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NET CLINICAL TRIAL OVERVIEW

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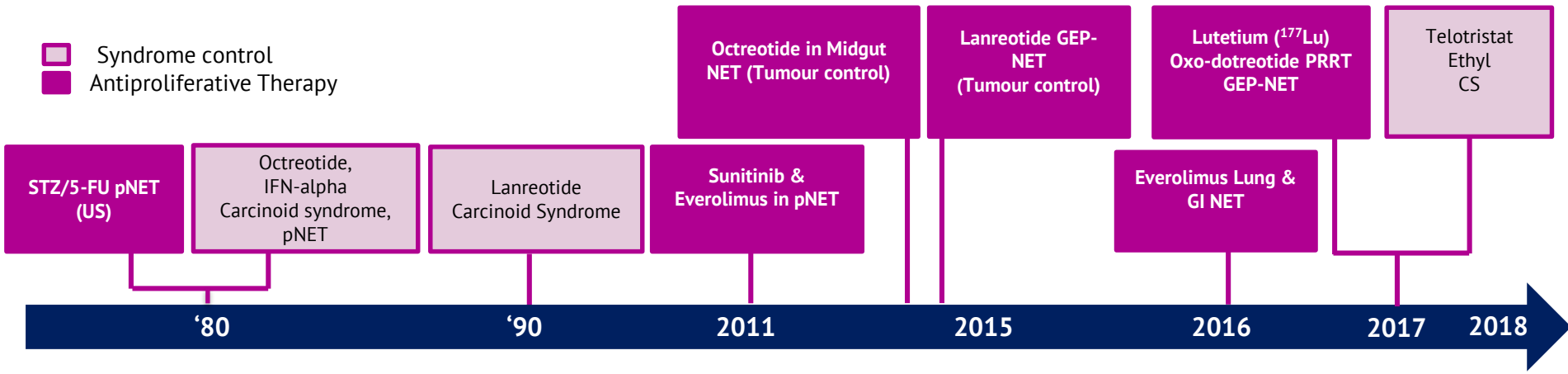
PRACTICE CHANGING CLINICAL TRIALS IN NET

APPROVED THERAPEUTIC OPTIONS IN NEUROENDOCRINE TUMOURS



CDK4/6, Cyclin-dependent kinase 4/6; CS, carcinoid syndrome; GEP-NET, gastroenteropancreatic neuroendocrine tumours; GI NET, gastrointestinal neuroendocrine tumour; HDAC, histone deacetylase; IFN, interferon; pNET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; STZ/5-FU, streptozotocin/ fluorouracil; TACE, transarterial chemoembolization; TAE, transarterial embolization; TKI, tyrosine kinase inhibitors; TMZ, Temozolomide. Slide provided by Prof. Marianne Pavel

NOVEL AGENTS FOR NEUROENDOCRINE TUMOURS

- In the past 10 years, a number of key trials reported resulting in the availability of new treatments for NETs:-
  - **PROMID:** Ocreotide
  - **RADIANT-3 & RADIANT-4:** Everolimus
  - **CLARINET:** Lanreotide
  - **NETTER-1:** ^{177}Lu-DOTATATE
  - **Study A6181111:** Sunitinib
  - **TELESTAR:** Telotristat Ethyl
- These trials have contributed to the current treatment recommendations and therapeutic algorithm.

Rinke, et al. J Clin Oncol 2009;27:4656-63; Yao, et al. N Engl J Med 2011;364:514-23; Yao, et al. Lancet 2016;387:968–77; Caplin, et al. N Engl J Med 2014;371:224-33; Strosberg, et al. N Engl J Med 2017;376:125-35 ; Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

ENETS CONSENSUS GUIDELINES

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Neuro endocrinology

ENETS Consensus Guidelines

Neuroendocrinology 2016;103:172–185
DOI: 10.1159/000443167

Published online: January 5, 2016

ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site

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E. Krenning[g] U. Knigge[h] R. Salazar[i] U.-F. Pape[a] K. Öberg[j]
all other Vienna Consensus Conference participants

Therapeutic options and conditions for preferential use as first-line therapy in advanced NEN

Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+/–	GI	Midgut	+	Lower tumor burden
Lanreotide	+/–	G1/G2 (–10%)	Midgut, pancreas	+	Low and high (>25%) liver tumor burden
IFN-alpha 2b	+/–	G1/G2	Midgut		If SSTR negative
STZ/5-FU	+/–	G1/G2	Pancreas		Progressive in short-term* or high tumor burden or symptomatic
TEM/CAP	+/–	G2	Pancreas		Progressive in short-term* or high tumor burden or symptomatic; if STZ is contraindicated or not available
Everolimus	+/–	G1/G2	Lung		Atypical carcinoid and/or SSTR negative
			Pancreas		Insulinoma or contraindication for CTX
			Midgut		If SSTR negative
Sunitinib	+/–	G1/G2	Pancreas		Contraindication for CTX
PRRT	+/–	G1/G2	Midgut	+ (required)	Extended disease; extrahepatic disease, e.g. bone metastasis
Cisplatin§/ etoposide	+/–	G3	Any		All poorly differentiated NEC

* ⩽6–12 months; §Cisplatin can be replaced by carboplatin.

CAP, capecitabine; TEM, temozolomide.
Pavel, et al. Neuroendocrinology. 2016;103:172-85.

PROMID: EFFICACY AND SAFETY OF OCTREOTIDE LAR COMPARED TO PLACEBO IN SMALL INTESTINAL NEUROENDOCRINE TUMOURS

Rinke, et al. J Clin Oncol 2009;27:4656-63.

PROMID: BACKGROUND & RATIONALE

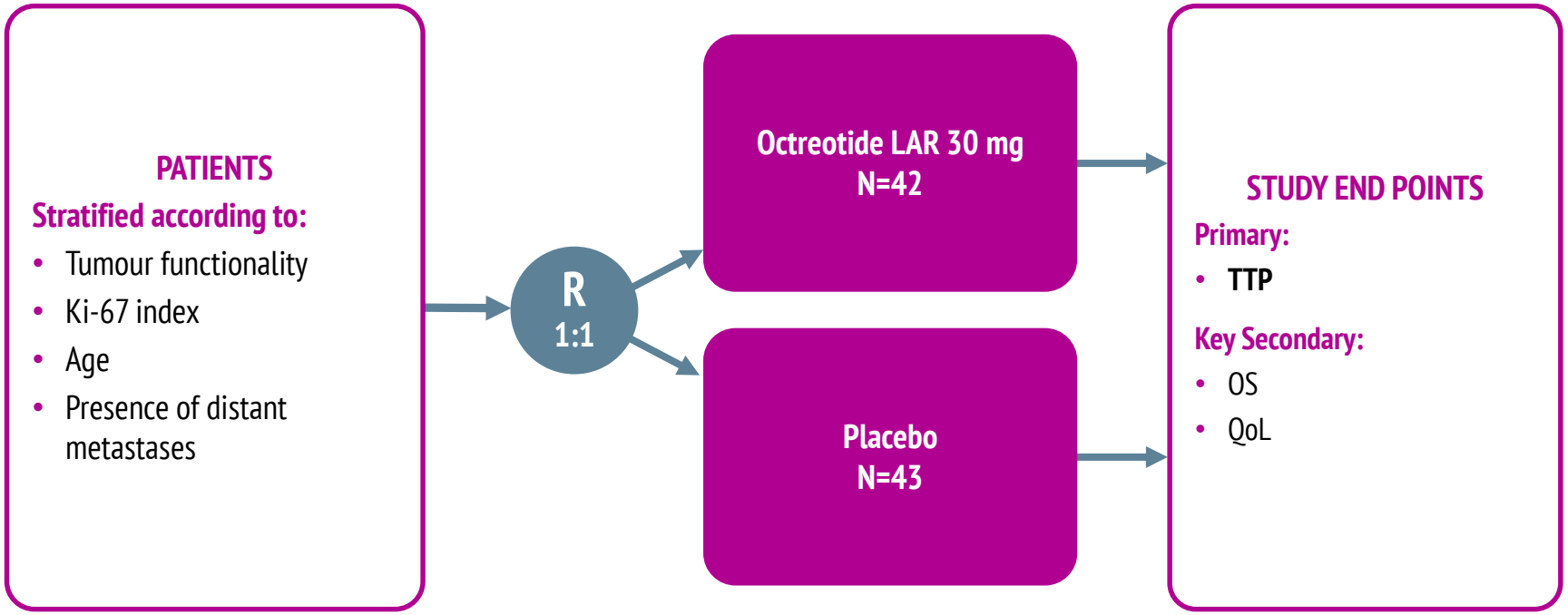
- Prior to this study there were no systemic therapies approved for patients with small intestinal NETs
- Somatostatin analogues have been used to treat symptoms associated with hormone hypersecretion caused by neuroendocrine tumours
- Whether or not somatostatin analogues may control the growth of well-differentiated metastatic NETs was under debate

NETs, neuroendocrine tumours.

Rinke, et al. J Clin Oncol 2009;27:4656-63

PROMID: STUDY DESIGN

Patient population: well-differentiated metastatic midgut tumours



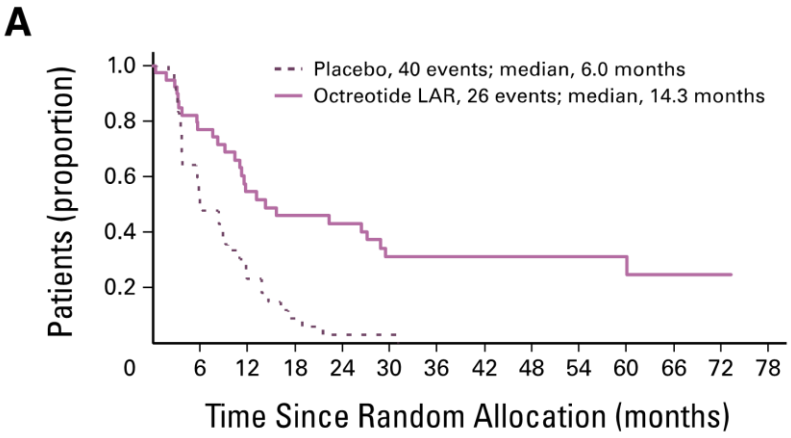
LAR, long acting release; OS, overall survival; QoL, quality of Life; R, randomisation; TTP, time to tumour progression.

Rinke, et al. J Clin Oncol 2009;27:4656-63.

PROMID: EFFICACY

OCTREOTIDE VS PLACEBO IN MIDGUT-NET

PRIMARY ENDPOINT: TTP

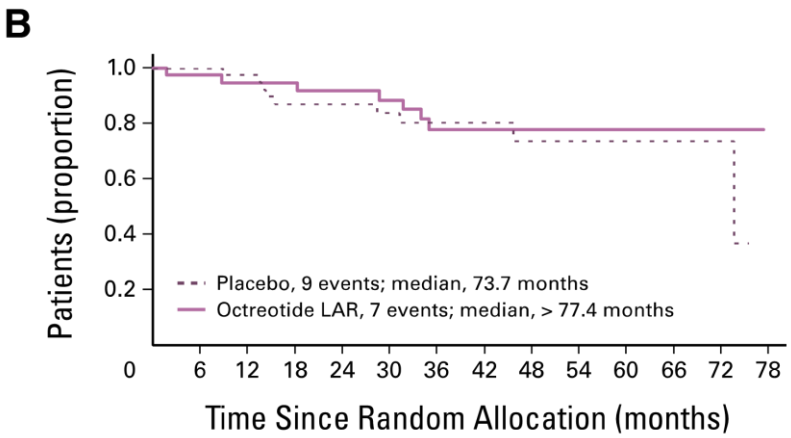


No. of patients at risk

Placebo	43	21	9	3	1	1	0	0	0	0	0	0	0	0
Octreotide LAR	42	30	19	16	15	10	10	9	9	6	5	3	1	0

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

SECONDARY ENDPOINT: OS



No. of patients at risk

Placebo	43	41	39	29	27	25	19	14	11	8	6	4	2	0
Octreotide LAR	42	39	32	31	29	27	20	16	16	10	9	7	2	0

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

- At the time of the planned interim analysis, overall survival data not mature

CI, confidence interval; HR, hazard ratio; LAR, long acting release; OS; overall survival; SI-NET, small intestine neuroendocrine tumour; TTP, time to tumour progression.

Rinke, et al. J Clin Oncol 2009;27:4656-63.

PROMID: EFFICACY

SECONDARY ENDPOINT: QOL

	Study Entry				Six Months				Change From Study Entry to Six Months						
	Octreotide LAR		Placebo		Octreotide LAR		Placebo		Octreotide LAR		Placebo				
Quality of Life	Total No. of Patients	EORTC QLQ-C30 score	Total No. of Patients	EORTC QLQ-C30 score	Total No. of Patients	EORTC QLQ-C30 score	Total No. of Patients	EORTC QLQ-C30 score	Total No. of Patients	EORTC QLQ-C30 score	Total No. of Patients	EORTC QLQ-C30 score	Δ (%)	95% CI (%)	*P*
EORTC QLQ-C30 score	38		42		29		24		25		24		2.1	-7.8 to 12.0	0.6738
Mean		64.0		65.7		68.1		64.2		0.0		−2.1			
SD		22.3		24.7		23.2		19.6		18.5		15.8			

- Both treatment groups had comparable levels of global quality of life at random assignment and after 6 months of follow-up

CI, confidence interval; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer quality-of-life questionnaire, 30-question survey; LAR, long acting release; QoL, Quality of Life.

Rinke, et al. J Clin Oncol 2009;27:4656-63

PROMID: SAFETY

Serious Adverse Events

	Octreotide LAR (N=42)	Placebo (N=43)
Serious adverse events	11	10
Affecting GI tract	6	8
Affecting haematopoietic system	5	1
Affecting general health status (fatigue and fever)	8	2
Treatment discontinuation due to AEs	5	0

AEs, adverse events; GI, gastrointestinal; LAR, long acting release.

Rinke, et al. J Clin Oncol 2009;27:4656-63.

PROMID: SUMMARY

PROMID suggests treatment with octreotide LAR 30 mg compared to placebo in patients with advanced mid-gut neuroendocrine tumours:-

- Prolongs PFS, HR 0.32 [95% CI 0.19 – 0.55]
- OS analysis did not attain a significant difference
- No difference in QoL between treatment arms

CI, confidence interval; HR, hazard ratio; LAR, long acting release; OS, overall survival; PFS, progression free survival; QoL, Quality of Life.

RADIANT-3: EFFICACY AND SAFETY OF EVEROLIMUS COMPARED TO PLACEBO IN PANCREATIC NETs

Yao, et al. N Engl J Med 2011;364:514-23.

RADIANT-3: BACKGROUND & RATIONALE

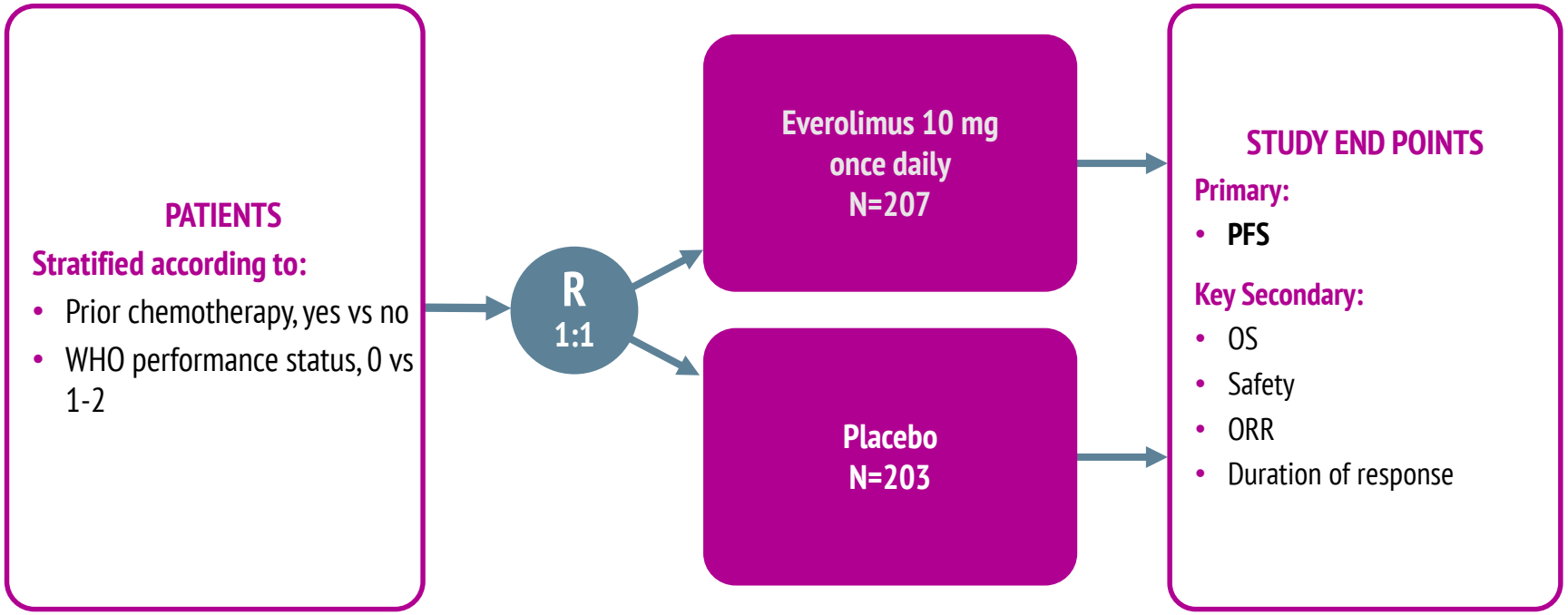
- Prior to this study the only approved agent for pancreatic neuroendocrine tumours was Streptozocin
- Everolimus showed efficacy in two phase II trials that included patients with pancreatic neuroendocrine tumours
- The purpose of this study was to evaluate the efficacy and safety of everolimus 10 mg daily versus placebo in pancreatic NETs

NETs, neuroendocrine tumours.

Yao, et al. N Engl J Med 2011;364:514-23.

RADIANT-3: STUDY DESIGN

Patient population: advanced and progressive pancreatic neuroendocrine of grade 1-2.



ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; WHO, World Health Organization.

Yao, et al. N Engl J Med 2011;364:514-23.

RADIANT-3: EFFICACY

EVEROLIMUS VS PLACEBO IN PAN-NET

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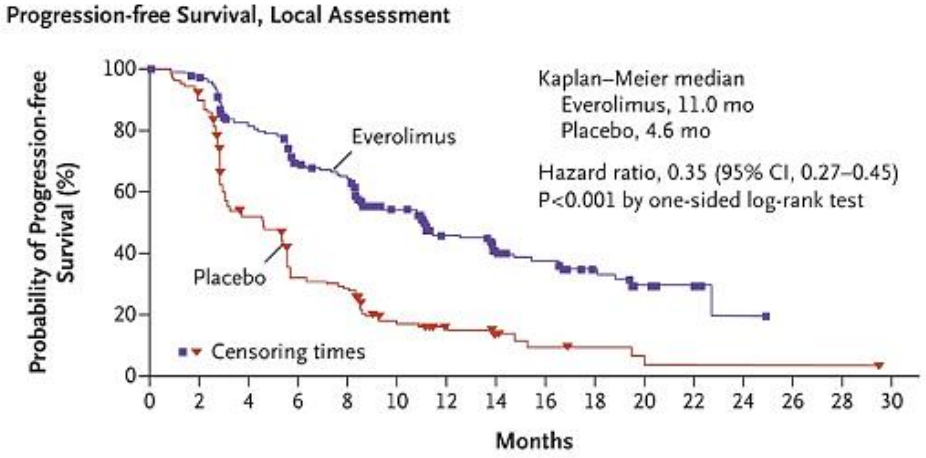
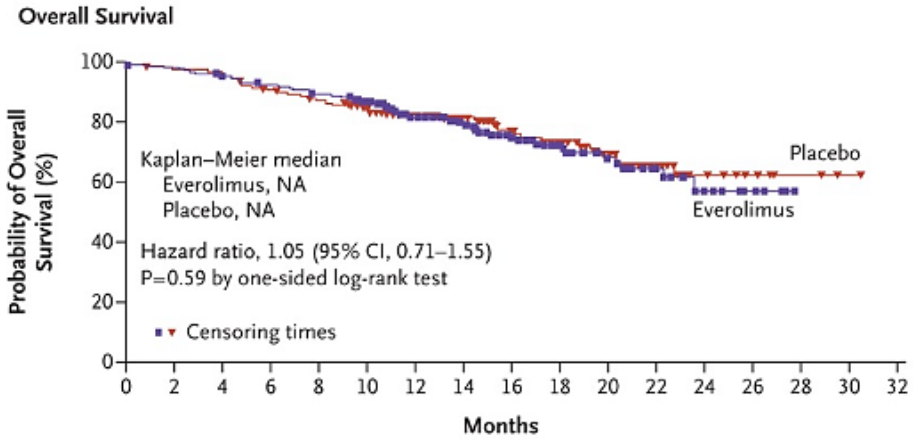
PRIMARY ENDPOINT: PFS

N = 410
Everolimus: 207
Placebo: 203



SECONDARY ENDPOINT: OS



- Prespecified subgroup analyses indicated that the PFS benefit was maintained across subgroups

CI, confidence interval; mo, months; NA, not available; OS, overall survival; PFS, progression-free survival.

Yao, et al. N Engl J Med 2011;364:514-23.

RADIANT-3: EFFICACY

SECONDARY ENDPOINT: CONFIRMED OBJECTIVE RESPONSE

	Everolimus (N=207)	Placebo (N=203)
Partial responses	5%	2%
Stable disease	73%	51%
Progressive disease	14%	42%

By local radiological evaluation.

Yao, et al. N Engl J Med 2011;364:514-23

RADIANT-3: SAFETY

DRUG-RELATED ADVERSE EVENTS OCCURRING IN AT LEAST 10% OF PATIENTS

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Adverse Event	Everolimus (N=204)		Placebo (N=203)	
	All grades, N(%)	Grade 3 or 4, N(%)	All grades, N(%)	Grade 3 or 4, N(%)
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10)	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis‡	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0
Vomiting	31 (15)	0	13 (6)	0
Pruritus	30 (15)	0	18 (9)	0
Hyperglycaemia	27 (13)	11 (5)	9 (4)	4 (2)
Thrombocytopenia	27 (13)	8 (4)	1 (<1)	0
Asthenia	26 (13)	2 (1)	17 (8)	2 (1)
Nail disorder	24 (12)	1 (<1)	2 (1)	0
Cough	22 (11)	0	4 (2)	0
Pyrexia	22 (11)	0	0	0
Dry skin	21 (10)	0	9 (4)	0

*includes stomatitis, mouth ulceration and tongue ulceration; † includes all types of infections; ‡ includes pneumonitis, interstitial lung disease, lung infiltration and pulmonary fibrosis

Yao, et al. N Engl J Med 2011;364:514-23.

RADIANT-3: SUMMARY

RADIANT-3 suggests treatment with everolimus 10 mg daily compared to placebo:-

- Significantly prolongs PFS, HR 0.35 [95% CI 0.27 – 0.45]
- OS analysis did not attain a significant difference
- QoL not investigated

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; QoL, Quality of Life.

Yao, et al. N Engl J Med 2011;364:514-23.

RADIANT-4: EFFICACY AND SAFETY OF EVEROLIMUS COMPARED TO PLACEBO IN LUNG AND GASTROINTESTINAL NETs

Yao, et al. Lancet 2016;387:968-77.

RADIANT-4: BACKGROUND & RATIONALE

- Prior to this study there were few systemic therapies available to patients with NET of the lungs or gastrointestinal tract. Antitumour effect of everolimus was demonstrated for pancreatic NETs in the RADIANT-3 trial[1]

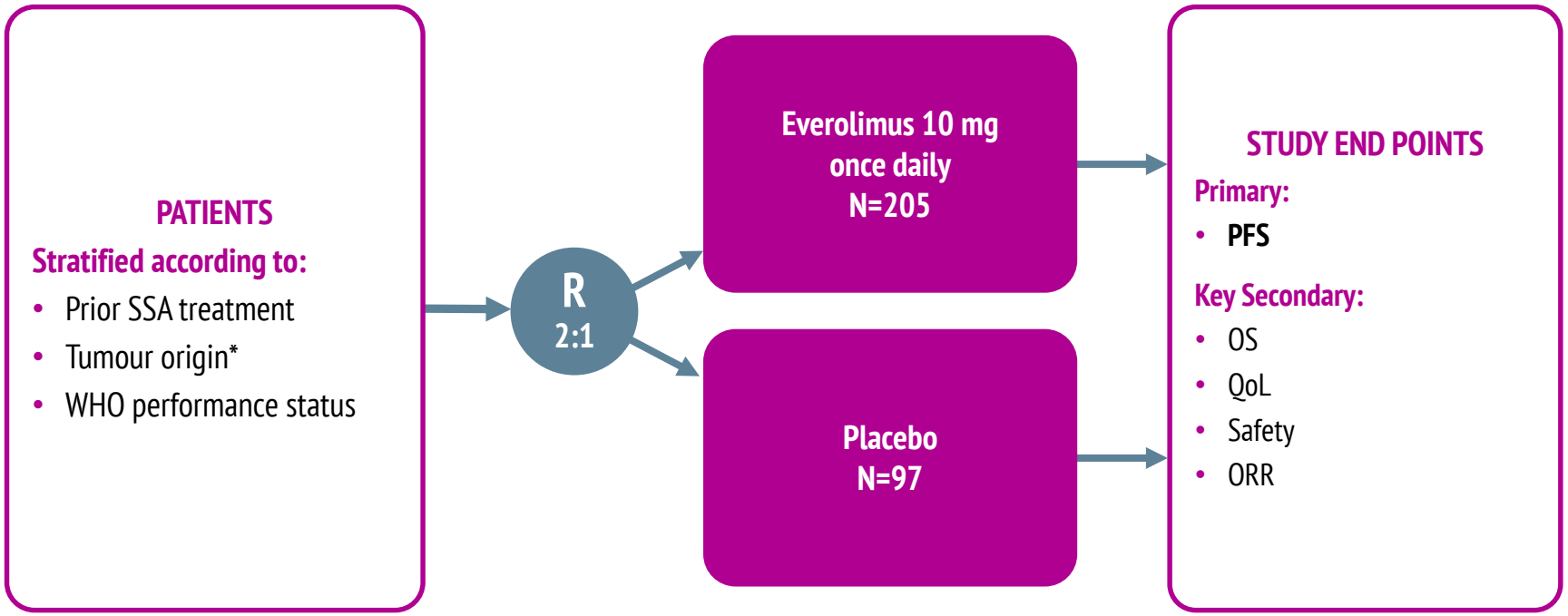
- The purpose of this study was to evaluate efficacy and safety of everolimus 10 mg daily versus placebo in patients with lung or GI NETs

GI, Gastrointestinal; NET, neuroendocrine tumour.

1. Yao, et al. N Engl J Med 2011;364:514-23.
Yao, et al. Lancet 2016;387:968–77.

RADIANT-4: STUDY DESIGN

Patient population: advanced (unresectable or metastatic), non-functional, NET grade 1-2 of lung or gastrointestinal origin.



*Patients categorized into Strata A, appendix, caecum, jejunum, ileum, duodenum or NET of unknown origin; Strata B, lung, stomach or colon.

NET, neuroendocrine tumour; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, Quality of Life; R, randomization; SSA somatostatin analogue. Yao, et al. Lancet 2016;387:968–77.

RADIANT-4: STUDY

EVEROLIMUS VS PLACEBO IN LUNG, INTESTINAL NET AND NET OF UNKNOWN ORIGIN

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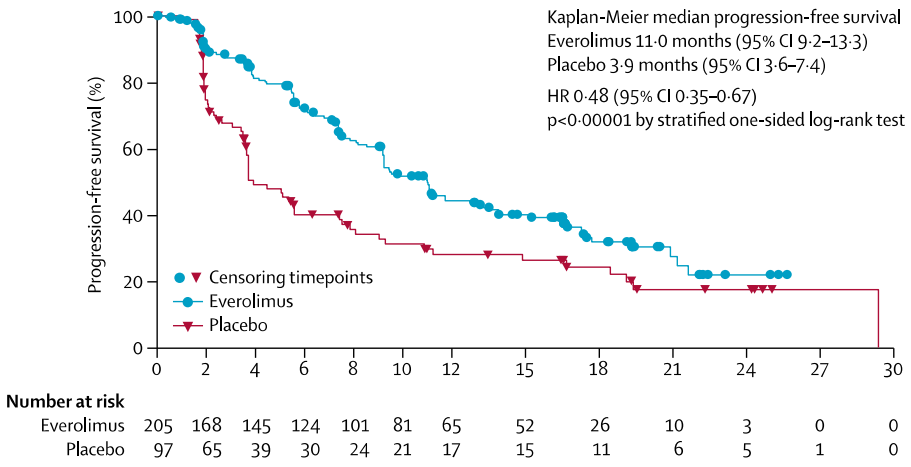
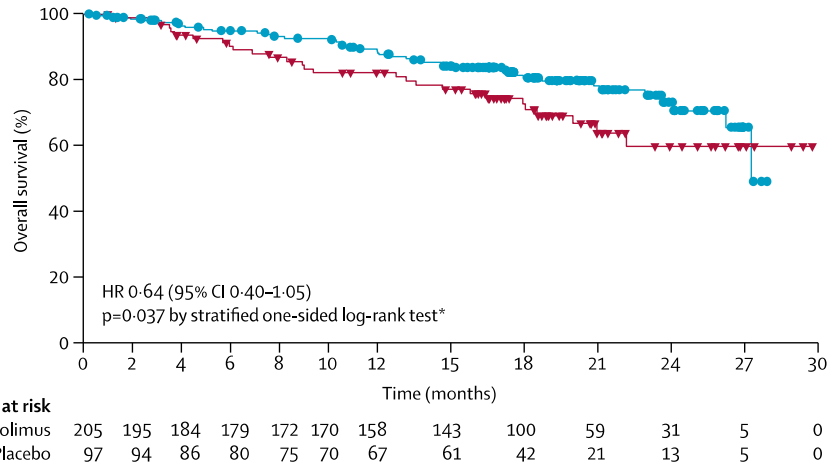
PRIMARY ENDPOINT: PFS



SECONDARY ENDPOINT: OS (premature)



* The Lan-DeMets O'Brian-Fleming boundary for significance at first interim analysis was 0.0002

PFS, by central radiology review; OS accordingly to interim analysis.

CI, confidence interval; HR, hazard ratio; NA, not available; OS, overall survival, PFS, progression-free survival.

Yao, et al. Lancet 2016;387:968–77.

RADIANT-4: EFFICACY

SECONDARY ENDPOINT: CONFIRMED OBJECTIVE RESPONSE

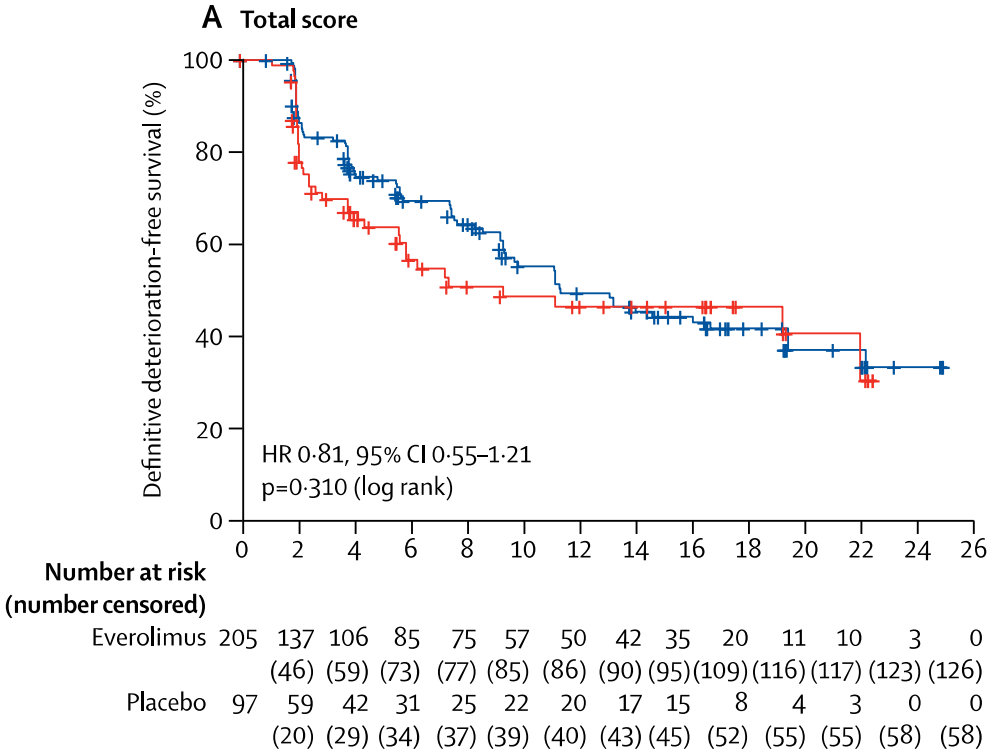
	Everolimus (N=205)	Placebo (N=97)
Partial responses	4 (2%)	1 (1%)
Disease stabilisation	165 (81%)	62 (64%)

By central radiological evaluation

Yao, et al. Lancet 2016;387:968–77

RADIANT-4: EFFICACY

SECONDARY ENDPOINT: HRQoL, TIME TO DEFINITIVE DETERIORATION



HRQoL defined as time to definitive deterioration (≥7 points) in FACT-G total score

CI, confidence interval; HR, hazard ratio; HRQoL, health related quality of life.

Pavel, et al. Lancet Oncol 2017;18:1411–22.

RADIANT-4: SAFETY

	Everolimus (n=202)					Placebo (n=98)				
	All grades	Grade 1	Grade 2	Grade 3	Grade 4	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis*	127 (63%)	72 (36%)	37 (18%)	18 (9%)	0	19 (19%)	17 (17%)	2 (2%)	0	0
Diarrhoea	63 (31%)	30 (15%)	18 (9%)	13 (6%)	2 (1%)	16 (16%)	10 (10%)	4 (4%)	2 (2%)	0
Fatigue	62 (31%)	35 (17%)	20 (10%)	5 (2%)	2 (1%)	24 (24%)	17 (17%)	6 (6%)	1 (1%)	0
Infections†	59 (29%)	12 (6%)	33 (16%)	10 (5%)	4 (2%)	4 (4%)	1 (1%)	3 (3%)	0	0
Rash	55 (27%)	42 (21%)	12 (6%)	1 (<1%)	0	8 (8%)	6 (6%)	2 (2%)	0	0
Peripheral oedema	52 (26%)	30 (15%)	18 (9%)	4 (2%)	0	4 (4%)	2 (2%)	1 (1%)	1 (1%)	0
Nausea	35 (17%)	26 (13%)	6 (3%)	2 (1%)	1 (<1%)	10 (10%)	7 (7%)	3 (3%)	0	0
Asthenia	33 (16%)	8 (4%)	22 (11%)	2 (1%)	1 (<1%)	5 (5%)	4 (4%)	1 (1%)	0	0
Anaemia	33 (16%)	5 (2%)	20 (10%)	8 (4%)	0	2 (2%)	0	1 (1%)	1 (1%)	0
Decreased appetite	32 (16%)	22 (11%)	9 (4%)	1 (<1%)	0	6 (6%)	2 (2%)	4 (4%)	0	0
Non-infectious pneumonitis‡	32 (16%)	5 (2%)	24 (12%)	3 (1%)	0	1 (1%)	0	1 (1%)	0	0
Dysgeusia	30 (15%)	26 (13%)	3 (1%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Pruritus	26 (13%)	19 (9%)	6 (3%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Cough	26 (13%)	18 (9%)	8 (4%)	0	0	3 (3%)	3 (3%)	0	0	0
Pyrexia	22 (11%)	14 (7%)	4 (2%)	2 (1%)	2 (1%)	5 (5%)	4 (4%)	1 (1)	0	0
Hyperglycaemia	21 (10%)	5 (2%)	9 (4%)	7 (3%)	0	2 (2%)	2 (2%)	0	0	0
Dyspnoea	21 (10%)	4 (2%)	15 (7%)	2 (1%)	0	4 (4%)	2 (2%)	1 (1)	0	1 (1)

*includes stomatitis, aphthous stomatitis, mouth ulceration and tongue ulceration; †includes all type of infections; ‡includes pneumonitis, interstitial lung disease, lung infiltration and pulmonary fibrosis.

Yao, et al. Lancet 2016;387:968–77

RADIANT-4: SUMMARY

RADIANT-4 suggests treatment with everolimus 10 mg daily compared to placebo:-

- Significantly prolongs PFS HR 0.48 (95% CI 0.35 – 0.67)
- OS did not attain a significant difference (interim analysis)
- Analysis of health related QoL did not attain a significant difference

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; QoL, Quality of Life.

Pavel, et al. Lancet Oncol 2017;18:1411–22; Yao, et al. Lancet 2016;387:968–77

CLARINET: EFFICACY AND SAFETY OF LANREOTIDE COMPARED TO PLACEBO IN PANCREATIC AND GASTROINTESTINAL NEUROENDOCRINE TUMOURS

Caplin, et al. N Engl J Med 2014;371:224-33.

CLARINET: BACKGROUND & RATIONALE

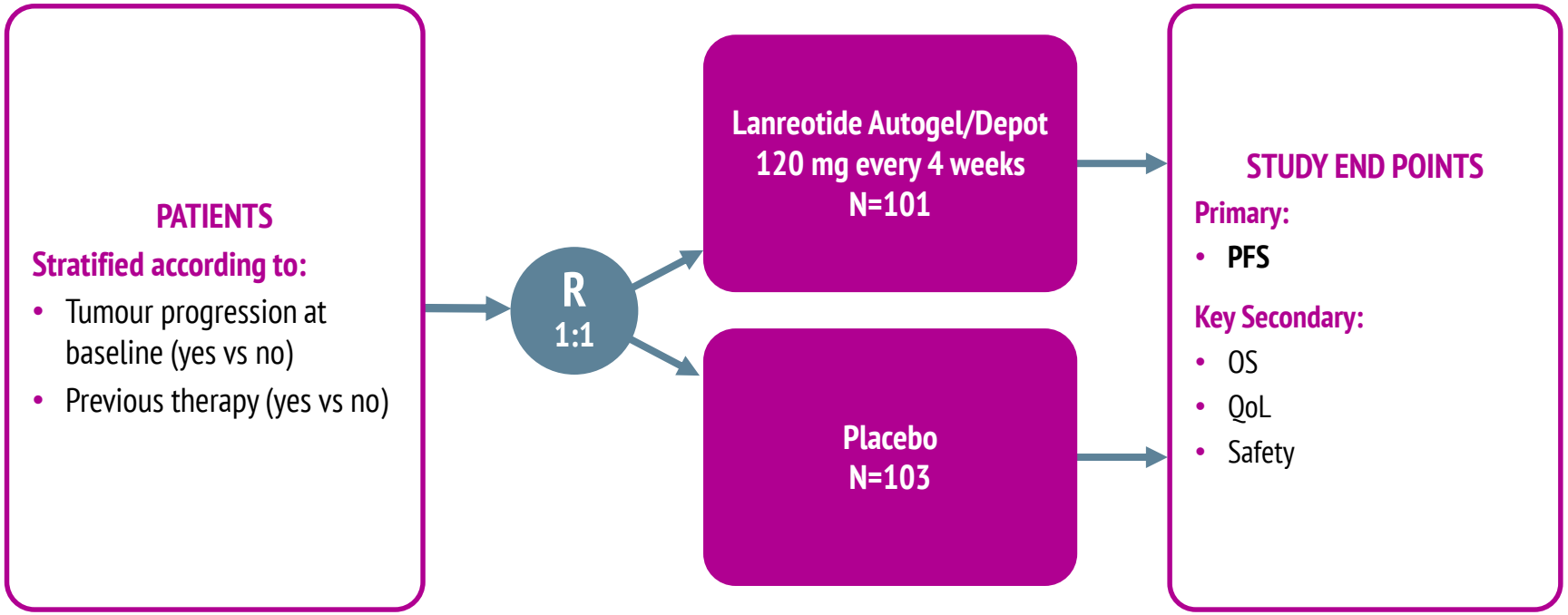
- Prior to this study there were few systemic therapies approved for patients with pancreatic and GI-NETs
- Somatostatin analogues have been used to treat symptoms associated with hormone hypersecretion from neuroendocrine tumours
- A randomized, controlled trial on small intestinal neuroendocrine tumours found that treatment with somatostatin analogue octreotide LAR was associated with an increased progression free survival as compared to placebo[1]

GI, Gastrointestinal; LAR, long acting release; NETs, neuroendocrine tumours

Caplin, et al. N Engl J Med 2014;371:224-33 1. Rinke et al. J Clin Oncol 27:4656-63.

CLARINET: STUDY DESIGN

Patient population: advanced, well or moderately differentiated, non-functioning, somatostatin receptor positive neuroendocrine tumours of grade 1 or 2 (Ki67 >10%).



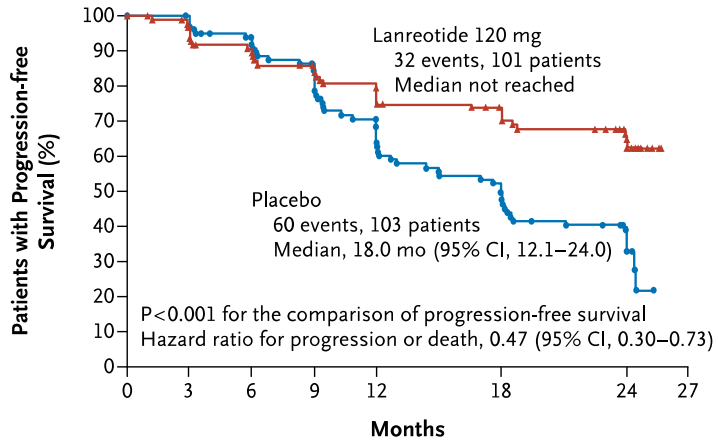
OS, overall survival; PFS, progression-free survival; QoL, Quality of Life; R, randomisation.

Caplin, et al. N Engl J Med 2014;371:224-33.

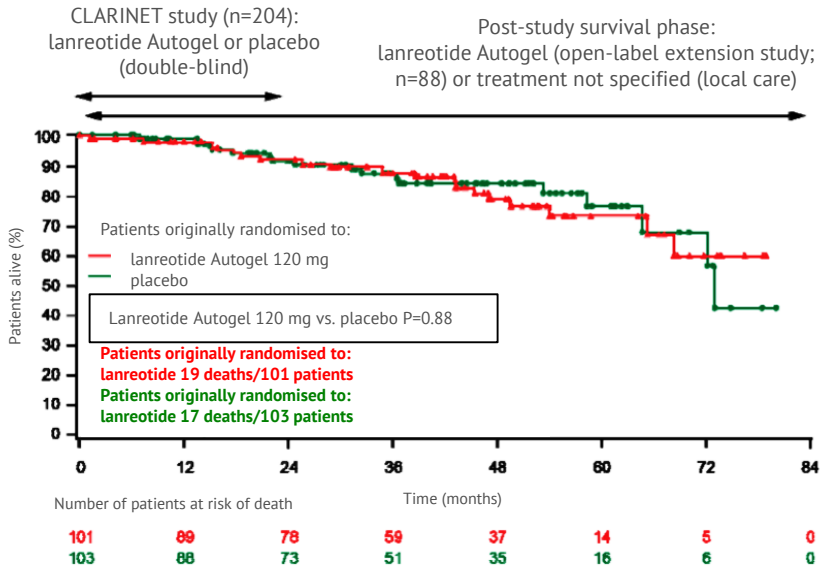
CLARINET: EFFICACY

LANREOTIDE VS PLACEBO IN GEP-NET

PRIMARY ENDPOINT: PFS



SECONDARY ENDPOINT: OS (premature)



PFS centrally assessed according to RECIST. OS accordingly to investigator follow up of patients
CI, confidence interval; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours
Caplin, et al. N Engl J Med 2014;371:224-33 (OS data from supplementary appendix)

CLARINET: EFFICACY

SECONDARY ENDPOINT: QoL

Secondary Efficacy End Points (Intention-to-Treat Population)

End Point	Lanreotide (N=101)	Placebo (N=103)	Between-Group Comparison (95% CI)
EORTC QLQ-C30 global health status score – least squares mean change from baseline to last post-baseline value available	−5.18±3.73	−4.87±3.7	−0.31±2.74 (−5.73 to 5.10)

CI, confidence interval; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer quality-of-life questionnaire, 30-question survey; QoL, quality of life.

Caplin, et al. N Engl J Med 2014;371:224-33.

CLARINET: SIDE EFFECTS

ADVERSE EVENTS (SAFETY POPULATION)

Event	Lanreotide (N=101)	Placebo (N=103)
	Number of patients (%)	
Any adverse event	89 (88)	93 (90)
Any adverse event related to study treatment	50 (50)	29 (28)
Any adverse event according to intensity		
Severe	26 (26)	32 (31)
Moderate	44 (44)	44 (43)
Mild	17 (17)	17 (17)
Any serious adverse event	25 (25)	32 (31)
Serious adverse event related to study treatment	3 (3)	1 (1)
Withdrawal from study because of any adverse event	3 (3)	3 (3)
Withdrawal because of adverse event related to study treatment	1 (1)	0

Caplin, et al. N Engl J Med 2014;371:224-33.

CLARINET: SIDE EFFECTS

TRAEs IN ≥5% OF PATIENTS (SAFETY POPULATION)

Event	Lanreotide (N=101)	Placebo (N=103)
	Number of patients (%)	
Study treatment–related adverse events in ≥5% of patients		
Diarrhea	26 (26)	9 (9)
Abdominal pain	14 (14)	2 (2)
Cholelithiasis	10 (10)	3 (3)
Flatulence	8 (8)	5 (5)
Injection-site pain	7 (7)	3 (3)
Nausea	7 (7)	2 (2)
Vomiting	7 (7)	0
Headache	5 (5)	2 (2)
Lethargy	5 (5)	1 (1)
Hyperglycaemia	5 (5)	0
Decreased level of pancreatic enzymes	5 (5)	0

TRAEs, treatment related adverse events

Caplin, et al. N Engl J Med 2014;371:224-33.

CLARINET: SUMMARY

CLARINET suggests treatment with lanreotide Autogel/Depot 120 mg every 4 weeks compared to placebo:-

- Significantly prolonged PFS, HR 0.47 (95% CI 0.30 – 0.73)
- OS analysis did not attain a significant difference
- QoL analysis did not attain a significant difference

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival, QoL, Quality of Life.

Caplin, et al. N Engl J Med 2014;371:224-33 (OS data from supplementary appendix)

NETTER-1: EFFICACY AND SAFETY OF ^{177}LU-DOTATATE PLUS OCTREOTIDE LAR 30 MG COMPARED TO OCTREOTIDE LAR 60 MG IN SMALL INTESTINAL NEUROENDOCRINE TUMOURS

Strosberg, et al. N Engl J Med 2017;376:125-35.

NETTER-1: BACKGROUND & RATIONALE

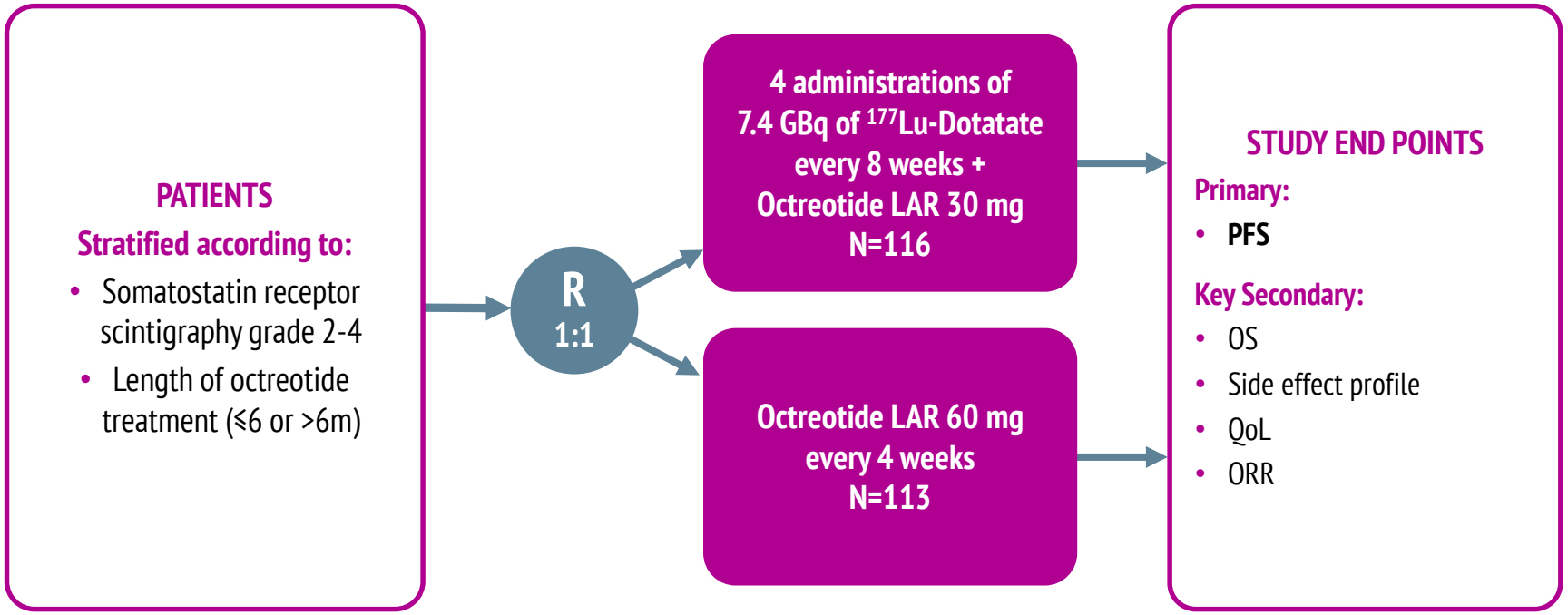
- Prior to this study there were few treatment options beyond first-line therapy with somatostatin analogues for patients with advanced small intestinal neuroendocrine tumour.
- Large retrospective materials have showed efficacy and tolerability of ^{177}Lu-DOTATATE in this setting[1]

Lu, lutetium.

1. Marincek, N et al. J Transl Med 2013: 11: 17; 2. Strosberg, et al. N Engl J Med 2017;376:125-35.

NETTER-1: STUDY DESIGN

Patient population: advanced, progressive, somatostatin-receptor positive midgut neuroendocrine tumours.



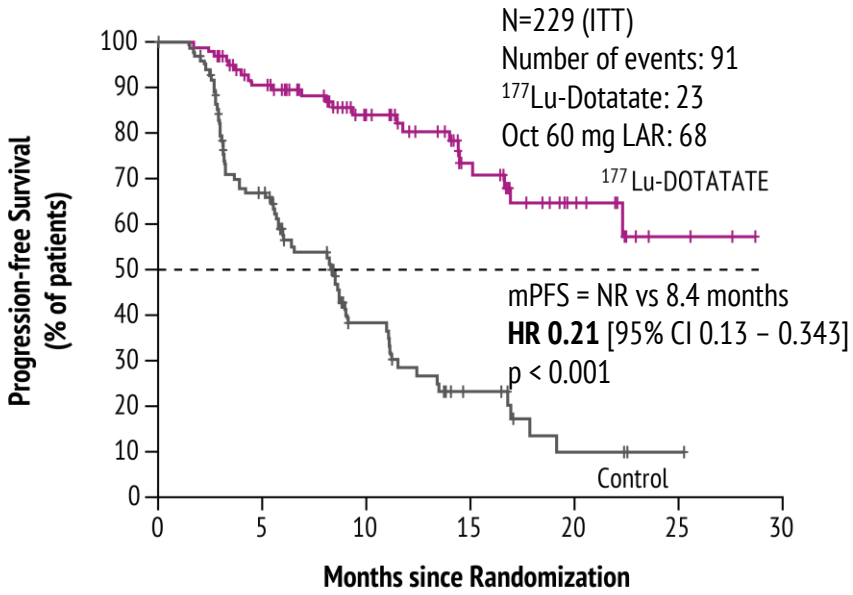
GBq, gigabecquerels; LAR, long acting release; Lu, lutetium; m, months; ORR, objective response rate; OS, overall survival; PFS, progression free survival; QoL, Quality of Life; R, randomisation.

Strosberg, et al. N Engl J Med 2017;376:125-35; Strosberg, et al. J Clin Oncol 2018;36:2578-84.

NETTER-1: EFFICACY

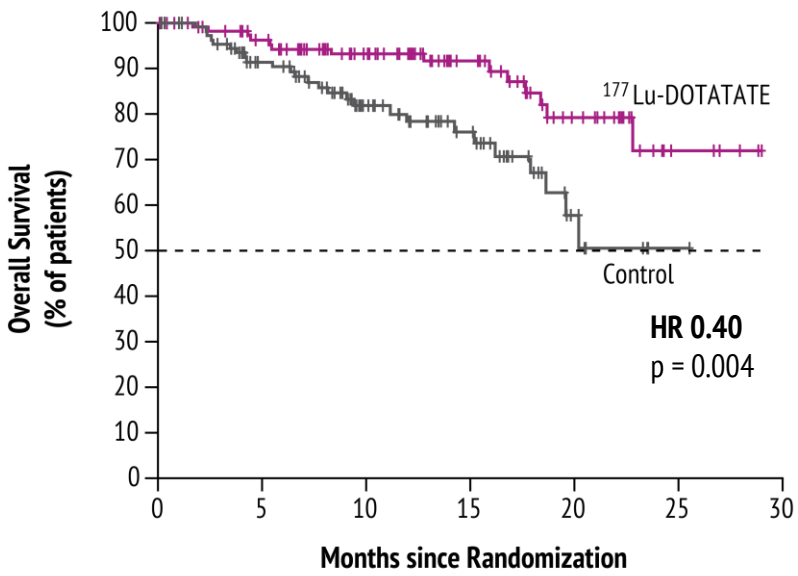
^{177}LU-DOTATATE VS HIGH DOSE OCTREOTIDE IN MIDGUT NET

PRIMARY ENDPOINT: PFS



No. at Risk											
^{177}Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

SECONDARY ENDPOINT: OS (premature)



No. at Risk											
^{177}Lu-DOTATATE group	116	108	96	79	64	47	31	21	8	3	0
Control group	113	103	83	64	41	32	17	5	1	0	0

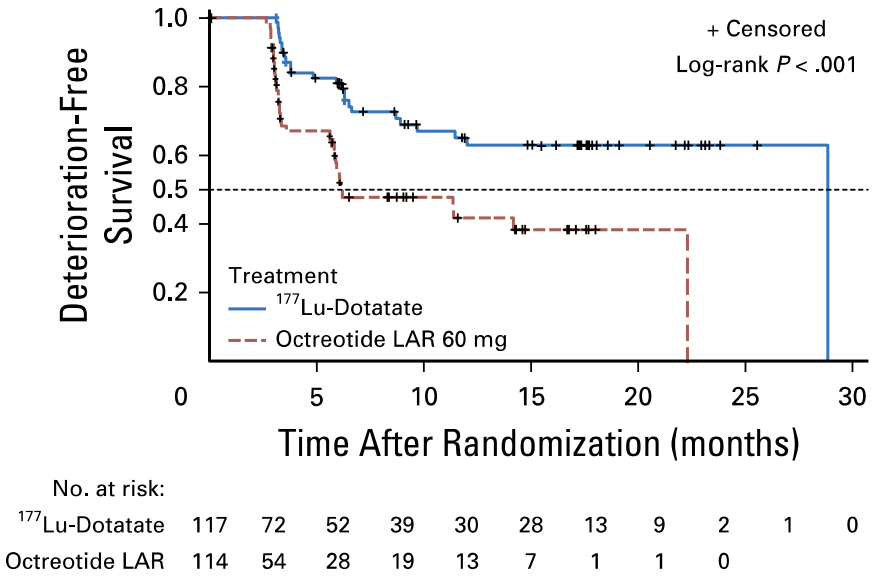
- Consistent treatment benefits on PFS associated with ^{177}Lu-Dotatate were observed irrespective of stratification factors and prognostic factors

Primary analysis of NETTER-1 with interim analysis of overall survival. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mPFS, median progression free survival; NR, not reached; LAR, long acting release; Lu, lutetium; Oct, octreotide, OS, overall survival.

Strosberg, et al. N Engl J Med 2017;376:125-35.

NETTER-1: EFFICACY

SECONDARY ENDPOINT: HRQoL time to deterioration of global health status



22.7 month difference between treatment arms
HR 0.41 [95% CI 0.24 – 0.69]
p < 0.001

Time to deterioration defined as the time from randomization to the first HRQoL deterioration ⩾ 10 points for each patient

CI, confidence interval; HR, hazard ratio; HRQoL, health-related quality of life; LAR, long acting release; Lu, lutetium.

Strosberg, et al. J Clin Oncol 2018;36:2578-84.

NETTER-1: EFFICACY

OBJECTIVE TUMOUR RESPONSE*

Response Category	^{177}Lu-Dotatate Group (N=101)	Control Group (N=100)	P Value†
Complete response – no. (%)	1 (1)	0	
Partial response – no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate – % (95% CI)	8 (10–25)	3 (0–6)	<0.001

*The objective response rate was defined as the percentage of patients who had a response according to Response Evaluation Criteria in Solid Tumors (RECIST) (sum of partial responses and complete responses). Patients for whom no post-baseline computed tomography (CT) or magnetic resonance imaging (MRI) scans or central response data were available (15 patients in the ^{177}Lu-Dotatate group and 13 patients in the control group) were excluded from this analysis (trial is still ongoing).

†The P value was calculated with the use of Fisher's exact text.

Primary analysis of NETTER-1 with interim analysis of overall survival. CI, confidence interval; Lu, lutetium.

Strosberg, et al. N Engl J Med 2017;376:125-35.

NETTER-1: SAFETY

OVERVIEW OF ADVERSE EVENTS (SAFETY POPULATION)*

Event	^{177}Lu-Dotatate Group (N=111)	Control Group (N=110)	P Value†
	Number of patients (%)		
Adverse event			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
Serious adverse event			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of adverse event			
Because of any adverse event	7 (6)	10 (9)	0.46
Because of adverse event related to treatment	5 (5)	0	0.06

*The safety population included all patients who underwent randomization and received at least one dose of trial treatment.
†P values were calculated with the use of Fisher's exact text.

- Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were reported in 1%, 2%, and 9% of patients, respectively, in the ^{177}Lu-Dotatate group versus no patients in the control group

Lu, lutetium.

Strosberg, et al. N Engl J Med 2017;376:125-35.

NETTER-1: SUMMARY

NETTER-1 suggests treatment with ^{177}Lu-DOTATATE plus Octreotide LAR 30 mg compared to Octreotide LAR 60 mg in advanced midgut neuroendocrine tumours:-

- Significantly prolonged PFS, HR 0.209 [95% CI 0.13 – 0.33]
- Improved OS in interim analysis, HR 0.40
- Improved time to deterioration for global health status (QoL), HR 0.41 [95% CI 0.24 – 0.69]

CI, confidence interval; HR, hazard ratio; LAR, long acting release; Lu, lutetium; OS, overall survival; PFS, progression free survival; QoL, quality of life.

Strosberg, et al. N Engl J Med 2017;376:125-35.

STUDY A6181111:
A PHASE 3, PLACEBO CONTROLLED STUDY OF SUNITINIB IN PATIENTS WITH ADVANCED, WELL-DIFFERENTIATED PANCREATIC NEUROENDOCRINE TUMOURS

Raymond, E et al. N Engl J Med 2011;364(6):501-13

STUDY A6181111: BACKGROUND & RATIONALE

- Treatment for panNETs has focussed on surgery as the main treatment, LDT for palliation of metastases and SSAs to relieve symptoms from hormone hypersecretion in functioning tumours

- Streptozocin alone or with doxorubicin has been the only approved chemotherapeutic option for patients with advanced panNETs

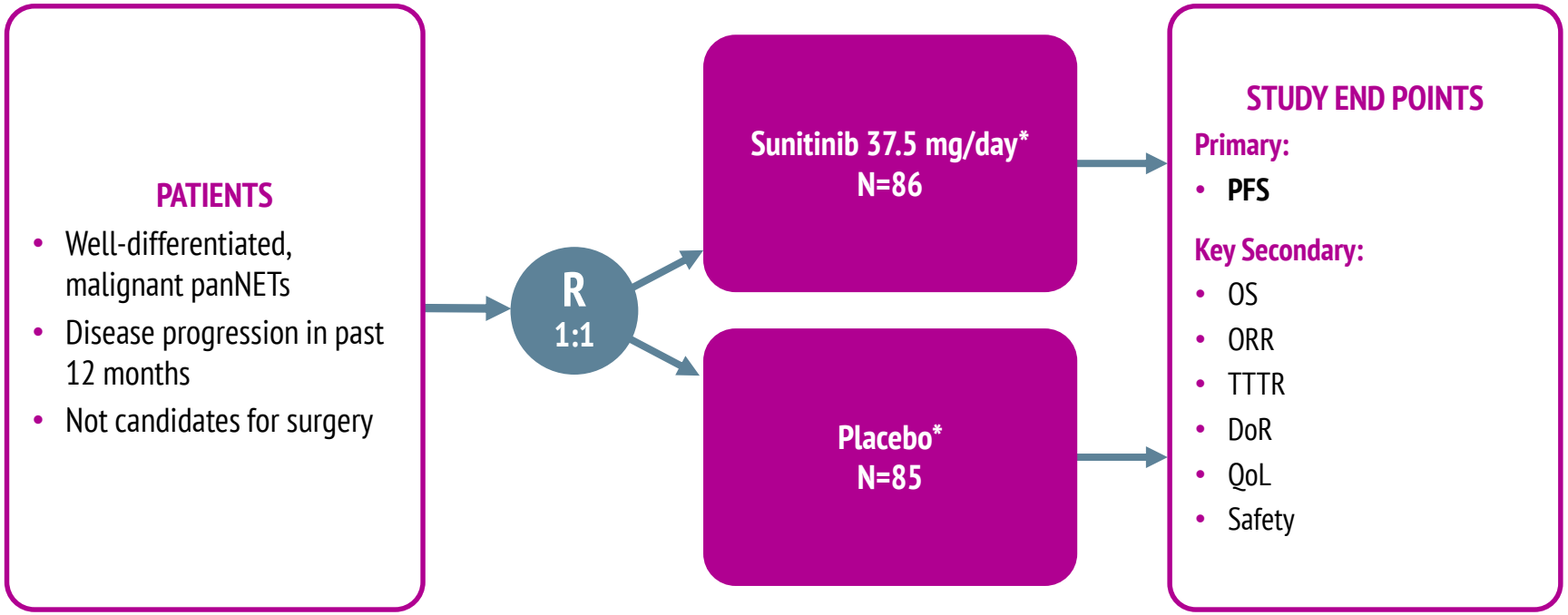
- Study A6181111 investigated whether inhibiting VEGFR and PDGFR signalling with sunitinib would have a clinical benefit for patients with advanced panNETs

LDT, liver directed therapy; panNETs, pancreatic neuroendocrine tumours; PDGFR, platelet derived growth factor receptor; SSA, somatostatin analogues; VEGFR, vascular endothelial growth factor receptor

Raymond, E et al. N Engl J Med 2011;364(6):501-13

STUDY A6181111 : STUDY DESIGN

Patient population: well-differentiated pancreatic neuroendocrine tumours that were advanced, metastatic or both



*with best supportive care. SSA were permitted

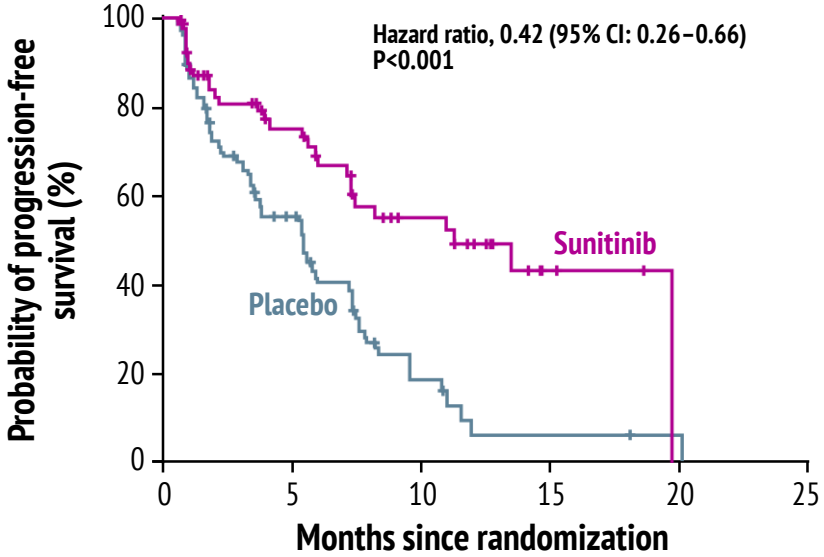
DoR, duration of response; ORR, objective response rate; OS, overall survival; panNETs, pancreatic neuroendocrine tumours; PFS, progression-free survival; QoL, Quality of Life; R, randomisation; TTTR, time to tumour response

Raymond, E et al. N Engl J Med 2011;364(6):501-13.

STUDY A6181111

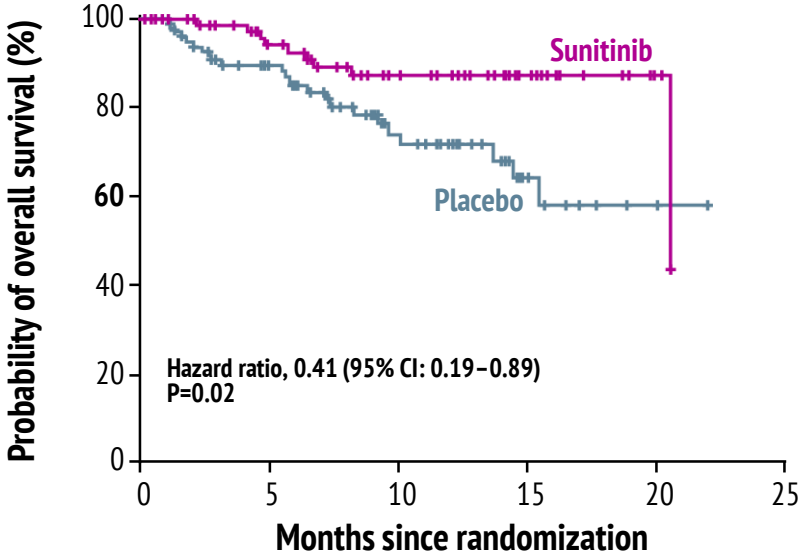
SUNITINIB VS PLACEBO IN PANCREATIC NET

PRIMARY ENDPOINT: PFS



No. at risk						
Sunitinib	86	39	19	4	0	0
Placebo	85	28	7	2	1	0

SECONDARY ENDPOINT: OS



No. at risk						
Sunitinib	86	60	38	16	3	0
Placebo	85	61	33	12	3	0

- A median PFS of 11.4 months was observed with sunitinib compared to 5.5 months with placebo

CI, confidence interval; NET, neuroendocrine tumour; PFS, progression free survival; OS, overall survival.

Raymond, E et al. N Engl J Med 2011;364(6):501-13.

STUDY A6181111: EFFICACY

OBJECTIVE TUMOUR RESPONSE

Response Category	Sunitinib (N=86)	Placebo (N=85)	P Value
Best observed RECIST response – no. (%)			
Complete response	2 (2)	0	
Partial response	6 (7)	0	
Stable disease	54 (63)	51 (60)	
Progressive disease	12 (14)	23 (27)	
Could not be evaluated	12 (14)	11 (13)	
Objective response rate (%)	9.3	0	0.007

QUALITY OF LIFE

- No overall difference between treatment arms in global health related quality of life

RECIST, response evaluation criteria in solid tumours

Raymond, E et al. N Engl J Med 2011;364(6):501-13.

STUDY A6181111: SAFETY

OVERVIEW OF ADVERSE EVENTS (SAFETY POPULATION)

Event	Sunitinib (N=83)			Placebo (N=82)		
	All grades	Grade 1 or 2	Grade 3 or 4	All grades	Grade 1 or 2	Grade 3 or 4
	Number of patients (%)					
Most common adverse events associated with sunitinib treatment (≥ 30% patients)						
Diarrhoea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Most common grade 3 or 3 adverse events in patients receiving sunitinib						
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)

- SAEs were reported in 26% of patients treated with sunitinib and 41% of patients in the placebo group
  - the DSMC recommended termination after a third unplanned interim analysis, after observation of more deaths and serious adverse events in the placebo arm of the study
- Findings for thyroid function were consistent with those reported previously for sunitinib

DSMC, data and safety monitoring committee; SAEs, serious adverse events

Raymond, E et al. N Engl J Med 2011;364(6):501-13.

STUDY A6181111: SUMMARY

Study A6181111 suggests treatment with sunitinib 37.5 mg compared to placebo in pancreatic neuroendocrine tumours:-

- Significantly prolonged PFS, HR 0.42 [95% CI 0.26 – 0.66]
- Improved OS in interim analysis, HR 0.41 [95% CI 0.19 – 0.89]
- QoL analysis did not attain a significant difference

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression free survival; QoL, quality of life

Raymond, E et al. N Engl J Med 2011;364(6):501-13.

TELESTAR:
A PHASE 3, PLACEBO CONTROLLED STUDY OF TELOTRISTAT ETHYL IN PATIENTS WITH CARCINOID SYNDROME

Kulke, et al. JCO 2017;35:14-23

TELESTAR: BACKGROUND & RATIONALE

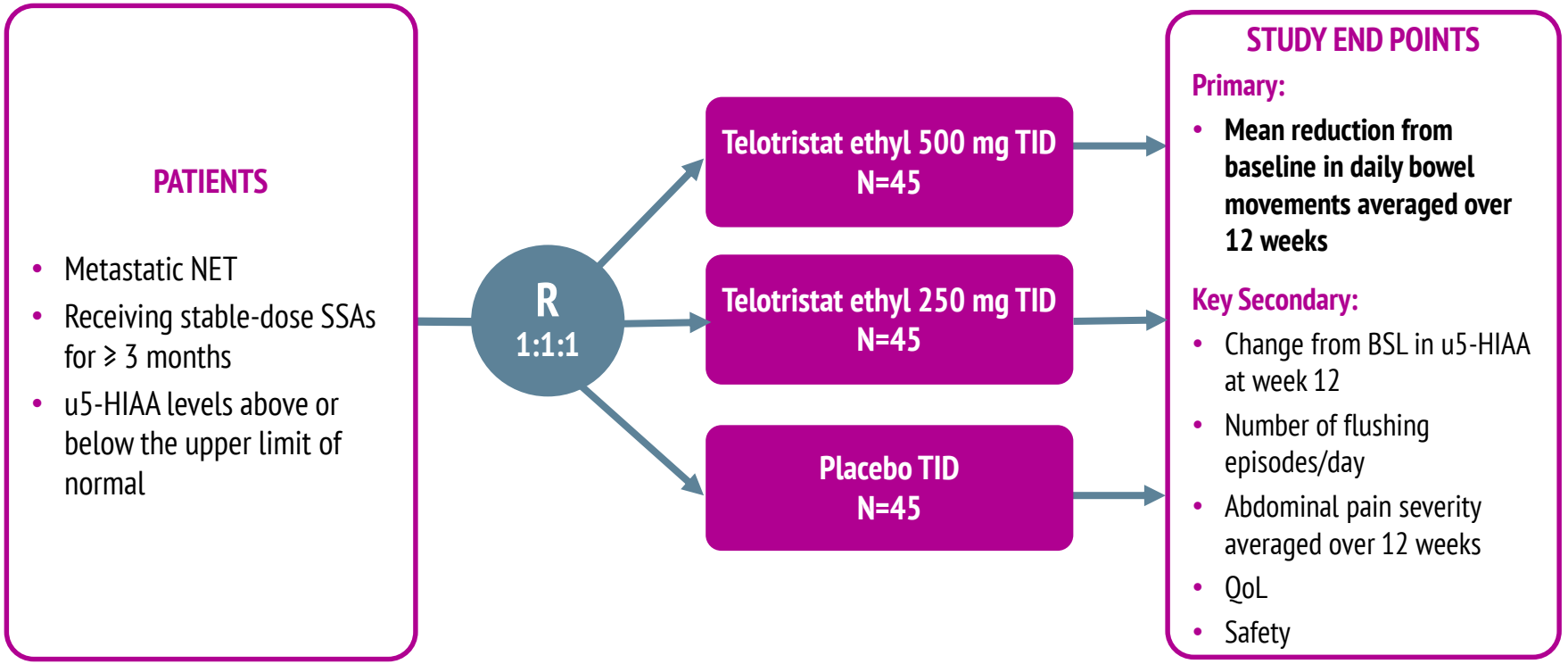
- Patients with advanced neuroendocrine tumours may develop carcinoid syndrome due to tumour secretion of serotonin
- High systemic serotonin levels, as reflected by elevated urinary 5-HIAA (u5-HIAA), most often in the setting of wide- spread tumour metastases, are associated with severe carcinoid syndrome, carcinoid heart disease, and poor prognosis
- Telotristat Ethyl is a tryptophan hydroxylase inhibitor, the rate-limiting enzyme in serotonin synthesis, that fails to penetrate the blood-brain barrier
- TELESTAR investigates the safety and efficacy of Telotristat Ethyl in patients with carcinoid syndrome not adequately controlled with somatostatin analogue therapy

u5-HIAA, urinary 5-hydroxyindoleacetic acid

Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

TELESTAR : STUDY DESIGN

Patient population: well-differentiated metastatic NET patients with carcinoid syndrome



- At end of 12 week double-blind period, patients received telotristat ethyl 500 mg during an open-label extension

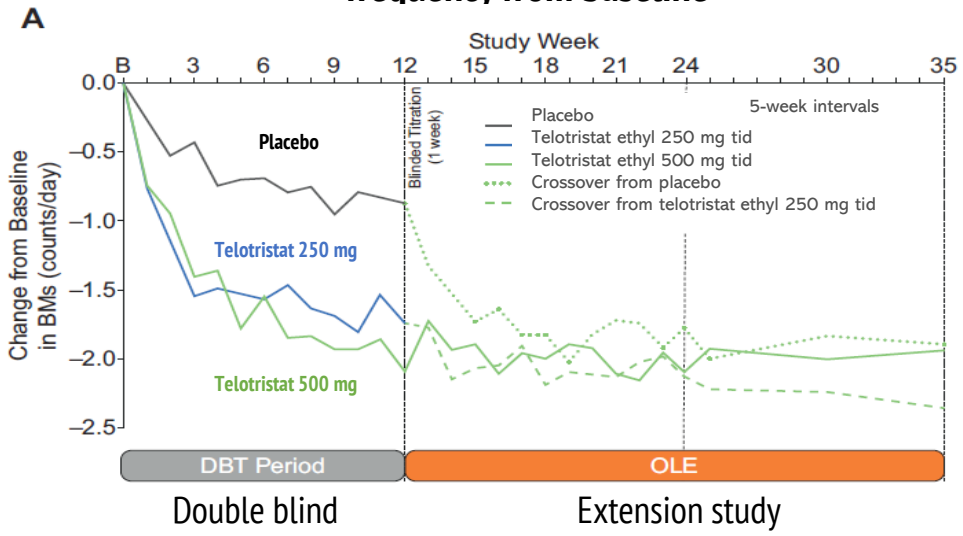
BSL, baseline; NET, neuroendocrine tumours; QoL, Quality of Life; R, randomisation; SSA, somatostatin analogues; TID, three times per day; u5-HIAA, urinary 5-hydroxyindoleacetic acid

Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

TELESTAR STUDY

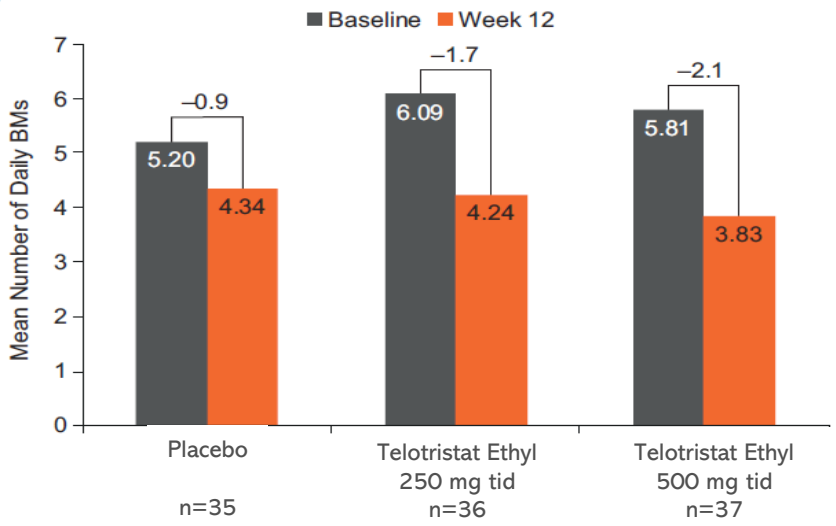
PRIMARY ENDPOINT: MEAN REDUCTION FROM BASELINE IN DAILY BOWEL MOVEMENTS AVERAGED OVER 12 WEEKS.

Reduction in mean daily BM frequency from baseline



- Placebo; n=35
- Telotristat ethyl 250 mg; n=36
- Telotristat ethyl 500 mg; n=37

Mean daily BM frequency at baseline and week 12



44 and 42% patients treated with Telotristat (250 mg and 500 mg respectively) had a durable benefit

(≥ 30% Reduction of diarrhea for ≥ 50% of the double-blind study period)

BM, bowel movement; DBT, double blind treatment; OLE, open-label extension; TID, three times per day

Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

TELESTAR: SAFETY

OVERVIEW OF ADVERSE EVENTS IN DBT PERIOD

Category, N (%)	Placebo TID (N=45)	Telotristat ethyl 250 mg TID (N=45)	Telotristat ethyl 500 mg TID (N=45)
Any TEAE	39 (86.7)	37 (82.2)	42 (93.3)
Study discontinuation as a result of TEAE*	6 (13.3)	3 (6.7)	3 (6.7)
TEAE resulting in death‡	3 (6.7)	1 (2.2)	1 (2.2)
AEs related to investigations			
Increased gamma-glutamyl transferase	0	4 (8.9)	4 (8.9)
Increased alanine aminotransferase	0	1 (2.2)	3 (6.7)
Increased alkaline phosphatase	0	0	3 (6.7)

*TEAEs leading to study discontinuation were anaemia, cardia arrest, nausea, vomiting, eructation, dyspepsia, chills, fatigue, general health deterioration, dehydration, disease progression, sepsis, rash and increased GGT

‡ All deaths occurred in the setting of advanced metastatic disease

AEs, adverse events; DBT, double blind treatment; GGT, gamma-glutamyl transferase; TEAE, treatment emergent adverse event; TID, three times per day

Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

TELESTAR: SAFETY

OVERVIEW OF ADVERSE EVENTS IN DBT PERIOD

Selected AE's occurring in ⩾ 5% of patients in any study arm, by preferred term; N(%)	Placebo TID (N=45)	Telotristat ethyl 250 mg TID (N=45)	Telotristat ethyl 500 mg TID (N=45)
Nausea	5 (11.1)	6 (13.3)	14 (31.1)
Abdominal pain	8 (17.8)	5 (11.1)	10 (22.2)
Vomiting	4 (8.9)	2 (4.4)	5 (11.1)
Abdominal distension	3 (6.7)	2 (4.4)	1 (2.2)
Diarrhoea	3 (6.7)	3 (6.7)	0
Dyspepsia	3 (6.7)	1 (2.2)	1 (2.2)
Fatigue	4 (8.9)	4 (8.9)	7 (15.6)
Nasopharyngitis	1 (2.2)	2 (4.4)	3 (6.7)
Pneumonia	0	0	3 (6.7)
Decreased appetite	2 (4.4)	3 (6.7)	7 (15.6)
Hypokalemia	3 (6.7)	3 (6.7)	5 (11.1)
Headache	2 (4.4)	5 (11.1)	4 (8.9)
Dizziness	2 (4.4)	0	4 (8.9)
Memory impairment	3 (6.7)	0	1 (2.2)
Depression-related	3 (6.7)	3 (6.7)	7 (15.6)
Confusional state	0	0	3 (6.7)
Dyspnea	0	2 (4.4)	4 (8.9)
Cough	1 (2.2)	1 (2.2)	3 (6.7)
Flushing	2 (4.4)	3 (6.7)	3 (6.7)

AEs, adverse events; DBT, double blind treatment; TID, three times per day. Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

TELESTAR: QOL

QoL was investigated using EORTC QLQ-C30 scores averaged during the treatment period

- No overall differences in the global health status subscale were observed between treatment arms
- Diarrhoea subscale scores, on a scale of 0 to 100, improved by:
  - 19.2 points in the 250 mg telotristat ethyl group (p=0.039)
  - 21.6 points in the 500 mg telotristat ethyl groups (p=0.051)
  - 8.5 points in the placebo group

EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL, quality of life

Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

TELESTAR: SUMMARY

TELESTAR suggests treatment with telotristat ethyl 250mg or 500mg compared to placebo in metastatic neuroendocrine tumours, resulted in:

- Significant reductions in bowel movements
- No overall differences in the global health status subscale
- Improved QoL through significantly lower EORTC QLQ-C30 diarrhoea subscale scores.

EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL, quality of life

Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

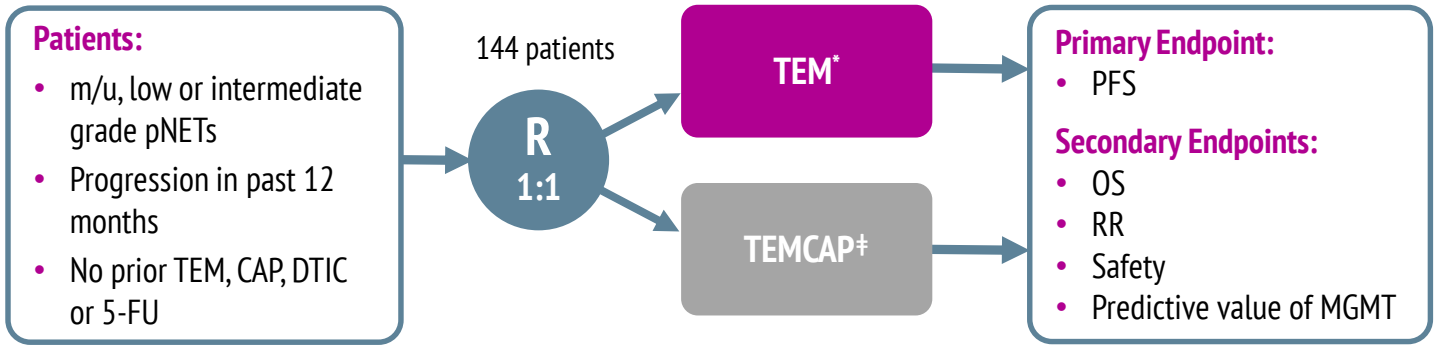
PRELIMINARY DATA FROM OTHER KEY TRIALS

ECOG-ACRIN (E2211): A PHASE 2 STUDY OF TEMOZOLOMIDE OR TEMOZOLOMIDE AND CAPECITABINE IN PATIENTS WITH ADVANCED PANCREATIC NEUROENDOCRINE TUMOURS

KUNZ, et al. ASCO 2018 ABSTRACT #4004

ECOG-ACRIN (E2211): STUDY DESIGN

ADVANCED PANCREATIC NET PATIENTS



*Temozolomide (200 mg/m^2 PO QD days 1-5)

‡Temozolomide (200 mg/m^2 PO QD days 10-14) plus capecitabine (750 mg/m^2 PO BID days 1-14)

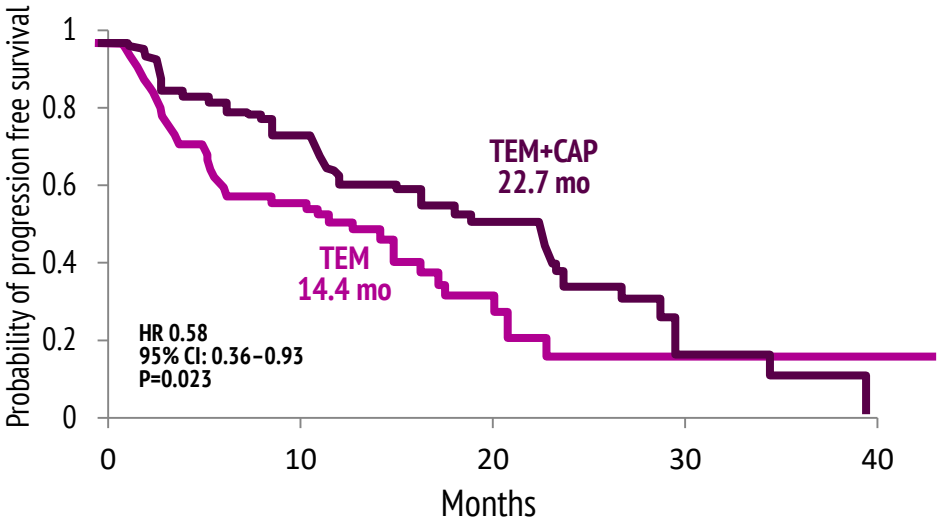
5-FU, 5-fluorouracil; ACRIN, American College of Radiology Imaging; CAP, capecitabine; DTIC, dacarbazine; ECOG, Eastern Cooperative Oncology Group; MGMT, O6-methylguanine DNA methyltransferase; m/u, metastatic or unresectable; OS, overall survival; PO, by mouth; PFS, progression free survival; pNETs, pancreatic neuroendocrine tumours; QD, every day; R, randomised; RR, response rate; TEM, temozolomide

Kunz, PL et al. ASCO 2018 Abstract #4004

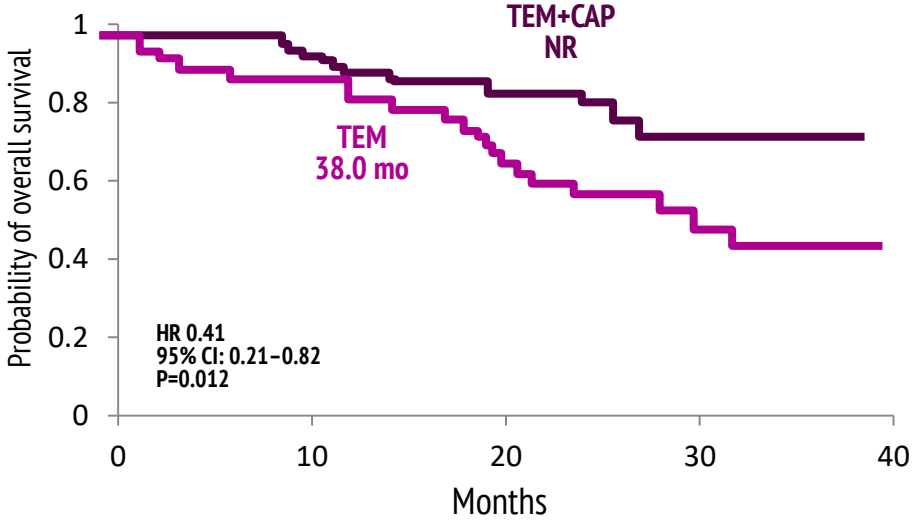
ECOG-ACRIN STUDY (E2211)

TEMOZOLOMIDE VS TEMOZOLOMIDE + CAPECITABINE IN PANCREATIC NET

PRIMARY ENDPOINT: PFS



SECONDARY ENDPOINT: OS



CAP, capecitabine; CI, confidence interval; NR, not reached; OS, overall survival; PFS, progression free survival; TEM, temozolomide

Kunz, PL et al. ASCO 2018 Abstract #4004

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

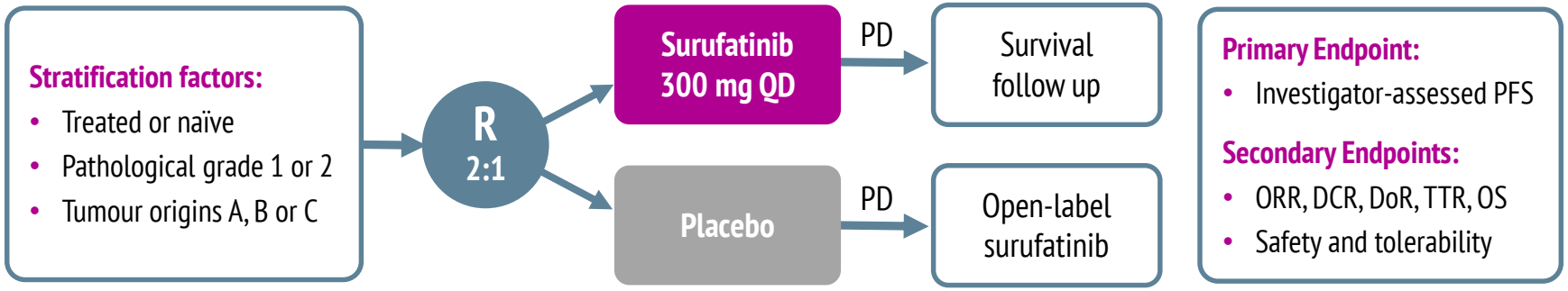
Xu, et al. ESMO 2019 Abstract #LBA76

NETs, neuroendocrine tumours

SANET-ep STUDY DESIGN

PROGRESSIVE ADVANCED EXTRA-PANCREATIC NET PATIENTS

198 patients randomised at time of interim analysis



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

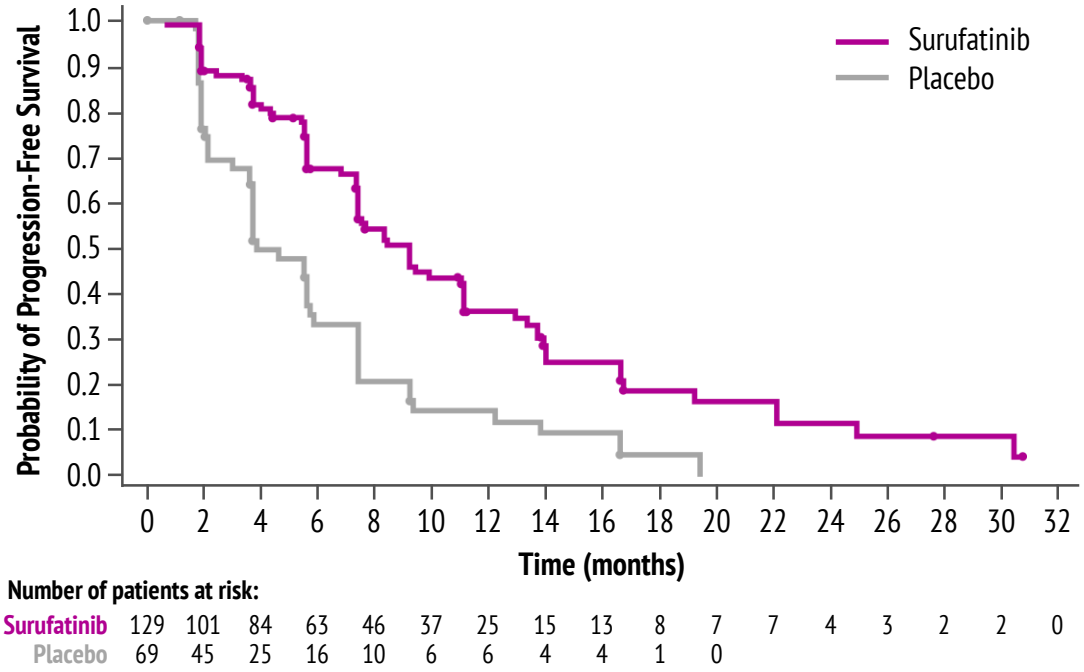
DCR, disease control rate; DoR, duration of response; NET, neuroendocrine tumours; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TTR, time to tumour response

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)



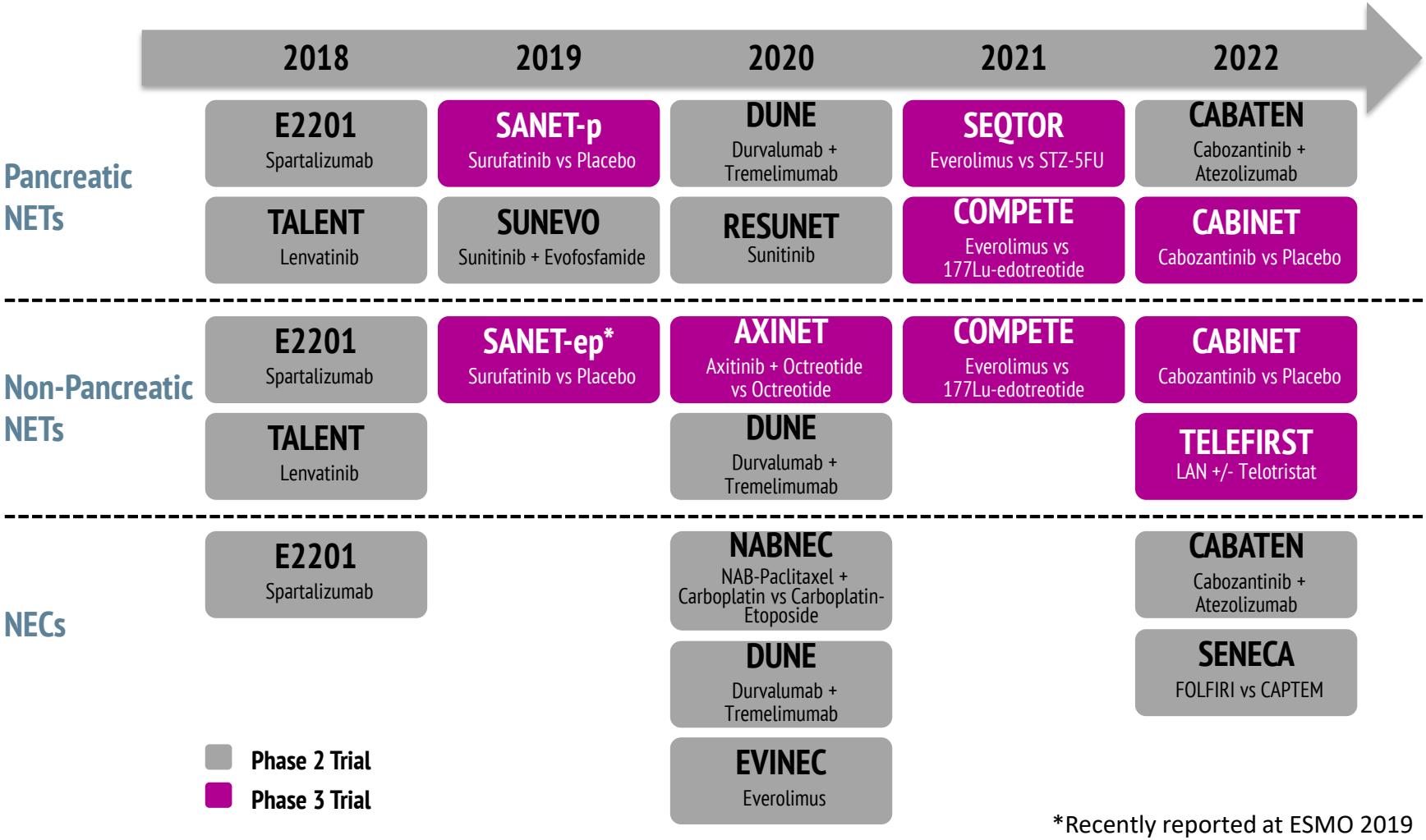
	surufatinib (N=129)	placebo (N=69)
Median PFS, months. (95% CI)	9.2 (7.4-11.1)	3.8 (3.7-5.7)
HR (95% CI)	0.334 (0.223-0.499)	
Stratified p-value < 0.0001		

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

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

FUTURE PRACTICE CHANGING TRIALS IN NET?

OVERVIEW OF KEY ON-GOING CLINICAL TRIALS IN NETS



*Recently reported at ESMO 2019

Presented by Dr. Enrique Grande, ESMO 2019

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