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#1712 EFFICACY AND SAFETY OF SURUFATINIB IN PATIENTS WITH WELL-DIFFERENTIATED ADVANCED PANCREATIC NEUROENDOCRINE TUMORS (NETS)

Results from the randomized phase III study (SANET-p) (NCT02589821)

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DISCLOSURE INFORMATION

Weiguo Su, James He, Jing Li and Di Zhang are employees of Hutchison MediPharma Ltd.

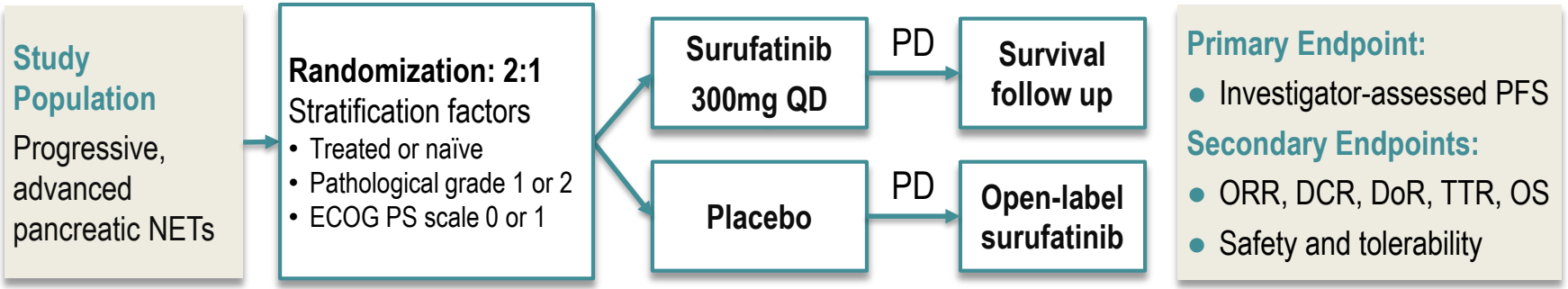
The remaining authors have no conflicts of interest.

SANET-p: BACKGROUND

- Surufatinib (HMPL-012, previously named sulfatinib) is a small-molecule kinase inhibitor targeting VEGFRs, FGFR1 and CSF-1R.
- Simultaneous targeting of angiogenesis through VEGFRs/FGFR1 and modulating tumor immune microenvironment through CSF-1R may be a uniquely potent strategy to enhance antitumor activity.
- Encouraging efficacy of surufatinib treating patients with advanced pancreatic NETs was reported (ORR 19%)[1].
- Surufatinib demonstrated significant improvement in progression-free survival in patients with NETs originating outside the pancreas in the pivotal phase III SANET-ep study[2].

1. Xu J, Li J, Bai C, et al. Surufatinib in Advanced Well-Differentiated Neuroendocrine Tumors: A Multicenter, Single-Arm, Open-Label, Phase Ib/II Trial. *Clin Cancer Res*. 2019;25(12):3486-3494. doi:10.1158/1078-0432.CCR-18-2994. Epub 2019 Mar 4.
2. Xu J, Shen L, Zhou Z, et al. Efficacy and safety of surufatinib in patients with well-differentiated advanced extrapancreatic neuroendocrine tumors (NETs): results from the randomized phase III study (SANET-ep). Presented at ESMO, Barcelona, Spain, 27 September – 1 October 2019; Abstract #4979. *Annals of Oncology* 2019;30(suppl_5):v851-v934. doi:10.1093/annonc/mdz394

SANET-p: PHASE III STUDY DESIGN



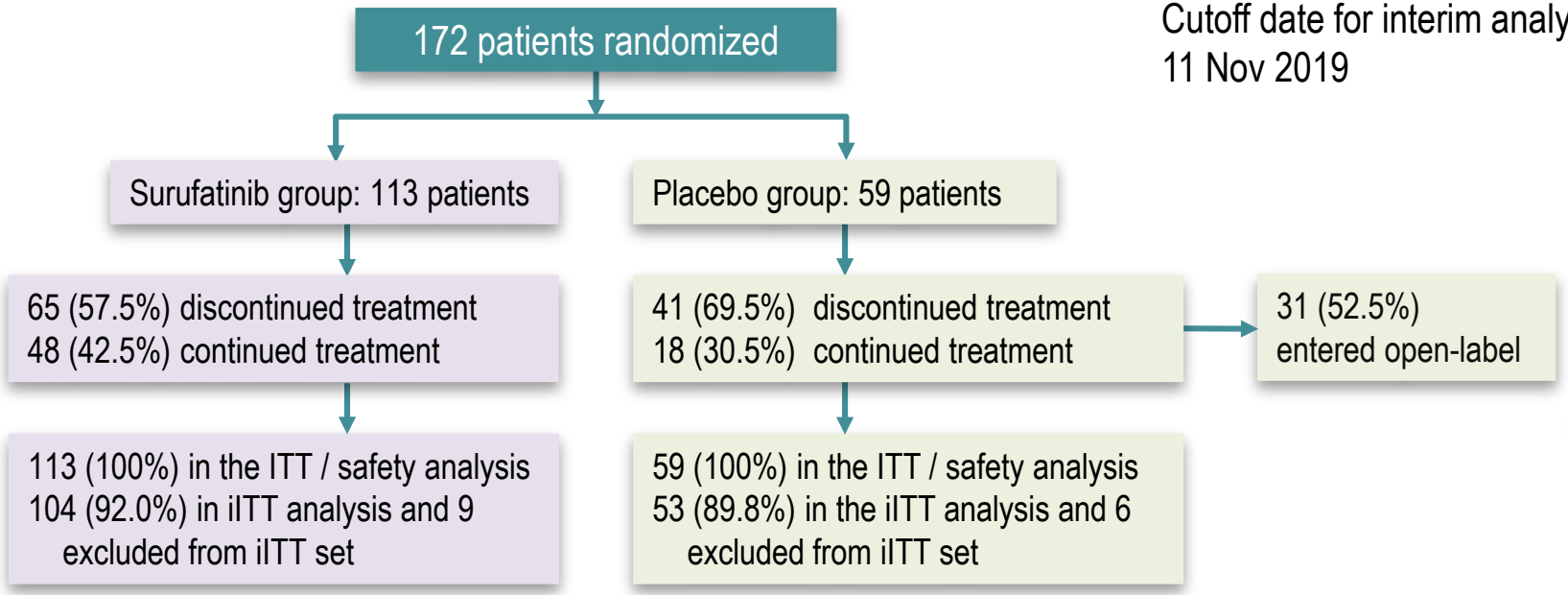
- Statistical assumption: 195 patients planned based on the assumption of the median PFS of 6 months in placebo arm, HR of surufatinib treatment is 0.55 with a two-sided alpha 0.05.
- Interim analysis was planned when 92 PFS events (i.e. 70% of the planned PFS events for final analysis) were observed; study early termination for superiority ($p<0.015$) was allowed.
- Tumor evaluation was conducted by investigators; a blinded independent image review committee (BIIRC) performed tumor assessment in parallel, which was used for sensitivity analysis of PFS.

KEY ELIGIBILITY CRITERIA

- Well-differentiated pancreatic NETs of pathological grade 1 or 2.
- Locally advanced disease or with distant metastasis.
- Documented radiological disease progression within past one year.
- Progression on two or fewer kinds of prior systemic therapies for advanced disease.
- No progression on prior VEGF/VEGFR inhibitors.
- Functional NETs that required treatment with long-acting SSAs were excluded.

*Prior systemic therapies included somatostatin analogues (SSAs), chemotherapy, interferon, mTOR inhibitor, peptide receptor radionuclide therapies; chemotherapies were considered as one kind of therapy, regardless of the regimens or lines.

PATIENT DISPOSITION



Cutoff date for interim analysis
11 Nov 2019

Interim Intent-to-Treat (iITT) Set included patients with at least one post-baseline tumor assessment performed ≥ 6 weeks from first dosing or patients discontinued for any reason. iITT Set was used for the analysis of objective response.

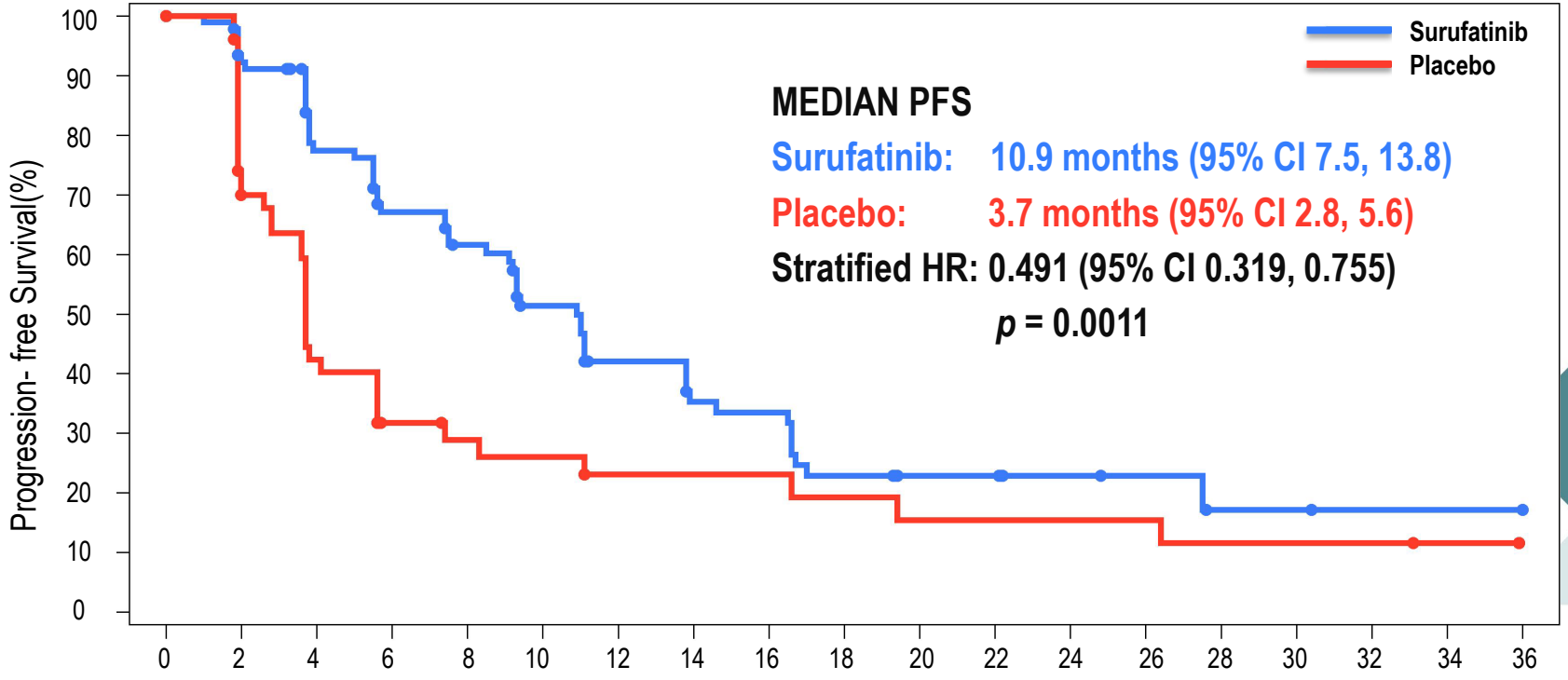
DEMOGRAPHICS AND BASELINE TUMOR CHARACTERISTICS

	Surufatinib (N=113)	Placebo (N=59)
Age, years median (range)	51.0 (25.0, 75.0)	48.0 (20.0, 77.0)
Male	53.1%	47.5%
ECOG PS 0/1	64.6% / 35.4%	72.9% / 27.1%
Pathological grade 1/2	12.4% / 87.6%	15.3% / 84.7%
Non-functional tumors	90.3%	93.2%

	Surufatinib (N=113)	Placebo (N=59)
Liver metastasis	95.6%	91.5%
Previous systemic anti-tumor treatment for advanced disease	65.5%	66.1%
Chemotherapy	29.2%	20.3%
Somatostatin analogue	42.5%	47.5%
Everolimus	10.6%	6.8%
Previous loco-regional therapy	23.9%	25.4%

INVESTIGATOR-ASSESSED PFS (PRIMARY)

SANET-p clearly succeeded in meeting the superiority criteria of PFS

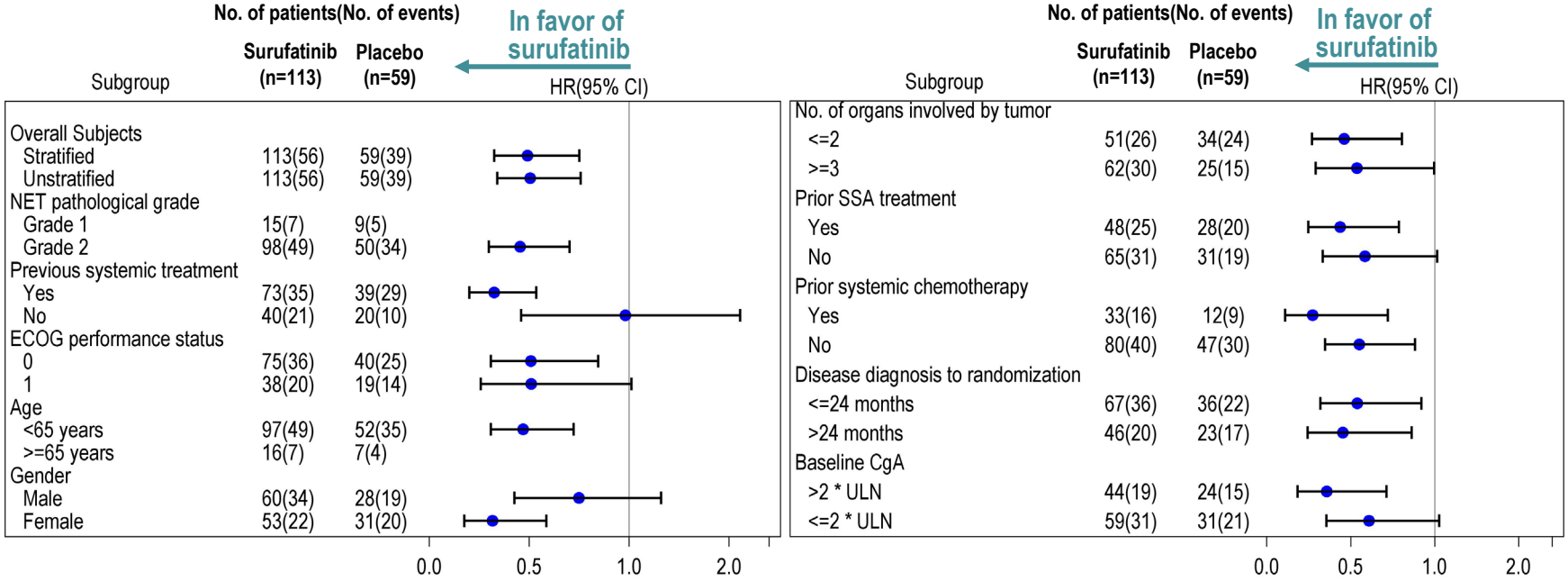


Number at risk (number censored)

Surufatinib	*113 (0)*	*79 (27)*	*61 (33)*	*50 (36)*	*43 (39)*	*33 (42)*	*25 (44)*	*20 (45)*	*19 (45)*	*13 (45)*	*8 (50)*	*8 (50)*	*5 (53)*	*4 (54)*	*2 (55)*	*2 (55)*	*1 (56)*	*1 (56)*	*1 (57)*
Placebo	*59 (0)*	*33 (10)*	*20 (11)*	*12 (14)*	*10 (15)*	*9 (15)*	*6 (17)*	*6 (17)*	*6 (17)*	*5 (17)*	*4 (17)*	*4 (17)*	*4 (17)*	*4 (17)*	*3 (17)*	*3 (17)*	*3 (17)*	*2 (18)*	*0 (20)*

SUBGROUP ANALYSIS OF INVESTIGATOR-ASSESSED PFS

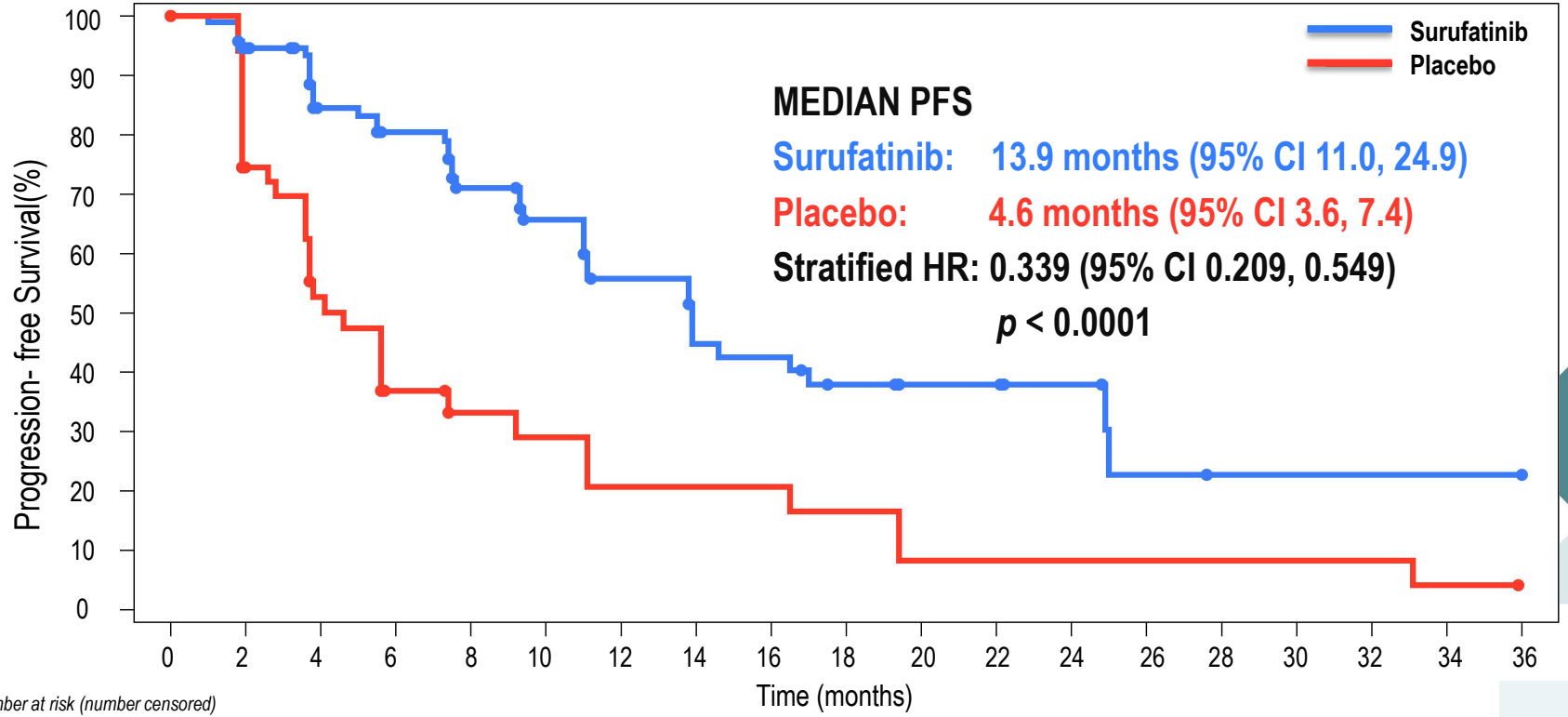
PFS benefit favored surufatinib across major subgroups



ULN: upper limit of normal; SSA: Somatostatin analogues; CgA: chromogranin A.

SUPPORTIVE ANALYSIS: BIIRC-ASSESSED PFS

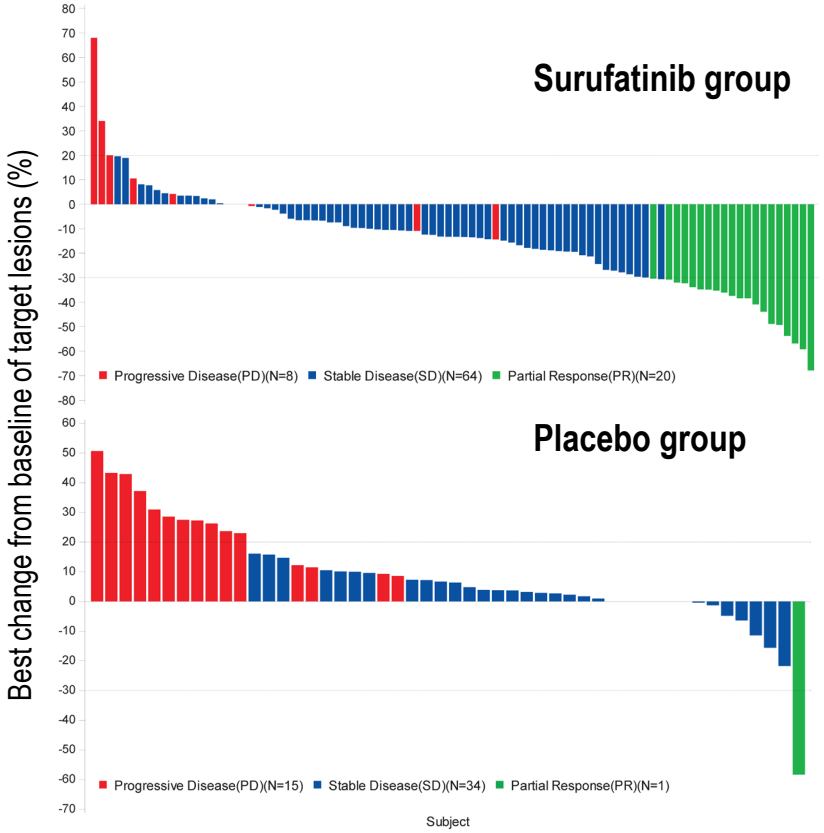
BIIRC-assessed PFS was consistent with investigator-assessed PFS



Number at risk (number censored)

Surufatinib	*113 (0)*	*80 (28)*	*62 (38)*	*54 (43)*	*42 (49)*	*34 (54)*	*26 (57)*	*20 (58)*	*19 (58)*	*14 (61)*	*10 (65)*	*10 (65)*	*7 (68)*	*3 (70)*	*1 (72)*	*1 (72)*	*1 (72)*	*1 (72)*	*1 (73)*
Placebo	*59 (0)*	*31 (14)*	*20 (17)*	*11 (20)*	*8 (22)*	*7 (22)*	*5 (22)*	*5 (22)*	*5 (22)*	*4 (22)*	*2 (22)*	*2 (22)*	*2 (22)*	*2 (22)*	*2 (22)*	*2 (22)*	*2 (22)*	*1 (22)*	*0 (23)*

SECONDARY ENDPOINTS: ORR, DCR, TTR, DOR, OS



	Investigator assessment in iITT#		
	Surufatinib (N=104)	Placebo (N=53)	*p* value
PR-n (%)	**20 (19.2)***	**1 (1.9)***	-
SD-n (%)	64 (61.5)	34 (64.2)	-
PD-n (%)	8 (7.7)	16 (30.2)	-
NE-n (%)	12 (11.5)	2 (3.8)	-
ORR- % (95% CI)	**19.2 (12.2, 28.1)**	**1.9 (0.0, 10.1)**	**0.0021**
DCR- % (95% CI)	80.8 (71.9, 87.8)	66.0 (51.7, 78.5)	0.0774
TTR, months (95% CI)	3.8 (2.3, 7.3)	7.4 (-, -)	-
DOR, months (95% CI)	7.4 (3.7, -)	-	-

* Surufatinib group: 13 PR confirmed, 7 PR unconfirmed. Placebo group: 1 PR confirmed.
# 15 patients were excluded from the iITT set (9 from the surufatinib arm and 6 from the placebo arm), who were on-treatment but had not yet received a post-baseline tumor evaluation.

OS was immature (16.9% events)

DRUG EXPOSURE: SAFETY ANALYSIS SET

	Surufatinib (N=113)	Placebo (N=59)
Exposure, days median (range)	229 (3, 1174)	123 (5, 1127)
Dose intensity, mg/day mean (std)	266.89 (40.623)	292.88 (15.791)
Relative dose intensity, % mean (std)	88.96 (13.541)	97.63 (5.263)

SAFETY SUMMARY-SAFETY ANALYSIS SET

Most TEAEs were manageable through dose interruption and modification

	Surufatinib (N=113) n (%)	Placebo (N=59) n (%)
Any treatment emergent adverse events (TEAEs)	108 (95.6)	54 (91.5)
CTC AE grade		
Grade 1	5 (4.4)	19 (32.2)
Grade 2	24 (21.2)	19 (32.2)
Grade 3	67 (59.3)	14 (23.7)
Grade 4	9 (8.0)	2 (3.4)
Grade 5	3 (2.7)	0
Any ≥ grade 3 TEAEs	79 (69.9)	16 (27.1)
Any serious adverse event (SAE)	29 (25.7)	5 (8.5)
Any TEAEs leading to dose interruption	51 (45.1)	14 (23.7)
Any TEAEs leading to dose reduction	44 (38.9)	3 (5.1)
Any TEAEs leading to dose discontinuation	12 (10.6)	4 (6.8)

TEAEs: treatment emergent adverse events

MOST COMMON TEAES (≥ 20%)-SAFETY ANALYSIS SET

The most common (≥20%) TEAEs were hypertension, proteinuria, diarrhoea

TEAEs	Surufatinib (N=113) n (%)		Placebo (N=59) n (%)	
	Any grade	≥ grade 3	Any grade	≥ grade 3
Hypertension	75 (66.4)	44 (38.9)	13 (22.0)	5 (8.5)
Proteinuria	74 (65.5)	11 (9.7)	32 (54.2)	1 (1.7)
Diarrhoea	58 (51.3)	5 (4.4)	15 (25.4)	1 (1.7)
Blood thyroid stimulating hormone increased	49 (43.4)	0	6 (10.2)	0
Hypertriglyceridaemia	42 (37.2)	8 (7.1)	9 (15.3)	0
Blood bilirubin increased	42 (37.2)	2 (1.8)	11 (18.6)	0
Hypoalbuminaemia	31 (27.4)	0	8 (13.6)	0
Occult blood positive	30 (26.5)	0	14 (23.7)	0
Aspartate aminotransferase increased	27 (23.9)	2 (1.8)	20 (33.9)	1 (1.7)
Abdominal pain	27 (23.9)	2 (1.8)	5 (8.5)	0
Hyperuricaemia	24 (21.2)	2 (1.8)	1 (1.7)	0

CONCLUSION

- Surufatinib treatment resulted in a statistically significant and clinically meaningful improvement in PFS with tolerable safety profile for advanced pancreatic NETs patients.
- The study was early terminated by the recommendation of the IDMC, based on superior efficacy observed at the pre-planned interim analysis.
- Results from SANET-p support surufatinib as an effective addition to the clinical armamentarium for treating well-differentiated pancreatic NETs.

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