An Open-Label Phase Ib/II Study of Sulfatinib in Patients with Advanced Neuroendocrine Tumors (NCT02267967)

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Disclosure

Jian Ming Xu is a consultant/advisory board member for Hutchison MediPharma Limited and has received speaker's bureau honoraria from Roche, Novartis, Merck, and Sanofi.

Ru Jia is an attending doctor from the same department of professor Xu and presents the study results on behalf of professor Xu and has no conflict of interest to declare.

Background

- Treatment options for advanced neuroendocrine tumors (NETs) are limited.
- Targeting VEGF pathways has been proven to provide clinical benefits to patients with advanced NETs, particularly pancreatic NET.
- FGF/FGFR signaling pathway activation may play a role in acquired resistance to anti-VEGF therapies.
- Evidence also shows FGFR and CSF1R can induce tumor-associated macrophage proliferation and differentiation, leading to tumor immune evasion.

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*Sulfatinib**

- Sulfatinib selectively inhibits VEGFR1-3, FGFR1 and CSF1R kinases.
- In preclinical models, sulfatinib prevents tumor angiogenesis and tumor immune evasion.
- Sulfatinib demonstrated encouraging clinical activity in NET (G1/2) patients in phase I study, with ORR of 38.1% and mPFS of 16.9 months against a variety of NETs.

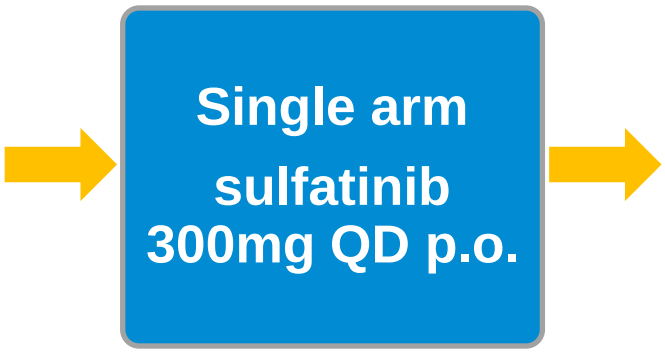
Kinase	IC_{50} (μM)
VEGFR 1	0.002
VEGFR 2	0.024
VEGFR 3	0.001
FGFR1	0.015
CSF1R	0.004
TrkB	0.041
FLT3	0.067
278 other kinases	>0.150

***Sulfatinib, a novel kinase inhibitor, in patients with advanced solid tumors: Results from a phase I study, Oncotarget, Feb 01 2017, published online**

Sulfatinib phase Ib/II study in G1/2 NET SANET-1

Study population:

- ECOG PS 0 or 1.
- Measurable disease.
- Unresectable or metastatic NET.
- Grade 1 or 2.
- Failed standard therapy or standard therapy unavailable.



Continuous treatment in 28-day cycles, until

- Disease progression.
- Unacceptable toxicity.
- Other reasons.

Primary Endpoints: ORR and safety (CTC AE 4.03).

Secondary Endpoints: DCR, DoR and PFS (RECIST1.1) and PK characteristics.

Demographics and baseline characteristics

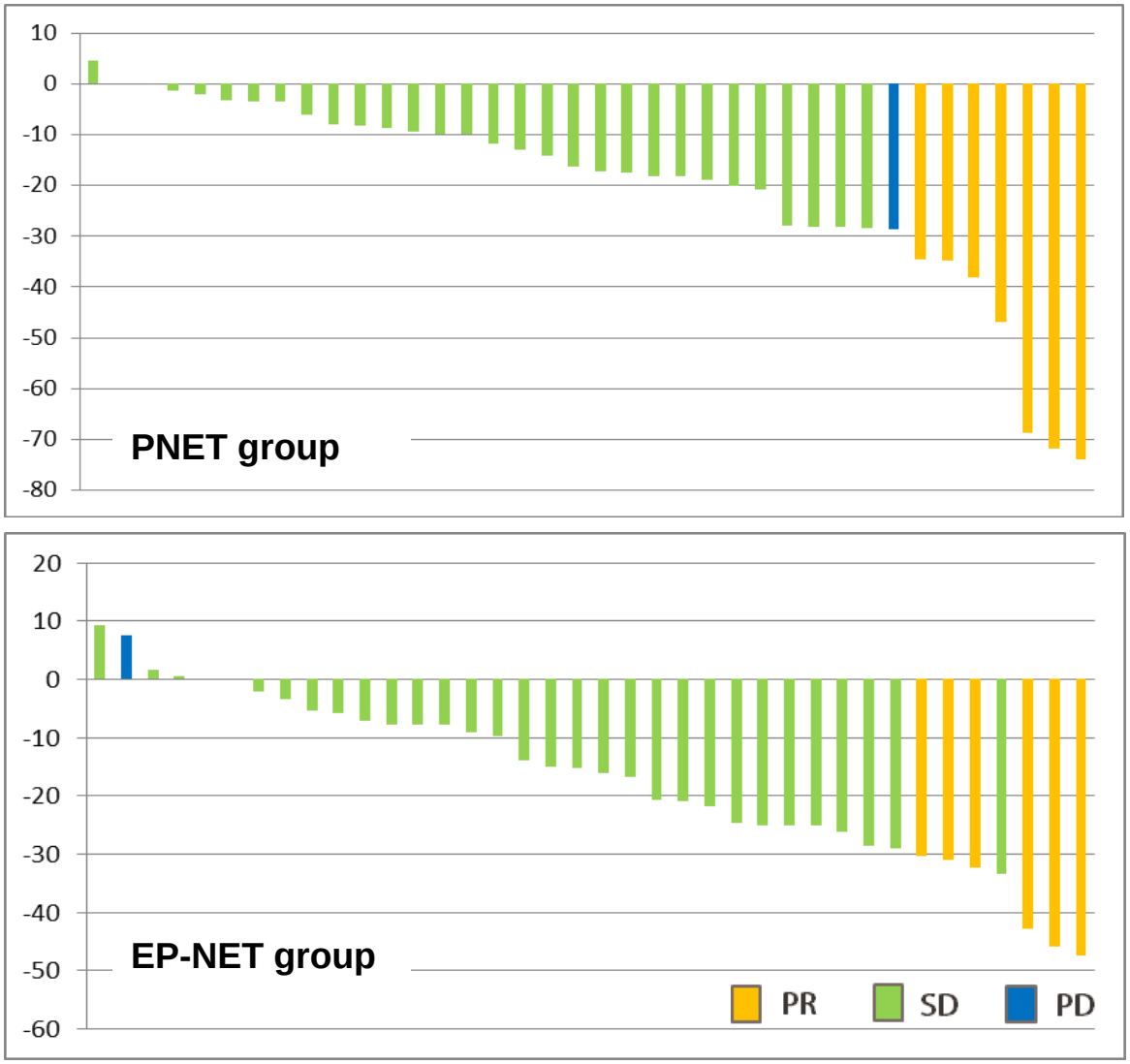
	PNET* N=41 n (%)	EP-NET** N=40 n (%)	Total N=81 n (%)
Age Median Years (min, max)	44 (21, 69)	55 (26, 72)	49 (21, 72)
ECOG PS			
0	31 (75.6)	22 (55.0)	53 (65.4)
1	10 (24.4)	18 (45.0)	28 (44.6)
Pathology grade			
G1	7 (17.1)	10 (25.0)	17 (21.0)
G2	34 (82.9)	30 (75.0)	64 (79.0)
Liver metastasis	37 (90.2)	33 (82.5)	70 (86.4)
Radiologically PD in past 1 year	34 (82.9)	35 (87.5)	69 (85.2)
Prior systemic treatment	26 (63.4)	27 (67.5)	53 (65.4)
Sunitinib	9 (22.5)	4 (10.0)	13 (16.5)
Everolimus	5 (12.2)	6 (15.0)	11 (13.6)
LAR-SSA	17 (41.5)	19 (47.5)	36 (44.4)
Chemotherapy	8 (19.5)	14 (35.0)	22 (27.2)

- **Enrollment:** Nov 2014 to Jan 2016
- **Most patients (95.1%) had non-functional NETs**
- **Primary site for EP-NET group:**
  - Colon/rectum, 14
  - Stomach, 5
  - Small intestine, 3
  - Lung, 4
  - Unknown, 14

* Pancreatic NET; **Extra-pancreatic NET

Best tumor response

as of 20 Jan 2017

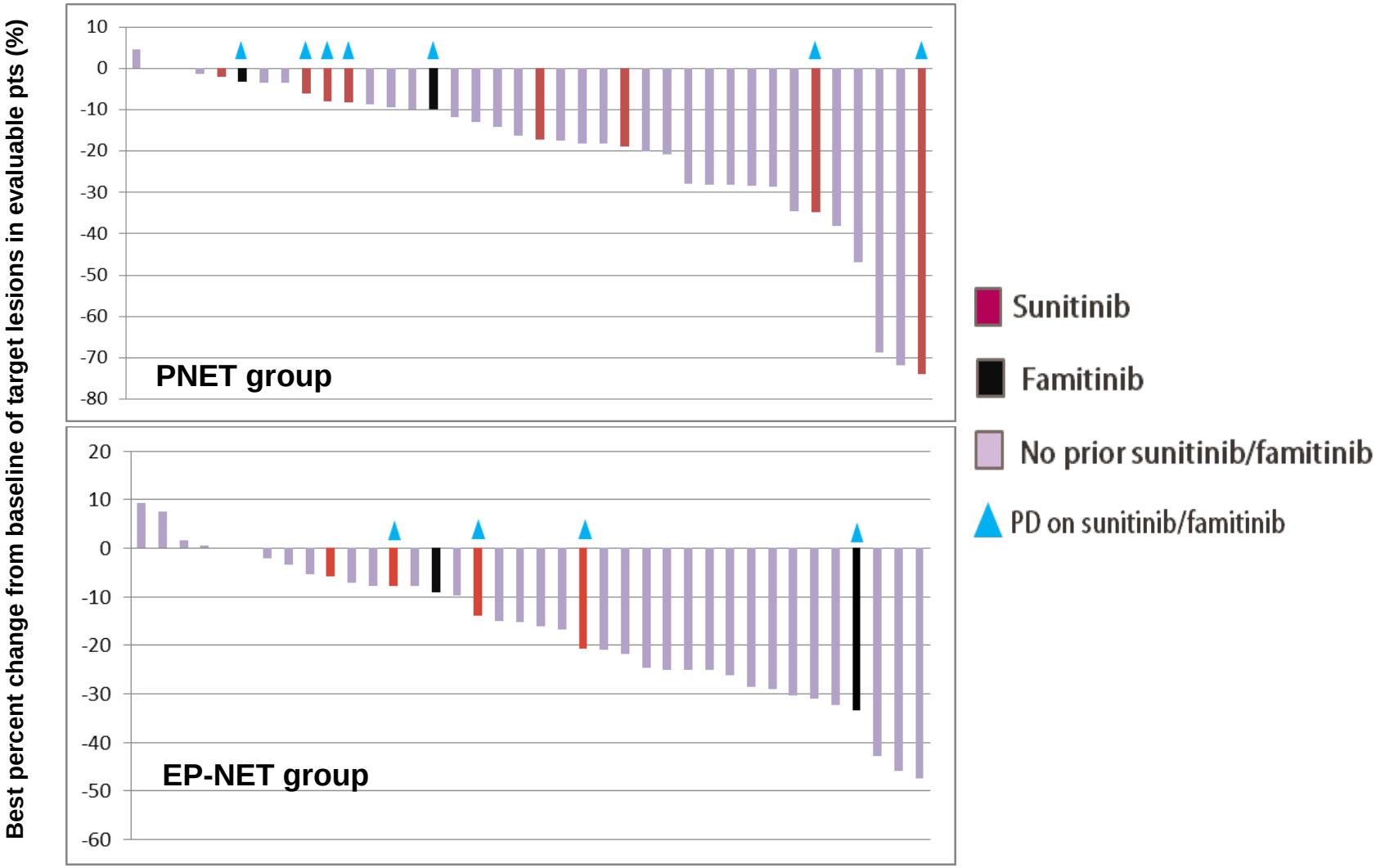


PNET	N=41 n (%)
PR (confirmed)	7 (17.1%)
SD	30 (73.2%)
PD	1 (2.4%)
NE*	3 (7.3%)
ORR (95% CI)	17.1% (7.2%-32.1%)
DCR (95% CI)	90.2% (76.9%-97.3%)

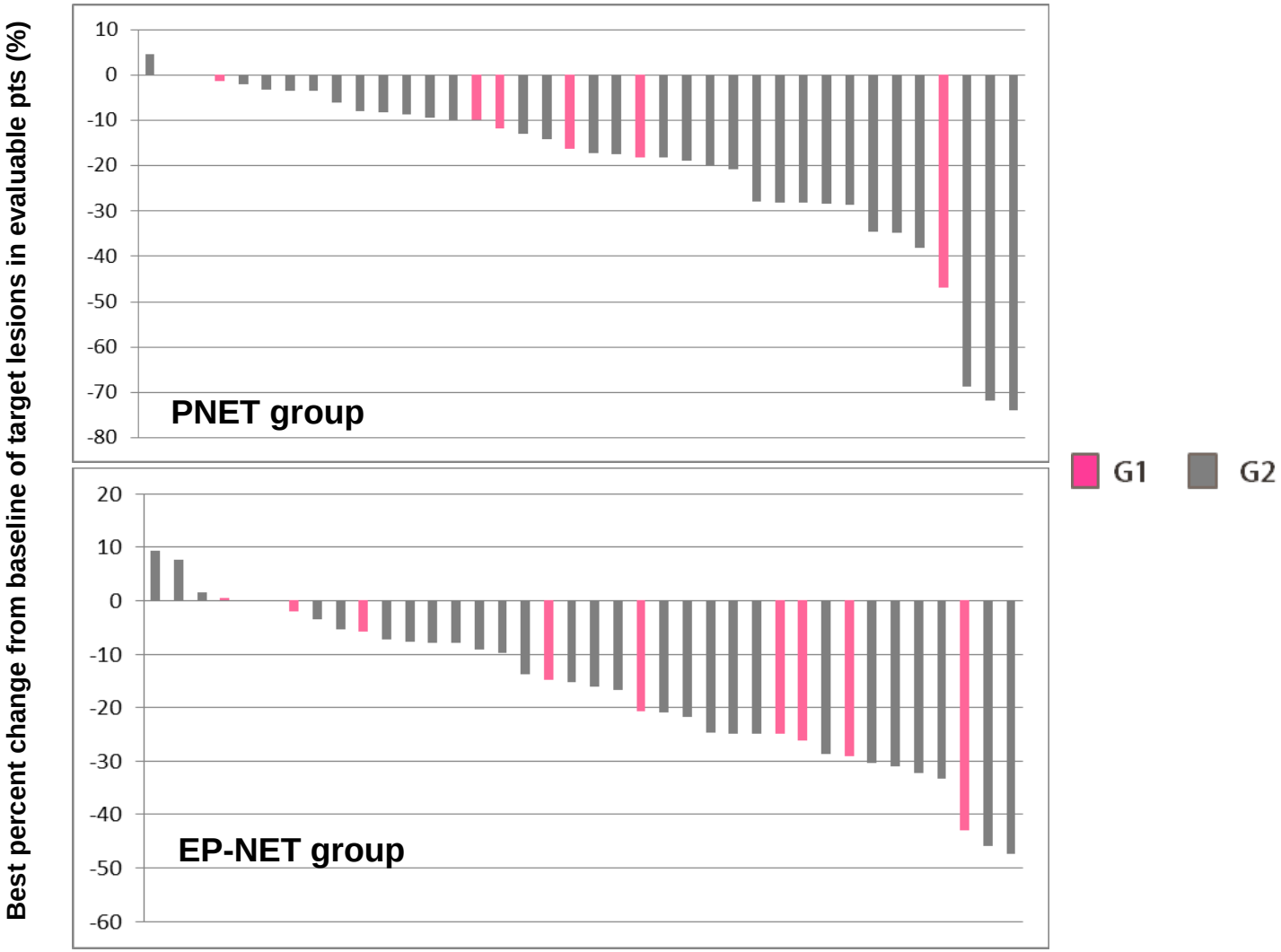
EP-NET	N=40 n (%)
PR (confirmed)	6 (15.0%)
SD	31 (77.5%)
PD	1 (2.5%)
NE*	2 (5.0%)
ORR (95% CI)	15.0% (5.7%-29.8%)
DCR (95% CI)	92.5% (79.6%-98.4%)

*NE: not evaluable

Sulfatinib showed anti-tumor activity in patients who failed sunitinib / famitinib

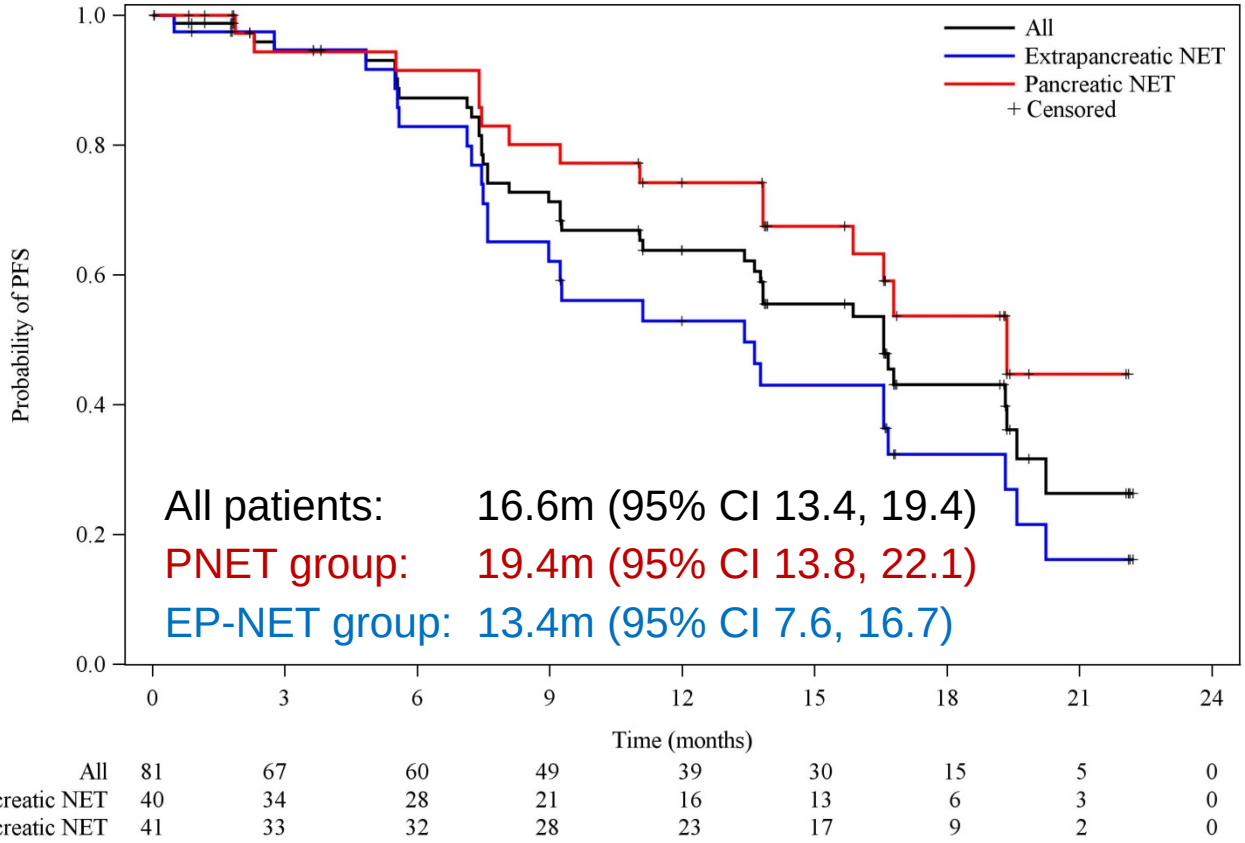


Sulfatinib showed anti-tumor activity in both G1/2 NET patients



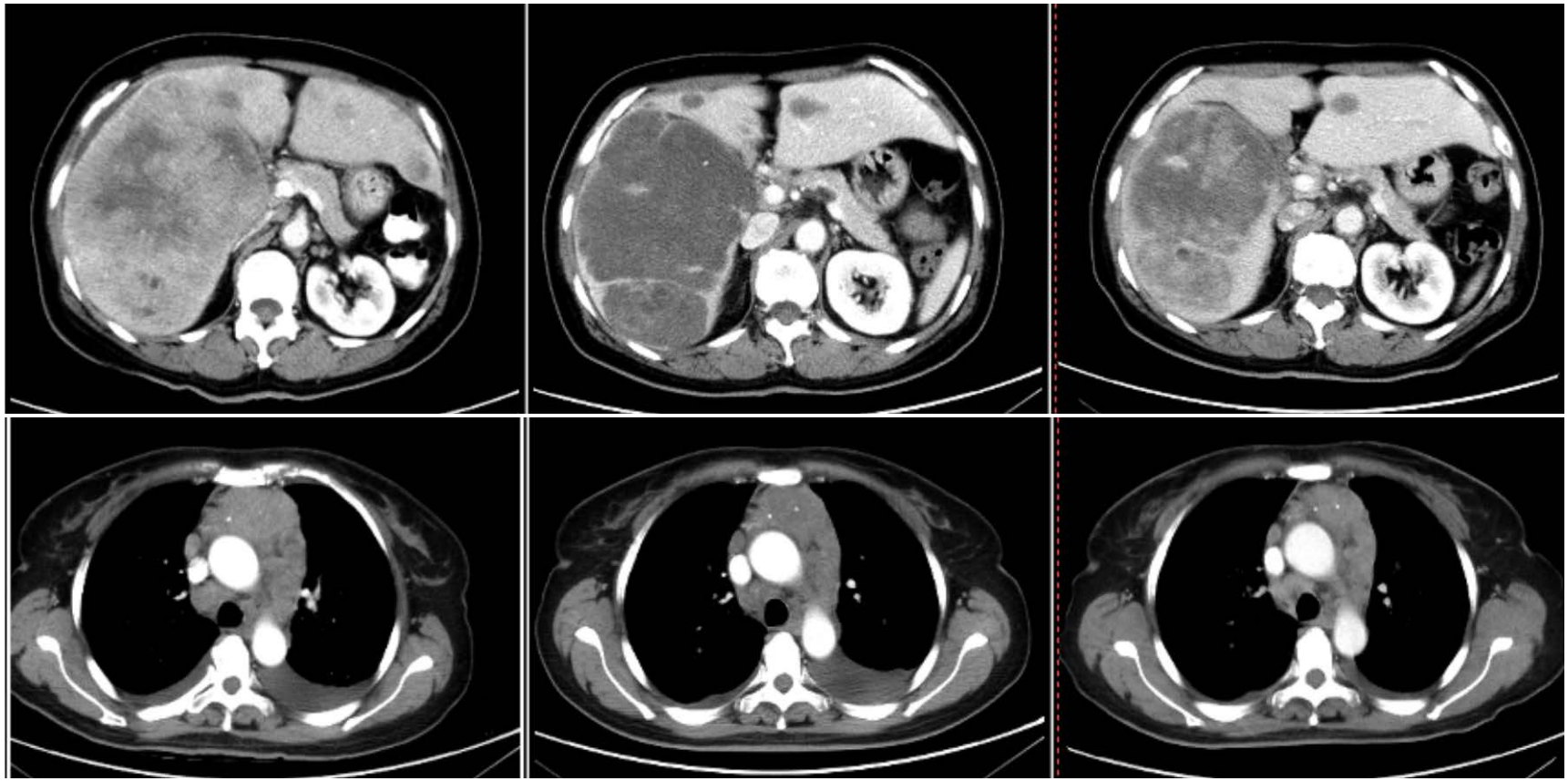
Progression free survival in ITT patients

as of 20 Jan2017



- **Among 41 PNET patients:** 18 (43.9%) still on treatment; 7 (17.1%) discontinued due to AE or withdrawal; 16 (39.0%) experienced PD/death.
- **Among 40 EP-NET patients:** 6 (15.0%) still on treatment; 8 (20.0%) discontinued due to AE or withdrawal; 26 (65.0%) experienced PD/death.

Thymus atypical carcinoid with multiple liver and lymph node metastasis

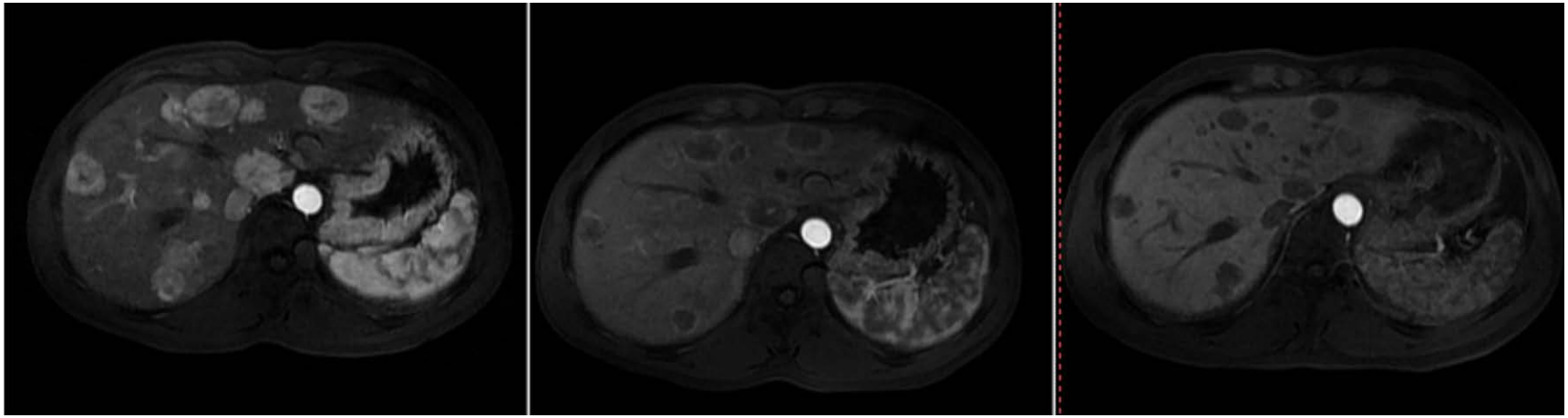


Baseline

Week 4

Week 24

Duodenum NET (G2) with multiple liver metastasis

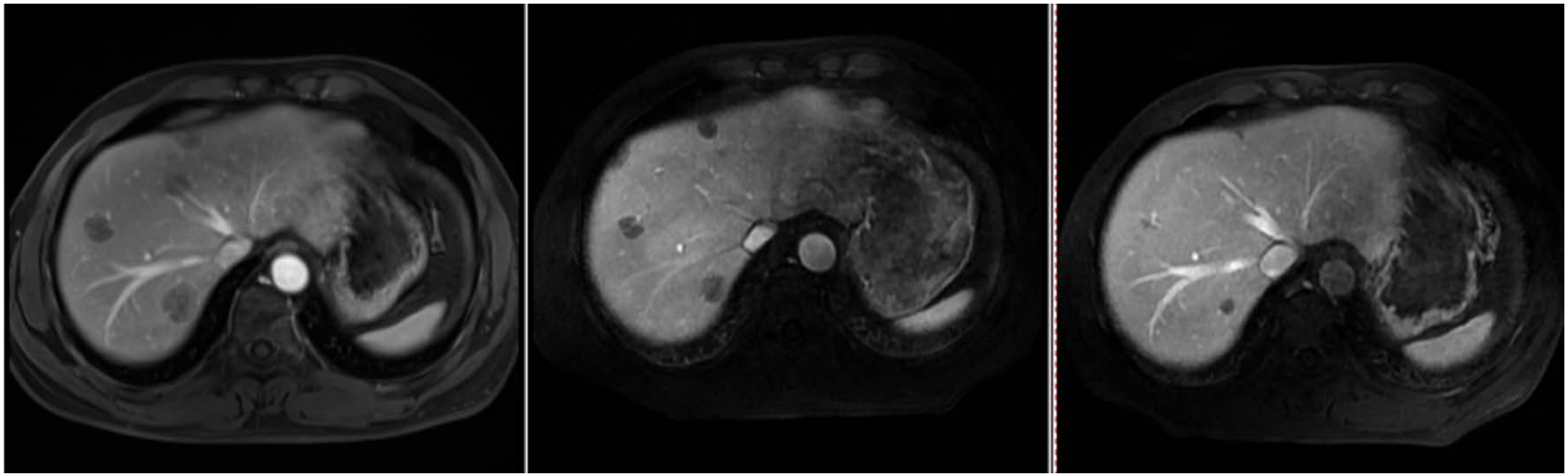


Baseline

Week 8

Week 52

Rectum NET (G2) with multiple liver metastasis



Baseline

Week 4

Week 56

AE summary

	N=81 n (%)
Any AE	81 (100)
Grade ≥3 AE	63 (77.8)
Any SAE	21 (25.9)
Any drug-related AE	81 (100)
Any drug-related grade ≥3 AE	58 (71.6)
Any drug related SAE	10 (12.3)
Drug related AE leading to:	
dose interruption	40 (49.4)
dose reduction	20 (24.7)
drug withdrawal	7 (8.6)

Most common adverse events
(regardless of causality)

	Any grade (≥25%) n (%)
Proteinuria	68 (84.0)
Diarrhea	59 (72.8)
Hypertension	48 (59.3)
TSH increased	41 (50.6)
Asthenia	40 (49.4)
AST increased	38 (46.9)
Hypertriglyceridemia	34 (42.0)
Blood bilirubin increased	33 (40.7)
ALT increased	32 (39.5)
Hypoalbuminemia	32 (39.5)
Hypocalcemia	26 (32.1)
Electrocardiogram T wave abnormal	24 (29.6)
Hyperuricemia	24 (29.6)
Decreased appetite	23 (28.4)
Anemia	22 (27.2)
Hyperbilirubinemia	21 (25.9)

	Grade ≥3 (≥4pts) n (%)
Hypertension	25 (30.9)
Proteinuria	11 (13.6)
Hyperuricemia	8 (9.9)
Hypertriglyceridemia	7 (8.6)
Diarrhea	6 (7.4)
ALT increased	5 (6.2)
Anemia	4 (4.9)
Hypokalemia	4 (4.9)
Hepatic function abnormal	4 (4.9)

- Sulfatinib was tolerable in NET patients and most drug related AEs were manageable.
- Dermatologic reactions were less common. Three (3.7%) pts had hand food syndrome, only one of which was grade 3.

Conclusion

- Sulfatinib, a selective VEGFR, FGFR1 and CSF1R kinase inhibitor, showed promising antitumor activity in NET patients with GEP, lung, other or unknown primary tumor origins.
- Sulfatinib is well tolerated in NET patients with a similar safety profile as other VEGFR targeted TKIs.
- Two phase III confirmatory trials of sulfatinib in PNET and EP-NET respectively are ongoing in China.

Acknowledgments

- Patients and their families who participated in the study.
- Clinical investigators/associates and clinical sites.
- Study sponsor: Hutchison MediPharma.