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A Multivariate Efficacy Analysis of [^{177}Lu]Lu-DOTA-TATE in the NETTER 2 Study

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DECLARATION OF INTERESTS

Marianne Pavel reports:

- Consulting fees from Advanced Accelerator Applications (a Novartis company), Novartis, Ipsen, Riemser and Hutchmed
- Honoraria from Ipsen, Advanced Accelerator Applications (a Novartis company), Novartis, Boehringer, MSD, Lilly, Recordati, Sanofi and Serb
- Advisory board participation for Crinetics, Advanced Accelerator Applications (a Novartis company) and Ipsen

NETTER-2: ^{177}Lu-DOTATATE as a first-line treatment for advanced, well-differentiated, G2/3 GEP-NETs

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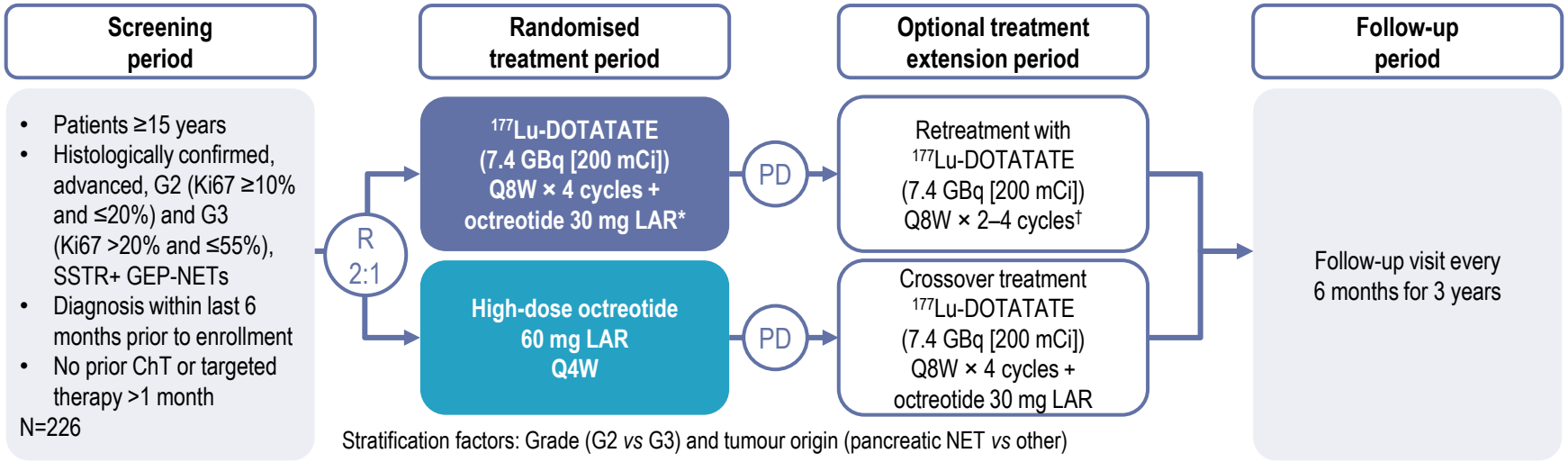

Median PFS (primary endpoint):
- **22.8 months** (^{177}Lu-DOTATATE group) and **8.5 months** (control group); stratified HR: 0.276 (95% CI: 0.182–0.418); p<0.0001[1]
- G2 NET: HR: 0.306 (95% CI: 0.176– 0.530)[2]
- G3 NET: HR: 0.266 (95% CI: 0.145–0.489)[2]

ORR (secondary endpoint):
- **43.0%** (^{177}Lu-DOTATATE group) and **9.3%** (control group); stratified OR: 7.81 (95% CI: 3.32–18.40); p<0.0001[1]
- G2 NET: OR: 5.83 (95% CI: 2.12–16.00)[2]
- G3 NET: OR: 11.57 (95% CI: 2.48–53.97)[2]

*Q8W during ^{177}Lu-DOTATATE treatment and then Q4W; †Octreotide LAR in retreatment phase is at the investigator's discretion.
ChT, chemotherapy; CI, confidence interval; G, grade; GEP, gastroenteropancreatic; HR, hazard ratio; LAR, long-acting repeatable; NET, neuroendocrine tumor; OR, odds ratio; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; Q#W, every # weeks; R, randomization; SSTR, somatostatin receptor.
1. Singh S, et al. Lancet 2024;403:2807–17; 2. Singh S, et al. Presented at ESMO GI 2024; June 26–29; Munich, Germany.
Figure reproduced from Singh S, et al. Lancet 2024;403:2807–17.

Baseline characteristics

Characteristic	^{177}Lu-DOTATATE arm (n=151)	High-dose octreotide arm (n=75)
Age (years), median (range)	61 (23–88)	60 (34–82)
Sex, n (%)		
Male	81 (54)	40 (53)
Female	70 (46)	35 (47)
Primary tumor site, n (%)		
Pancreas	**82 (54)**	**41 (55)**
Small intestine	45 (30)	21 (28)
Other	24 (16)	13 (17)
NET grade at diagnosis, n (%)		
G2	**99 (66)**	**48 (64)**
Low G3	32 (21)	16 (21)
High G3	20 (13)	11 (15)

Characteristic	^{177}Lu-DOTATATE arm (n=151)	High-dose octreotide arm (n=75)
Ki67 index (%), median (range)	**17 (10–50)**	**16 (10–50)**
Metastases in liver only, n (%)		
Yes	65 (43)	38 (51)
No	**85 (56)**	**36 (48)**
CgA, n*	143	68
≤2 × ULN, n (%)	43 (30)	24 (35)
>2 × ULN, n (%)	100 (70)	44 (65)
Highest SSTR uptake,† n (%)		
Score 3	56 (37)	25 (33)
Score 4	**95 (63)**	**50 (67)**

*Baseline CgA data were not available for 8 patients in the ^{177}Lu-DOTATATE arm and 7 patients in the high-dose octreotide arm; †Based on local assessment.
CgA, chromogranin A; G, grade; NET, neuroendocrine tumor; SSTR, somatostatin receptor; ULN, upper limit of normal.
Table adapted from Singh S, et al. Lancet 2024;403:2807–17.

NETTER-2 multivariate efficacy analysis

Aim: assess the effect of ^{177}Lu-DOTATATE when adjusted for baseline covariates (including disease spread) and identify potential prognostic factors

A multivariate Cox regression model (for PFS) and logistic regression model (for ORR) were applied to select baseline covariates of:

- Age (<65 vs ≥65 years)
- Sex (male vs female)
- Primary NET site (pancreas vs small intestine vs other)
- NET grade (G2 vs G3 low [Ki67 ≤30%] vs G3 high [Ki67 >30%])
- Ki67 as a continuous variable
- Metastatic spread (liver metastases only [± lymph nodes] vs other metastases)
- CgA (≤2 × ULN vs >2 × ULN)
- SSTR uptake score (3 [>liver, <spleen] vs 4 [>spleen])

CgA, chromogranin A; G, grade; NET, neuroendocrine tumor; ORR, objective response rate; PFS, progression-free survival; SSTR, somatostatin receptor; ULN, upper limit of normal.

Treatment effects on PFS and ORR were minimally affected when adjusted for covariates

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PFS

Analysis	Treatment effect: ^{177}Lu-DOTATATE vs high-dose octreotide	
	Hazard ratio (95% CI)	p value
Primary analysis[1,*]	0.276 (0.182, 0.418)	<0.0001
Exploratory analysis[†]	0.212 (0.134, 0.337)	<0.0001

ORR

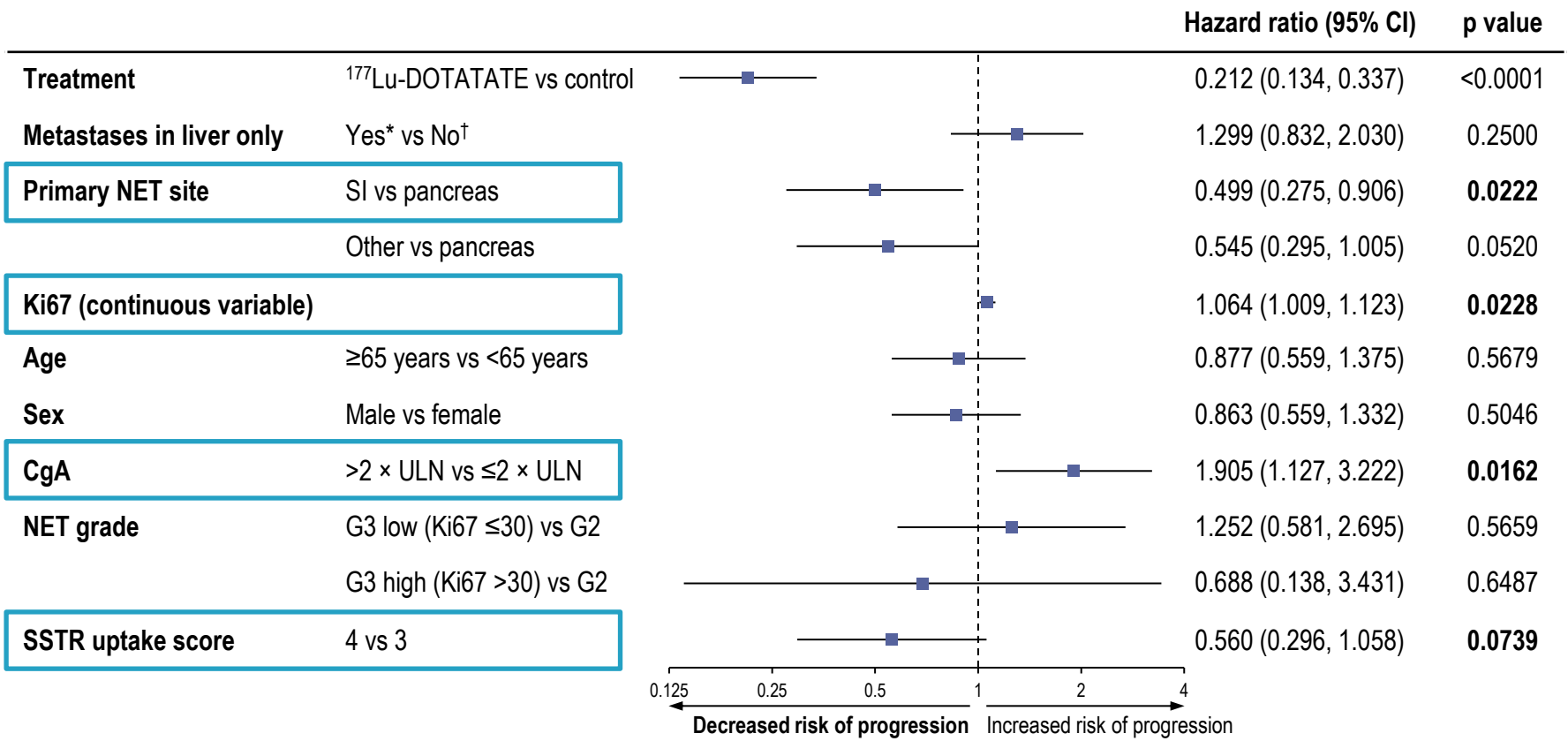
Analysis	Treatment effect: ^{177}Lu-DOTATATE vs high-dose octreotide	
	Odds ratio (95% CI)	p value
Primary analysis[1,*]	7.81 (3.32, 18.40)	<0.0001
Exploratory analysis[†]	10.43 (3.98, 27.29)	<0.0001

*No adjustment by additional covariates; †Multivariate Cox regression model (for PFS) and logistic regression model (for ORR) with adjustment by baseline covariates.
CI, confidence interval; ORR, objective response rate; PFS, progression-free survival.

1. Singh S, et al. Lancet 2024;403:2807–17.

Baseline characteristics that may impact PFS

Potential impact on PFS



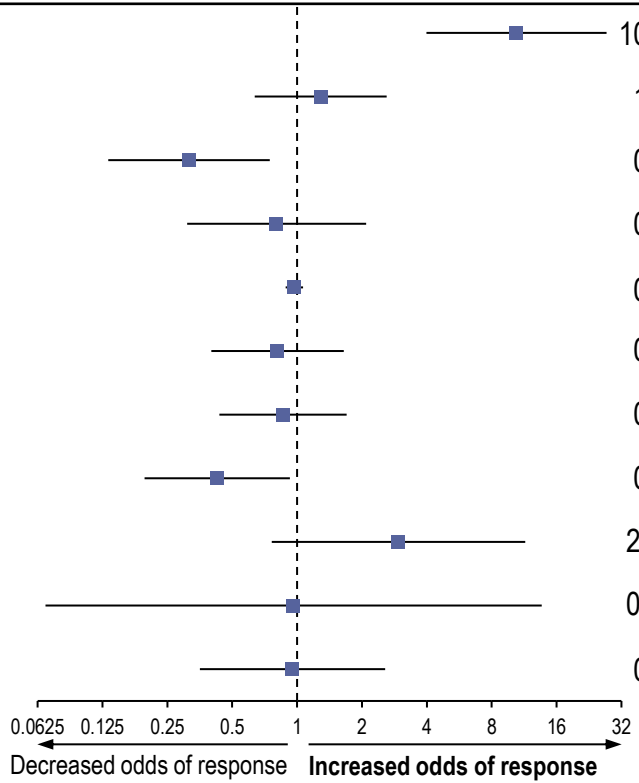
*Patients who had liver metastases only ± lymph nodes involved; †Patients who had no liver metastases or had both liver and other organ metastases involved.

CgA, chromogranin A; CI, confidence interval; G, grade; NET, neuroendocrine tumor; PFS, progression-free survival; SI, small intestine; SSTR, somatostatin receptor; ULN, upper limit of normal.

Baseline characteristics that may impact ORR

Potential impact on ORR

		Odds ratio (95% CI)	p value
Treatment	^{177}Lu-DOTATATE vs control	10.428 (3.984, 27.294)	<0.0001
Metastases in liver only	Yes* vs No†	1.287 (0.636, 2.604)	0.4831
Primary NET site	SI vs pancreas	0.315 (0.133, 0.747)	**0.0087**
	Other vs pancreas	0.804 (0.309, 2.092)	0.6549
Ki67 (continuous variable)		0.971 (0.885, 1.066)	0.5353
Age	≥65 years vs <65 years	0.812 (0.400, 1.647)	0.5638
Sex	Male vs female	0.861 (0.436, 1.698)	0.6649
CgA	>2 × ULN vs ≤2 × ULN	0.427 (0.196, 0.926)	**0.0312**
NET grade	G3 low (Ki67 ≤30) vs G2	2.955 (0.763, 11.449)	0.1169
	G3 high (Ki67 >30) vs G2	0.964 (0.068, 13.655)	0.9783
SSTR uptake score	4 vs 3	0.953 (0.354, 2.563)	0.9243



*Patients who had liver metastases only ± lymph nodes involved; †Patients who had no liver metastases or had both liver and other organ metastases involved.
CgA, chromogranin A; CI, confidence interval; G, grade; NET, neuroendocrine tumor; ORR, objective response rate; SI, small intestine; SSTR, somatostatin receptor; ULN, upper limit of normal.

Conclusions

- In patients with advanced, well-differentiated, G2/3 GEP-NETs, efficacy benefits with ^{177}Lu-DOTATATE vs high-dose octreotide in the first-line setting were consistent after adjustment for baseline covariates
- Treatment benefit of ^{177}Lu-DOTATATE (i.e. PFS and ORR) was consistent across all pre-specified subgroups in the primary PFS analysis. Nevertheless, there were potential prognostic factors identified for PFS/response regardless of study treatment in this *post hoc* analysis:
  - Small intestine NET origin, lower CgA, lower Ki67 score, and higher SSTR uptake score improved PFS to varying degrees
  - Pancreatic NET origin and lower CgA improved objective response to varying degrees
  - Disease spread had limited impact on PFS and ORR

CgA, chromogranin A; G, grade; GEP, gastroenteropancreatic; NET, neuroendocrine tumor; ORR, objective response rate; PFS, progression-free survival; SSTR, somatostatin receptor.

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