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MEETING SUMMARY
ESMO 2019, Barcelona, Spain

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NEUROENDOCRINE TUMOUR UPDATE

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TOP 3 HIGH-IMPACT NEUROENDOCRINE TUMOUR PRESENTATIONS AT ESMO 2019

SANET-ep: A PHASE 3 STUDY OF SURUFATINIB IN PATIENTS WITH WELL-DIFFERENTIATED ADVANCED EXTRA-PANCREATIC NETs

Xu, et al. ESMO 2019 Abstract #LBA76

NETs, neuroendocrine tumours

BACKGROUND

- surufatinib is an anti-angiogenic tyrosine kinase inhibitor that selectively inhibits VEGFR, FGFR and CSF-1R

- Anti-VEGF signaling pathway is a proven strategy for treatment of pancreatic NETs but its effect in extra-pancreatic NETs has yet to be proven

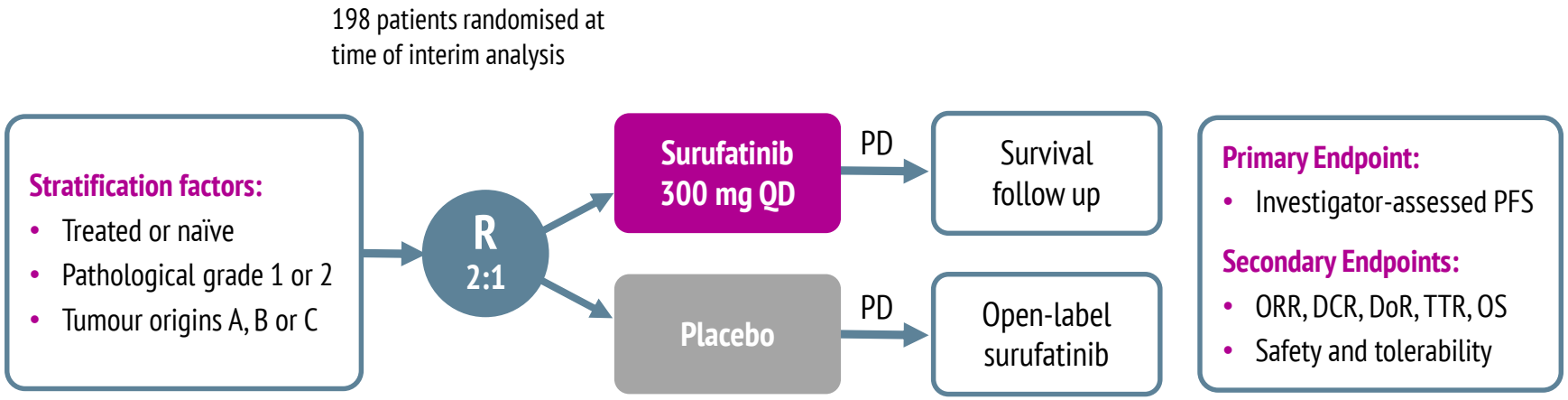
- SANET-ep investigates the effect of surufatinib in patients with advanced, well differentiated extra-pancreatic NETs

CSF-1R, colony stimulating factor-1 receptor; FGFR, fibroblast growth factor receptor; NET, neuroendocrine tumour; VEGF(R), vascular endothelial growth factor (receptor)

1. Raymond E, et al. N Engl J Med 2011;364:501–13; 2. Xu J, et al. Presented at ESMO 2019. Abstract #LBA76

SANET-ep STUDY DESIGN

PROGRESSIVE ADVANCED EXTRA-PANCREATIC NET PATIENTS



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

- Study was terminated due to superiority following a pre-planned interim analysis at 127 PFS events

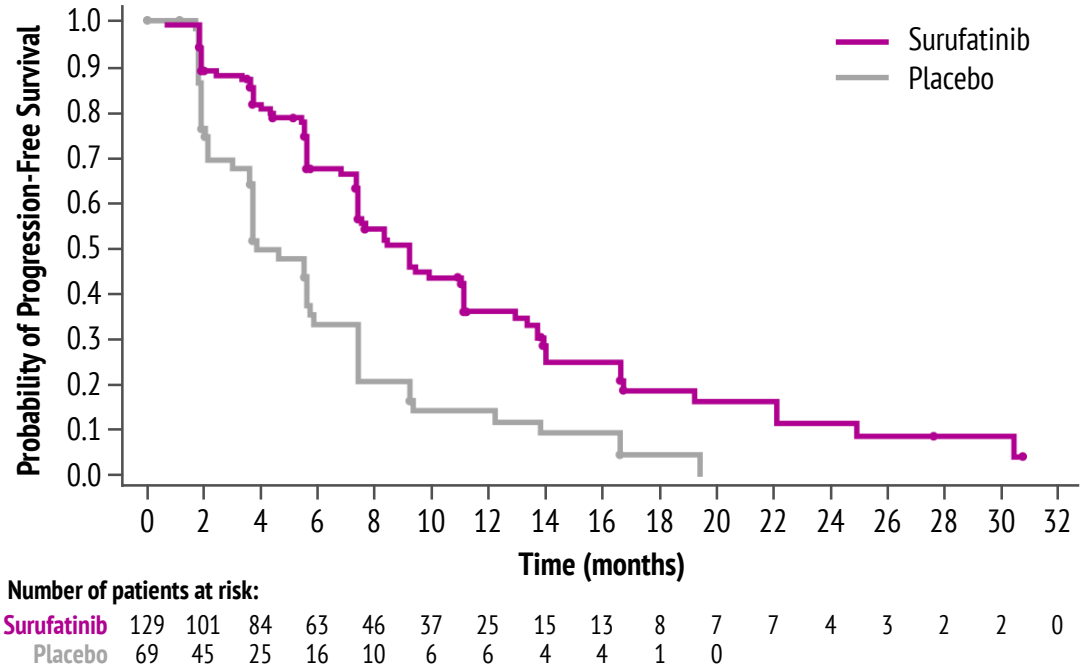
DCR, disease control rate; DoR, duration of response; NET, neuroendocrine tumours; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TTR, time to tumour response

Xu J, et al. Presented at ESMO 2019. Abstract #LBA76

SANET-ep PRIMARY ENDPOINT RESULTS

PROGRESSION FREE SURVIVAL (INVESTIGATOR ASSESSED)

- PFS 9.2 months (surufatinib) vs 3.8 months (placebo)



	surufatinib (N=129)	placebo (N=69)
Median PFS, months. (95% CI)	9.2 (7.4-11.1)	3.8 (3.7-5.7)
HR (95% CI)	0.334 (0.223-0.499)	
Stratified p-value < 0.0001		

CI, confidence interval; HR, hazard ratio; PFS, progression free survival

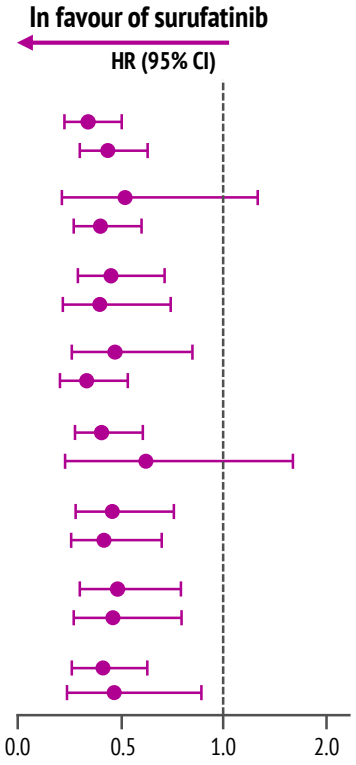
Xu J, et al. Presented at ESMO 2019. Abstract #LBA76

SANET-ep SUB-GROUP ANALYSIS

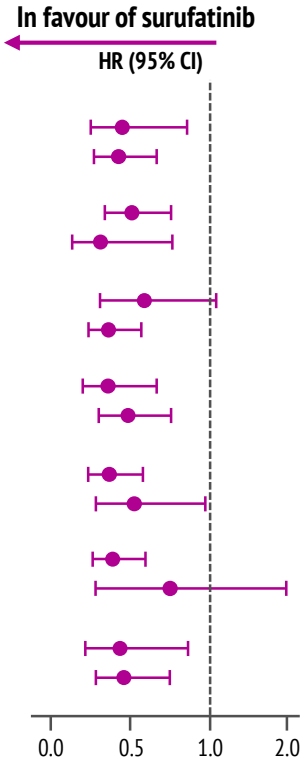
PROGRESSION FREE SURVIVAL (INVESTIGATOR ASSESSED)

- Benefit was observed across all subgroups

Subgroup	Surufatinib N (Events)	Placebo N (Events)
Overall Subjects		
Stratified	129 (77)	69 (51)
Unstratified	129 (77)	69 (51)
NET pathological grade		
Grade 1	21 (12)	12 (8)
Grade 2	108 (65)	57 (43)
Previous systemic treatment		
Yes	87 (50)	45 (33)
No	42 (27)	24 (18)
Primary lesion of tumour		
A+C	57 (32)	31 (20)
B	72 (45)	38 (31)
Age		
<65 years	115 (69)	56 (42)
≥65 years	14 (8)	13 (9)
Gender		
Male	73 (44)	35 (25)
Female	56 (33)	34 (26)
Primary tumour site		
Gastrointestinal	61 (36)	32 (30)
Others	68 (41)	37 (21)
ECOG performance status		
0	72 (47)	46 (37)
1	57 (30)	23 (14)



Subgroup	Surufatinib N (Events)	Placebo N (Events)
No. of organs involved by tumour		
⩽2	43 (25)	25 (19)
⩾3	86 (52)	44 (32)
Liver metastasis		
Yes	97 (59)	53 (42)
No	32 (18)	16 (9)
Prior SSA treatment		
Yes	44 (25)	19 (17)
No	85 (52)	50 (34)
Prior systemic chemotherapy		
Yes	52 (29)	27 (19)
No	77 (48)	42 (32)
Disease diagnosis to randomisation		
⩽24 months	84 (52)	45 (33)
>24 months	45 (25)	24 (18)
Latest progression to randomisation		
⩽3 months	114 (67)	58 (44)
>3 months	15 (10)	11 (7)
Baseline CgA		
>2 ULN	43 (28)	22 (13)
⩽2 ULN	71 (38)	36 (29)



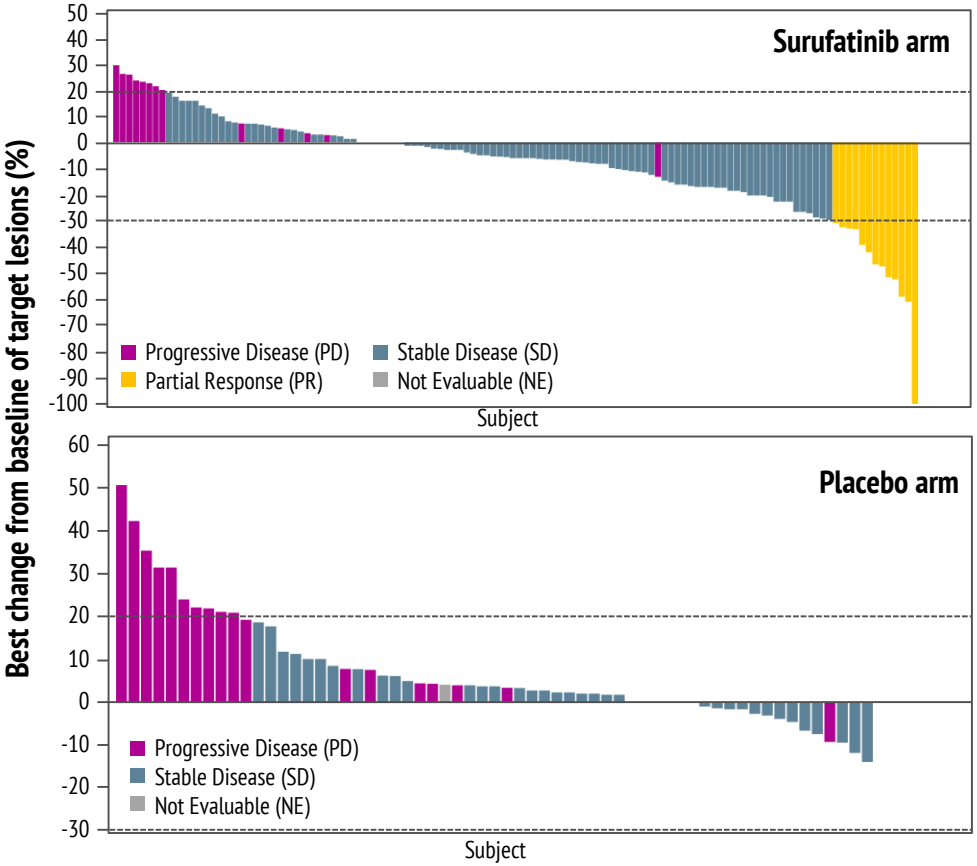
Tumour origin: A, jejunum; ileum, duodenum, thymus, cecum; B: lung, stomach, liver, appendix, colon, rectum; C: others or unknown origin.

CgA, chromogranin A; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NET, neuroendocrine tumour; PFS, progression free survival; SSA, somatostatin analogues; ULN, upper limit of normal

Xu J, et al. Presented at ESMO 2019. Abstract #LBA76

SANET-ep SECONDARY ENDPOINTS

ORR, DCR, TTR, DoR RESULTS



	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)	-	-	-

*11 PR confirmed, 2 PR unconfirmed

- OS was immature (18.7% events)

CI, confidence interval; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; iITT, interim intent-to-treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease; TTR, time to tumour response

Xu J, et al. Presented at ESMO 2019. Abstract #LBA76

SANET-ep SAFETY ANALYSIS

MOST COMMON TEAEs WITH FREQUENCY ⩾ 20%

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)

- Surufatinib was generally well tolerated. However, 36.4% of the patients treated with surufatinib experienced ⩾ grade 3 toxicity of hypertension

TEAEs, treatment emergent adverse events

Xu J, et al. Presented at ESMO 2019. Abstract #LBA76

SUMMARY

- **Surufatinib significantly improved PFS** in patients with advanced extra-pancreatic NETs[1]
- One limitation of the SANET-ep study is that it was **conducted in an Asian population only**
- **A poster presentation at ESMO 2019** reported on the safety profile of surufatinib in solid tumours in a western population[2]
  - **The safety profile in the western population** was shown to be **similar to that reported in the Asian population**
- **Further data is required** in a western population **before implementing in clinical practice**
- However, this is a step forward in delivering new options for patients with NETs

NET, neuroendocrine tumours

1. Xu J, et al. Presented at ESMO 2019. Abstract #LBA76 ; 2. Hamilton E, et al. Presented at ESMO 2019. Abstract #1393P

NETTER-1 (POST HOC ANALYSIS): RELATION BETWEEN OBJECTIVE TUMOUR SHRINKAGE AND PFS

Pavel, et al. ESMO 2019 Abstract #1382PD

PFS, progression free survival

BACKGROUND

- **NETTER-1** investigated the effect of **^{177}Lu-DOTATATE plus octreotide** in patients with **progressive midgut NETs**[1]
- The **NETTER-1 trial was instrumental in PRRT** now **being part of the treatment pathway** for patients with NET
- **Treatment efficacy** has often been **associated with early reduction of tumour size**
- This **post-hoc analysis of NETTER-1** examined whether achieving **objective tumour shrinkage predicts duration of PFS**

Lu, lutetium; NET, neuroendocrine tumour; PFS, progression free survival; PRRT, peptide receptor radionuclide therapy

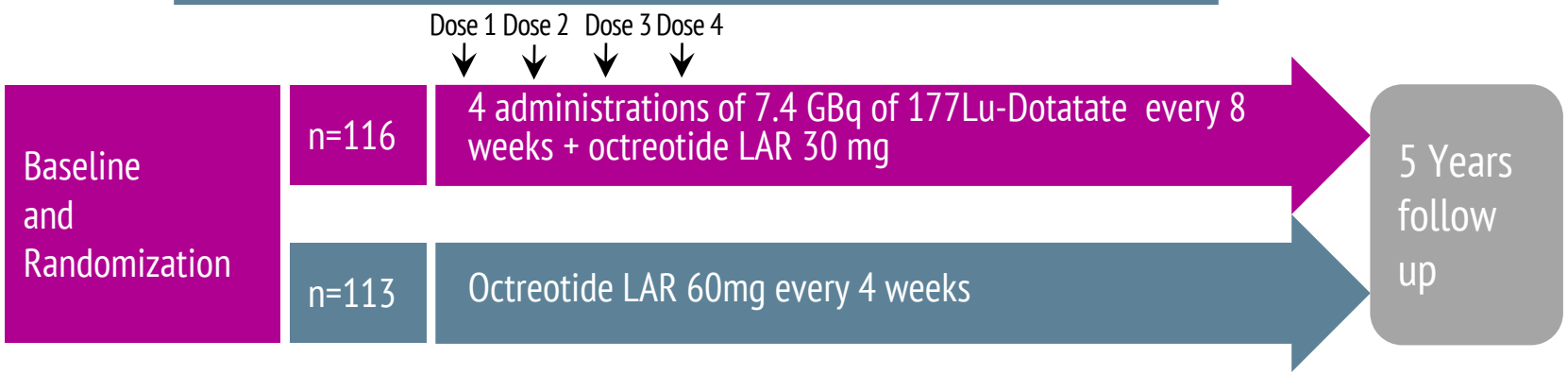
1. Strosberg J. NEJM 2017; 376:125-35; 2. Pavel M. ESMO 2019 Abstract #1382PD

NETTER-1 PHASE III TRIAL

MAIN STUDY DESIGN

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate plus octreotide 30 mg compared to octreotide LAR 60mg (off-label use) in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group

Treatment and Assessments
Progression free survival (RECIST criteria) every 12 weeks



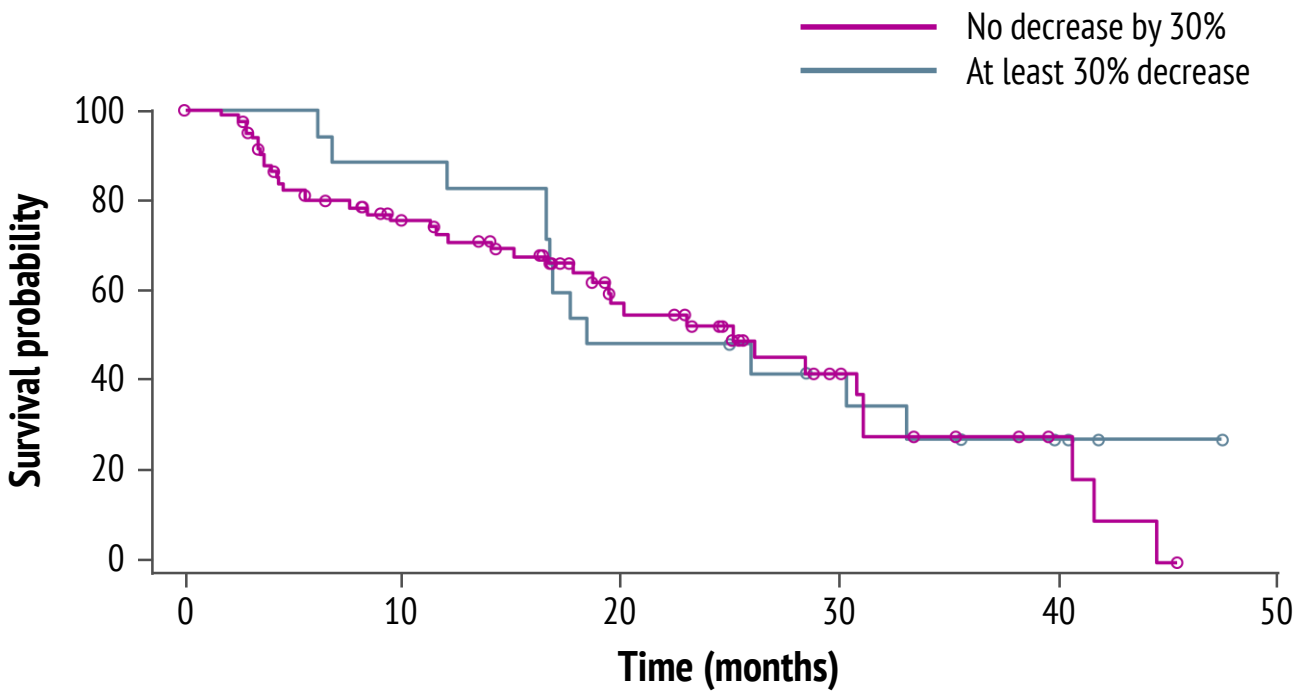
- Primary post hoc analysis for tumour shrinkage was based on the time interval between baseline and **150 days from baseline** and conducted on the full analysis set of **229 patients**

GBq, gigabecquerels; LAR, long acting release; Lu, lutetium; RECIST, response evaluation criteria in solid tumors

Strosberg J. NEJM 2017;376:125-35

NETTER-1 (POST-HOC ANALYSIS)

PFS IN RELATION TO TUMOUR RESPONSE IN THE ^{177}Lu-DOTATATE GROUP



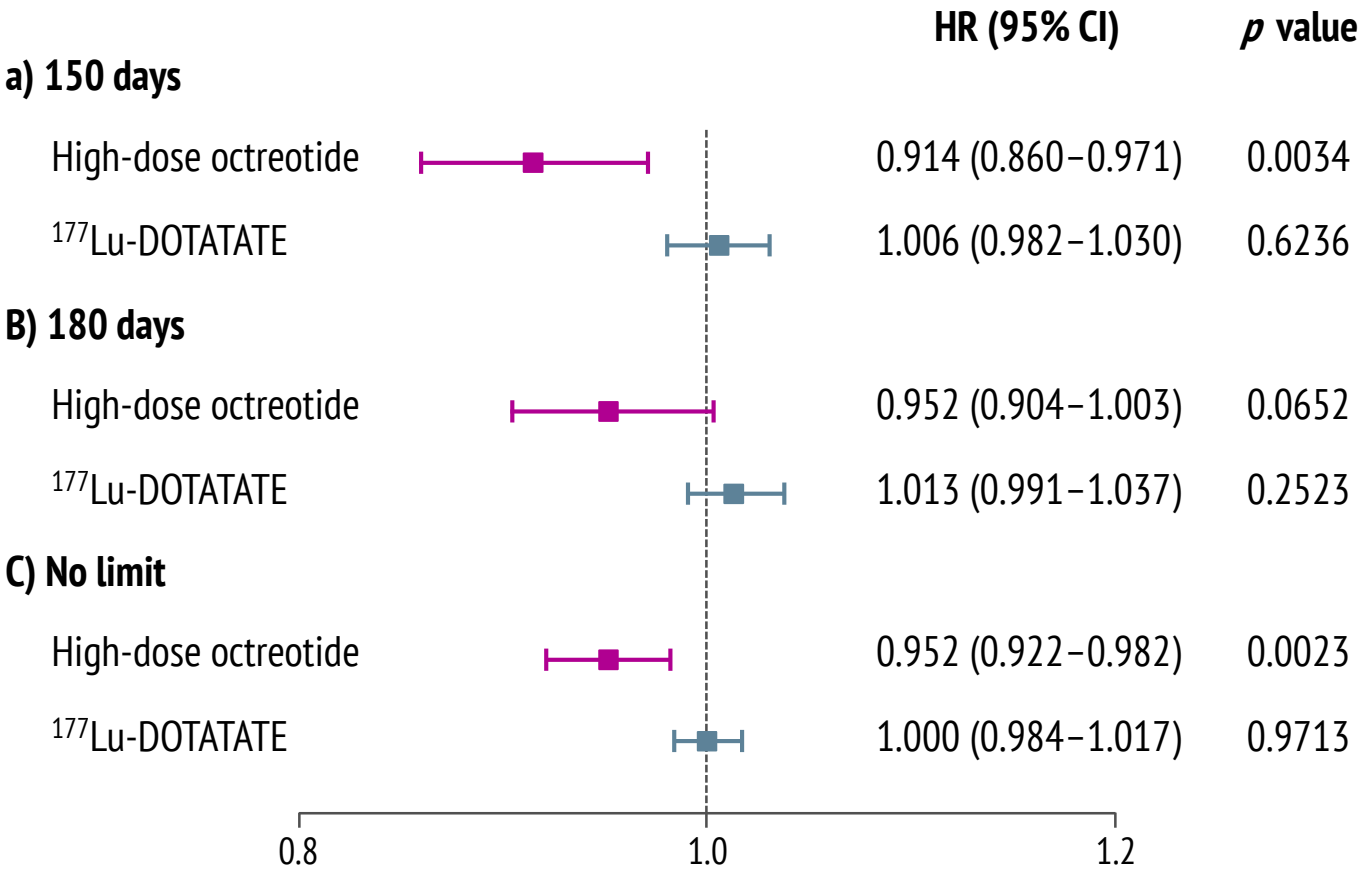
At least 30% decrease	19	17	10	7	3	0
No decrease by 30%	98	56	28	11	4	0

PFS, progression free survival

Pavel, M. ESMO 2019 Abstract #1382PD

NETTER-1 (POST-HOC ANALYSIS)

^{177}LU-DOTATATE PROLONGED PFS EVEN IN ABSENCE OF DETECTABLE TUMOUR RESPONSE



CI, confidence interval; HR, hazard ratio; PFS, progression free survival

Pavel M. ESMO 2019 Abstract #1382PD

SUMMARY

- **All patients benefitted from treatment with PRRT regardless of tumour shrinkage**
  - Benefit of 4 cycles of PRRT treatment should not only be assessed by tumour shrinkage

PRRT, peptide receptor radionuclide therapy

Pavel M. ESMO 2019 Abstract #1382PD

HEPAR PLUS: A PHASE 2 OPEN LABEL STUDY OF ^{177}LU-DOTATATE PLUS ^{166}HO-RADIOEMBOLISM IN PATIENTS WITH NETs

Braat, et al. ESMO 2019 Abstract #13800

NETs, neuroendocrine tumours

BACKGROUND

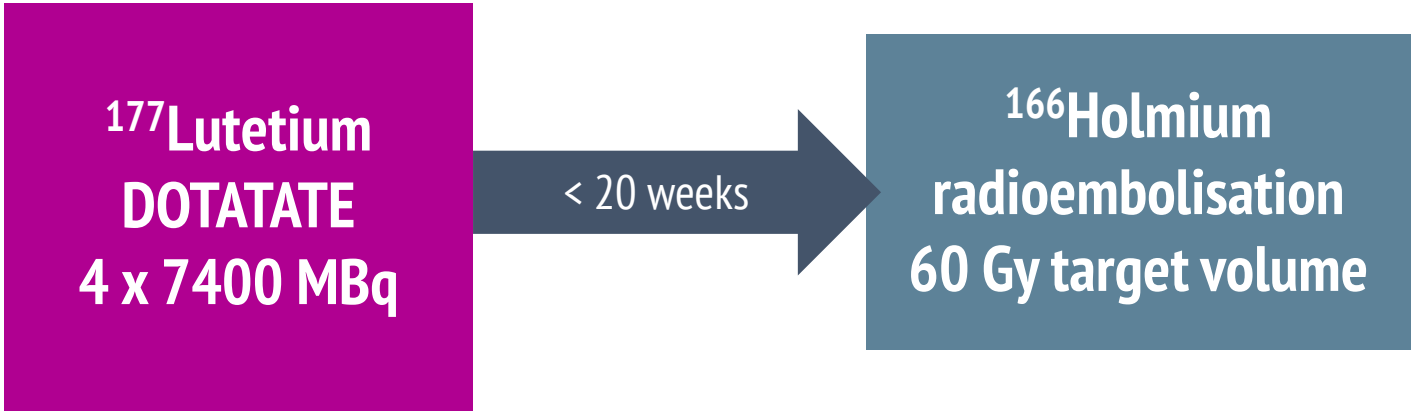
- **At diagnosis 21%** of the patients with a **grade 1 NET** and **30%** with a **grade 2 NET have distant metastases**[1]
- The **liver** is the **most commonly affected organ in metastatic disease** and is the most incriminating factor for patient survival[1]
- **Treatment with** peptide receptor radionuclide therapy (**PRRT**) shows a **high objective response rate** and **long median survival** after treatment However, **complete remission is almost never achieved**[1,2]
- **Additional treatment of liver disease** after PRRT **may improve outcome in NET patients**[2]
  - Radioembolization is an established therapy for liver metastasis

NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy

1. Braat A, et al. BMC Gastroenterology 2018;18:84; Braat A, et al. ECIO 2019 Abstract #1902.3

HEPAR PLUS STUDY DESIGN

- Non-randomised, single arm, phase 2 study
  - 34 patients included
  - 31 patients treated
  - 30 patients evaluable



- **Primary objectives:** objective response rate (RECIST 1.1) 3 months after ^{166}Ho-RE
- **Secondary endpoints:** toxicity profile, biochemical response, QoL, biodistribution and dosimetry

QoL, quality of life; RE, radioembolization

Braat A, et al. BMC Gastroenterology 2018;18:84; Braat A, et al. Presented at ESMO 2019 Abstract #1380O

HEPAR PLUS STUDY

OBJECTIVE TUMOUR RESPONSE

- An objective response rate of 40% was achieved

RECIST 1.1	Treatment volume			Non-treatment liver volume	Extrahepatic disease	Patient-based
	#1	#2	Mean			
Complete response	0%	0%	0%	0%	0%	40%
Partial response	40%	43%	43%	0%	0%	40%
Stable disease	60%	57%	57%	30%	63%	47%
Progressive disease	0%	0%	0%	7%	13%	13%
Not applicable				63%	24%	

mRECIST				Additional CR/PR after PRRT
Complete response	10%	10%	10%	0%
Partial response	47%	43%	50%	0%
Stable disease	30%	30%	27%	20%
Progressive disease	0%	0%	0%	0%
Not applicable	13%	17%	13%	80%

CR, complete response; mRECIST, modified response evaluation criteria in solid tumors; PR, partial response; PRRT, peptide receptor radionuclide therapy

Braat A, et al. Presented at ESMO 2019 Abstract #13800

HEPAR PLUS STUDY

CLINICAL TOXICITY

	CTCAE v4.03 grade				
Related toxicity	**0**	**1**	**2**	**3**	**4**
Hepatic failure	30				1
Abdominal pain	8	9	11	3	
Fatigue	12	10	8	1	
Nausea	11	12	7	1	
Back pain	22	7	2		
Vomiting	18	7	6		
Malaise	24	6	1		
(sub) febrile	27	3	1		
Weight loss	29	2			

	CTCAE v4.03 grade				
Unrelated toxicity	**0**	**1**	**2**	**3**	**4**
Constipation	27	3	1		
Insomnia	30		1		
Urinary retention	30		1		
Coughing	30		1		
Pruritis	30		1		
Sweating	28	3			
Shivering	29	2			
Diarrhea	29	2			
Oedema	29	1			
Joint pain	30	1			
Headache	30	1			
Cramps	30	1			

- Toxicity profile comparable to literature
- QoL temporarily decreased but fully recovered at 3 months

CTCAE, common terminology criteria for adverse events; QoL, quality of life

Braat A, et al. Presented at ESMO 2019 Abstract #1380O

SUMMARY

- **HEPAR PLUS is the first trial in this setting** and suggests that radioembolization after treatment with PRRT may benefit patients with NETs
- **Promising results** seen from HEPAR PLUS **but must be confirmed in a randomised phase 3 trial**

NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy

Braat A, et al. Presented at ESMO 2019 Abstract #1380O

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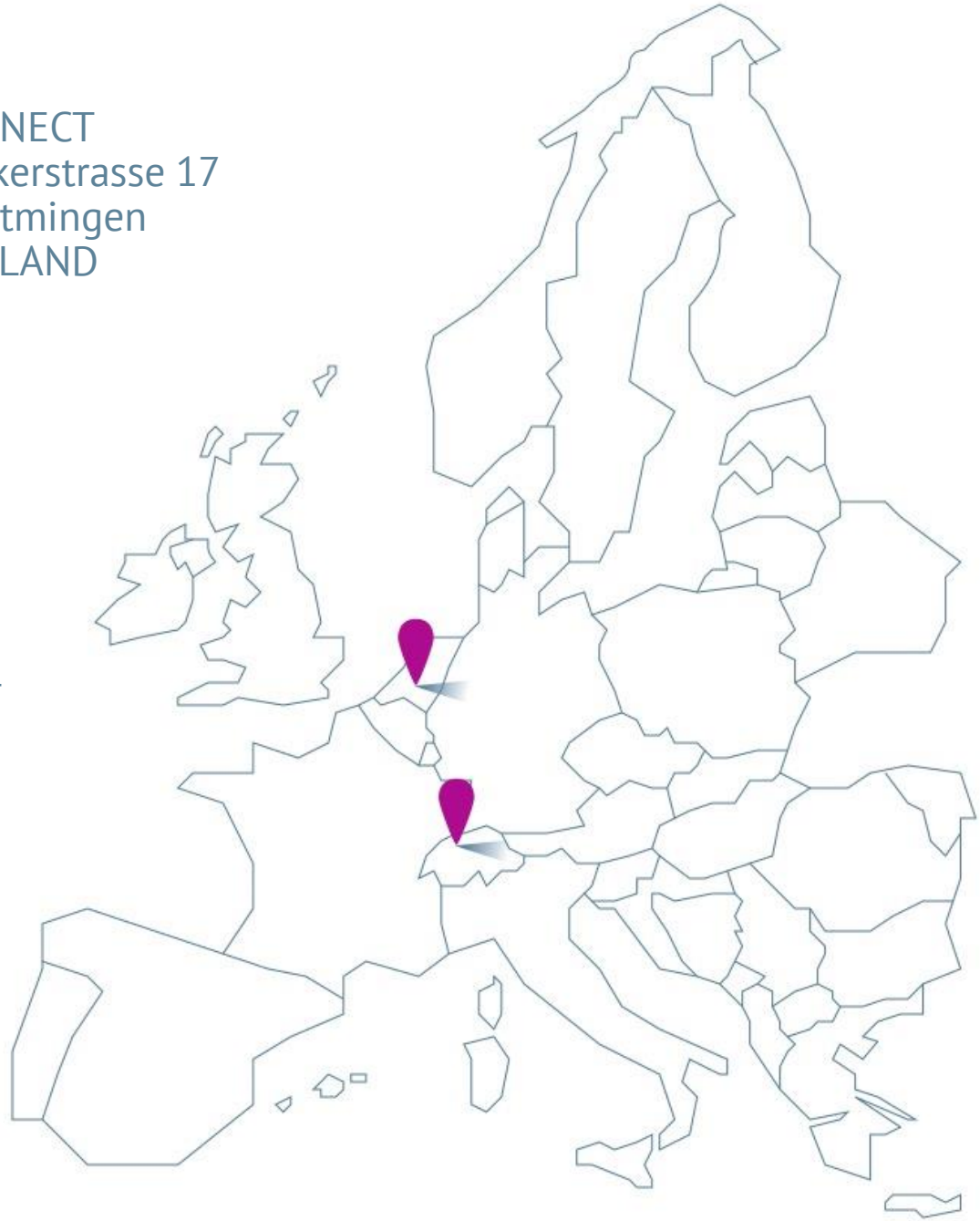

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