Gastric NETs

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10ο Πειραϊκό Συνέδριο 02/11/19

NET: Wide Spectrum of Malignancies

NET arise from neuroendocrine cells throughout the body

Pancreatic NET
(formerly called islet cell tumors[a])

Functional (<10%)

- Gastrinoma
- Insulinoma
- Glucagonoma
- VIPoma
- Somatostatinoma

Nonfunctional (~60-90%)

Carcinoid tumors (other NET)

Foregut

- Lungs
- Stomach
- Duodenum

Midgut

- Jejunum
- Ileum
- Transverse, right colon
- Appendiceal

Hindgut

- Left, sigmoid colon
- Rectum

Additional Sites

- Ovary
- Medulla
- Adrenal medulla
- Paraganglia

Unknown Primary

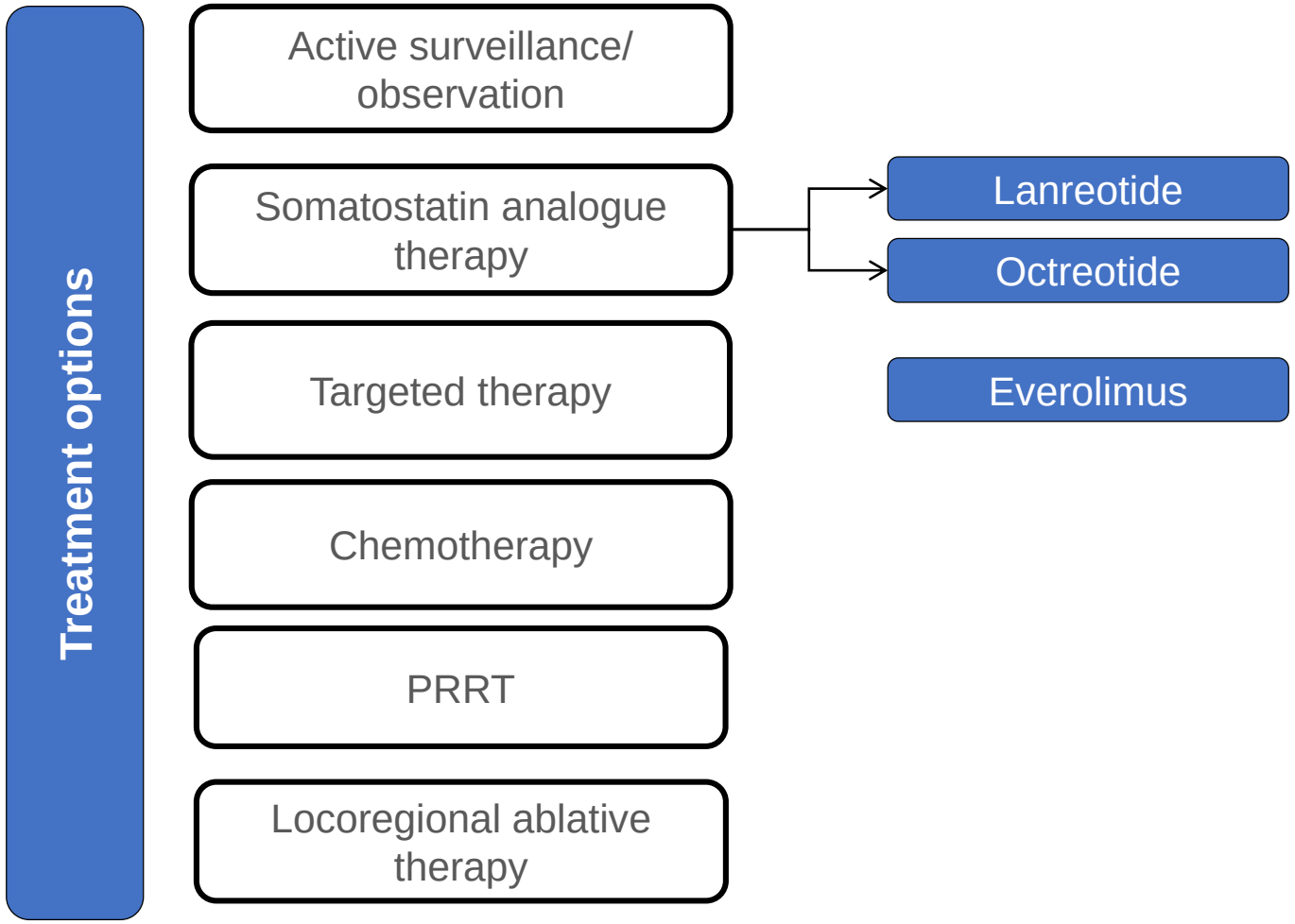
Introduction

- NETs are most frequently located in the digestive tract (68%) and broncho-pulmonary area (25%)
- NETs are relatively rare
  - Estimated overall incidence in the US is 5.25 cases per 100,000 people
- Most NET are slow-growing
- High index of suspicion needed
- Most GEPNETs are non-functioning and present with mass effects of the primary tumour or metastases – usually liver
- Diagnosis often delayed for years

Therapeutic challenges in NETs

- Extremely heterogeneous group
- Few randomised trials in the field
- Rare neoplasms- require international efforts
- Until 2011 no new drugs approved for 20 years
- No predictive biomarkers so far for better patient selection

Treatment options available for the management of patients with unresectable, advanced GEP-NETs



Key factors influencing treatment decisions

Tumour grade (Ki-67)	• High grade/low grade • Progressive or stable disease – Pace of progression

Tumour stage	• Extent/burden of disease
	  – Localised or metastatic disease
	  – Low tumour burden/high tumour burden

Tumour functionality	• Functional tumour • Non-functional tumour

Key factors influencing treatment decisions

Patient Factors	• Comorbidities • Performance status • Patient preference
Geography	• Multidisciplınary board availability • Access to drugs and techniques

Treatment decisions: criteria for choosing treatment for advanced NETs

Criteria for choosing somatostatin analogues	• Functional tumours • Low-volume disease • G1 and subset of G2 (Ki-67 <10%) • Non-progressive disease • **Aim is to delay time to disease progression**
Criteria for choosing targeted therapies	• Moderate–low volume disease • G1/G2 tumours (Ki-67 <20%) • Moderate-low rate of disease progression • **Aim is to delay time to disease progression**
Criteria for choosing chemotherapy	• Bulky disease/high volume disease • More rapid disease progression • G2/G3 tumours (occasionally G1 tumours) • **Response required**

WHO Pathological classification -revised 2017

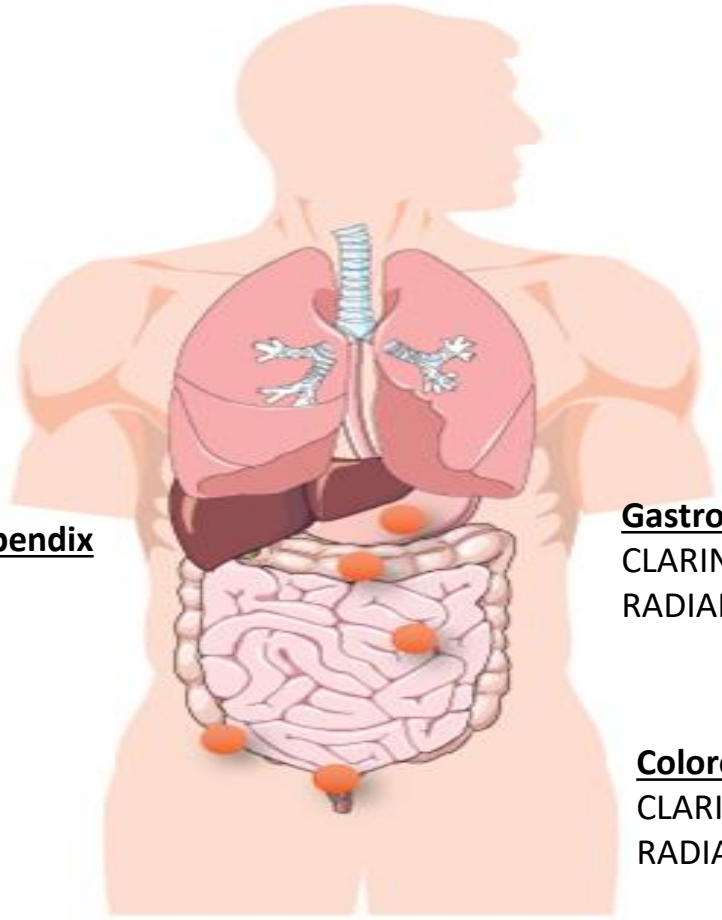
Table 1 World Health Organization's classification of neuroendocrine tumors [2010]

Grade	Mitotic rate (/10 HPF)	Ki-67 index (%)	5 yr survival
NET G1 (low grade)	<2	≤2	96%
NET G2 (intermediate grade)	2–20	3–20	73%
NEC G3 (high grade)	>20	>20	23%

Neuroendocrine neoplasm	Morphology (differentiation)	Grading G1-G3 (Ki-67 index in %)	Abbreviation
Neuroendocrine tumor Grade 1	Well-differentiated	G1 (≤2%)	NET G1
Neuroendocrine tumor Grade 2	Well-differentiated	G2 (3–20%)	NET G2
Neuroendocrine tumor Grade 3	Well-differentiated	G3 (>20%)	NET G3
Neuroendocrine carcinoma	Poorly-differentiated (large or small cell)	G3 (>20%)	NEC

Focus on GI NET

Small intestine/appendix
PROMID
CLARINET
RADIANT-4
NETTER-1



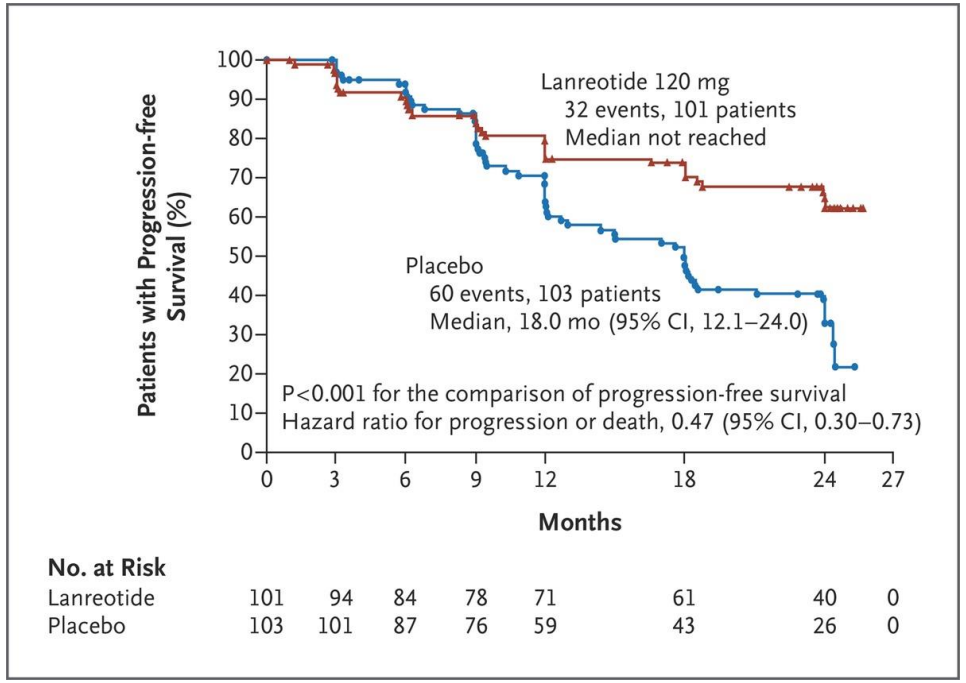
Gastroduodenal
CLARINET
RADIANT-4

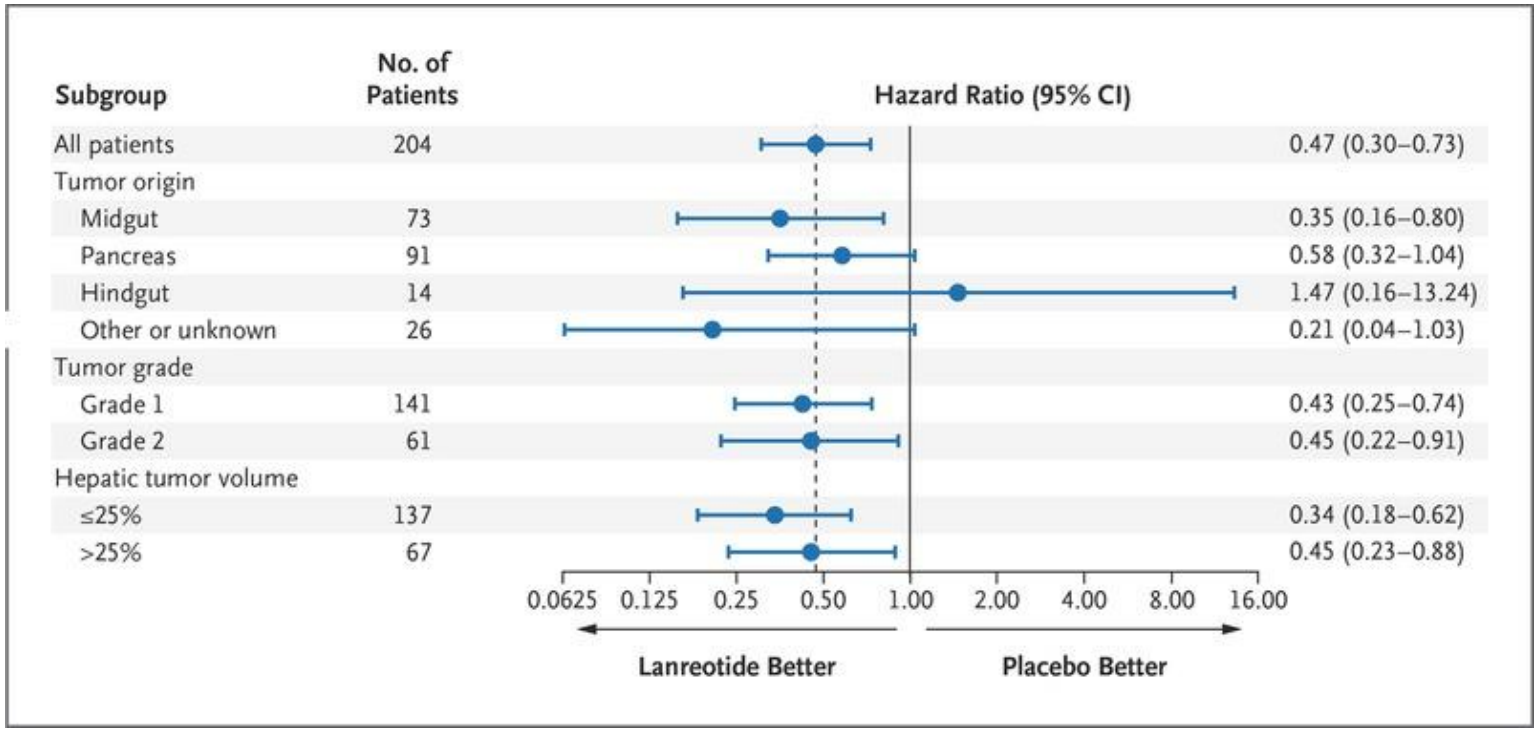
Colorectal
CLARINET
RADIANT-4

CLARINET

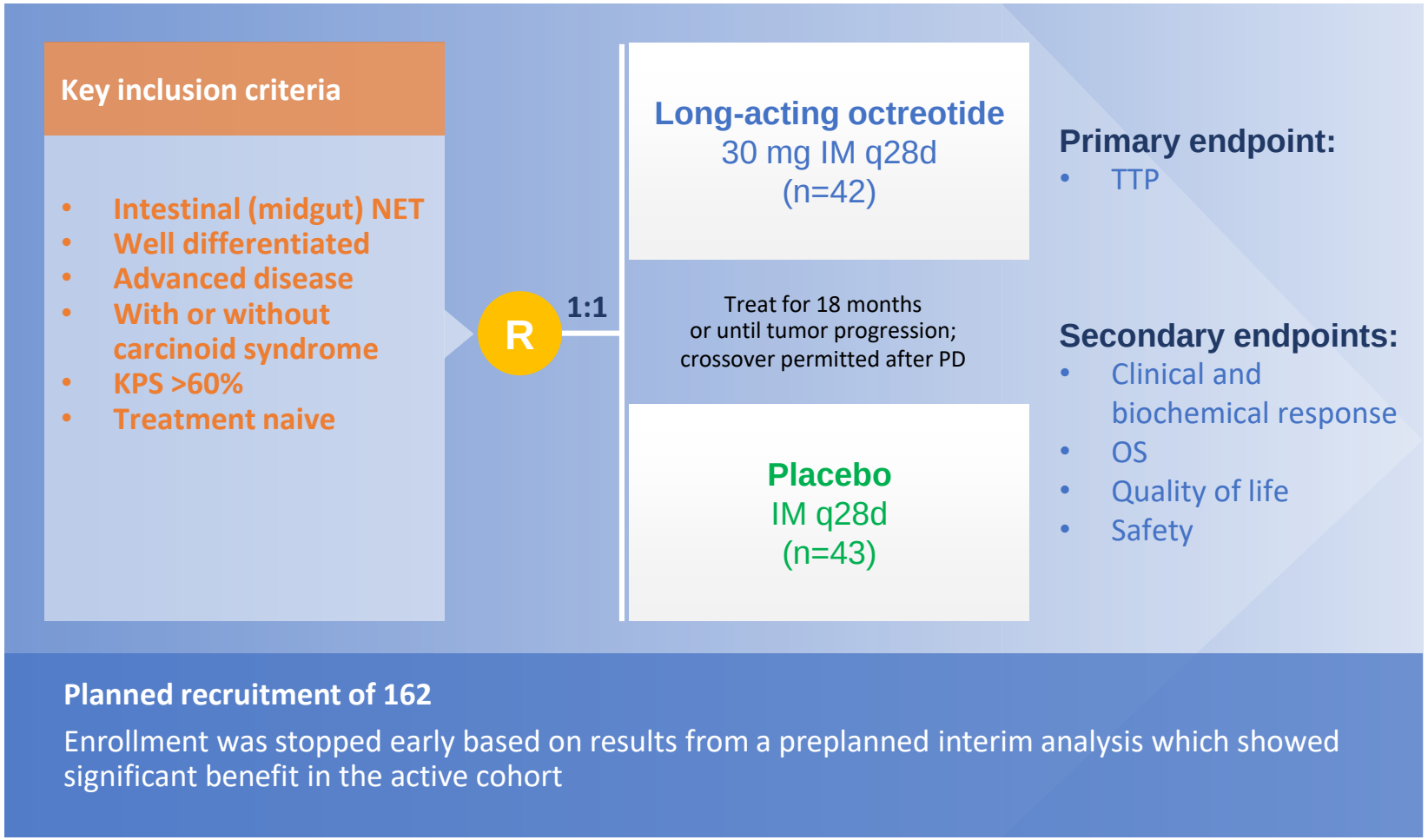
- Phase 3
- 204 pt non functioning GEP NETs
- Well/moderately differentiated
- Lanreotide 120mg Q28d vs Placebo
- 81% treatment-naive

Caplin *et al* NEJM 2014





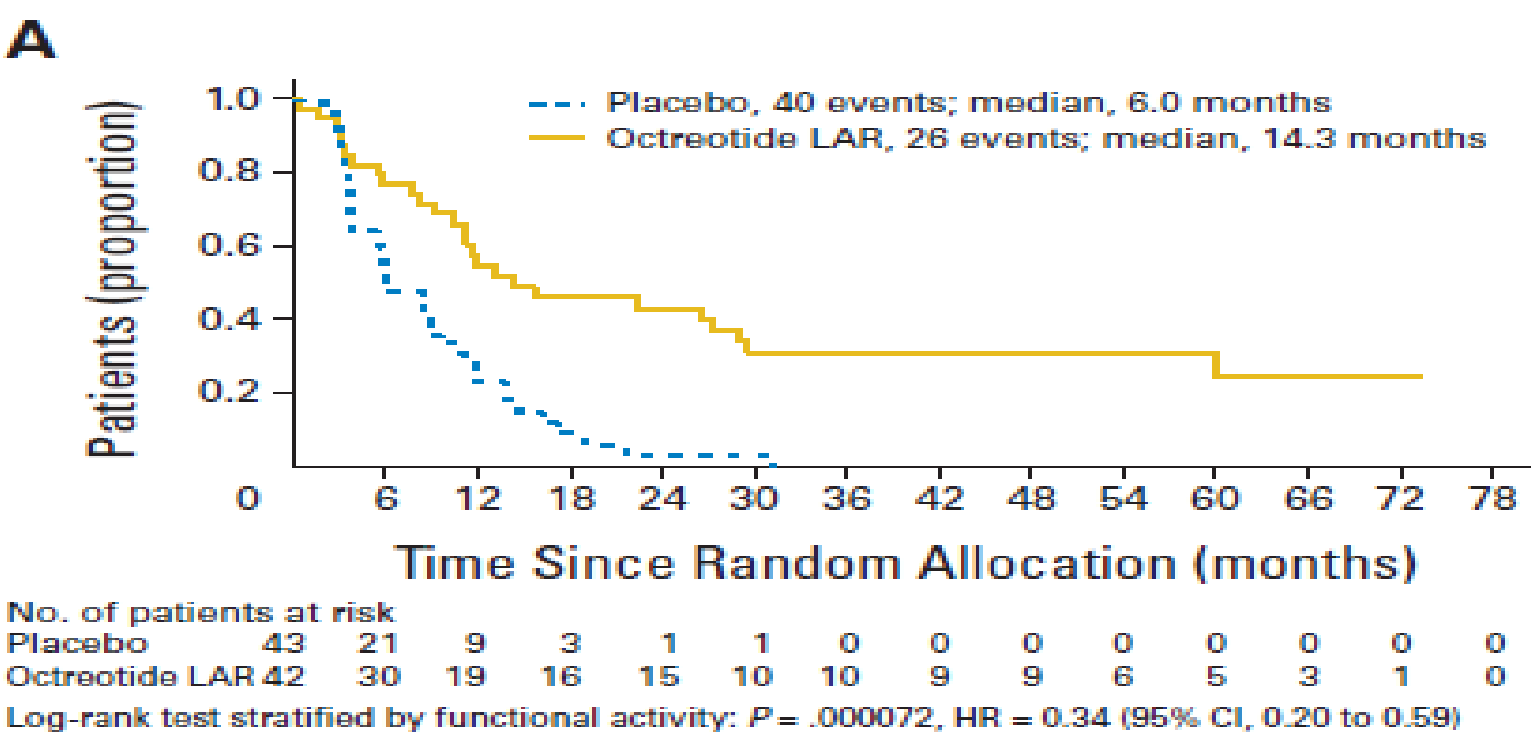
PROMID: Evaluation of the antiproliferative effect of octreotide LAR



KPS, Karnofsky performance status; PD, progressive disease; q28d, every 28 days; TTP, time to tumor progression.
Rinke A et al. *J Clin Oncol*. 2009;27:4656-4663.

PROMID: Octreotide LAR 30 mg significantly extends TTP compared to placebo

66% reduction in the risk of tumor progression[1]

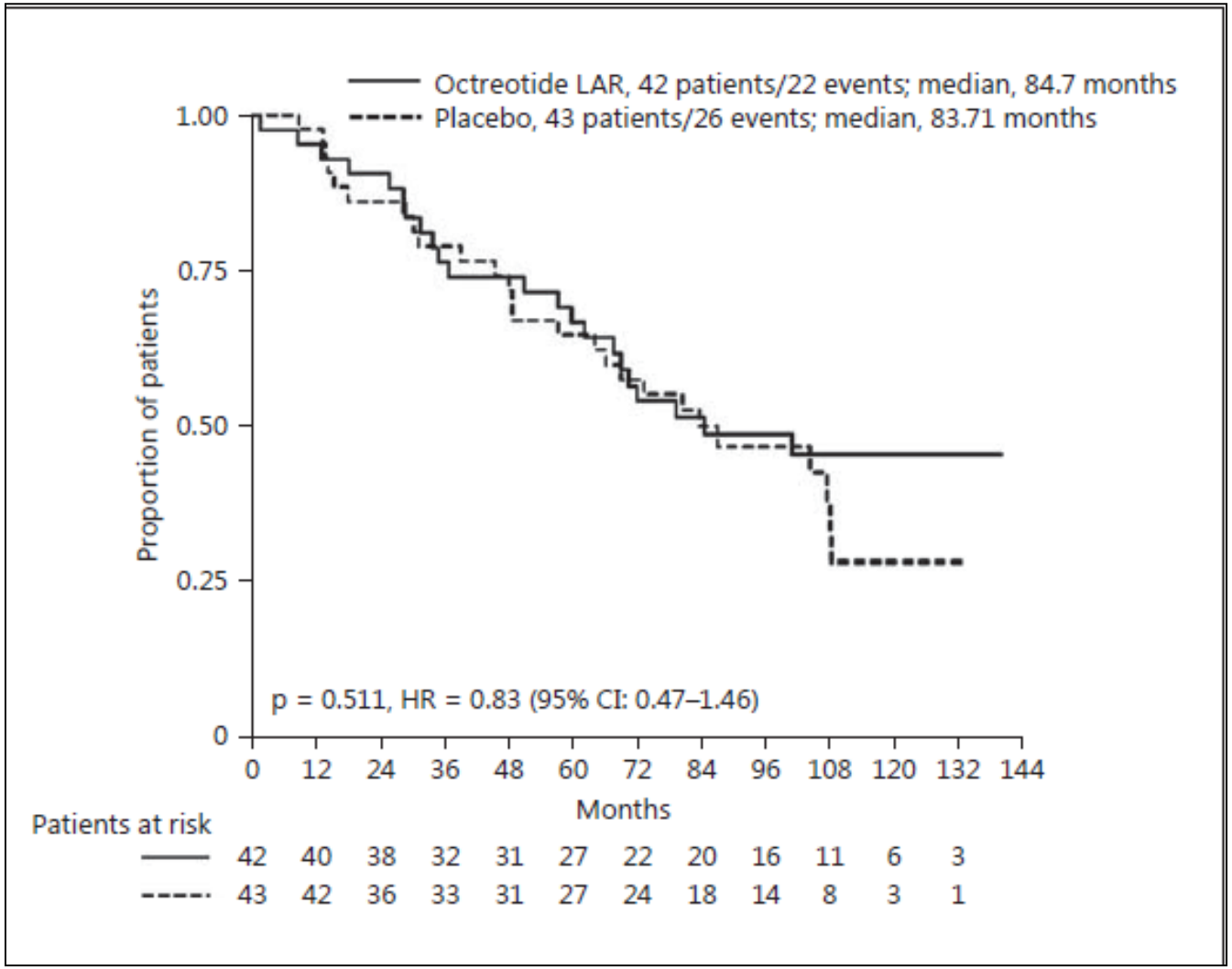


HR, hazard ratio.

Rinke A et al. *J Clin Oncol*. 27(28), 2009:4656-4663.

PROMID: Final OS by Treatment

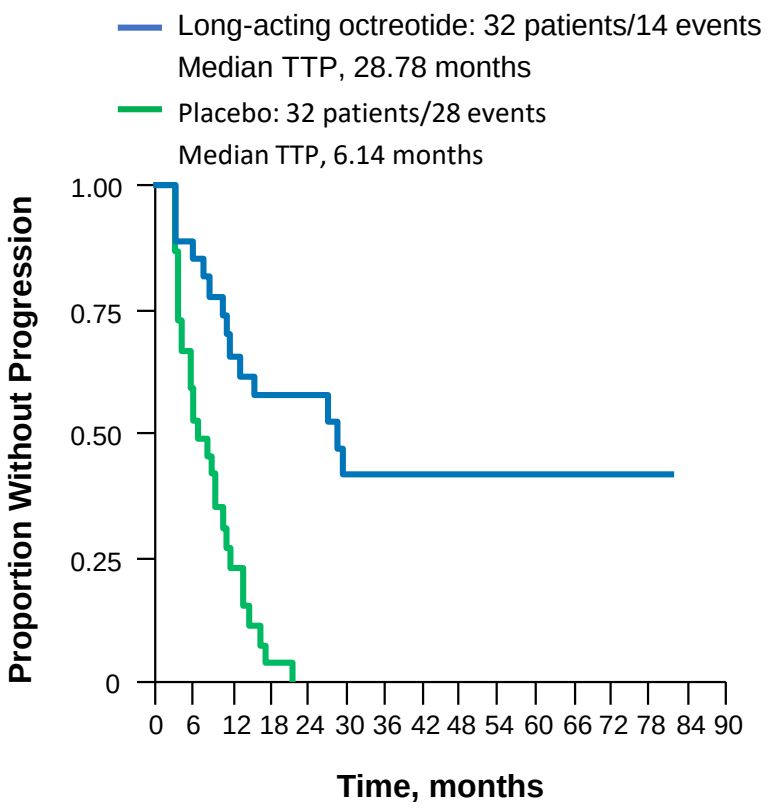
Upon disease progression, 38 out of 43 placebo patients (88.4%) received octreotide LAR



Rinke A et al. *Neuroendocrinology*. 2017;104:26-32

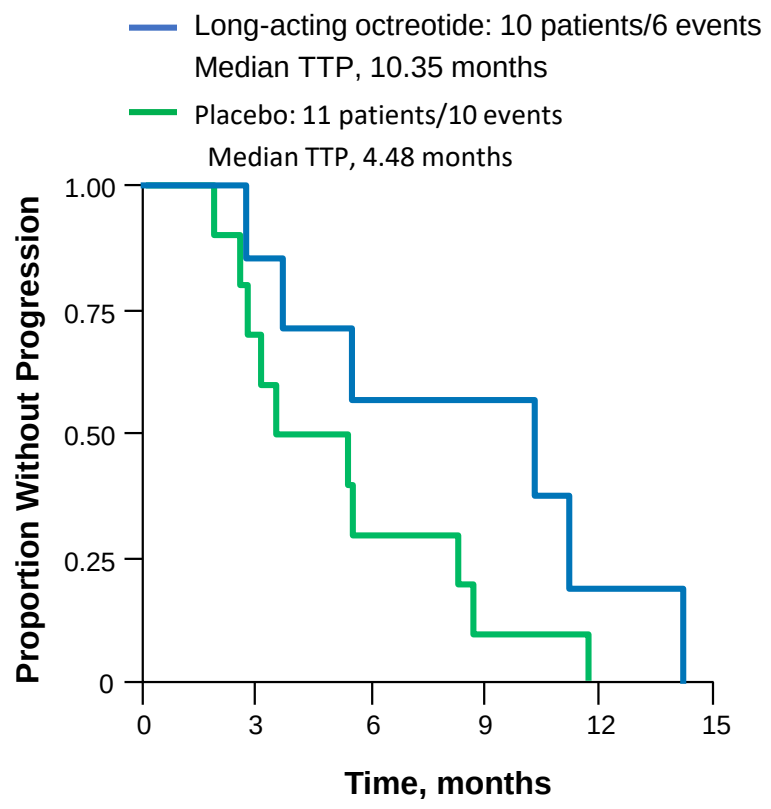
PROMID: TTP Subgroup Analysis By Hepatic Tumor Load

Patients with tumor load ≤10%



HR: 0.21 (95% CI: 0.10-0.44) *P*<0.0001

Patients with tumor load >10%



HR: 0.45 (95% CI: 0.15-1.35) *P*=0.1381

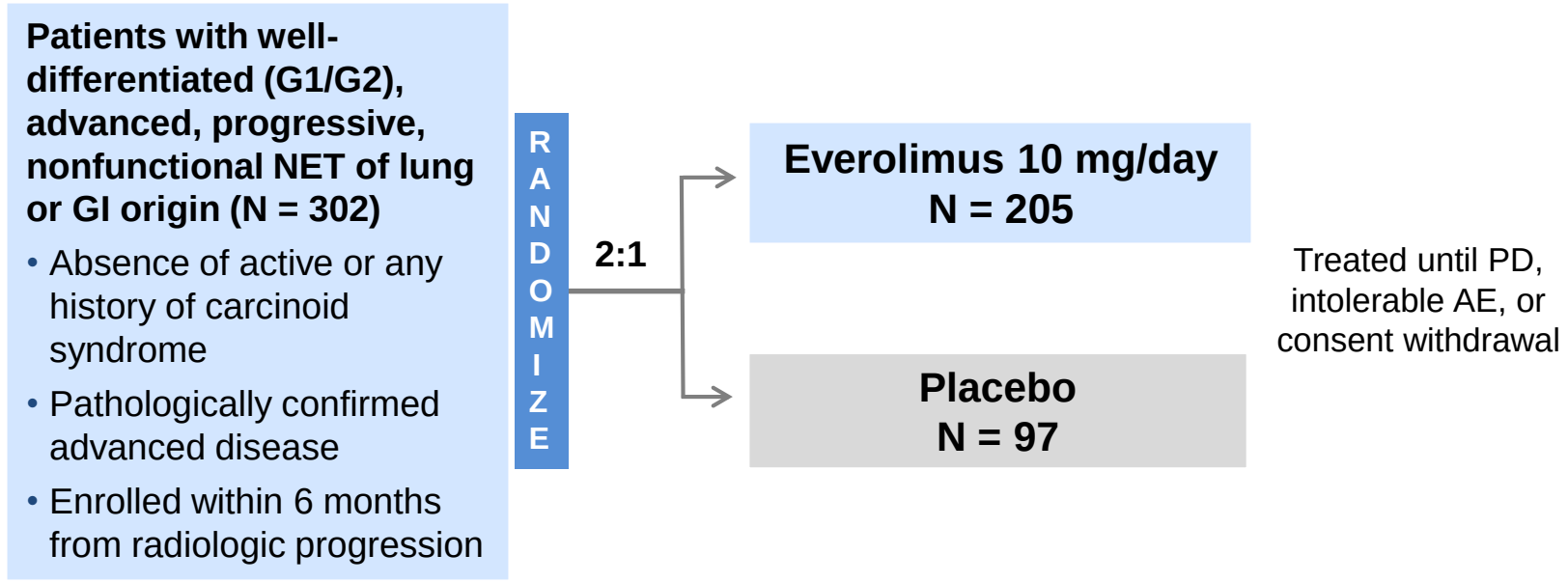
1. Arnold R et al. Presented at: ASCO 2009 Annual Meeting; May 29-June 2, 2009; Orlando, FL. Abstract 4508.
2. Rinke A et al. J Clin Oncol 2009;27:4656–4663

Clinical trials results confirm the antitumor activity of SSAs in NETs of GI origin

	PROMID[1]	CLARINET[2]
Somatostatin analogue	Octreotide	Lanreotide
N	85	204[3]
Population	Midgut **(No pNET)**	All GEP **(45% pNET)**
Functional status	Functional or Nonfunctional	Nonfunctional
Progression status at baseline?	Unknown	96% stable disease
Prior therapy received	0%	16%
Tumour grade 1	95% (Ki-67 <2%)	69% (Ki-67 ≤2%)
Tumour grade 2	5% (Ki-67 20%)	30% (Ki-67 <10%)
Time since diagnosis (median)	7.5 mos (Oct)/ 3.3 mos (placebo)[3]	13.2 mos (Lan)/ 16.5 mos (placebo)[3]
Primary endpoint	TTP (WHO)[3]	PFS (RECIST)[3]
Hepatic tumour volume	≤10%	≤25% (137); ≥25% (67)

1. Rinke A *et al. J Clin Oncol* 2009;27:4656–4663; 2. Caplin ME *et al*. *N Engl J Med* 2014;371:224–233;

RADIANT-4 Study Design



Endpoints:

- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:

- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** – lung, stomach, rectum, and colon except caecum.
Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

Yao JC et al. *Lancet*. 2016;387:968-977.

RADIANT-4: Baseline and Disease Characteristics (1/2)

Characteristic	Everolimus N = 205	Placebo N = 97
Age, median (range)	65 (22 – 86)	60 (24 – 83)
Male / female	43% / 57%	55% / 45%
WHO performance status		
0 / 1	73% / 27%	75% / 25%
Race		
Caucasian	79%	70%
Asian	16%	19%
Other*	5%	11%
Primary tumor site		
Lung	31%	28%
Ileum	23%	25%
Rectum	12%	16%
Jejunum	8%	6%
Stomach	3%	4%
Duodenum	4%	2%
Colon	2%	3%
NET of unknown primary	11%	13%

*Included Black.

1. Yao JC et al. *Lancet*. 2016;387:968-977. 2. Yao JC et al. *Eur J Cancer*. 2015;51(supplement 3):S709-S711.

RADIANT-4: Baseline and Disease Characteristics (2/2)

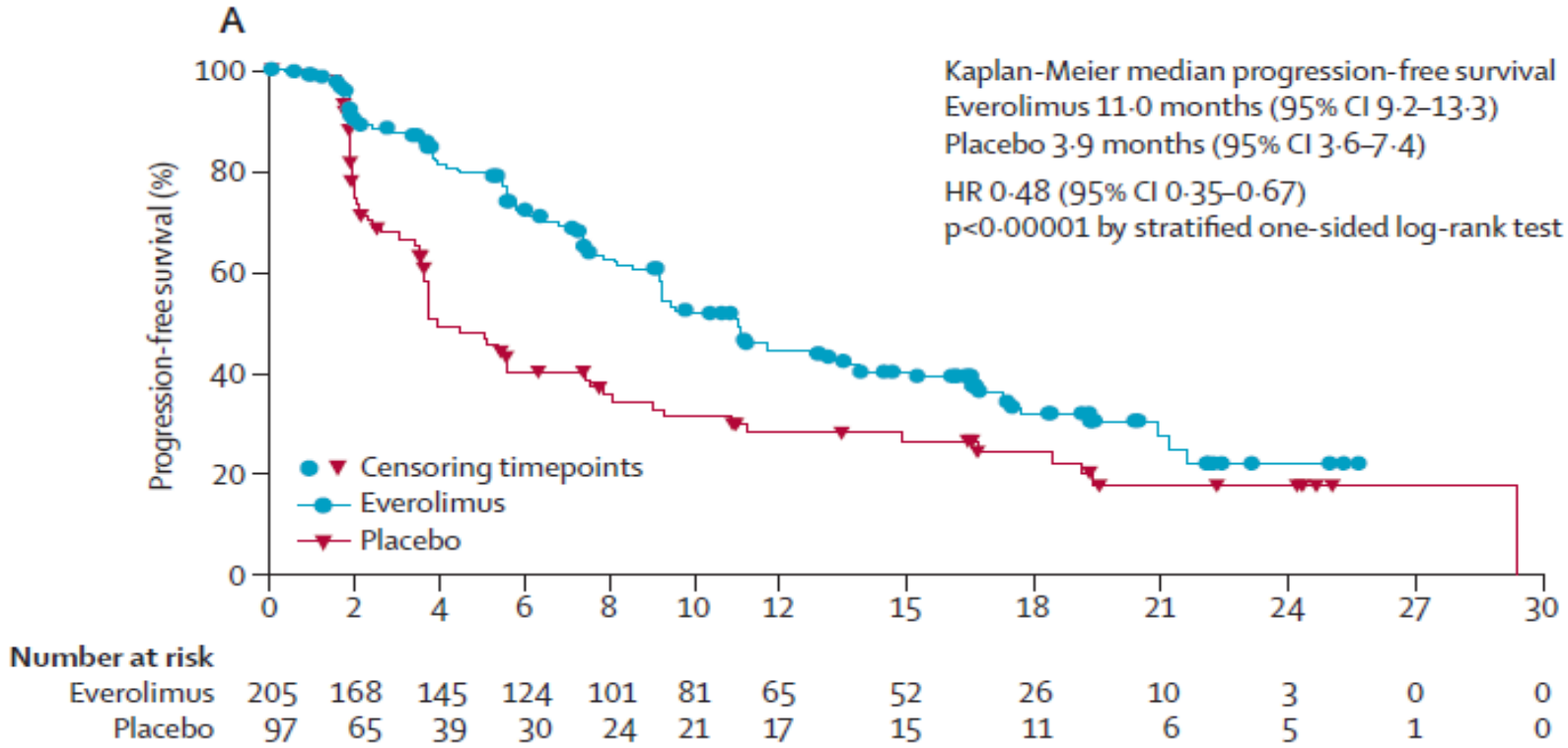
Characteristic	Everolimus N = 205	Placebo N = 97
Tumor grade		
Grade 1 / grade 2	63% / 37%	67% / 33%
Metastatic extent of disease†		
Liver	80%	78%
Lymph node or lymphatic system	42%	46%
Lung	22%	21%
Bone	21%	16%
Median time from initial diagnosis to randomization, months (range)	29.9 (0.7-258.4)	28.9 (1.1-303.3)
Median time from most recent progression until enrolment, months (range)‡	1.68 (0.0-7.8)	1.45 (0.2-11.8)
Prior treatments		
Somatostatin analogues	53%	56%
Surgery	59%	72%
Chemotherapy	26%	24%
Radiotherapy including PRRT	22%	20%
Locoregional and ablative therapies	11%	10%

†Organs as per target and non-target lesion locations observed at baseline by central radiology review.
‡Patients were expected to have disease progression in ≤ 6 months prior to enrolment as per inclusion criteria. Protocol deviation was reported in 7 patients.

1. Yao JC et al. *Lancet*. 2016;387:968-977. 2. Yao JC et al. *Eur J Cancer*. 2015;51(supplement 3):S709-S711.

RADIANT-4: PFS by Central Review Primary Endpoint

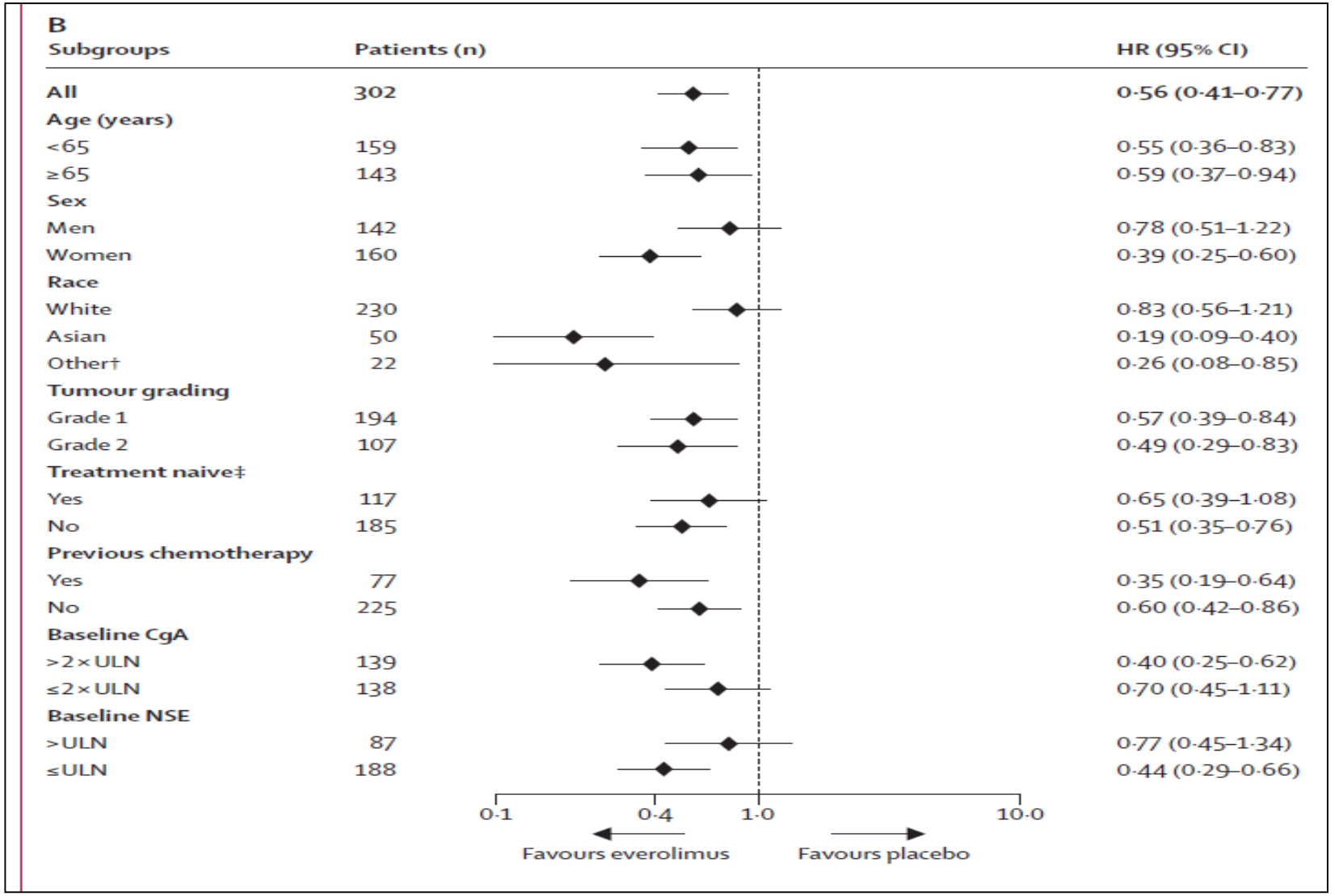
52% reduction in the relative risk of progression or death with everolimus vs placebo
HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001[1]



P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

1. Yao JC et al. *Lancet*. 2016;387:968-977.

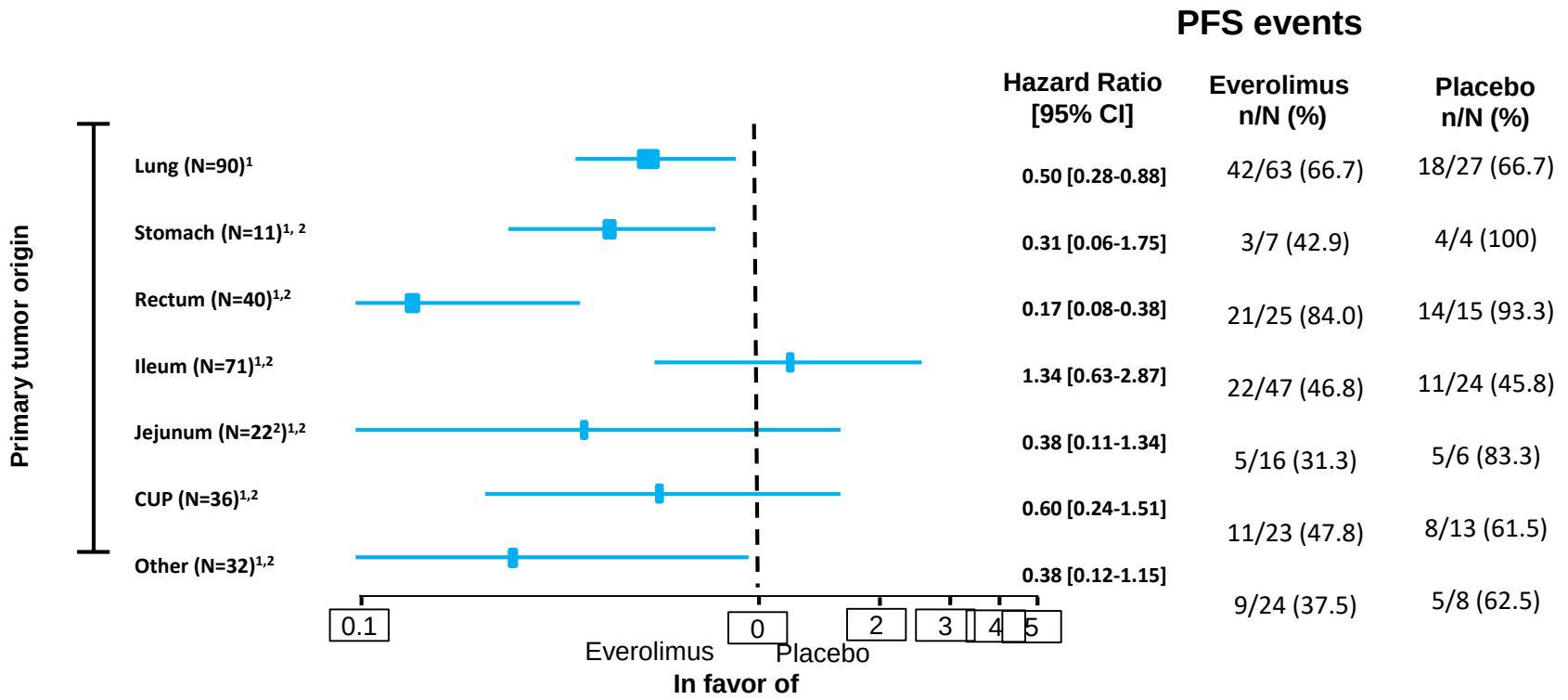
RADIANT-4: PFS HR by Pre-defined Subgroups Central Review



*Defined as no prior chemotherapy or no SSA therapy continuously for ≥12 weeks any time before study.
Hazard ratio is obtained from unstratified Cox model.
CgA, chromogranin A; NSE, neuron-specific enolase; ULN, upper limit of normal.

1. Yao JC et al. *Lancet*. 2016;387:968-977.

RADIANT-4: PFS Treatment Effect by Primary Tumor Per Central Review



All hazard ratios presented for these subgroup analyses were unstratified and unadjusted for any covariates.

- Everolimus demonstrated a consistent positive treatment effect across multiple primary tumor locations
- In the ileum subgroup only 22 progression events were reported out of 47 patients in the everolimus arm vs 11 out of 24 patients in the placebo arm
- The better prognosis for the ileum subgroup in relation to the median duration of follow-up may have been insufficient to demonstrate the potential benefit of treatment

1. Singh S et al. 2016 European Neuroendocrine Tumor Society (ENETS), Barcelona, Spain. Abstract L20
2. Singh S, et al. *Neuroendocrinology*. 2017 May 24. doi: 10.1159/000477585. [Epub ahead of print]

Chemotherapy for Advanced GEP-NEN -G3

- In high-grade neuroendocrine carcinomas (G3) Platinum-based chemotherapy is generally indicated
- The combination of cisplatin and etoposide, or alternative regimens substituting carboplatin for cisplatin, or irinotecan for etoposide, are recommended as first-line therapy
- Response rates of these regimens are lower in patients with Ki-67 in the lower range of G3 (21–55%)
- Efficacy of chemotherapy in NET G3 is presently uncertain.

Platinum-based chemo in G3 NEN

Table 3. Response to platinum-based therapy among NEN-G3.

Author	Objective	Number	Response rate to platinum-based therapy	
			NET-G3	NEC-G3
Hijioka S 2017 [8]	Pan NEN-G3	70 NET-G3;21 NEC-G3;49	0% (first line) 0% (total line)	55.9% (total line) 61.3% (first line)
Raj N 2016 [11]	Pan NEN-G3	45 NET-G3;16 NEC-G3;29	10% (total line)	37% (total line)
Heetfeld 2015 [7]	GEP-NEN-G3 (pancreas; 65, non pancreas; 60)	125 GEP-NET-G3;37 (pNET-G3;24) GEP-NEC-G3;167 (pNEC-G3;41)	17%* (first line)	35%** (first line)
Fritz-line 2013 [5]	GEP-NEN-G3 (pancreas; 9, non pancreas; 19)	28 GEP-NET-G3;12 (pNET-G3;7) GEP-NEC-G3;16 (pNEC-G3;2)	0%* (first line)	31%** (first line)
Average		**67**	**9%(0-17%)**	**40%(31-56%)**

NEC neuroendocrine carcinoma; NET neuroendocrine tumor,

*result of GEP-NETG3

** result of GEP-NECG3

Hijioka et al 2018 JOP, S[3]:346-353

Molecular characteristics of NEN-G3

Table 2. Genetic mutations and molecular abnormalities.

Molecular abnormalities	Well-diff.NET (NET G1/2)	NET-G3	NEC-G3
Authors	Jiao et al. [39] Raj et al. [11]	Hijioka et al. [8] Tang et al. [13] Konukiewitz et al. [44]	Yachida et al. [44, 45] Hijioka et al. [8] Tang et al. [13] Shida et al. [50]
KRAS	0%	0%	29-49%
Rb1	0%	0%	55-89%
P53	3%	0%	18-100%
mTOR (PTEN, TSC2) Or p-mTOR	7-18%	NA	67%
Bcl2	18%	NA	50-100%
MEN1	44-61%	75%	33%
DAXX/ATRX	18-41%	75%	20%

NEC neuroendocrine carcinoma; NET neuroendocrine tumor

Hijioka et al 2018 JOP, S[3]:346-353

MUNICH 2018 ESMO congress

Activity & Safety of Spartalizumab (PDR001) in Patients With Advanced Neuroendocrine Tumors of Pancreatic, Gastrointestinal, Thoracic Origin, & Gastroenteropancreatic Neuroendocrine Carcinoma Who Have Progressed on Prior Treatment

Yao JC[1*], Strosberg J[2], Fazio N[3], Pavel M[4], Ruszniewski P[5], Bergsland E[6], Li D[7], Tafuto S[8], Raj N[9], Campana D[10], Hijioka S[11], Raderer M[12], Guimbaud R[13], Gajate P[14], Pusceddu S[15], Reising A[16], Degtyarev E[17], Mookerjee B[16], Aimone P[17], Singh S[18]

[1]University of Texas/MD Anderson Cancer Center, Houston, Texas, USA; [2]Department of Medicine, Moffitt Cancer Center, Tampa, Florida, USA; [3]European Institute of Oncology, Milan, Italy; [4]University of Erlangen-Nuremberg, Erlangen, Germany; [5]Gastroenterology and Pancreatology Department, Beaujon Hospital, Clichy, France; [6]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California, USA; [7]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, California, USA; [8]Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, ENETS Center of Excellence, Naples, Italy; [9]Memorial Sloan Kettering Cancer Center, New York, New York, USA; [10]Policlinico Sant'Orsola-Malpighi, Bologna, Italy; [11]Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan; [12]Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria; [13]CHU de Toulouse, Toulouse, France; [14]Hospital Universitário Ramón y Cajal, Clinical Oncology Department, Madrid, Spain; [15]Fondazione IRCCS Istituto Naz, Milan, Italy; [16]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [17]Novartis Pharma AG, Basel, Switzerland; [18]Sunnybrook Health Sciences Centre, Toronto, Canada.

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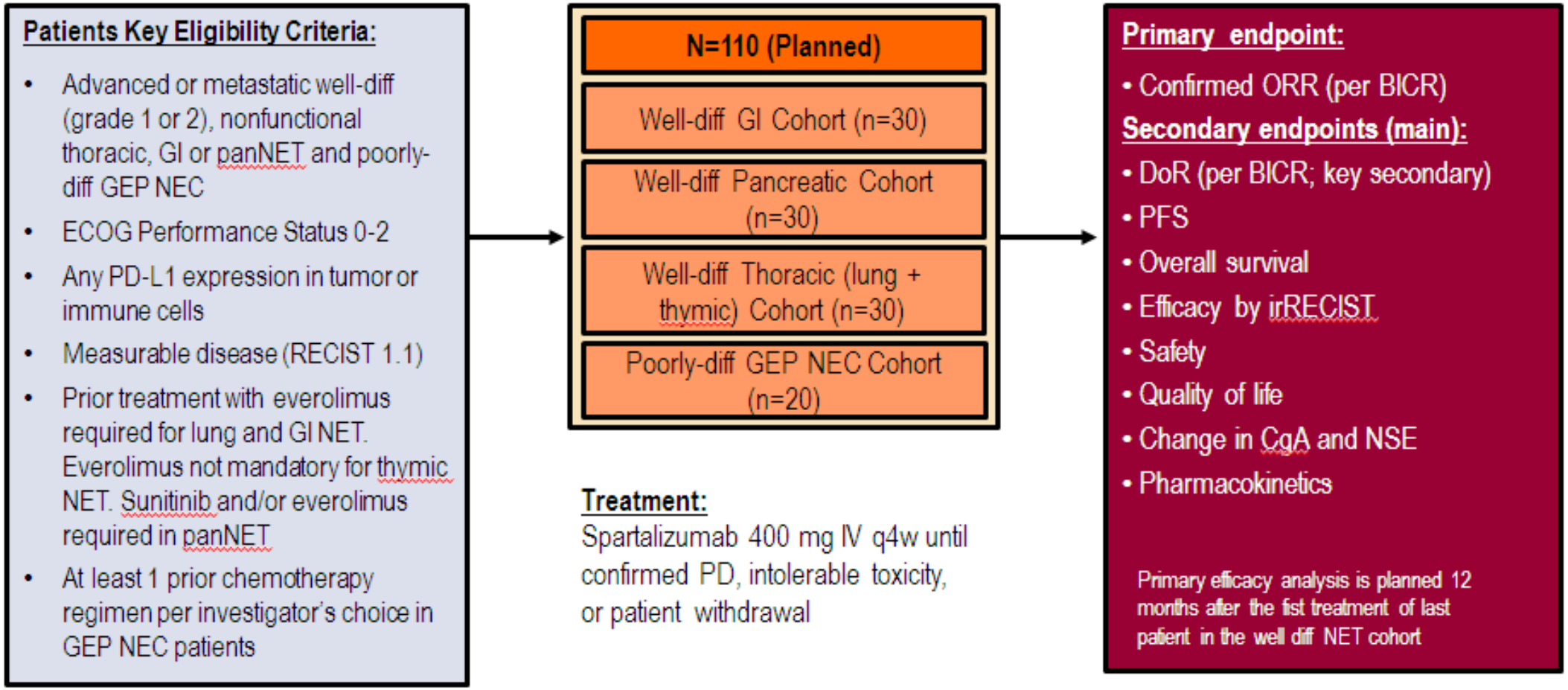
*Presenting author

Study Design



BICR, blinded-independent central review; CgA, chromogranin A; DoR, duration of response; ECOG, eastern cooperative oncology group; NEC, neuroendocrine carcinoma; ir, immune related; NSE, neurone specific enolase; ORR, overall response rate; q4w, every 4 weeks; RECIST, response evaluation criteria in solid tumours.

Yao et al, ESMO 2018

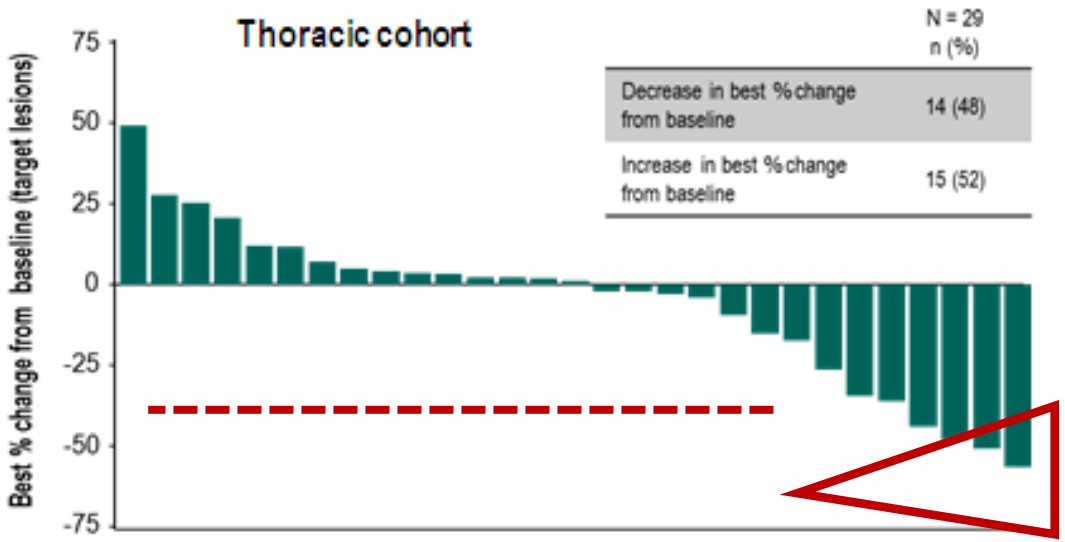
Confirmed Overall Response Rate by BICR

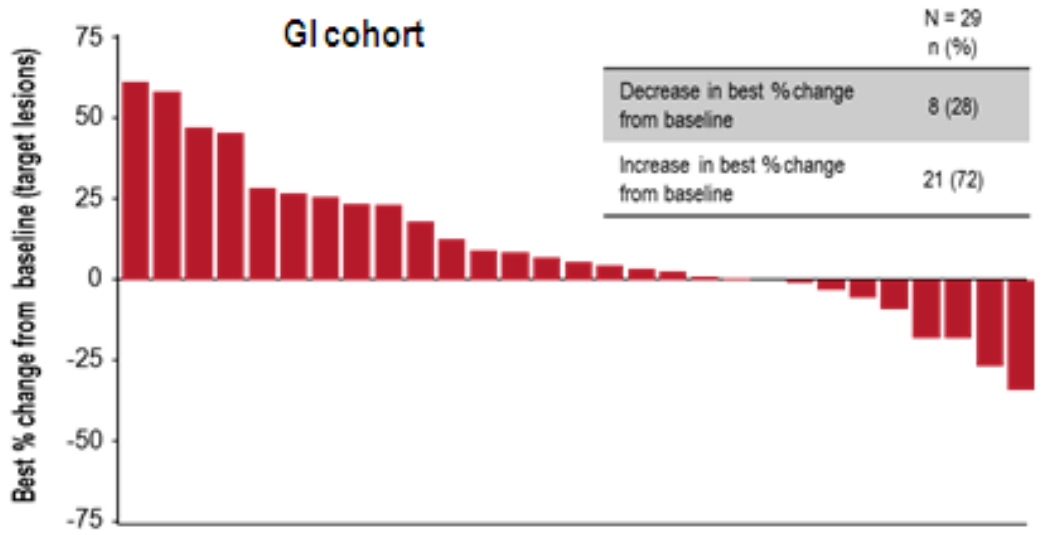
Variable	Well-diff NET				Poorly-diff GEP NEC N=21
	Thoracic cohort N=30	Pancreatic cohort N=33	GI cohort N=32	Overall N=95	
PR, n (%)	6 (20)	1 (3)	0	7 (7)	1 (5)
SD, n (%)	16 (53)	17 (52)	19 (59)	52 (55)	3 (14)
PD, n (%)	5 (17)	13 (39)	11 (34)	29 (31)	14 (67)
Unknown, n (%)	3 (10)	1 (3)	2 (6)	6 (6)	3 (14)
Confirmed ORR, n (%)	6 (20)*	1 (3)	0†	7 (7)	1 (5)
DCR, n (%)	22 (73)	19 (58)	19 (59)	60 (63)	4 (19)

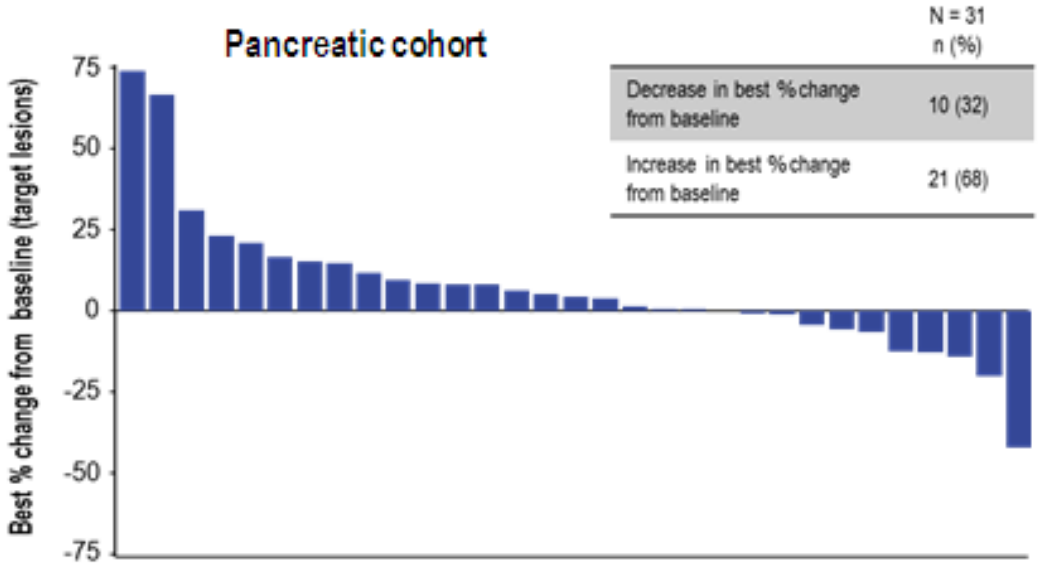
Median follow-up, months (range): 8 (6.0-10.9) for NET and 6 (4.7-6.9) for NEC

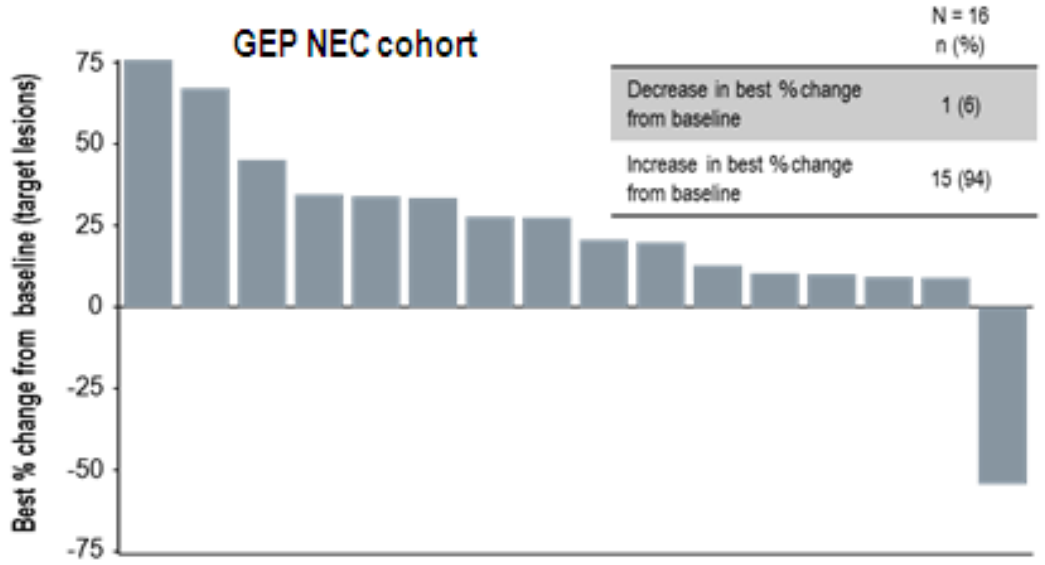
DCR, disease control rate; PR, partial response; SD, stable disease.
Yao et al, ESMO 2018

Best % Change From Baseline in Target Lesions









Yao et al, ESMO 2018

TALENT Trial: A phase II Trial to Assess the efficacy of LENvatinib in metastatic neuroendocrine Tumors (GETNE 1509)

Lenvatinib 24 mg qd

N = 110 pts

Cohort A

Patients with advanced/metastatic G1/G2 **neuroendocrine tumors of the pancreas** after progression to a previous targeted agent

Cohort B

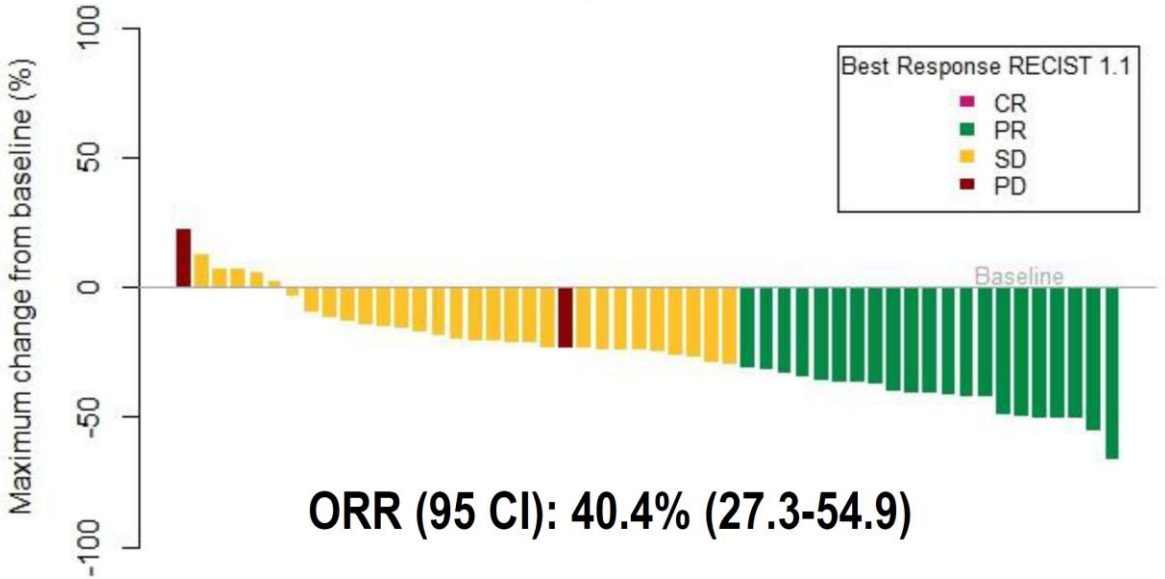
Patients with advanced/metastatic G1/G2 **neuroendocrine tumors of the gastrointestinal tract** after progression to somatostatin analogs

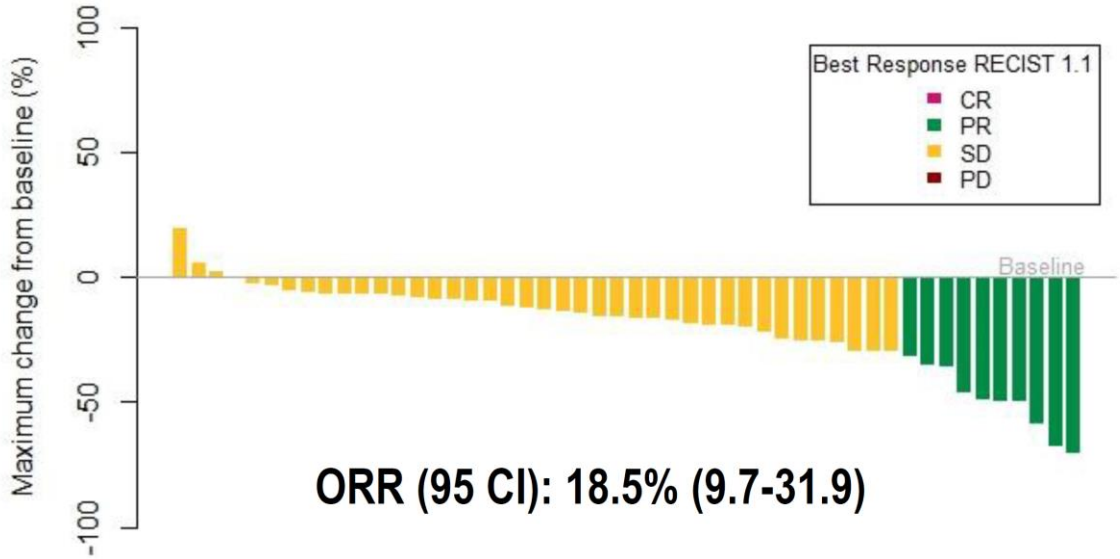
Lenvatinib inhibits: VEGFR1-3, FGFR 1-4, PDGFRα, cKIT and RET

Capdevilla et al, ESMO 2018

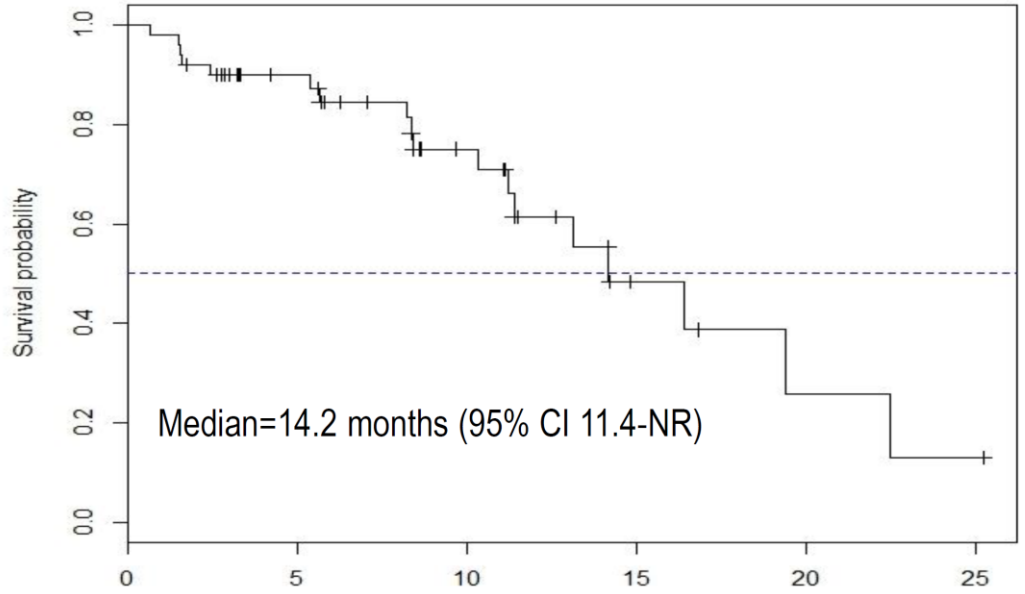
	PanNETs (n=55)	GI-NETs (n=56)	Total (n=111)
Patients with tumor assessments	52	54	106*
Best overall response n(%)			
Complete response (CR)	0	0	0
Partial response (PR)	21 (40.4%)	10 (18.5%)	31 (**29.2%**)
Stable disease (SD)	29 (55.8%)	41 (76%)	70 (66%)
Progressive disease (PD)	2 (3.8%)	0	2 (2%)
Not evaluable	0	3** (5.5%)	3 (2.8%)

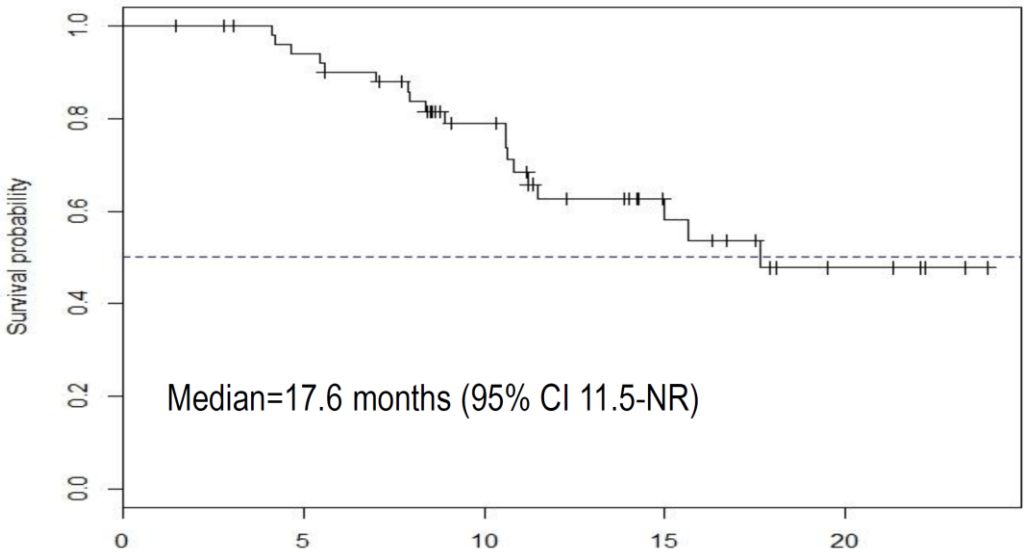
*Five patients withdrew the Informed Consent before the first post-basal tumor assessment.
**Central radiologist confirms that 3 patients did not have evaluable target lesions. They have been considered as not evaluable.





Capdevilla et al, ESMO 2018



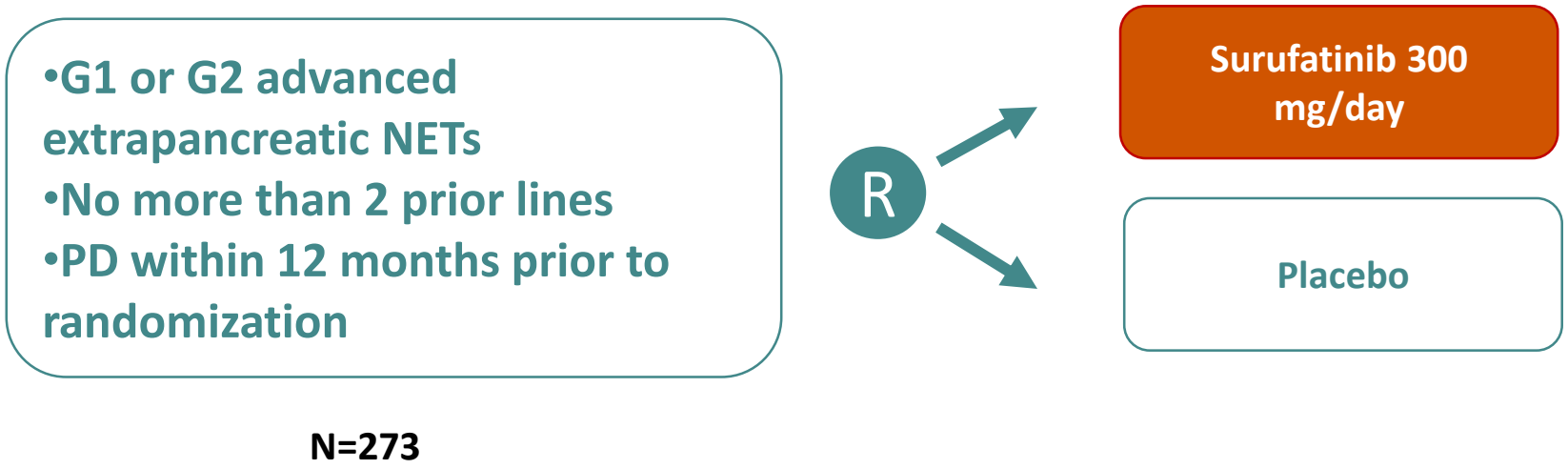


	Pancreatic NETs (n=55)	Gastrointestinal NETs (n=56)
Dose modifications Pts (%)		
Dose reduction/interruption	47 (88.6%)	51 (91.1%)
Definitive drug interruption due to side effects	6 (10.9%)	10 (17.8%)
Total number of adverse events (%)		
Grade 1/2	894 (90.7%)	862 (89.8%)
Grade 3	85 (8.6%)	92 (9.6%)
Grade 4	5 (0.5%)	6 (0.6%)
Grade 5*	1 (0.1%)	0

Pts: patients;
*1 patient presented grade 5 toxicity: Acute renal insufficiency;

Capdevilla et al, ESMO 2018

SANET-ep Trial: Phase III study of Surufatinib (VEGFR, FGFR, and CSF1R) in Treating WD Advanced Extrapancreatic NETs



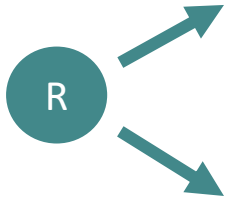
N=273

Primary endpoint: Progression-free survival
Primary completion date: December 2019

NCT02588170

Phase III study of PRRT vs everolimus in WD GEP-NETs: COMPETE (n=300)

- **G1 or G2 metastatic or locally advanced well diff, functioning or non-functioning GEP-NETs**
- **SSTR +ve**
- **PD as per RECIST 1.1**
- **Randomization 2:1**



^{177}Lu-DOTA-TOC 7.5 Gbq (4 cycles; 1 dose/12wks)

Everolimus 10 mg PO OD

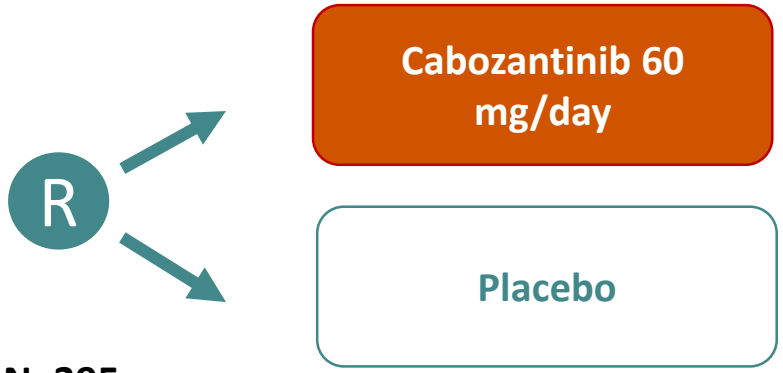
Primary endpoint: Progression free survival at 2 years

Primary completion date: Dec 2020

NCT03049189

CABINET trial: Double-blinded phase III study Cabozantinib vs placebo in advanced NETs that have progressed to Everolimus

- Well or moderate differentiated NETs
- Target lesions must have shown disease progression within 6 months prior to randomization.
- Patient should have failed at least one prior line of treatment that included everolimus.



N=395

Primary endpoint: PFS
Estimated Primary completion date: January 2021

NCT03375320

Conclusions

- The assessment of patients with advanced GEP NET includes evaluation of symptoms, tumour progression, tumour proliferation and disease extent
- Accurate path assessment of proliferation index is critical
- Awareness of NET G3–justifies re-analysis of histopath
- SSA for low grade/functional tumours
- Everolimus for progressive G1/G2 GI NETs
- Cisplatin-Etoposide remains the standard for G3 NECs

(Efficacy in well-differentiated G3 NETs is presently uncertain)

Conclusions

- Several questions remain unanswered, especially regarding the place of chemotherapy versus targeted agents and optimal sequencing of agents
- Rare disease- Collaborative international efforts required
- Understanding the molecular biology will lead to better treatments & predictive biomarkers.

  e.g. Rb and KRAS as predictors of response to platinum-based chemo


THANK YOU