BARCELONA 2019 ESMO congress

#4979 EFFICACY AND SAFETY OF SURUFATINIB IN PATIENTS WITH WELL-DIFFERENTIATED ADVANCED EXTRAPANCREATIC NEUROENDOCRINE TUMORS (NETS)

Results from the randomized phase III study (SANET-ep) (NCT02588170)

Jianming Xu, Lin Shen, Zhiwei Zhou, Jie Li, Chunmei Bai, Yihebali Chi, Zhiping Li, Nong Xu, Ru Jia, Eenxiao Li, Tianshu Liu, Yuxian Bai, Ying Yuan, Xingya Li, Xiuwen Wang, Jia Chen, Jieer Ying, Xianjun Yu, Shukui Qin, Tao Zhang, Xianglin Yuan, Dianrong Xiu, Yanhong Deng, Ying Cheng, Min Tao, Jing Li, Songhua Fan, Weiguo Su

Study Sponsored by Hutchison MediPharma Ltd.,
a subsidiary of Hutchison China MediTech.

DISCLOSURE

Weiguo Su, Songhua Fan and Jing Li are employees of Hutchison MediPharma Ltd.

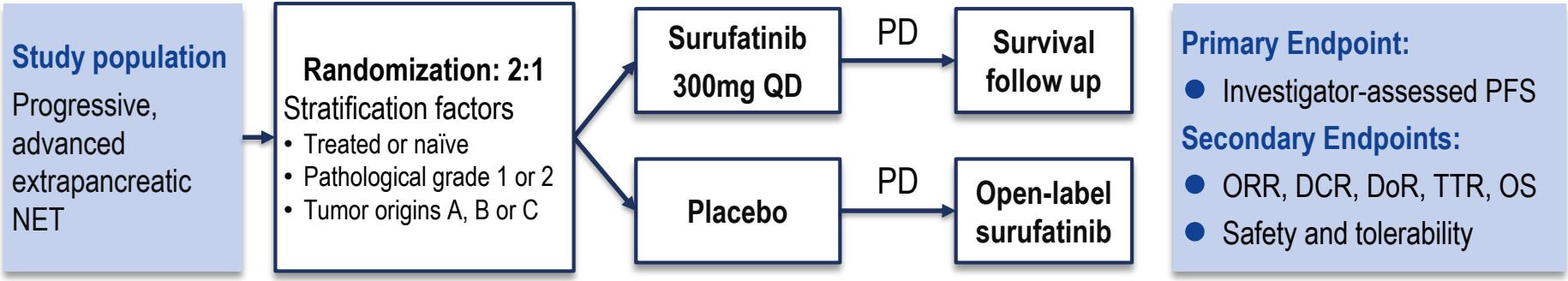
The remaining authors have no conflicts of interest.

SANET-ep: BACKGROUND

- Treatment options remain limited for patients with extrapancreatic neuroendocrine tumors (NETs).
- Anti-VEGF signalling pathway is a proven strategy for the treatment of pancreatic NETs. However efficacy in extrapancreatic NETs has not yet been proven. [1]
- Surufatinib (HMPL-012, previously named sulfatinib) is a small-molecule kinase inhibitor targeting VEGFRs, FGFR1 and CSF-1R.
- Encouraging efficacy of surufatinib treating patients with advanced NETs regardless of tumor origin was reported (ORR of 19% in pancreatic NETs and 15% in extrapancreatic NET). [2]

1. Raymond E, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501–13.
2. Xu J, et al. Surufatinib in Advanced Well-Differentiated Neuroendocrine Tumors: A Multicenter, Single-Arm, Open-Label, Phase Ib/II Trial. Clin Cancer Res. 2019 Jun 15;25(12):3486-3494. doi: 10.1158/1078-0432.CCR-18-2994. Epub 2019 Mar 4.

SANET-ep: PHASE III STUDY DESIGN



- Statistical assumption: 273 patients planned based on the assumption of the median PFS of 8 months in placebo arm, HR of surufatinib treatment is 0.6 with a two sided alpha 0.05.
- Interim analysis was planned when 127 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 retrospectively in parallel, which was used for sensitivity analysis of PFS.

Tumor origin A: jejunum, ileum, duodenum, thymus, cecum; B: lung, stomach, liver, appendix, colon, rectum; C: others or unknown origin.

KEY ELIGIBILITY CRITERIA

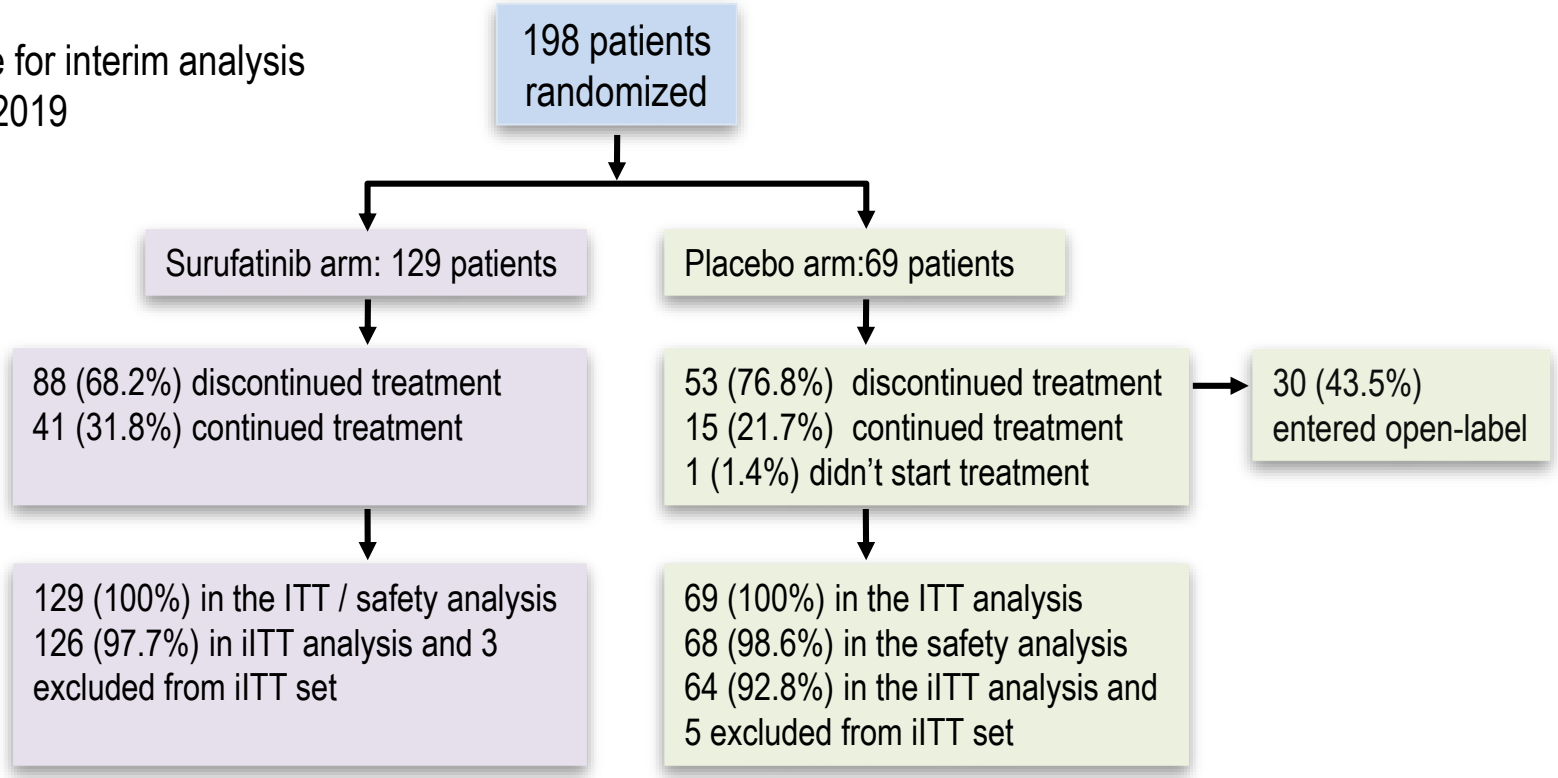
- Well-differentiated extrapancreatic NETs of pathological grade 1 or 2.
- Locally advanced disease or with distant metastasis.
- Documented radiological disease progression within past one year.
- Progression on two or fewer kinds of prior systemic therapies for advanced disease.
- No progression on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

BARCELONA 2019 ESMO congress

*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
31 March 2019



BARCELONA 2019 ESMO congress

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 overall response.

DEMOGRAPHICS AND BASELINE TUMOR CHARACTERISTICS

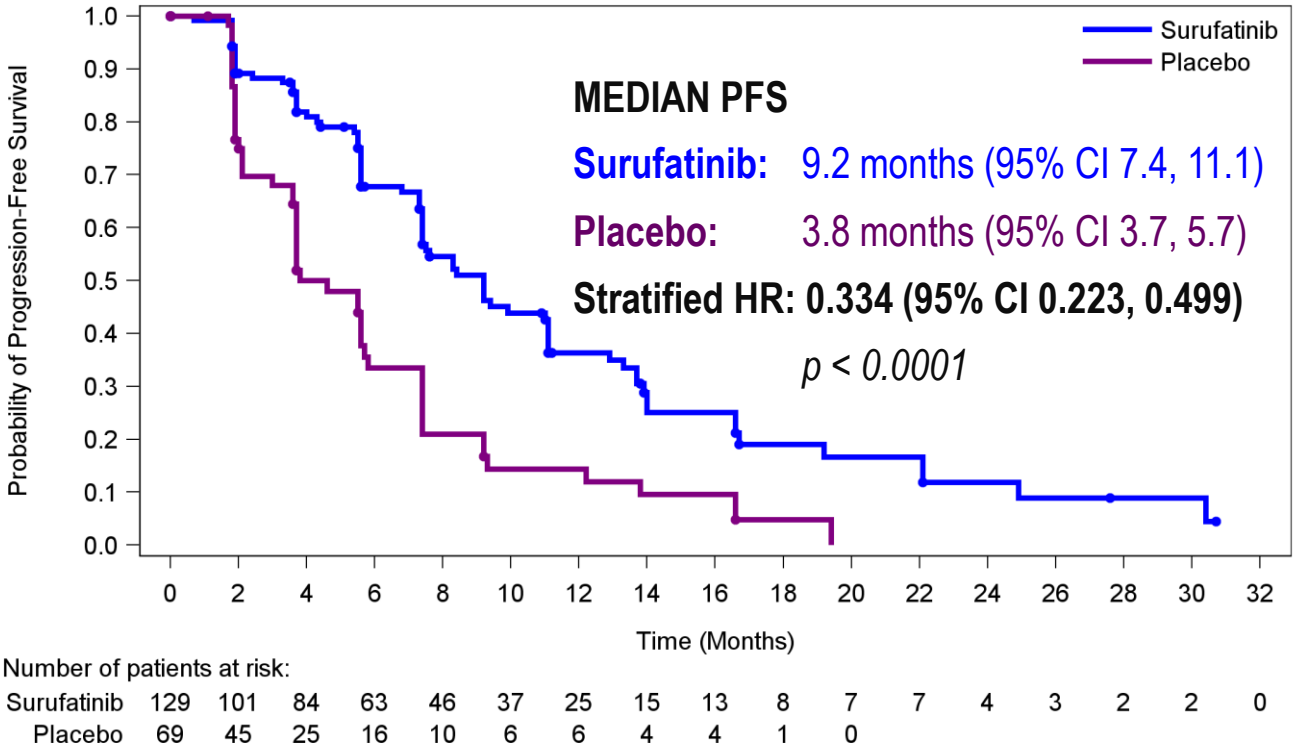
	Surufatinib (N=129)	Placebo (N=69)
Age, median (range), years	52.0 (19.0, 72.0)	54.0 (25.0, 79.0)
Male	56.6%	50.7%
ECOG PS 0/1	55.8% / 44.2%	66.7% / 33.3%
Pathological grade 1/2	16.3% / 83.7%	15.9% / 84.1%
Non-functional tumors	94.6%	97.1%
Primary tumor origins		
Gastrointestinal tract (Rectum / stomach / 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%
Previous loco-regional therapy	34.1%	23.3%

BARCELONA 2019 ESMO congress

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

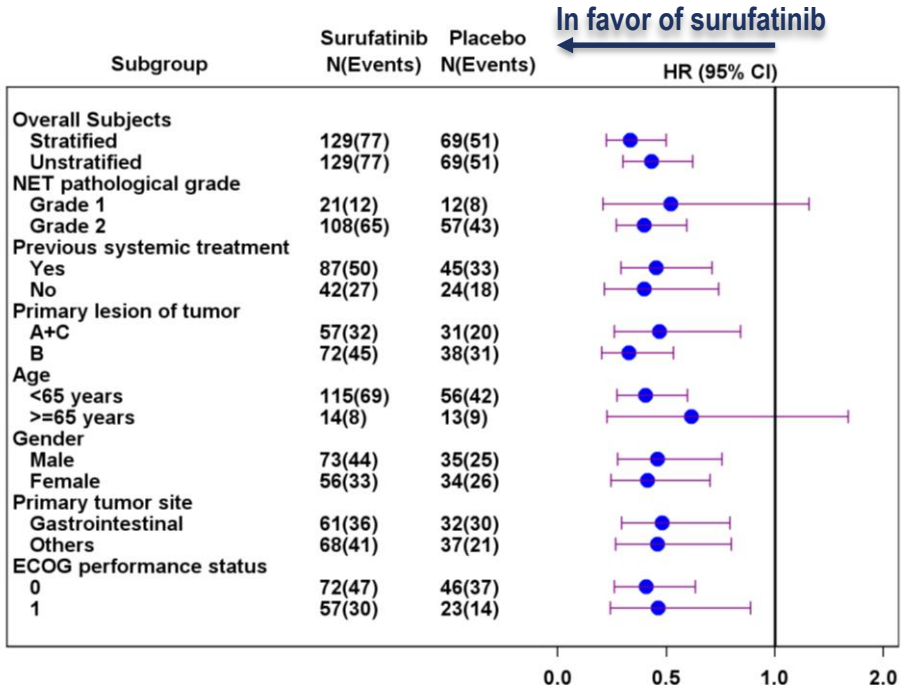
INVESTIGATOR-ASSESSED PFS (PRIMARY)

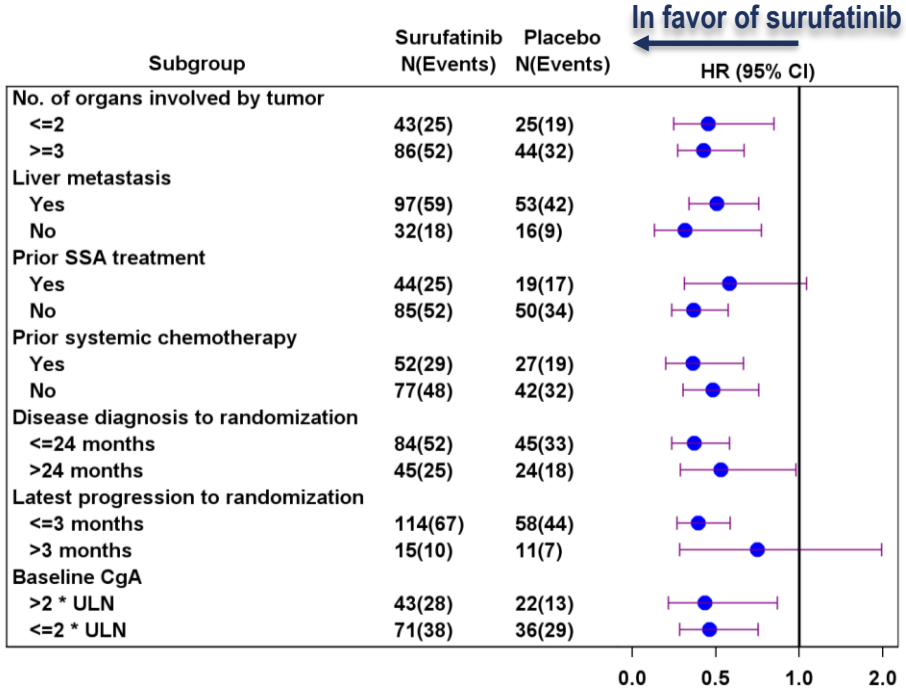
SANET-ep clearly succeeded in meeting the superiority criteria of PFS



BARCELONA 2019 ESMO congress

SUBGROUP ANALYSIS OF INVESTIGATOR-ASSESSED PFS



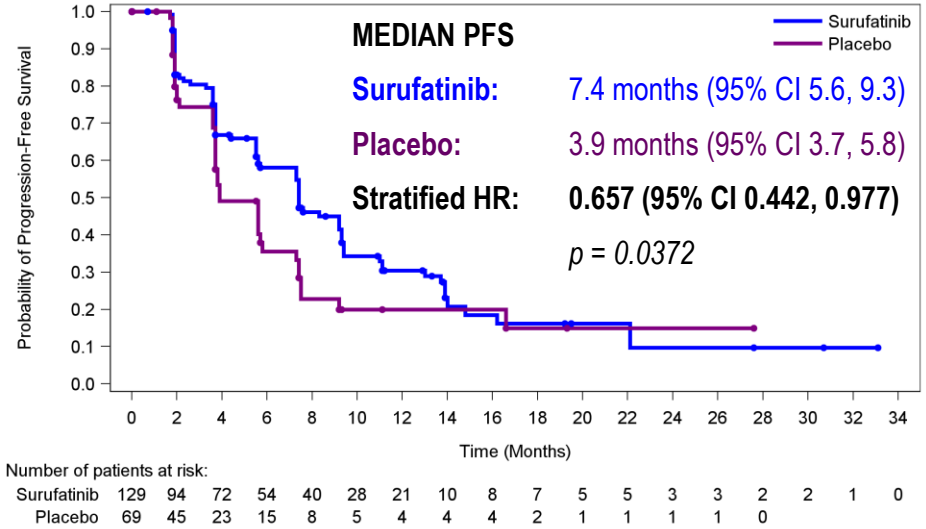


BARCELONA 2019 ESMO congress

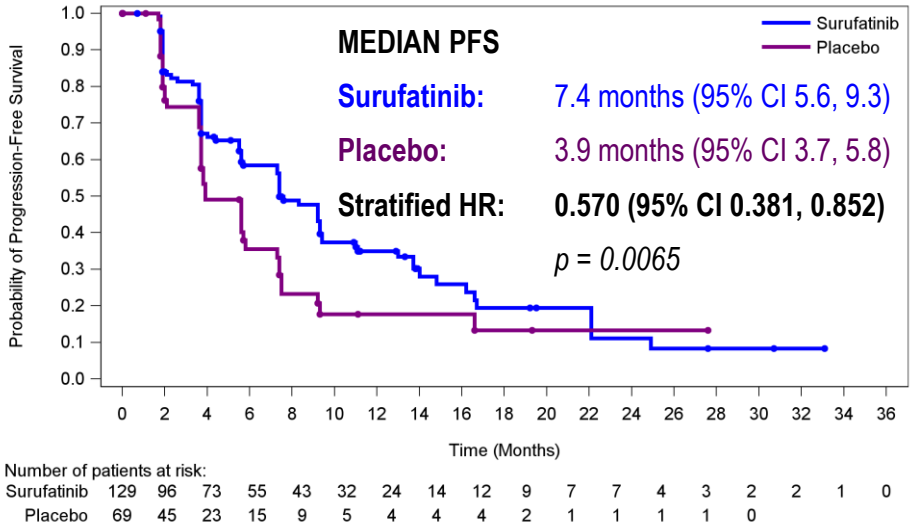
Tumor origin A: jejunum, ileum, duodenum, thymus, cecum; B: lung, stomach, liver, appendix, colon, rectum; C: others or unknown origin.

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

SUPPORTIVE ANALYSIS: BIIRC-ASSESSED PFS



POST-HOC ANALYSIS: ADJUDICATED BIIRC-ASSESSED PFS



Post-hoc blinded image adjudication conducted for 35 patients with PFS discrepancy ≥ 4 cycles (28 days/cycle) between BIIRC and investigators

BARCELONA 2019 ESMO congress

POST-HOC SENSITIVITY ANALYSIS OF PFS

Potential reasons for assessment difference between investigators and BIIRC:

- Prior loco-regional therapies (34.1% vs. 23.3%) may have posed challenges to central reviewers.
- The characteristics of liver lesion in CT/MRI likely led to false new lesion / non-target lesion progression (e.g. equidensity at baseline, low-density after treatment).

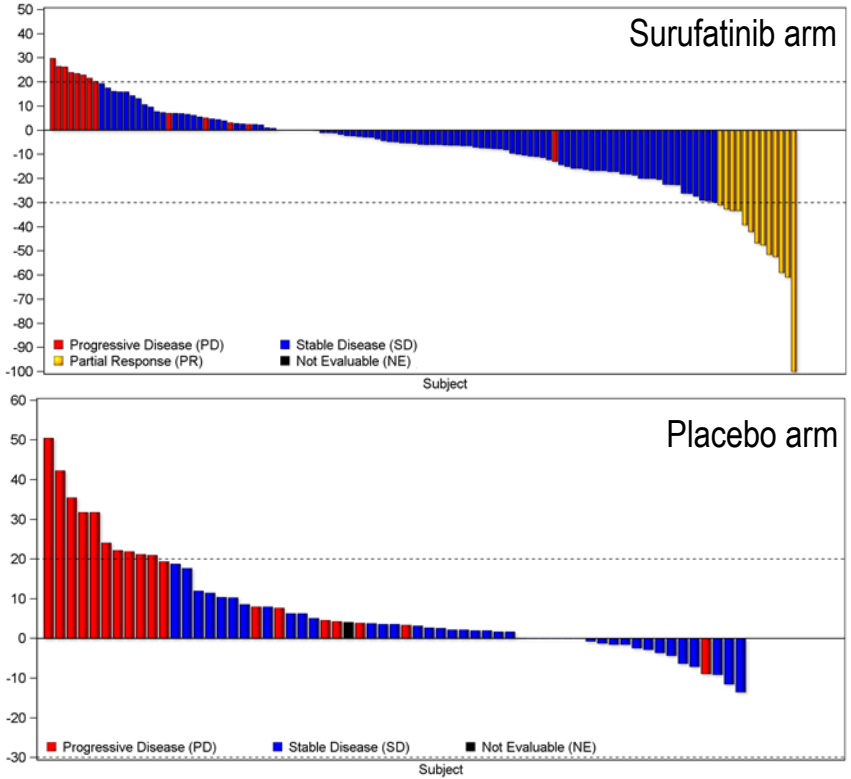
Excluding 60 patients with prior loco-regional therapy

	Surufatinib (N=85)	Placebo (N=53)	Surufatinib vs. Placebo	
	Median PFS (months)	Median PFS (months)	HR (95% CI)	*P*-value
Investigator	9.9	5.5	0.307 (0.188, 0.502)	<0.0001
BIIRC	9.2	3.9	0.514 (0.319, 0.829)	0.0063

Excluding 17 patients with prior loco-regional therapy and PFS event status discordance

	Surufatinib (N=115)	Placebo (N=66)	Surufatinib vs. Placebo	
	Median PFS (months)	Median PFS (months)	HR (95% CI)	*P*-value
Investigator	9.2	4.6	0.323 (0.212, 0.492)	<0.0001
BIIRC	7.4	3.9	0.546 (0.362, 0.825)	0.0041

SECONDARY ENDPOINTS: ORR, DCR, TTR, DOR



	Investigator assessment in iITT			
	Surufatinib (N=126)	Placebo (N=64)	Odds Ratio	*P* value
PR-n (%)	13 (10.3)*	0	-	-
SD-n (%)	96 (76.2)	42 (65.6)	-	-
PD-n (%)	13 (10.3)	18 (28.1)	-	-
NE-n (%)	4 (3.2)	4 (6.3)	-	-
ORR- % (95% CI)	10.3 (5.6, 17.0)	0	-	0.0051
DCR- % (95% CI)	86.5 (79.3, 91.9)	65.6 (52.7, 77.1)	3.3 (1.5, 7.3)	0.0022
TTR, months (95% CI)	3.7 (1.8, 5.5)	-	-	-
DOR-months (95% CI)	5.6 (2.0, 17.5)	-	-	-

- **OS was immature (18.7% events)**

BARCELONA 2019 ESMO congress

* 11 PR confirmed, 2 PR unconfirmed

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 overall response.

DRUG EXPOSURE-SAFETY ANALYSIS SET

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

SAFETY SUMMARY-SAFETY ANALYSIS SET

	Surufatinib (N=129)	Placebo (N=68)
	n (%)	n (%)
Any treatment emergent adverse events (TEAE)	127 (98.4)	65 (95.6)
CTC AE grade		
Grade 1	7 (5.4)	16 (23.5)
Grade 2	21 (16.3)	26 (38.2)
Grade 3	82 (63.6)	19 (27.9)
Grade 4	14 (10.9)	3 (4.4)
Grade 5	3 (2.3)	1 (1.5)
Any ≥ grade 3 TEAE	99 (76.7)	23 (33.8)
Any serious adverse event (SAE)	34 (26.4)	12 (17.6)
Any TEAE leading to dose interruption	62 (48.1)	15 (22.1)
Any TEAE leading to dose reduction	62 (48.1)	5 (7.4)
Any TEAE leading to dose discontinuation	23 (17.8)	4 (5.9)

MOST COMMON TEAES WITH FREQUENCY ≥ 20% (SAFETY ANALYSIS SET)

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
Hypertriglyceridemia	41 (31.8)	3 (2.3)	6 (8.8)	0
Hypoalbuminemia	37 (28.7)	0	4 (5.9)	0
Alanine aminotransferase increased	32 (24.8)	4 (3.1)	19 (27.9)	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)

TEAEs: treatment emergent adverse events

CONCLUSION

- Surufatinib significantly improved PFS for the advanced extrapancreatic NETs patients in this study.
- Surufatinib was generally well tolerated in this study and the safety profile consistent with that previously reported for surufatinib.
- The study was terminated by the recommendation of the Independent Data Monitoring Committee based on the interim analysis.
- Global clinical development of surufatinib in NETs is ongoing, including a phase III trial of surufatinib in pancreatic NETs being conducted in China.

ACKNOWLEDGEMENT

The authors thank all the patients and families for their participation in this study.

The authors thank all the investigators and staff involved in this study.

The authors thank Dr. Haesun Choi from MD Anderson Cancer Center, Houston, TX and Dr. Marianne Pavel from Friedrich-Alexander-University of Erlangen-Nürnberg, Germany for the independent image adjudication.

This study was sponsored by Hutchison MediPharma Ltd., a subsidiary of Hutchison China MediTech.

ACKNOWLEDGEMENT

All study centers participating in this study

- Department of Gastrointestinal Oncology, The Fifth Medical Center, General Hospital of the People's Liberation Army, Beijing, China.
- Department of Gastrointestinal Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China.
- 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, China.
- Department of Oncology, Peking Union Medical College Hospital, Beijing, China.
- Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.
- Department of Abdominal Oncology, West China Hospital, Sichuan University, Chengdu, China.
- Department of Medical Oncology, The First Affiliated Hospital of Zhejiang University, Hangzhou, China.
- Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.
- Department of Oncology, Zhongshan Hospital of Fudan University, Shanghai, China.
- Department of Gastrointestinal Oncology, Harbin Medical University Cancer Hospital, Harbin, China.
- Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.
- Department of Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.
- Department of Medical Oncology, Qilu Hospital of Shandong University, Jinan, China.
- Department of Oncology, Jiangsu Cancer Hospital, Nanjing, China.
- Department of Abdominal Oncology, Zhejiang Cancer Hospital, Hangzhou, China, Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China.
- Department of Oncology, 81 Hospital of Chinese People's Liberation Army, Nanjing, China.
- Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.
- Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.
- Department of General Surgery, Peking University Third Hospital, Beijing, China.
- Department of Medical Oncology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.
- Department of Thoracic Oncology, Jilin Provincial Cancer Hospital, Jilin, China.
- Department of Oncology, The First Affiliated Hospital of Soochow University, Suzhou, China.