

**Overall survival and long-term safety  
data from the NETTER-1 trial:  
<sup>177</sup>Lu-DOTATATE vs. high-dose  
octreotide in patients with progressive  
midgut NETs**

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# Disclosures

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# Introduction

- Midgut NETs, also known as carcinoid tumours, are the most common subtype of advanced, well-differentiated GEP-NET, the majority of which express somatostatin receptors.<sup>1,2</sup>
- <sup>177</sup>Lu-DOTATATE is a  $\beta$ -emitting radionuclide coupled to a high-affinity somatostatin analogue.<sup>3</sup>
- In the primary analysis of NETTER-1, <sup>177</sup>Lu-DOTATATE significantly prolonged PFS versus high-dose long-acting octreotide (HR, 0.18 [95% CI: 0.11, 0.29];  $p < 0.0001$ ), in patients with advanced, progressive, well-differentiated, somatostatin receptor-positive midgut NETs.<sup>4</sup>
- Here we report the final OS and long-term safety results in the NETTER-1 trial.

CI, confidence interval; GEP-NET, gastro-entero-pancreatic neuroendocrine tumour; HR, hazard ratio; NET, neuroendocrine tumour; OS, overall survival; PFS, progression-free survival.

1. Yao JC *et al.* *J Clin Oncol* 2008;26:3063–72; 2. Kwekkeboom DJ *et al.* *Endocr Relat Cancer* 2010;17:R53–73; 3. Das S *et al.* *Expert Rev Gastroenterol Hepatol* 2019;13:1023–31; 4. Advanced Accelerator Applications. Lutathera. Summary of product characteristics. 2017.

# NETTER-1: an international, randomized, open-label, comparator-controlled, phase 3 trial

## Key eligibility criteria

- Advanced, inoperable, well-differentiated (Ki67 index  $\leq 20\%$ ) midgut NETs
- Somatostatin receptor-positive on all target lesions (OctreoScan)
- Radiographic disease progression (RECIST, version 1.1) while taking a fixed dose of long-acting octreotide 20 or 30 mg every 3–4 weeks
- Karnofsky performance status  $\geq 60$

R (1:1)

N = 117

Four administrations of  $^{177}\text{Lu}$ -DOTATATE 7.4 GBq (200 mCi) Q8W + long-acting octreotide 30 mg Q4W\*†

N = 114

High-dose long-acting octreotide 60 mg Q4W\*

## Stratification

- Highest tumour uptake on OctreoScan (Krenning grade 2, 3 or 4)
- Duration on most recent constant dose of long-acting octreotide ( $\leq 6$  months or  $> 6$  months).

## Endpoints

**Primary:** PFS (blinded independent central review)‡

**Secondary:** ORR,‡ OS,‡ TTP, safety, HRQoL

**Exploratory:** DoR, PFS2, correlation analyses

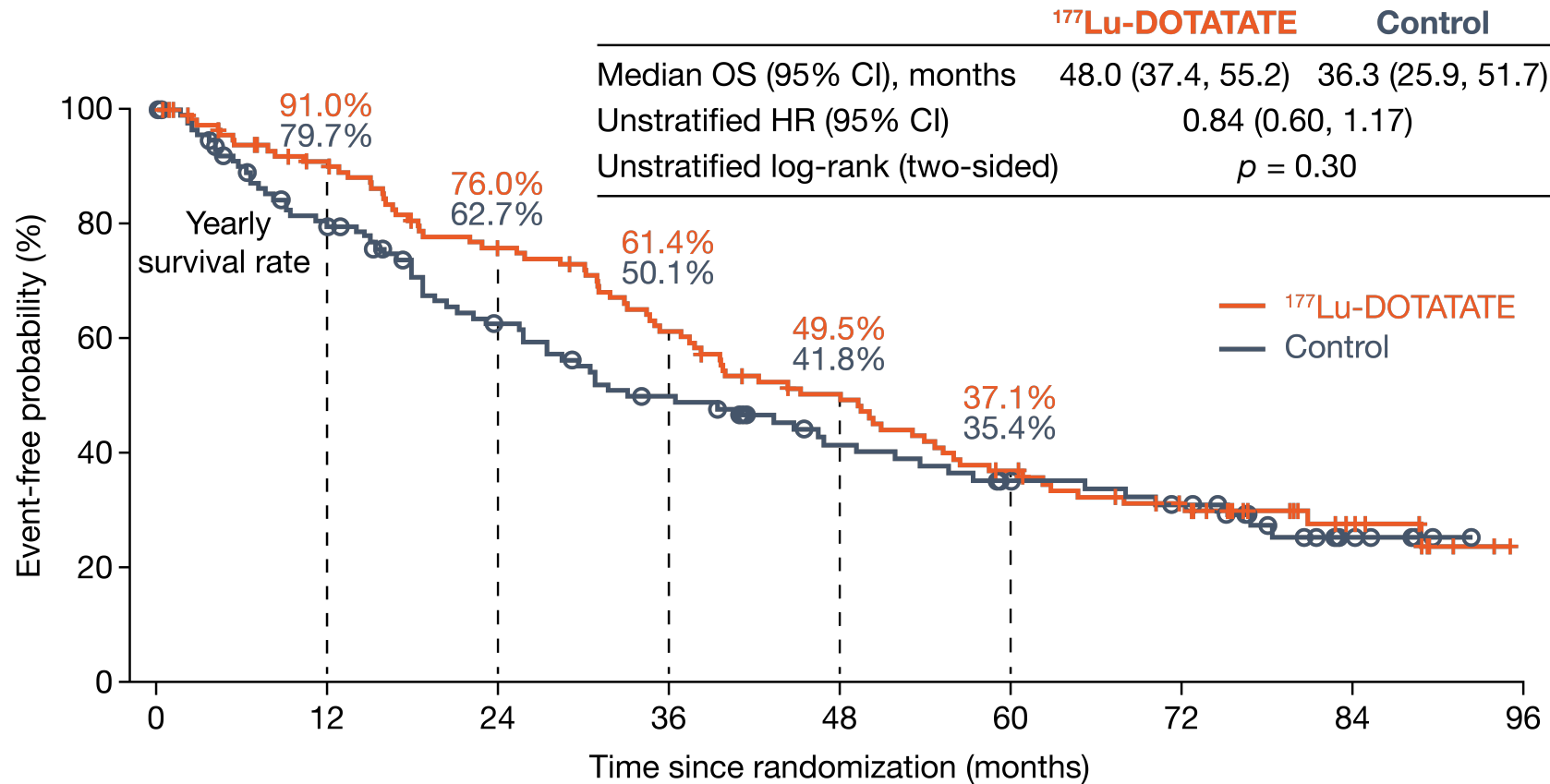
Final analysis of OS was pre-specified to occur either after 158 deaths, or 5 years after last patient was randomized, whichever occurred first.

\*After centrally confirmed disease progression, discontinuing study treatment without confirmed progression or completion of the 18-month treatment period (regardless of progression after the primary PFS analysis) patients entered long-term follow-up and could receive further anti-cancer treatments; †Long-acting octreotide 30 mg was administered Q8W during  $^{177}\text{Lu}$ -DOTATATE treatment; ‡Controlled for type I error within a hierarchical testing procedure. DoR, duration of response; HRQoL, health-related quality of life; GBq, giga-becquerel; mCi, millicurie; ORR, objective response rate; OS, overall survival, PFS, progression-free survival, PFS2, time to second progression or death; Q3W, every 3 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; RECIST, response evaluation criteria in solid tumors; TTP, time to progression.

# NETTER-1: prespecified final analysis

- Data cut-off for the final OS analysis was **18 January 2021**, triggered by **5 years time elapsed** after the last patient was randomized (142 death events observed).
- Median study follow-up: **76.3 months** (range, 0.4–95.0 months) in the  $^{177}\text{Lu}$ -DOTATATE arm and **76.5 months** (range, 0.1–92.3 months) in the control arm.

# NETTER-1: overall survival in the intention-to-treat population

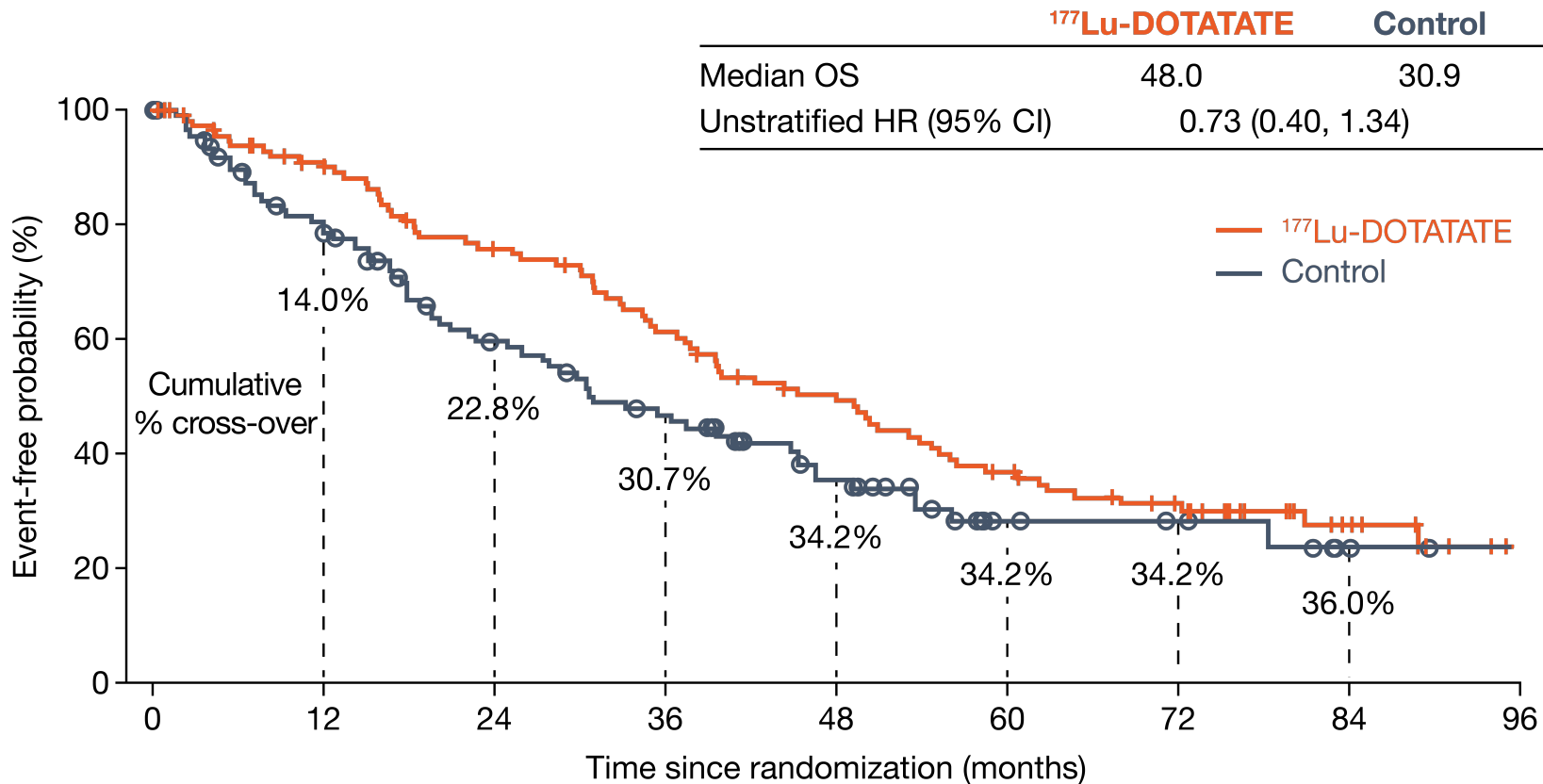


No. patients still at risk:

—	117	98	79	63	48	35	25	10	0
—	114	84	61	45	33	25	21	6	0

CI, confidence interval; HR, hazard ratio; OS, overall survival.

# NETTER-1: overall survival accounting for cross-over to radioligand therapy in the control arm (RPSFT method)



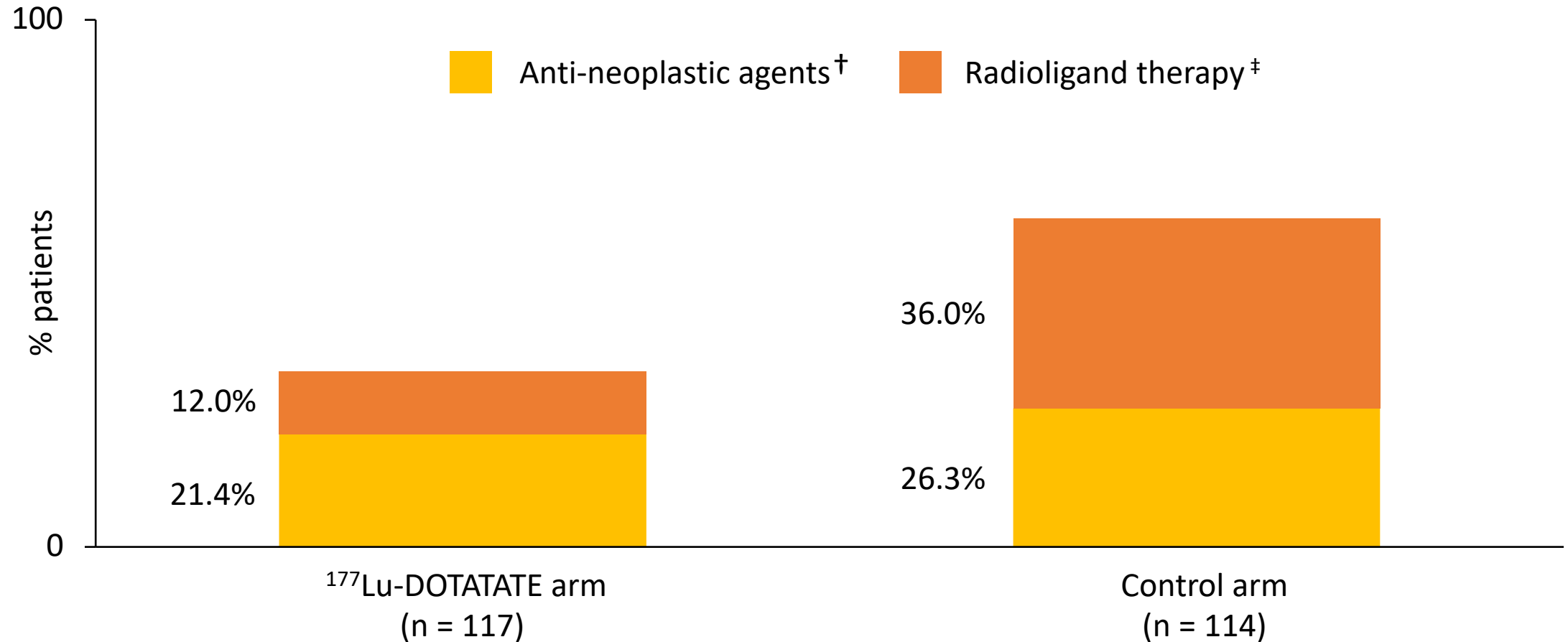
In the control arm, 41/114 patients (36.0%) crossed over to radioligand therapy during long-term follow-up.

No. patients still at risk:

Time (months)	0	12	24	36	48	60	72	84	96
<sup>177</sup> Lu-DOTATATE	117	98	79	63	48	35	25	10	0
Control	114	84	57	42	26	9	7	2	0

CI, confidence interval; HR, hazard ratio; OS, overall survival; RPSFT, rank-preserving structural failure time.

# Subsequent systemic anti-cancer treatments during long-term follow-up\*



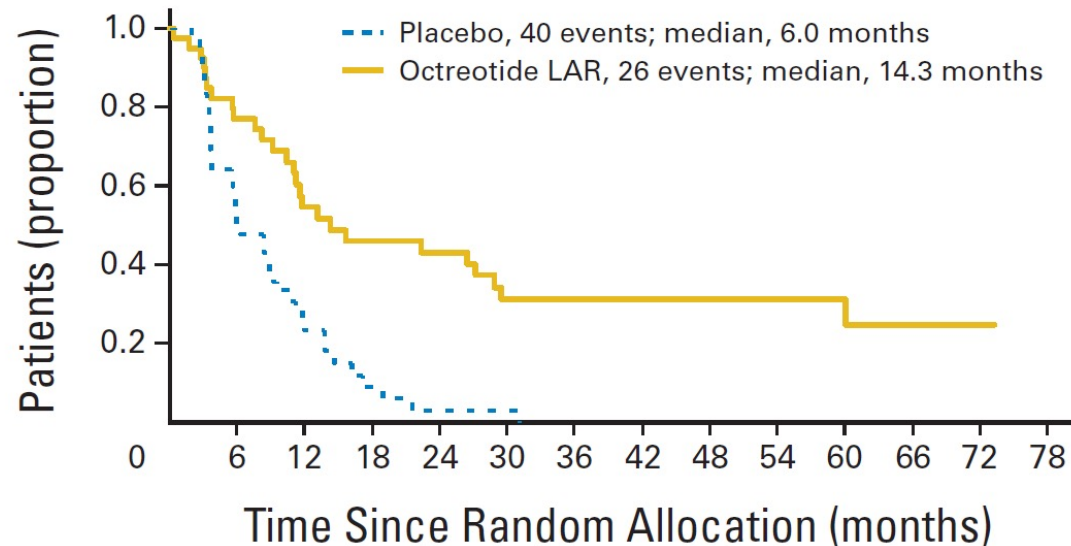
\*Not including somatostatin analogues; <sup>†</sup>Includes all systemic chemotherapeutic agents and protein kinase inhibitors; <sup>‡</sup>Includes 8/117 patients (6.8%) in the <sup>177</sup>Lu-DOTATATE arm and 36/114 patients (31.6%) in the control arm who specifically received <sup>177</sup>Lu-DOTATATE.

# NETTER-1: safety update

- No new cases of MDS or acute leukaemia were reported during long-term follow-up.
- A total of 2/111 <sup>177</sup>Lu-DOTATATE-treated patients (1.8%) developed MDS.
  - One patient developed unilineage dysplasia, confirmed as MDS.
  - One patient developed refractory cytopenia with multilineage dysplasia.
- During the study, the rate of  $\geq$  grade 3 nephrotoxicity in <sup>177</sup>Lu-DOTATATE-treated patients was low and similar to the control arm (6/111 patients [5.4%] and 4/112 patients [3.6%], respectively).
  - No additional patients in the <sup>177</sup>Lu-DOTATATE arm had  $\geq$  grade 3 nephrotoxicity during long-term follow-up.

# Other key phase 3 studies in midgut NETs: PROMID

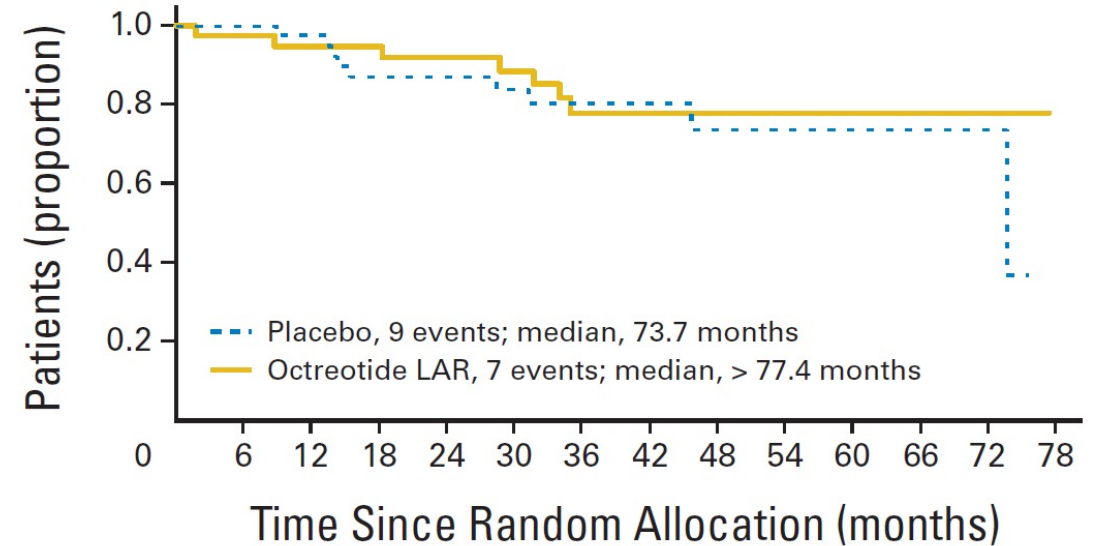
### Progression-free survival



No. of patients at risk													
Placebo	43	21	9	3	1	1	0	0	0	0	0	0	0
Octreotide LAR	42	30	19	16	15	10	10	9	9	6	5	3	1

Log-rank test stratified by functional activity:  $P = .000072$ , HR = 0.34 (95% CI, 0.20 to 0.59)

### Overall survival

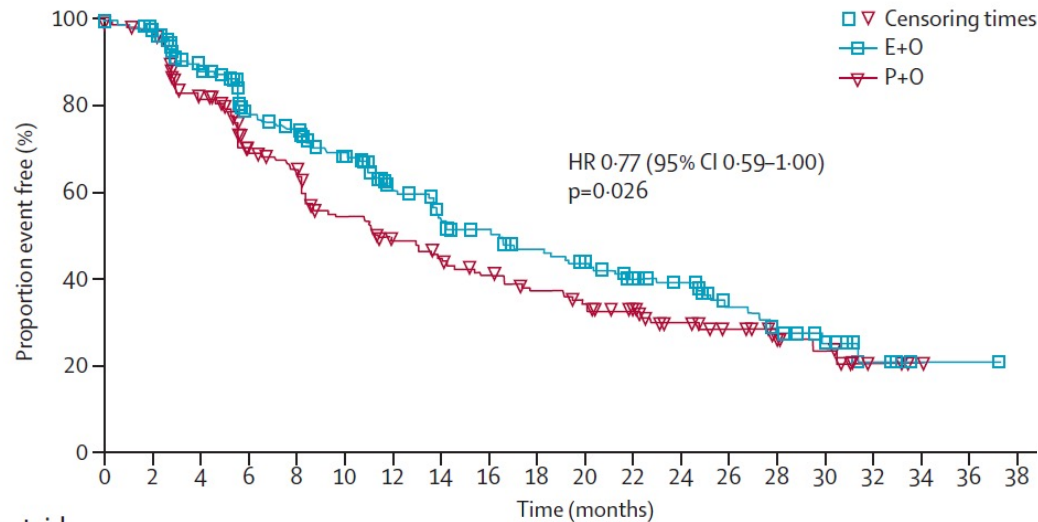


No. of patients at risk													
Placebo	43	41	39	29	27	25	19	14	11	8	6	4	2
Octreotide LAR	42	39	32	31	29	27	20	16	16	10	9	7	2

Log-rank test stratified by functional activity:  $P = .77$ , HR = 0.81 (95% CI, 0.30 to 2.18)

# Other key phase 3 studies in midgut NETs: RADIANT-2

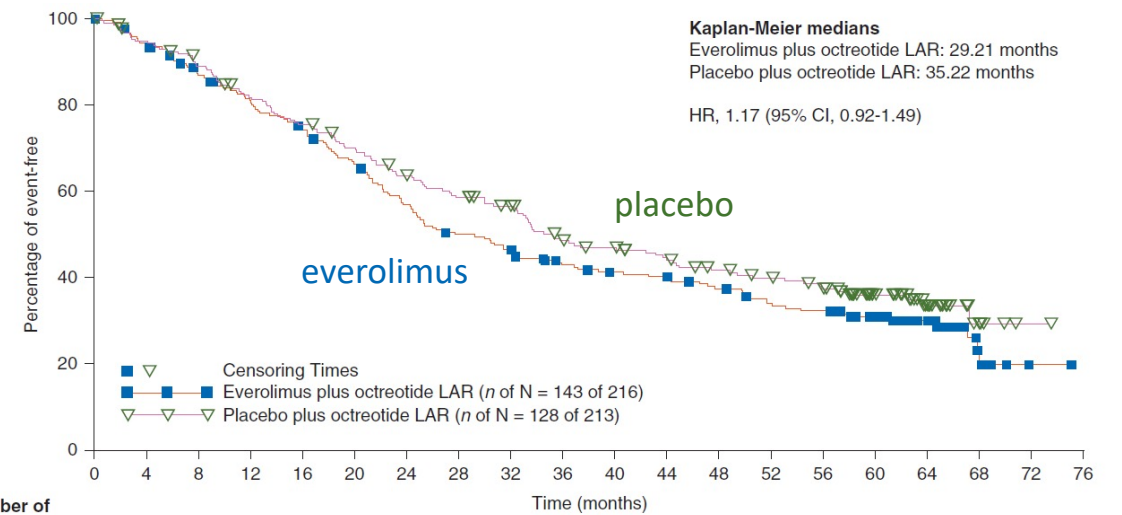
## Progression-free survival<sup>1</sup>



Number at risk

E+O	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
P+O	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0

## Overall survival<sup>2</sup>



Number of patients still at risk

Everolimus plus octreotide LAR	216	202	181	166	152	135	115	100	93	81	76	74	67	59	56	40	22	6	1	0
Placebo plus octreotide LAR	213	199	185	168	155	142	127	117	108	89	84	77	70	64	58	37	20	4	1	0

1. Pavel ME *et al.* *Lancet* 2011;378:2005–12; 2. Pavel ME *et al.* *Ann Oncol* 2017;28(7):1569–75.

# NETTER-1: conclusions

- The prespecified final analysis of OS, with a median follow-up of more than 6.3 years, did not reach statistical significance (HR, 0.84 [95% CI: 0.60, 1.17];  $p = 0.30$ ).
  - This was likely impacted by a variety of confounding factors, including 36% cross-over to radioligand therapy in the control arm (primarily  $^{177}\text{Lu}$ -DOTATATE).
- Median OS was 48.0 months in the  $^{177}\text{Lu}$ -DOTATATE arm and 36.3 months in the control arm.
  - This difference in median OS of 11.7 months may be considered clinically meaningful.
- No new safety signals emerged during long-term follow-up.

# Acknowledgements

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