, double-blinded phase III study** (NCT02588170) to evaluate the efficacy and safety of surufatinib in patients with progressive, unresectable or metastatic, well-differentiated (WHO pathological grade 1 or 2) extrapancreatic NETs.
- Tumor evaluation was conducted every 8 weeks in 1st year, and every 12 weeks thereafter (RECIST 1.1).
- **Post-hoc analysis** of investigator-assessed progression-free survival (PFS) and objective response rate (ORR) by the following categories was conducted in intent-to-treat population (all randomized patients):
  - **Ki-67 subcategories** (<3%, 3-10%, >10%).
  - **Primary tumor origins** (foregut, midgut, hindgut, others, unknown).

Figure 1: Study design



RESULTS

PATIENT CHARACTERISTICS

- As of 31 Mar 2019, a total of 198 patients with advanced extrapancreatic NETs were randomized.
- 129 in the surufatinib group (S) versus 69 in the placebo group (P).

Table 1: Baseline characteristics in subgroups by Ki-67 category

	Ki-67 <3%		Ki-67 3-10%		Ki-67 >10%	
	S N=21	P N=11	S N=78	P N=44	S N=30	P N=14
Age, median (range), years	51.0 (30, 72)	55.0 (30, 72)	52.5 (19, 72)	54.0 (25, 79)	53.0 (19, 67)	45.0 (26, 69)
Male / Female	47.6% / 52.4%	45.5% / 54.5%	57.7% / 42.3%	52.3% / 47.7%	60.0% / 40.0%	50.0% / 50.0%
ECOG PS 0 / 1	57.1% / 42.9%	54.5% / 45.5%	55.1% / 44.9%	72.7% / 27.3%	56.7% / 43.3%	57.1% / 42.9%
WHO Pathological grade 1 / 2*	90.5% / 9.5%	81.8% / 18.2%	2.6% / 97.4%	2.3% / 97.7%	0 / 100.0%	7.1% / 92.9%
Non-functional tumors	90.5%	90.9%	96.2%	97.7%	93.3%	100.0%
Liver metastasis	66.7%	72.7%	79.5%	81.8%	70.0%	64.3%
Prior systemic antitumor treatment						
Chemotherapy	42.9%	27.3%	35.9%	36.4%	30.0%	57.1%
Somatostatin analogue	42.9%	45.5%	32.1%	25.0%	33.3%	21.4%
Everolimus	4.8%	18.2%	9.0%	6.8%	6.7%	21.4%

For lung or thymus origin, grading was based on mitotic rate and necrosis status; for other extrapancreatic origins, both ki-67 & mitotic rate. Abbreviations: NETs: neuroendocrine tumors, PFS: progression-free survival, ORR: objective response rate, DCR: Disease Control Rate, DoR: Duration of Response, TTR: Time to response, OS: Overall survival, CI: Confidence interval, S: surufatinib, P: placebo.

Table 2: Baseline characteristics in subgroups by tumor origin

	Foregut		Midgut		Hindgut		Others		Unknown	
	S N=49	P N=29	S N=12	P N=6	S N=40	P N=17	S N=8	P N=5	S N=20	P N=12
Age, median (range), years	51.0 (19,71)	54.0 (25, 79)	49.5 (39, 72)	48.5 (36, 51)	56.0 (25, 70)	59.0 (26, 69)	49.5 (26, 70)	48.0 (30, 69)	52.5 (28, 72)	53.5 (32, 71)
Male / Female	63.3% / 36.7%	62.1% / 37.9%	58.3% / 41.7%	50.0% / 50.0%	50.0% / 50.0%	41.2% / 58.8%	62.5% / 37.5%	20.0% / 80.0%	50.0% / 50.0%	50.0% / 50.0%
ECOG PS 0 / 1	53.1% / 46.9%	65.5% / 34.5%	75.0% / 25.0%	100.0% / 0	55.0% / 45.0%	58.8% / 41.2%	62.5% / 37.5%	60.0% / 40.0%	50.0% / 50.0%	66.7% / 33.3%
WHO Pathological grade 1 / 2	18.4% / 81.6%	24.1% / 75.9%	8.3% / 91.7%	16.7% / 83.3%	12.5% / 87.5%	5.9% / 94.1%	25.0% / 75.0%	20.0% / 80.0%	20.0% / 80.0%	8.3% / 91.7%
Non-functional tumors	93.9%	100.0%	100.0%	100.0%	97.5%	100.0%	75.0%	80.0%	95.0%	91.7%
Liver metastasis	55.1%	58.6%	91.7%	100.0%	100.0%	100.0%	50.0%	60.0%	75.0%	83.3%
Prior systemic antitumor treatment										
Chemotherapy	55.1%	51.7%	25.0%	0	32.5%	23.5%	25.0%	60.0%	35.0%	41.7%
Somatostatin analogue	34.7%	27.6%	58.3%	66.7%	37.5%	41.2%	12.5%	0	20.0%	0
Everolimus	12.2%	6.9%	0	33.3%	7.5%	17.6%	0	0	5.0%	8.3%

SUBGROUP ANALYSIS BY KI-67 CATEGORY

- **Median PFS was significantly prolonged in the subgroup Ki-67 3-10% and Ki-67 >10%** with surufatinib versus placebo (figure 2).
- **Numerical PFS improvement in the subgroups of Ki-67 <3%** with surufatinib versus placebo (figure 2).
- **ORR in the subgroups of Ki-67 <3%, 3-10%, >10% were 4.8%** (95% CI 0.1, 23.8)**, 7.7%** (95% CI 2.9, 16.0) **and 20.0%** (95% CI 7.7, 38.6) respectively with surufatinib, versus none in the placebo arm.
- **Greater percentage of patients experienced tumor shrinkage** with surufatinib versus placebo across Ki-67 subgroups (table 3).

Figure 2: Progression-free survival in subgroups by Ki-67 category

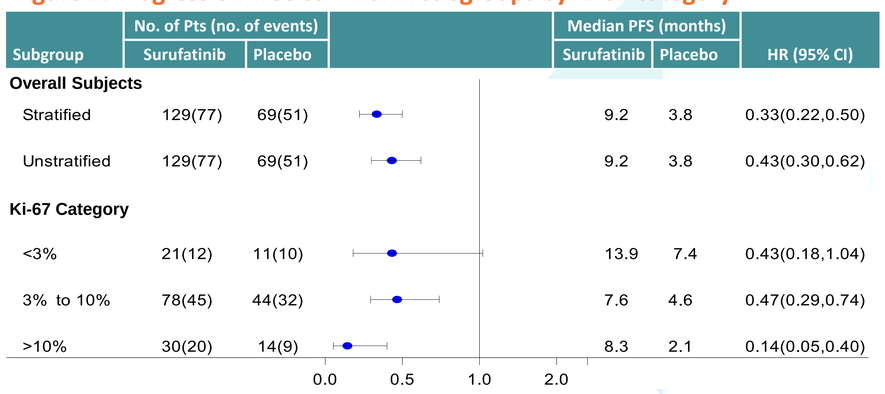


Table 3: Shrinkage of target lesions in subgroups by Ki-67 category

Ki-67 category	Ki-67 <3%		Ki-67 3-10%		Ki-67 >10%	
	S N=21	P N=11	S N=78	P N=44	S N=30	P N=14
Any shrinkage, n (%)	12 (57.1)	5 (45.5)	48 (61.5)	9 (20.5)	19 (63.3)	0
>10% shrinkage, n (%)	6 (28.6)	0	28 (35.9)	2 (4.5)	11 (36.7)	0

SUBGROUP ANALYSIS BY PRIMARY TUMOR ORIGIN

- **Median PFS was significantly prolonged in the subgroups of foregut and hindgut** with surufatinib versus placebo (figure 3).
- **Numerical PFS improvement in the subgroup of unknown origin** with surufatinib versus placebo (figure 3).
- **ORR in the subgroups of foregut, midgut and unknown origin were 18.4%** (95% CI 8.8, 32.0)**, 16.7%** (95% CI 2.1, 48.4) **and 10.0%** (95% CI 1.2, 31.7) respectively with surufatinib, versus none in the placebo arm. No partial response was observed in subgroups of hindgut or other origins.
- **Greater percentage of patients experienced tumor shrinkage** with surufatinib versus placebo across subgroups by tumor origin (table 4).

Figure 3: Progression-free survival in subgroups by tumor origin

Table 4: Shrinkage of target lesions in subgroups by tumor origin

Tumor origins	Foregut		Midgut		Hindgut		Others		Unknown	
	S N=49	P N=29	S N=12	P N=6	S N=40	P N=17	S N=8	P N=5	S N=20	P N=12
Any shrinkage, n (%)	36 (73.5)	4 (13.8)	9 (75.0)	3 (50.0)	19 (47.5)	2 (11.8)	3 (37.5)	3 (60.0)	12 (60.0)	2 (16.7)
>10% shrinkage, n (%)	21 (42.9)	1 (3.4)	7 (58.3)	1 (16.7)	7 (17.5)	0	2 (25.0)	0	8 (40.0)	0

CONCLUSION

- Surufatinib demonstrated clinically significant benefits for patients with advanced well-differentiated extrapancreatic NETs compared to placebo.
- Results of this post-hoc analysis were consistent with those reported for the SANET-ep primary analysis, and improved outcomes were observed across major subgroups.

Declaration of interests of first/correspondence author: No conflicts of interest. Email address: zhouzhw@sysucc.org.cn

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