BALI
A-PHPBA 2021
VIRTUAL CONGRESS

The 8th Biennial Congress of The Asian-Pacific Hepato-Pancreato-Biliary Association (A-PHPBA 2021)

Indonesia, 8-11 September 2021 Virtual

SYSTEMIC TREATMENT OF METASTATIC AND UNRESECTABLE PNETS

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Hospital Universitário Presidente Dutra
São Luiz - Brazil

SITES OF PRIMARY AND METASTASES

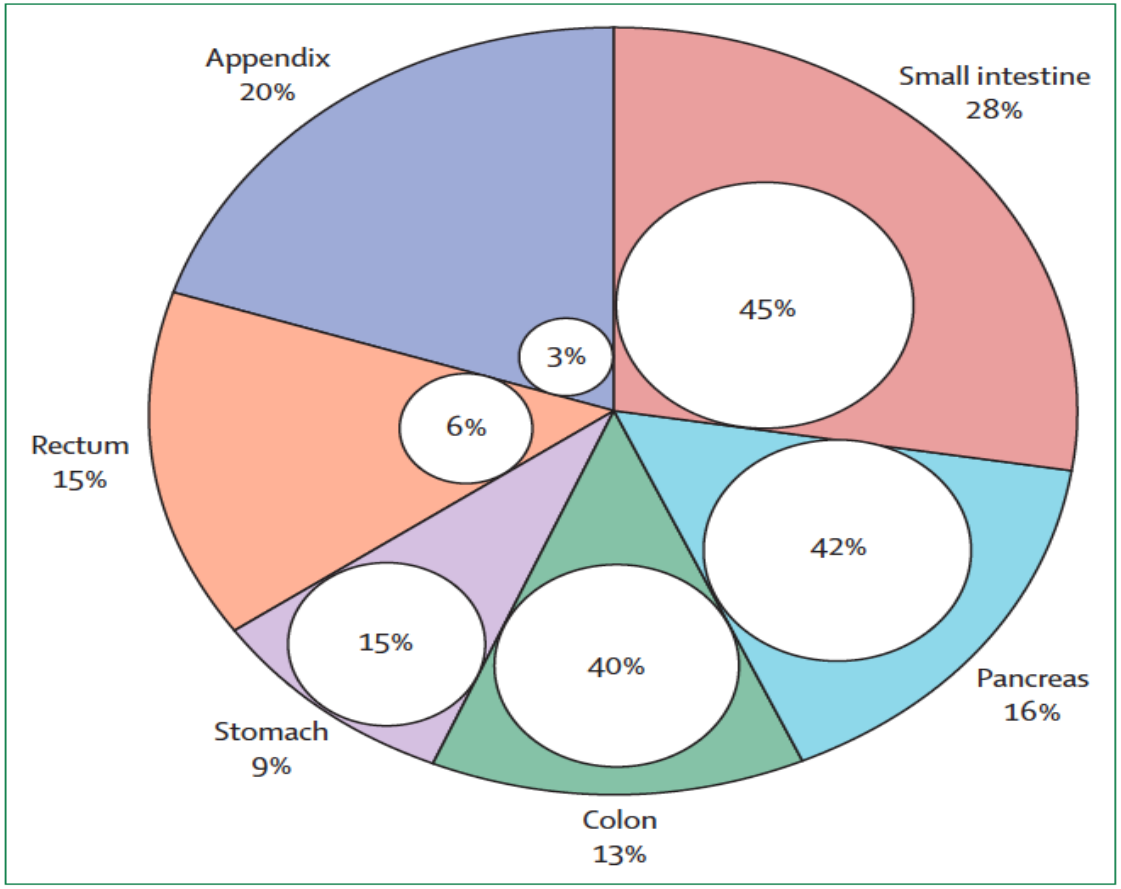


Figure 1: Sites of primary GEP NETs (segments) and metastases (circles)

Frilling A, et al. Lancet, 2015

No surgery

- **Technical contraindication** (cavernoma…)
- **Patient contraindication** (poor general status)
- **Extrahepatic metastatic disease**
- **pNEC G3**

Observation possible

- **Sporadic asymptomatic NF pNET G1 < 2 cm**
- **MEN-1 asymptomatic NF pNET G1 < 2 cm**
- **NEM-1 gastrinoma < 2 cm**

Surgery required

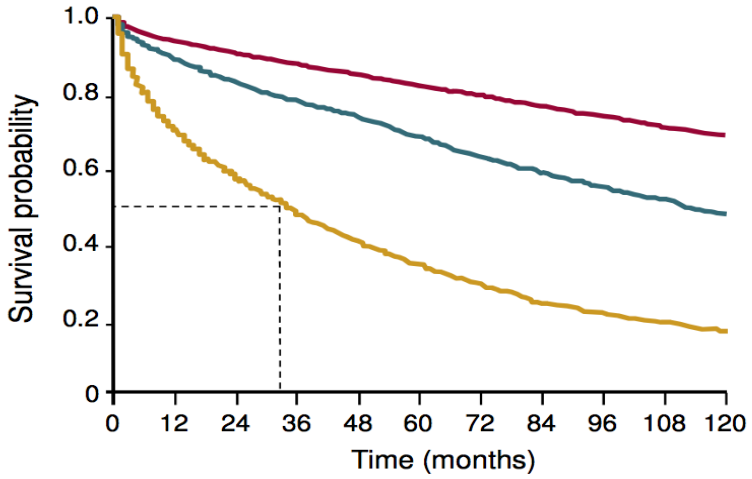
Basically all other!!!

METASTATIC AND UNRESECTABLE

Souche R, et al. J. Clin. Med. 2020

PROGNOSIS OF METASTATIC NETS

Tumours with well- and moderately differentiated histology[1]



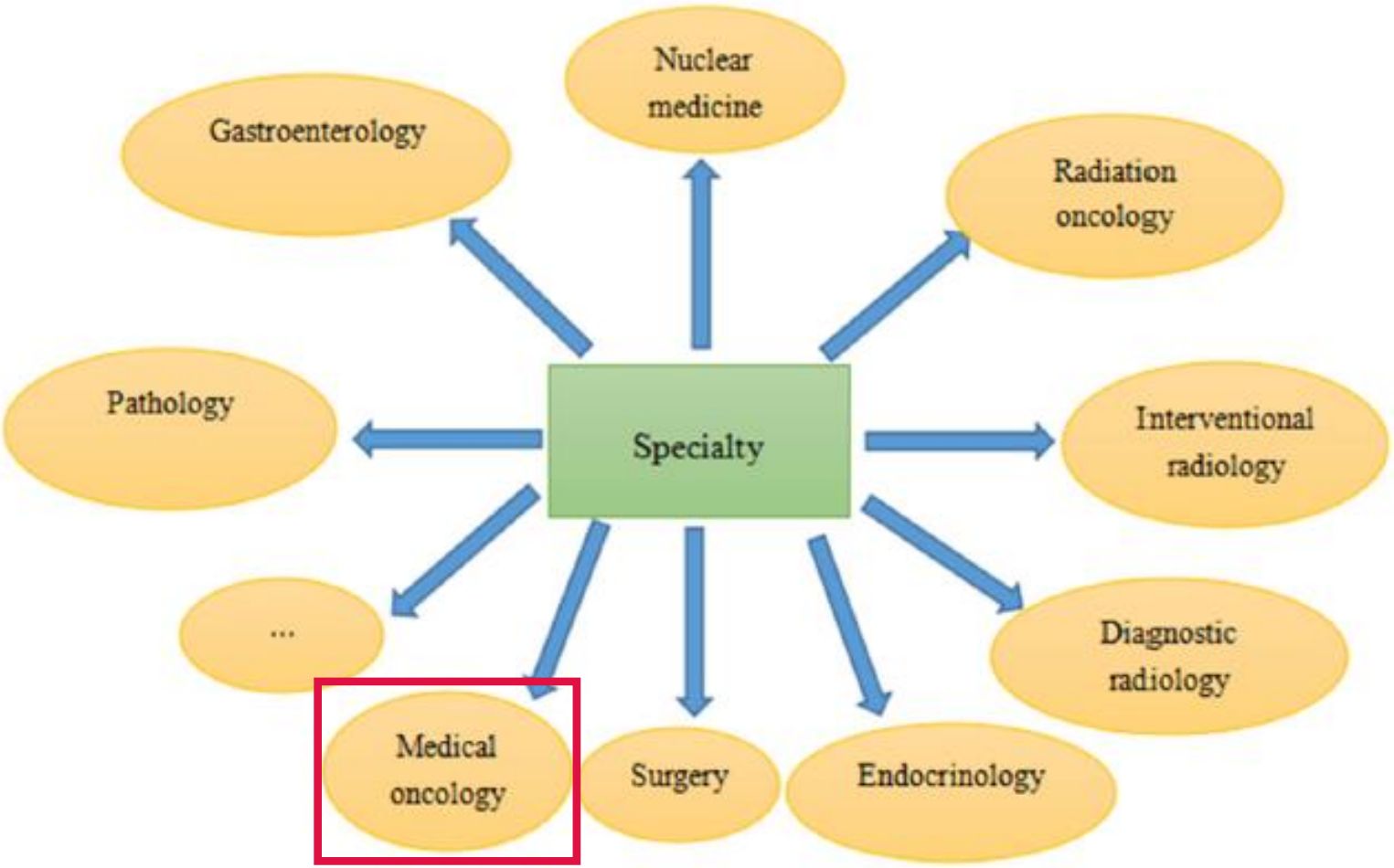
Stage	Median survival	
	Month	95% CI
Localized	223	208-238
Regional	111	104-118
Distant	33	31-35

CI = confidence interval

- 5-year survival rate in metastatic NET is similar to that in other metastatic cancers
  - Poorly differentiated NET: 4%[1]
  - Well/moderately differentiated NET: 35%[1]
  - Lung: 4%[2]
  - Colorectal, breast, and prostate: 11%, 23%, and 31%, respectively[2]
- 65% of patients with advanced NET will not be alive in 5 years

[1]Yao J, et al. *J Clin Oncol.* 2008;26:3063-3072; [2]Jemal A, et al. *CA Cancer J Clin.* 2010;60:277-300.

MULTIDISCIPLINARITY



Courtesy: Prof. Renata D'Alpino
(São Paulo – Brazil)

TREATMENT

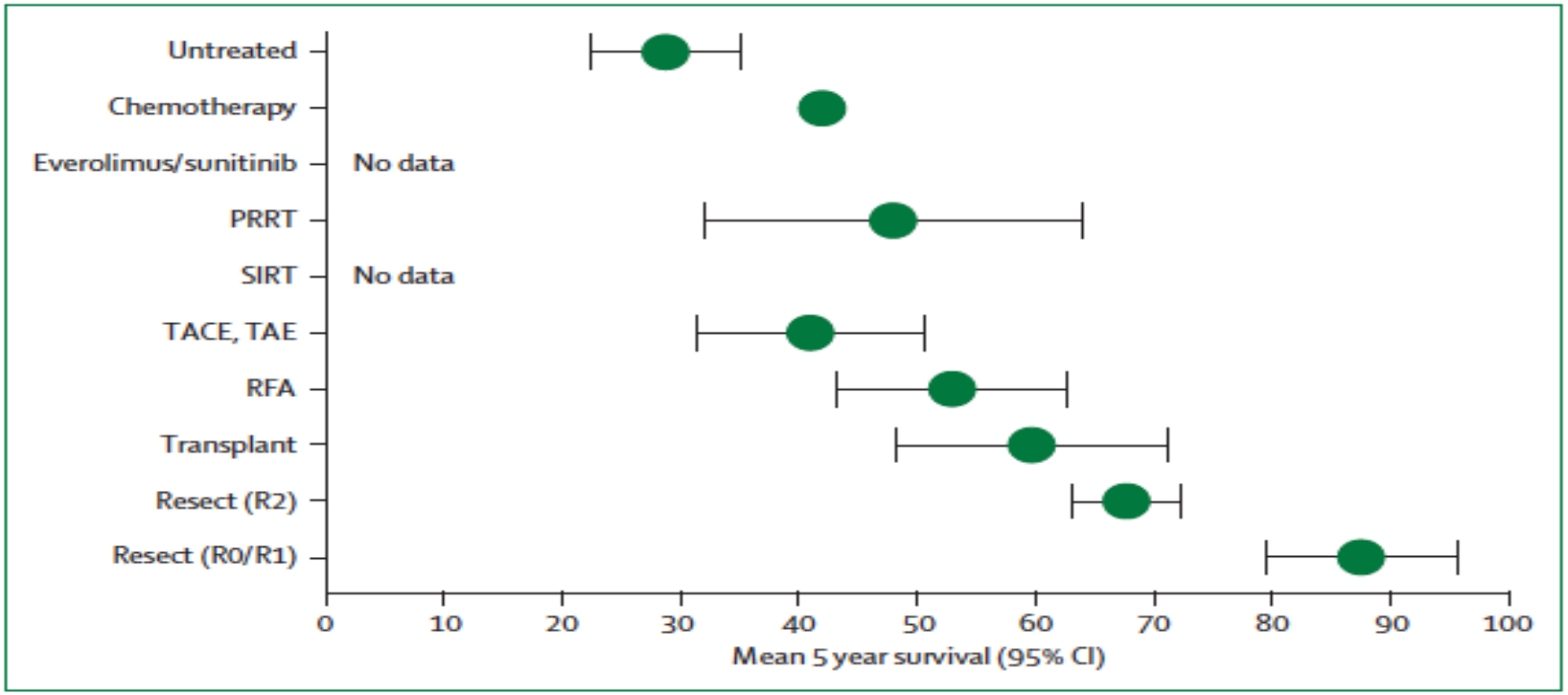


Figure 4: **Rates of 5 year survival by treatment method**

Frilling A, et al. Lancet, 2015

TREATMENT

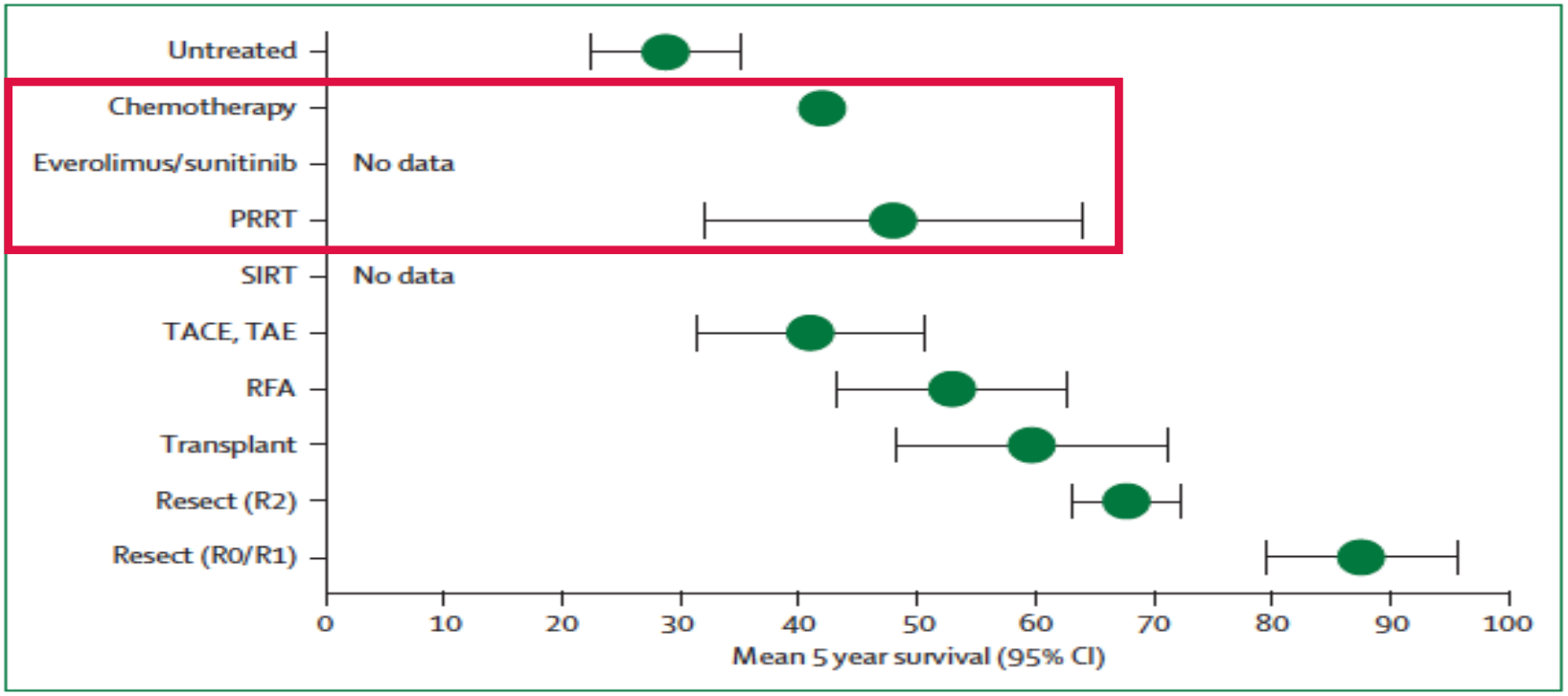


Figure 4: **Rates of 5 year survival by treatment method**

Frilling A, et al. Lancet, 2015

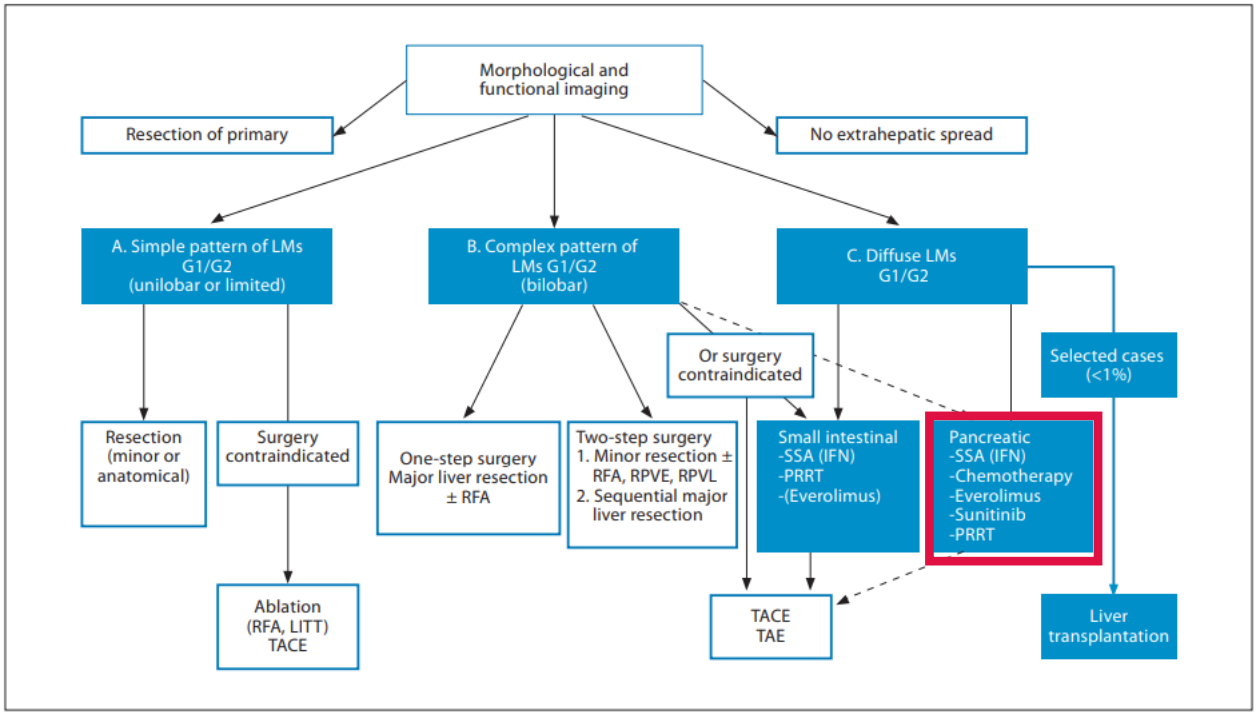
ENETS Consensus Guidelines

Neuro
endocrinology

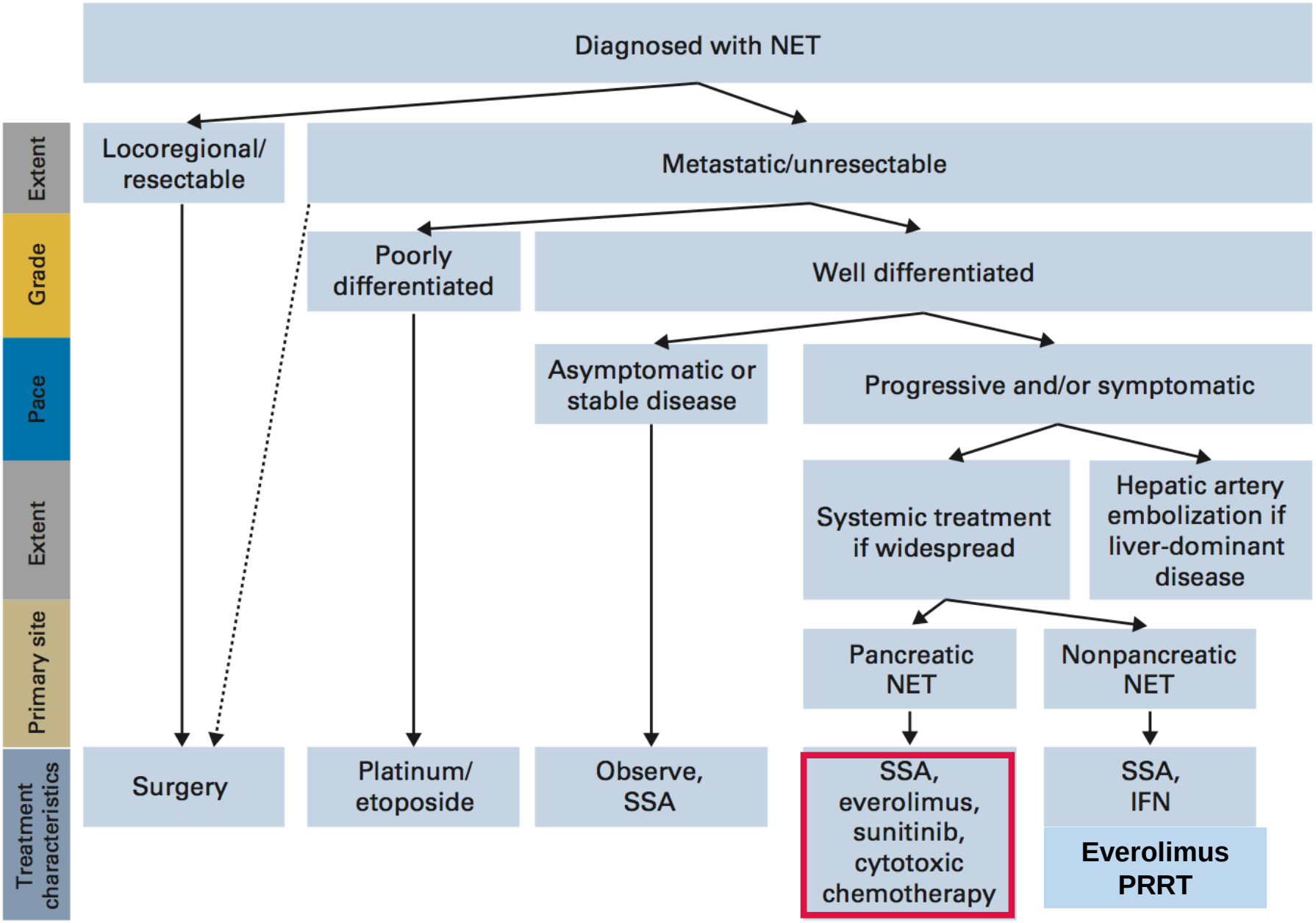
Neuroendocrinology 2012;95:157–176
DOI: 10.1159/000335597

Published online: February 15, 2012

ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary



Pavel M, et al. Neuroendocrinology 2012



Frilling A, et al. Lancet, 2015

Guide 38. Treatment for locally advanced or metstatic disease of the pancreas

Disease status	Treatment	Next steps
Complete surgery is possible	• Resect primary tumor and metastases	• Refer to *Surveillance*, Guide 36
No symptoms, low tumor burden, and stable disease	• Observe with tumor marker tests and CT or MRI of abdomen and pelvis every 3–12 months, and CT of chest as needed or • Consider octreotide or lanreotide	◦ For disease progression, follow the path below
Symptoms, major tumor burden, or disease progression	• Manage symptoms as needed • If disease progression, consider octreotide or lanreotide (if none before)	If disease progression: • Everolimus • Sunitinib • PRRT with ^{177}Lu-dotatate, if somatostatin receptor-positive imaging • Chemotherapy • Consider a hepatic-directed therapy for disease in the liver: ◦ Arterial embolization ◦ Chemoembolization ◦ Radioembolization ◦ Cytoreductive surgery/ablative therapy

ENETS Consensus Guidelines

Neuro
endocrinology

Neuroendocrinology 2012;95:157–176
DOI: 10.1159/000335597

Published online: February 15, 2012

ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary

Table 1. Therapeutic options and conditions for preferential use as first-line therapy

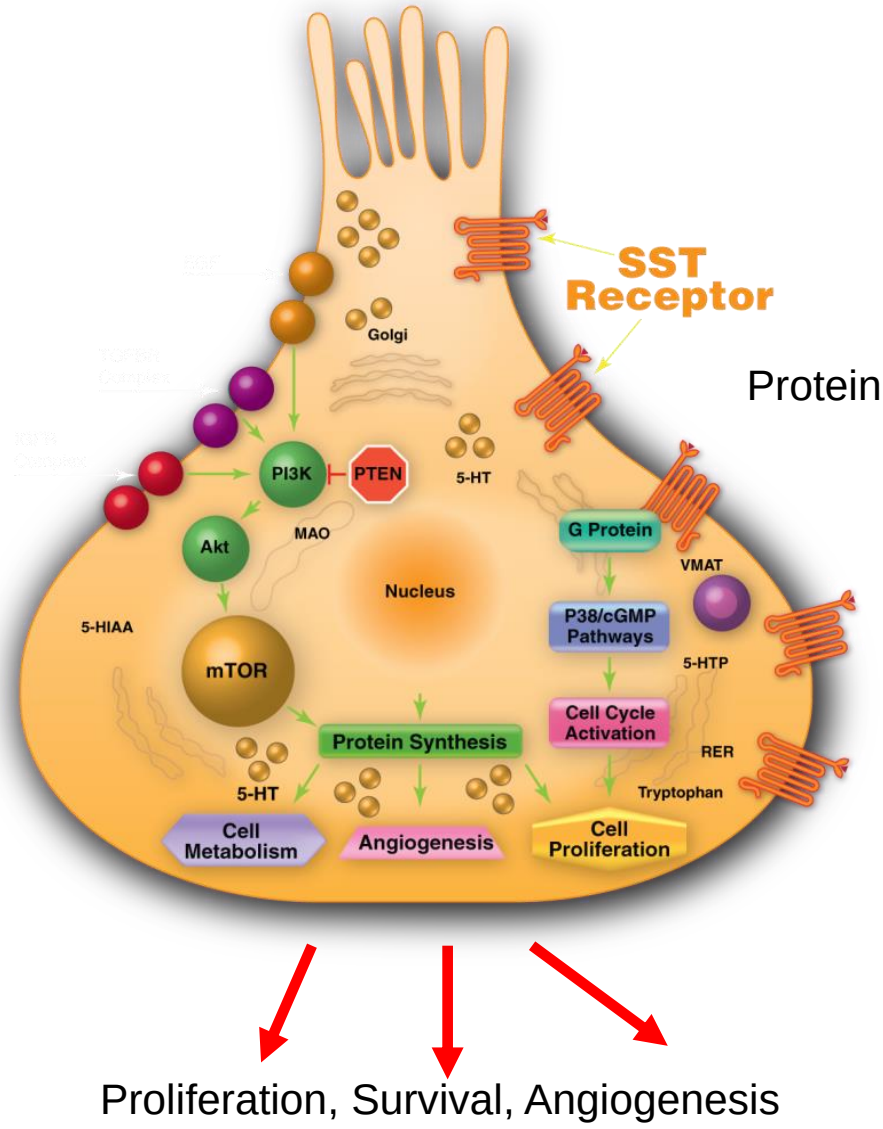
Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+	G1	midgut	+	low tumor burden
Lanreotide	+	G1		+	placebo-controlled data on antiproliferative activity pending
STZ+5-FU	+/–	G1-G2	pancreas		progressive in short-term[1] or high tumor burden or symptomatic
TEM/CAP	+/–	G2	pancreas		progressive in short-term[1] or high tumor burden or symptomatic; contraindication for STZ-based regimen
Everolimus	+/–	G1-G2	pancreas		insulinoma; contraindication for CTX
Sunitinib	+/–	G1-G2	pancreas		contraindication for CTX
PRRT	+/–	G1-G2	any	+	extended disease; extrahepatic disease, e.g. bone metastases (if tumor burden not too high); high uptake of tumor lesions on Octreoscan and limited disease amenable to surgery after down-staging
Cisplatin + etoposide	+/–	G3	any	+/–	all poorly differentiated NEC

CTX = Chemotherapy; STZ = streptozotocin; SSTR = somatostatin receptor.
[1] 3–6 months.

Pavel M, et al. Neuroendocrinology 2012

- **SOMATOSTATIN ANALOGUES**
  - Octreotide LAR
  - Lanreotide
- **TARGET THERAPY**
  - Everolimus
  - Sunitinib
- **CHEMOTHERAPY**
  - Temozolamide
  - Capecitabine
- **PRRT**
  - 177 Lutetium

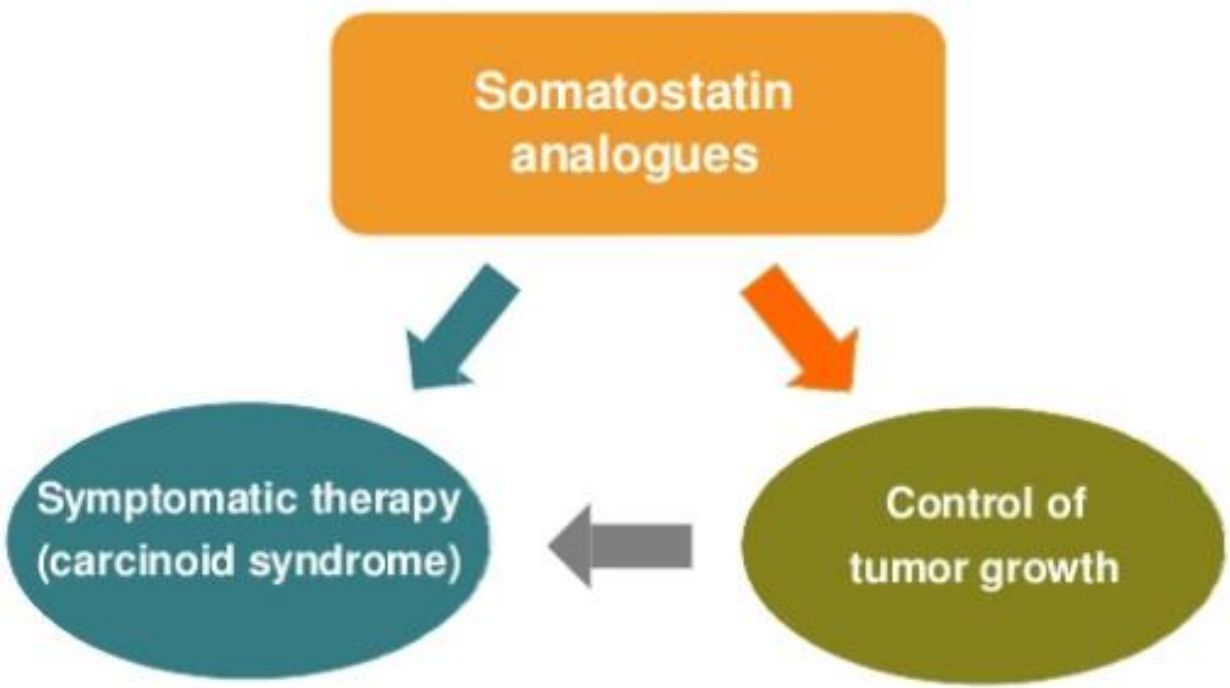
SOMATOSTATIN ANALOGUES



Protein G ativation

Proliferation, Survival, Angiogenesis

Somatostatin analogues and liver metastasis

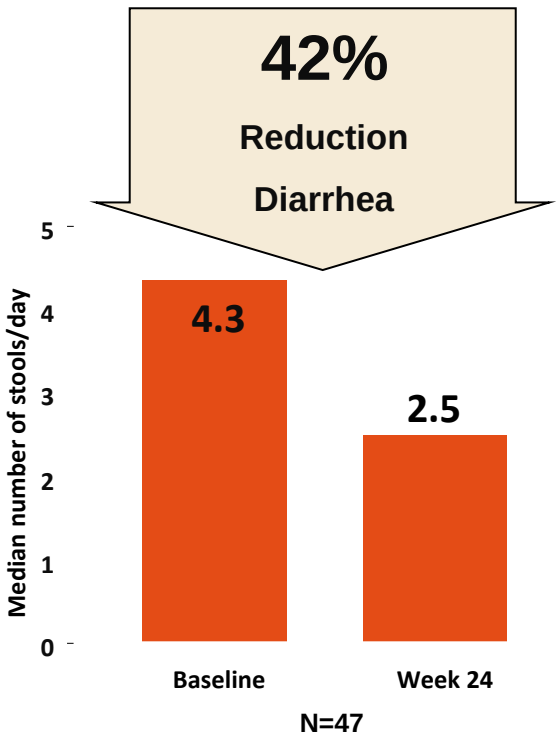


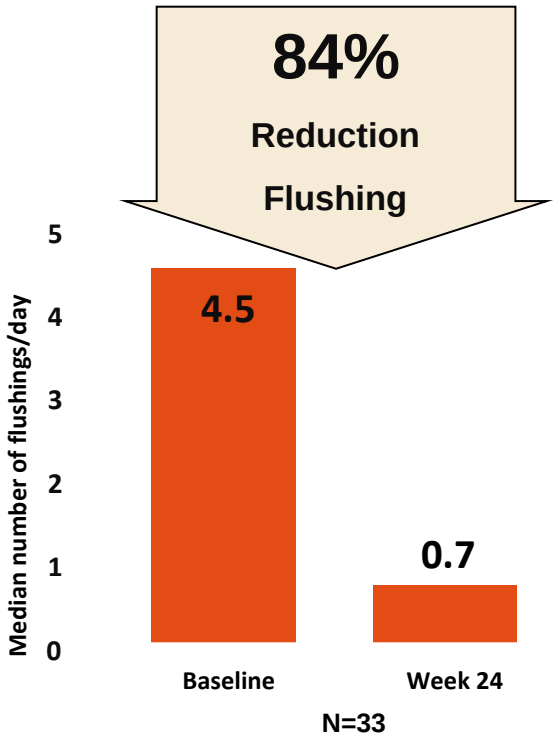
Courtesy: Prof. Renata D'Alpino (São Paulo – Brazil)

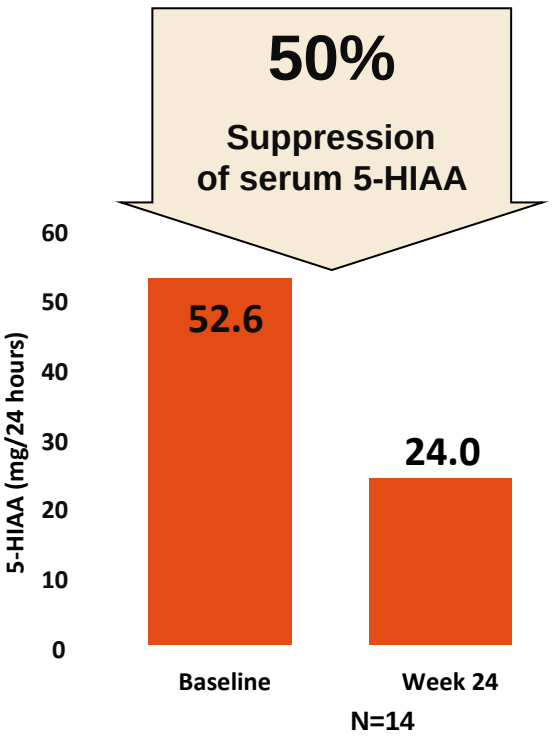
- **SOMATOSTATIN ANALOGUES**
  - Octreotide LAR (PROMID)
  - Lanreotide (CLARINET)

SOMATOSTATIN ANALOGUES

FUNCTIONAL PNETs







1. Rubin J et al. J Clin Oncol 1999;17:600–606
2. Arnold R et al. Gut 1996;38:430–438

Advances in the Management of Unresectable or Metastatic Pancreatic Neuroendocrine Tumors: Chemotherapy, Targeted Therapy, Hormonal Treatment, and Future Directions

Table 3. Selected Trials of Somatostatine Analogues in Patients with Advanced pNET

References	Regimen	No. of patients	Response rate,%	Median PFS/TTP and OS, months
Panzuto et al.	Oct LAR 30 mg q28day	21	SD:45	NA
Shojamanesh et al.	Oct sc or OCT LAR	15	PR:4; SD:28	NA
Aparicio et al.	Oct sc 100μg t.i.d. or Lan i.m 30 mg q14 day to q7 day or both	35	PR:2.9; SD:57.1	NA
Rinke et al.	Oct LAR 30 mg q28 day *vs* placebo	85	SD:66.7 *vs* 37.2	PFS, 14.3 *vs* 6.0
Caplin et al.	Lan 120 mg q28 day *vs* placebo	204	NA	PFS, NR *vs* 18

**pNET: pancreatic neuroendocrine tumors,, Oct: octreotide; Lan: lanreotide; BSC: Best supportive care; sc: subcutaneous; i.m: intramuscular;NA: not applicable; PFS: progression-free survival; OS: overall survival; TTP: time-to progression, SD:stable disease; PR: partial response; NR: not reached

Bilici A, et al. Asian Pac J Cancer Prev 2015

Original Paper

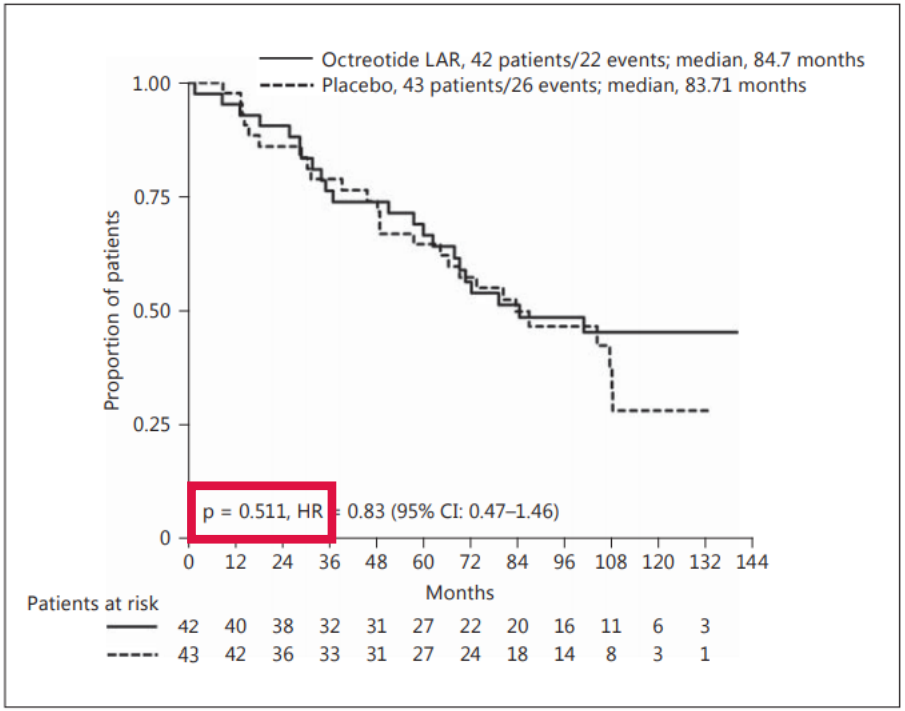
Neuro
endocrinology

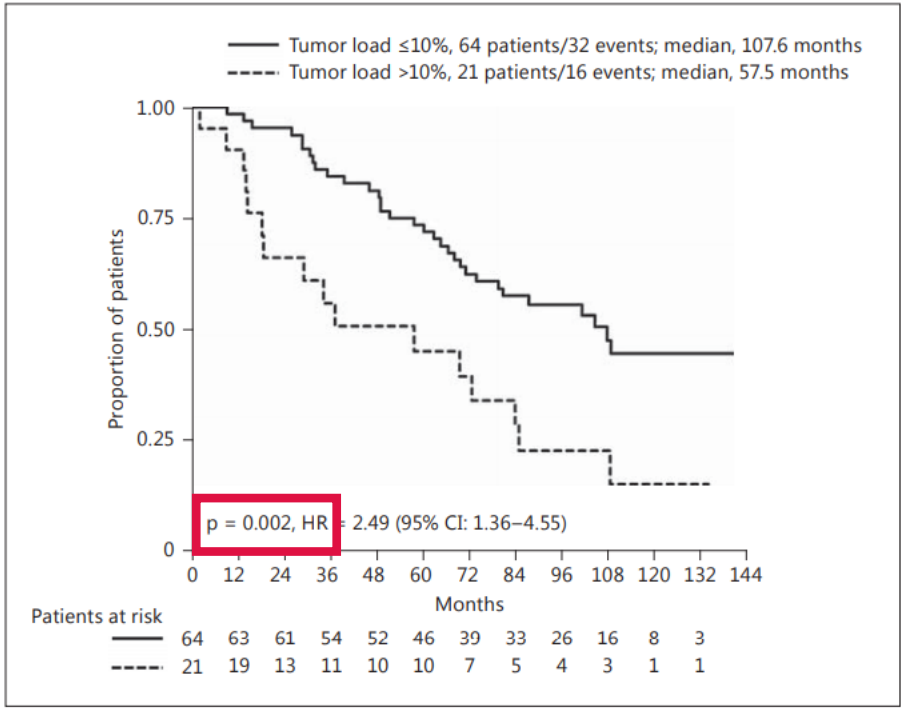
Neuroendocrinology 2017;104:26–32
DOI: 10.1159/000443612

Received: June 22, 2015
Accepted after revision: December 20, 2015
Published online: January 6, 2016

PROMID STUDY

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival



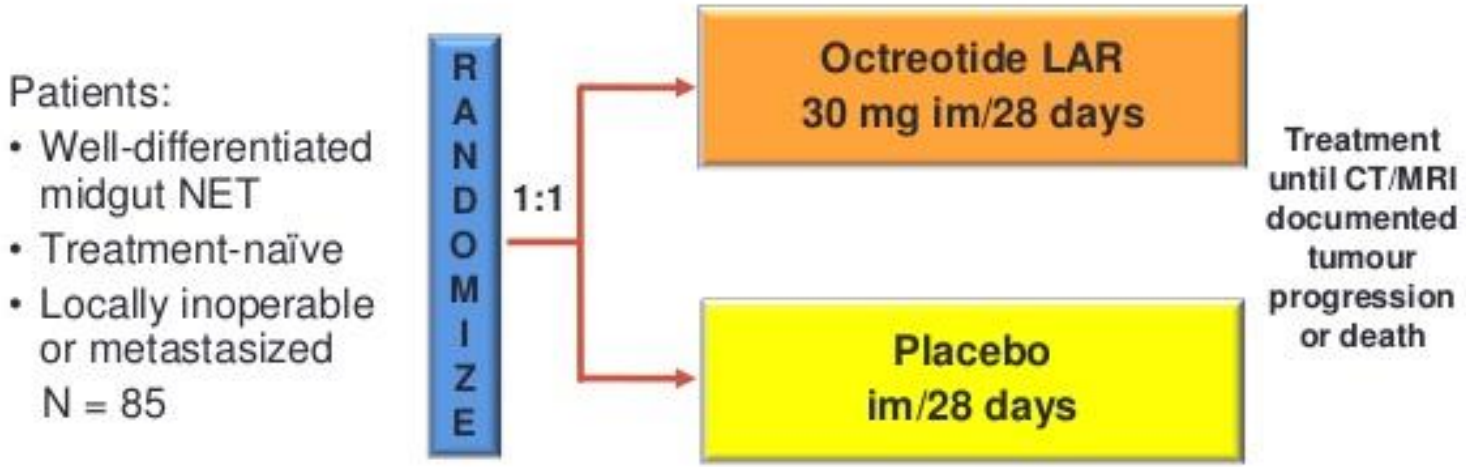


Rinke A, et al. J Clin Oncol 2009

PROMID STUDY

Phase III Study of Octreotide LAR:

Randomized, Double-blind, Placebo-controlled Study



Ki67 ≤ 2%

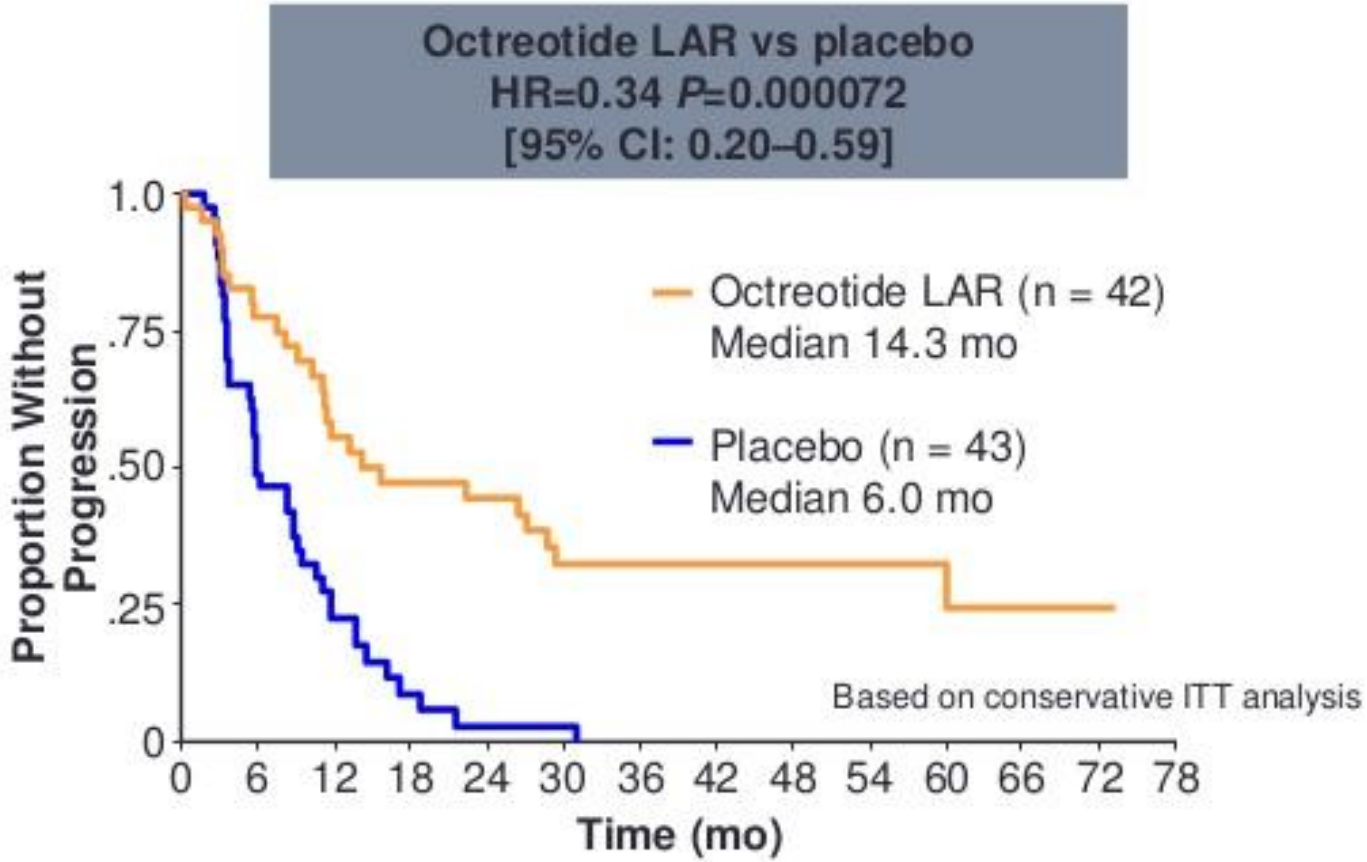
Primary endpoint:
- Median time to tumour progression

Secondary endpoints:
- Objective tumour response rate
- Symptom control
- Overall survival

Rinke A, et al. J Clin Oncol 2009

Courtesy: Prof. Renata D'Alpino (São Paulo – Brazil)

Octreotide LAR 30 mg Significantly Prolongs TTP:



Rinke A, et al. J Clin Oncol 2009

CLARINET STUDY

Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study

Ki67 ≤ 10%

Patients with nonfunctioning advanced NETs (N = 204)

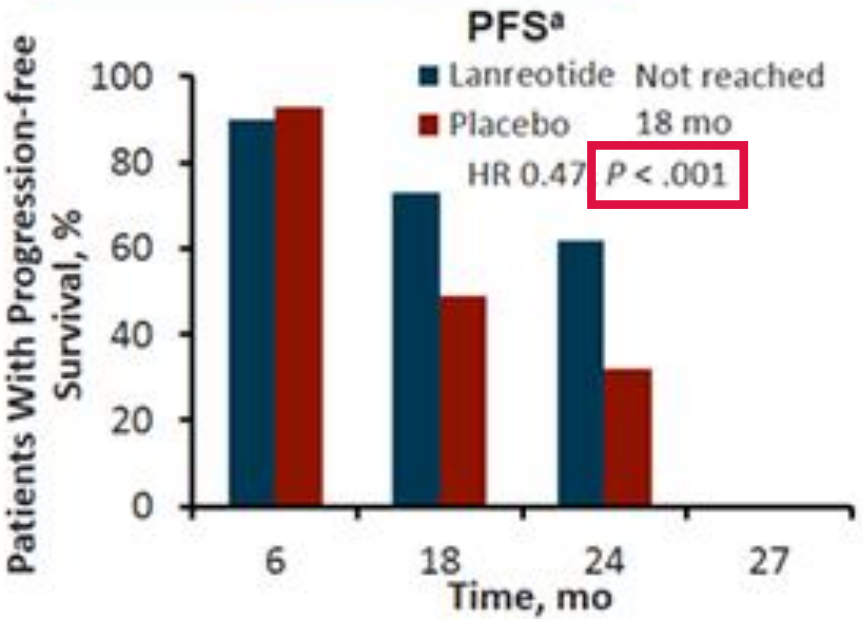
- Lanreotide 120 mg Via deep SC Q4W (n = 101)
- Placebo Q4W (n = 103)

*Primary tumor site:

- Pancreas, 45%
- Midgut, 36%
- Hindgut, 7%
- Unknown/other, 13%

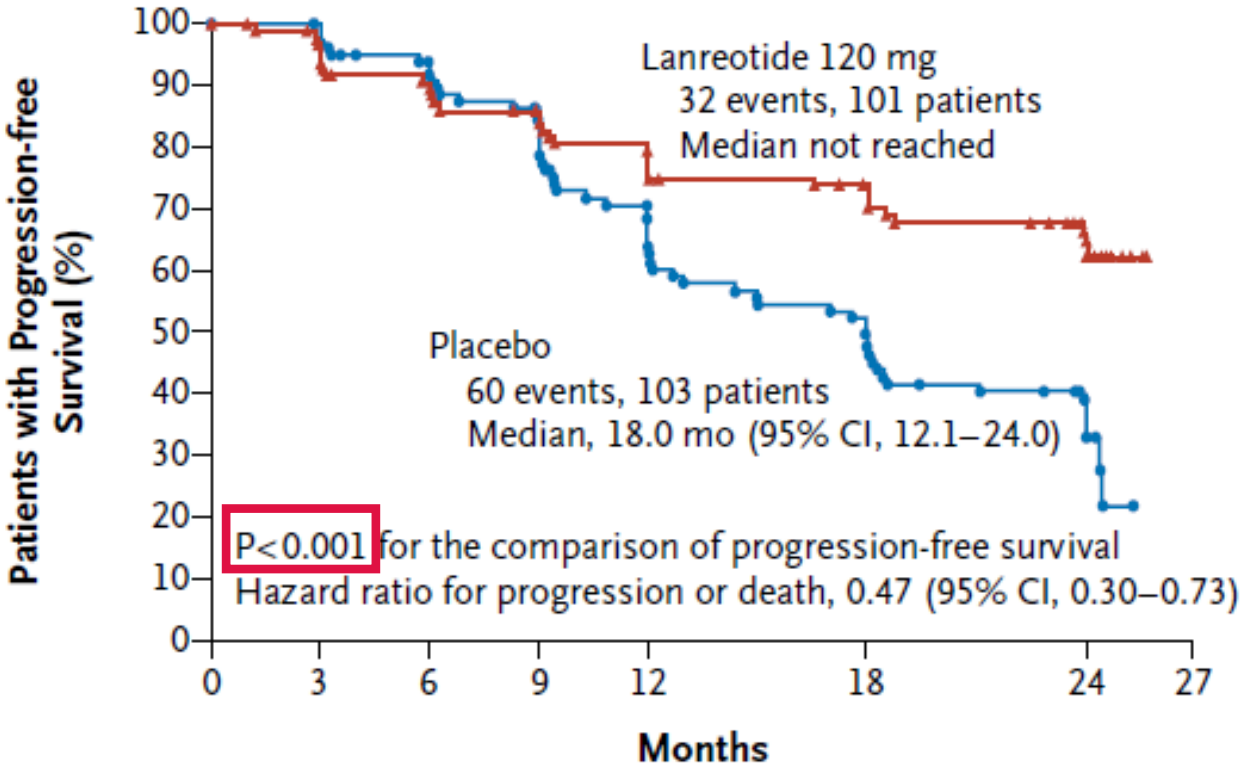
Other key points:

- Crossover allowed
- OS not reached at time of initial report
- 88 pts on extension study:[b] median PFS 32.8 mo



Caplin ME, et al. Endocrine-Related Cancer. 2016

CLARINET study

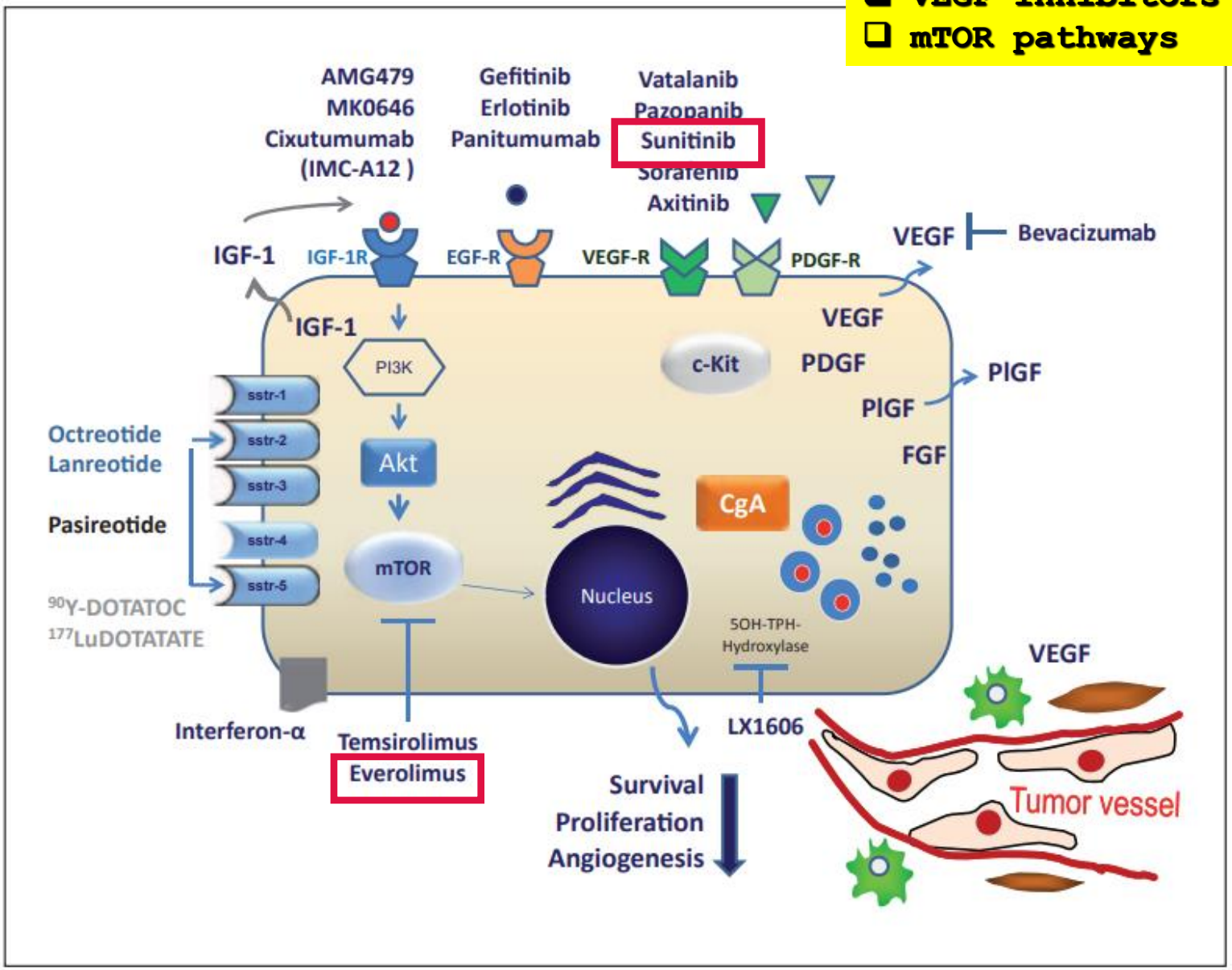


No. at Risk								
Lanreotide	101	94	84	78	71	61	40	0
Placebo	103	101	87	76	59	43	26	0

Caplin ME, et al. N Engl J Med 371:224,2014

TARGET THERAPY

- VEGF inhibitors
- mTOR pathways



Pavel M. Neuroendocrinology 2012

TARGET THERAPIES

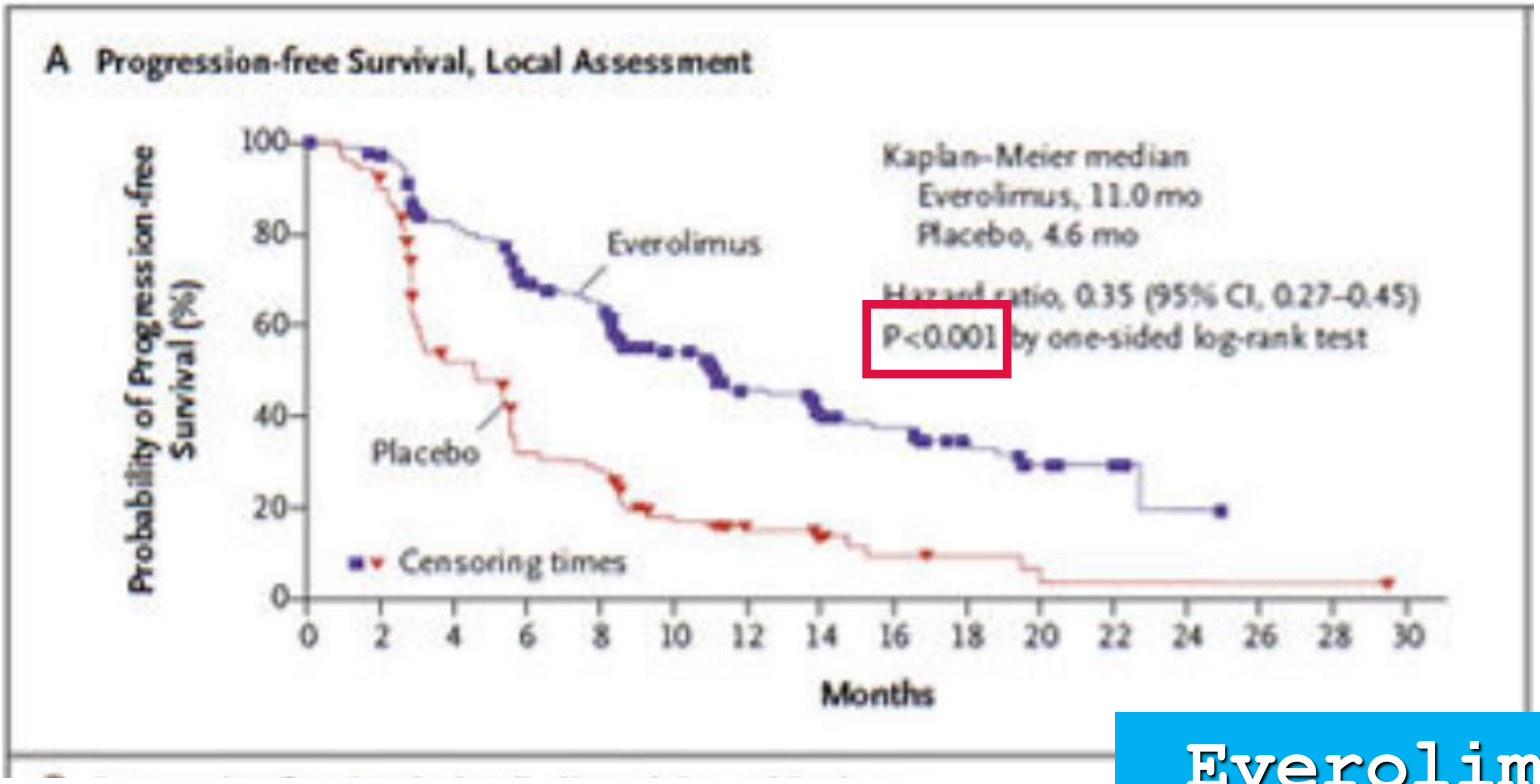
- TARGET THERAPY
  - Everolimus (RADIANT 3)
  - Sunitinib (A6181202)

N Engl J Med. 2011 February 10; 364(6): 514–523. doi:10.1056/NEJMoa1009290.

RADIANT -3 STUDY

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and **Kjell Öberg, M.D., Ph.D. for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group**



Everolimus

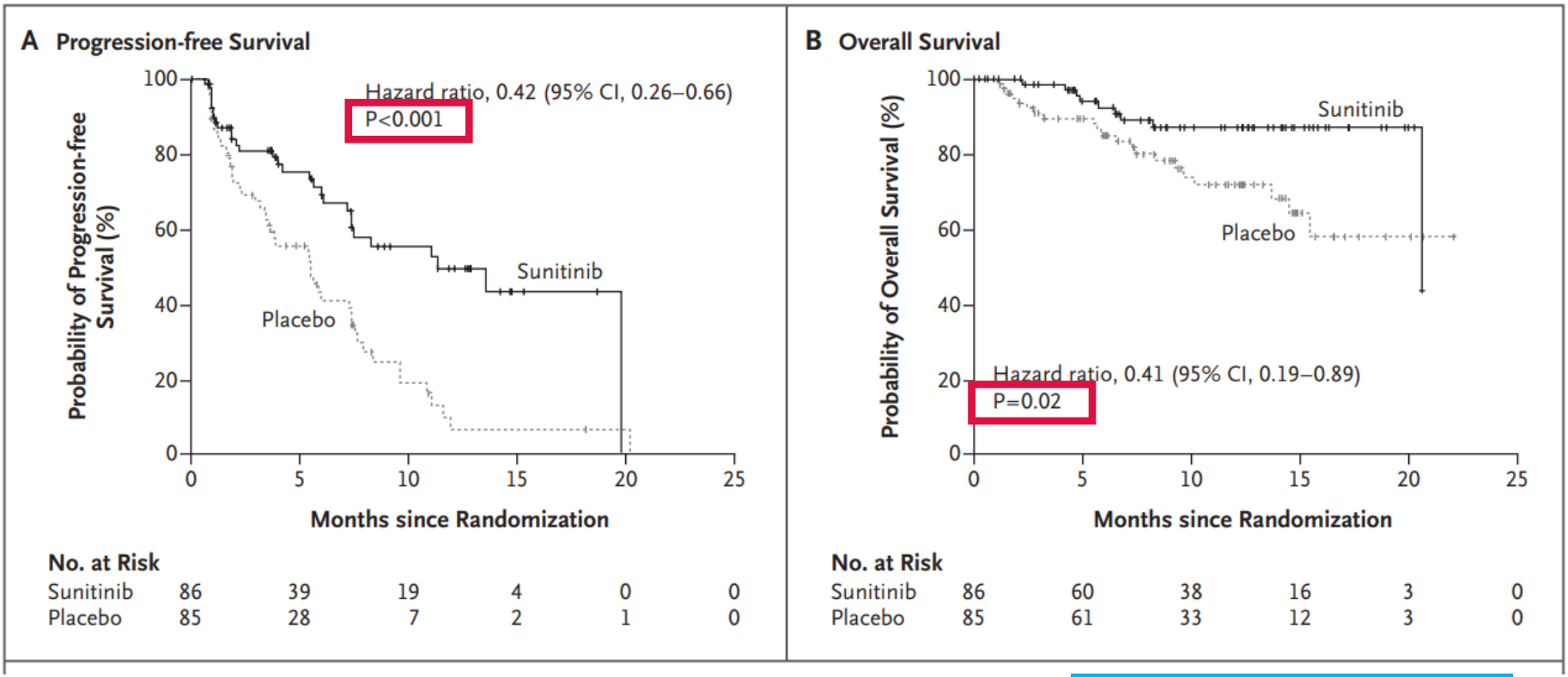
Yao JC, et al. N Engl J Med. 2011;364:514-23.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2011 VOL. 364 NO. 6

A6181202 STUDY

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors



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

Sunitinib

Advances in the Management of Unresectable or Metastatic Pancreatic Neuroendocrine Tumors: Chemotherapy, Targeted Therapy, Hormonal Treatment, and Future Directions

Table 2. Selected Phase II and III Clinical Trials of Targeted Therapies for Patients with Advanced pNET

References	Study/Setting	Treatment	No. of patients	Response rate, %	Median PFS/TTP and OS, months
mTOR inhibitors					
Yao et al.	Phase II	Everolimus *vs* everolimus-octreotide	160	9 *vs* 4	PFS, 9.7 *vs* 17
Yao et al	Phase III	Everolimus-BSC *vs* placebo-BSC	410	5 *vs* 2	PFS, 11 *vs* 4.6
Duran et al.	Phase II	Temsirolimus	37	7	PFS, 10.6
Hobday et al.	Phase II	Temsirolimus-BEV	55	37	NA
TK inhibitors					
Kulke et al.	Phase II	Sunitinib	107	18	PFS, 7.7
Raymond et al.	Phase III	Sunitinib *vs* placebo	171	9.3 *vs* 0	PFS, 11.4 *vs* 5.5
Raymond et al.	Phase II	Sorafenib	43	9	PFS, 11.9
Phan et al.	Phase II	Pazopanib-octreotide	31	17	11-Jul

pNET, pancreatic neuroendocrine tumor; BSC, best supportive care; PFS, Progression-free survival; TTP,Time-to progression; OS, overall survival, NA, not applicable

Bilici A, et al. Asian Pac J Cancer Prev 2015

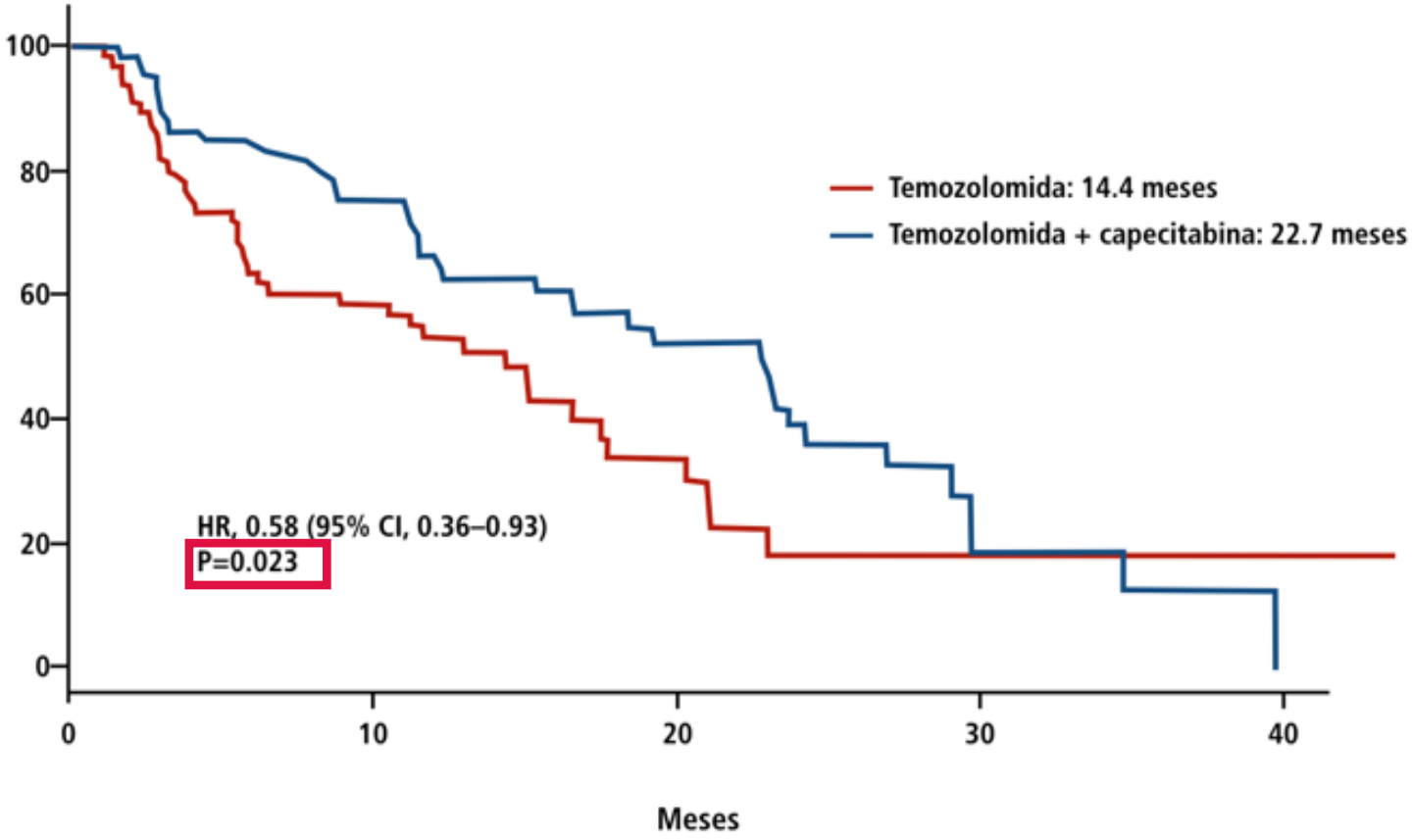
CHEMOTHERAPY

❑ CHEMOTHERAPY

Streptozocin
Temozolamide
Capecitabine
Oxaliplatin

N Engl J Med, 303:1189-94, 1980
Eur J Cancer. 2015 Jul;51(10):1253-62
Clin Cancer Res, 13:2986-2991, 2007
J Clin Oncol, 23:4762-4771, 2004
J Clin Oncol, 24:401-406, 2006
Cancer 117:268-275, 2011

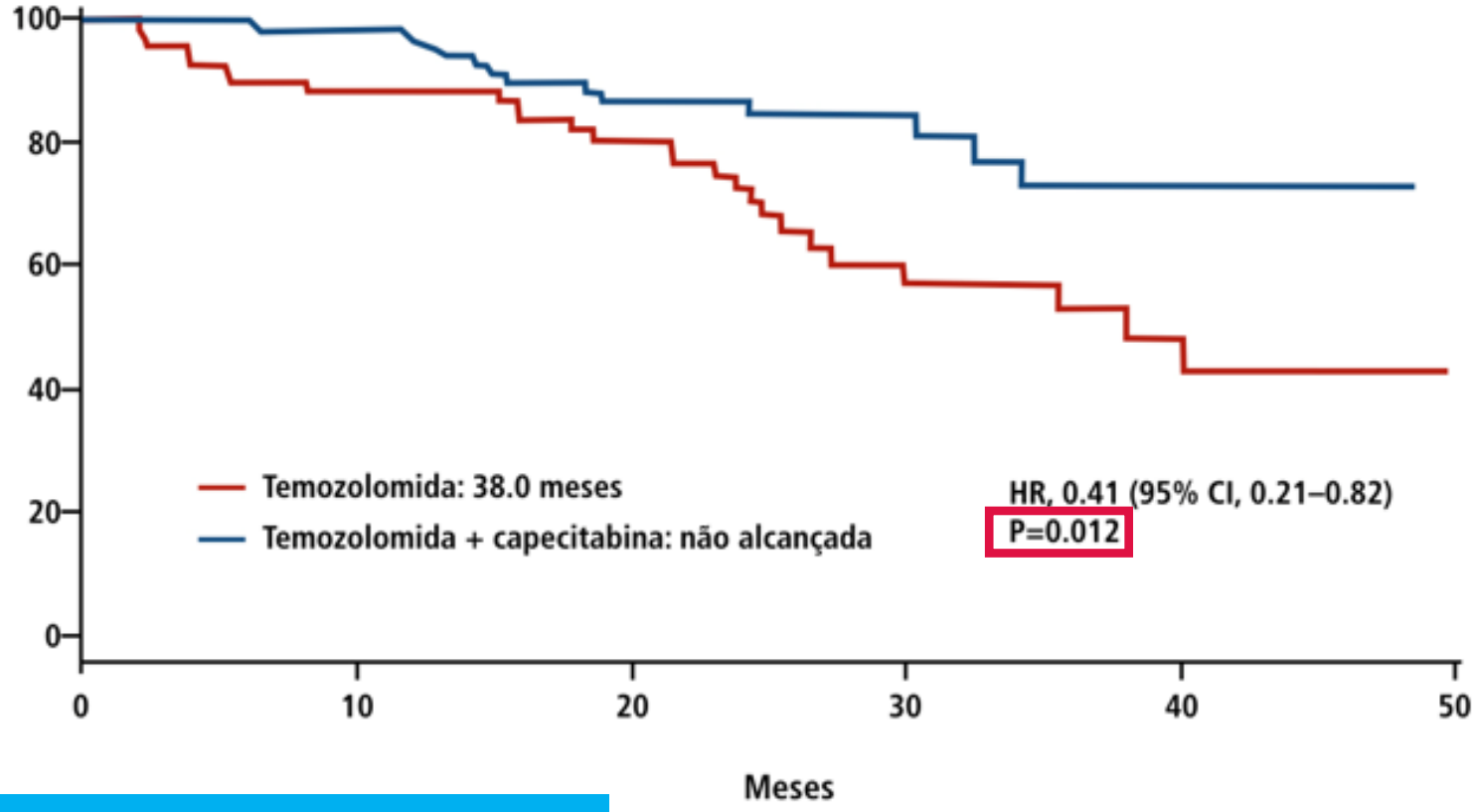
Temozolomide + Capecitabine



Progression free survival

J Clin Oncol 36, 2018 (suppl; abstr 4004)

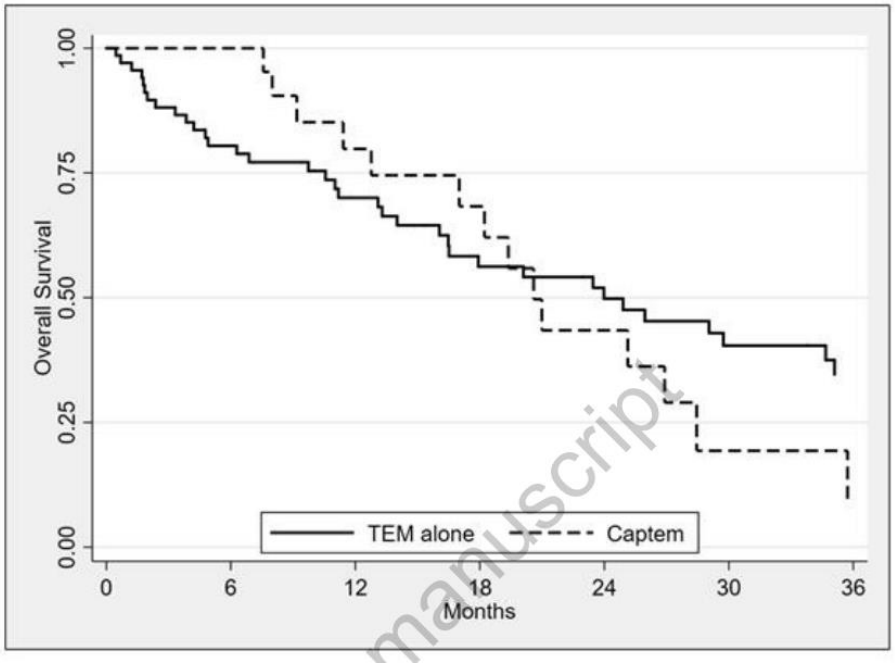
Temozolomide + Capecitabine

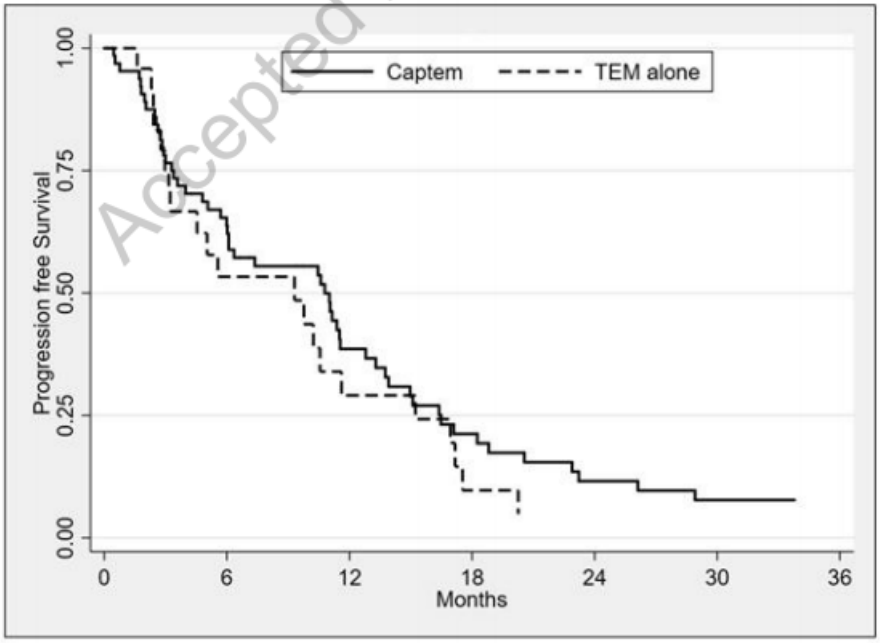


Overall survival

J Clin Oncol 36, 2018 (suppl; abstr 4004)

Temozolomide Alone or Combined with Capecitabine





(p=0.585)

Bongiovanni A, et al. Neuroendocrinology 2020

Advances in the Management of Unresectable or Metastatic Pancreatic Neuroendocrine Tumors: Chemotherapy, Targeted Therapy, Hormonal Treatment, and Future Directions

Table 1. Selected Clinical Trials of Systemic Chemotherapy in Patients with Advanced Pancreatic Neuroendocrine Tumors

Regimen		No. patients	Response rate,%	Median PFS and OS, months
Moertel et al.	STZ-DOX *vs* STX-5-FU *vs* Chloro	105	69 *vs* 45 *vs* 30	PFS, 18 *vs* 14 *vs* 17; OS, 26.4 *vs* 16.8 *vs* 18
Kouvaraki et al.	STZ-5-FU-DOX	84	39	PFS, 18;OS, 37
Ramanathan et al.	DTIC	42	33	PFS, NR; OS, 19.3
Strosberg et al.	TEM-CAP	30	70	PFS, 18; OS, NR
Kulke et al.	TMZ-TALD	11	45	PFS, NR; OS, NR
Chan et al.	TMZ-BEV	15	33	PFS, 14.3; OS, 41.7
Fine et al.	TMZ-CAP	11	36	PFS, >20; OS, >24.4

STZ, streptozocin; DOX, doxorubicin; 5-FU, 5- fluorouracil; Chloro, chlorozotocin; DTIC, dacarbazine; CAP, capecitabine; TALD, thalidomide; BEV, bevacizumab; PFSm progression-free survival; OSm overall survival; NR, not reached

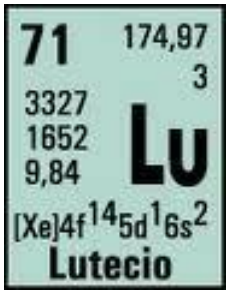
Bilici A, et al. Asian Pac J Cancer Prev 2015

Selected Randomized Controlled Trials for the Treatment of Pancreatic Neuroendocrine Tumors							
Trial	**Year**	**Enrollment**	**Patients Enrolled**	**Intervention**	**Comparator**	**Progression Free Survival**	**Response rate**
Moertel et al.	1980	Unresectable, metastatic PNETs	84	STZ 500mg/m^2 + FU 400mg/m^2 daily × 5 days, q6w	STZ 500mg/m^2 daily × 5 days, q6w	Not reported	63% vs 36% (p<0.01)
Raymond et al.	2011	Well-differentiated, progressive, unresectable PNETs	171	Sunitinib 37.5mg daily	Placebo	11.4 vs 5.5 months (p<0.001)	9.3% vs 0% (p=0.007)
RADIANT-3	2011	Low or intermediate-grade, unresectable, progressive PNETs	410	Everolimus 10mg daily	Placebo	11.0 vs 4.6 months (p<0.001)	5% vs 2% (p<0.001)
CLARINET	2014	Nonfunctioning enteropancreatic NETs or Gastrinoma, SSR+, Unresectable, Ki-67 <10%, 96% stable disease	204 (45% PNETs)	Lanreotide 120mg q28d	Placebo	65.1% vs 33.0% at 24 months (p<0.001)	Not reported
NETTER-1	2017	Well-differentiated, unresectable, progressive midgut NETs, SSR+, Ki-67 <20%	229	177Lu-Dotatate PRRT 7.4 GBq q8w + Octreotide LAR 30mg q4w	Octreotide LAR 60mg q4w	65.2% vs 10.8% at 20 months (p<0.001)	18% vs 3% (p<0.001)
E2211	2018	Low or intermediate-grade, unresectable, progressive PNETs	144	CAP 750 mg/m^2 daily × 14 days + TMZ 200 mg/m^2 daily × 5 days	TMZ 200 mg/m^2 daily × 5 days	22.7 vs 14.4 months (p=0.023)	Not reported

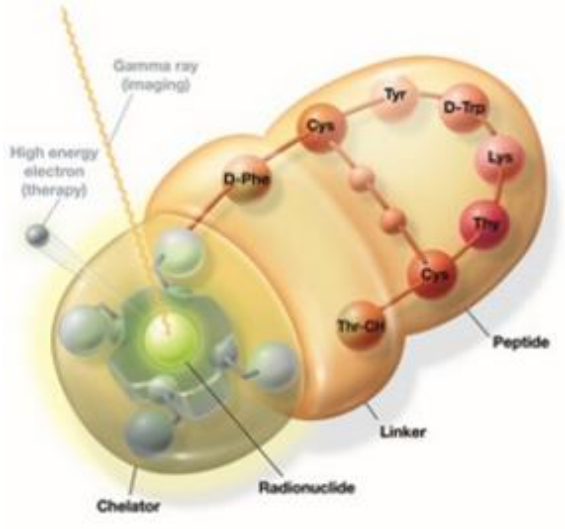
Scott AT, et al. Surg Clin North Am 2019;99:793–814

Peptide receptor radionuclide therapy

177 Lutetium



- Peptide Receptor Radionuclide Therapy (PRRT)
- Somatostatin analogue radionucleotide (beta radiation)



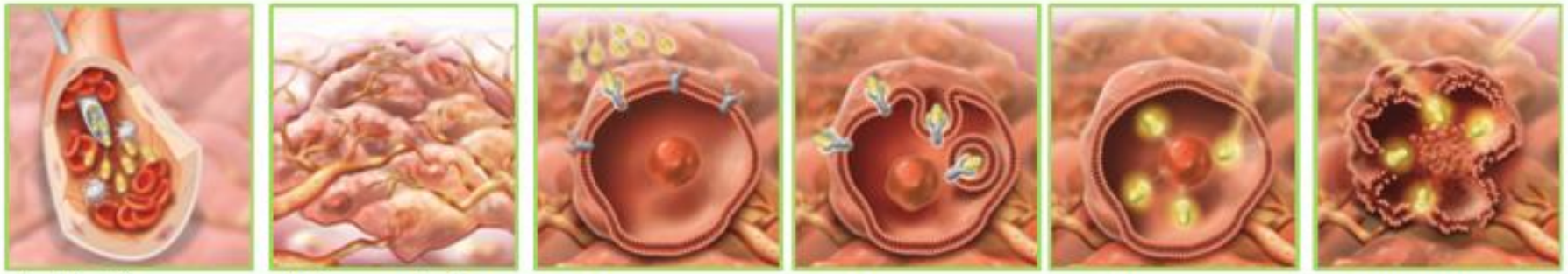
❑ PRRT

177 Lutetium

Kwekkeboom DJ A, et al. J Clin Oncol 2008

Peptide receptor radionuclide therapy

177 Lutetium

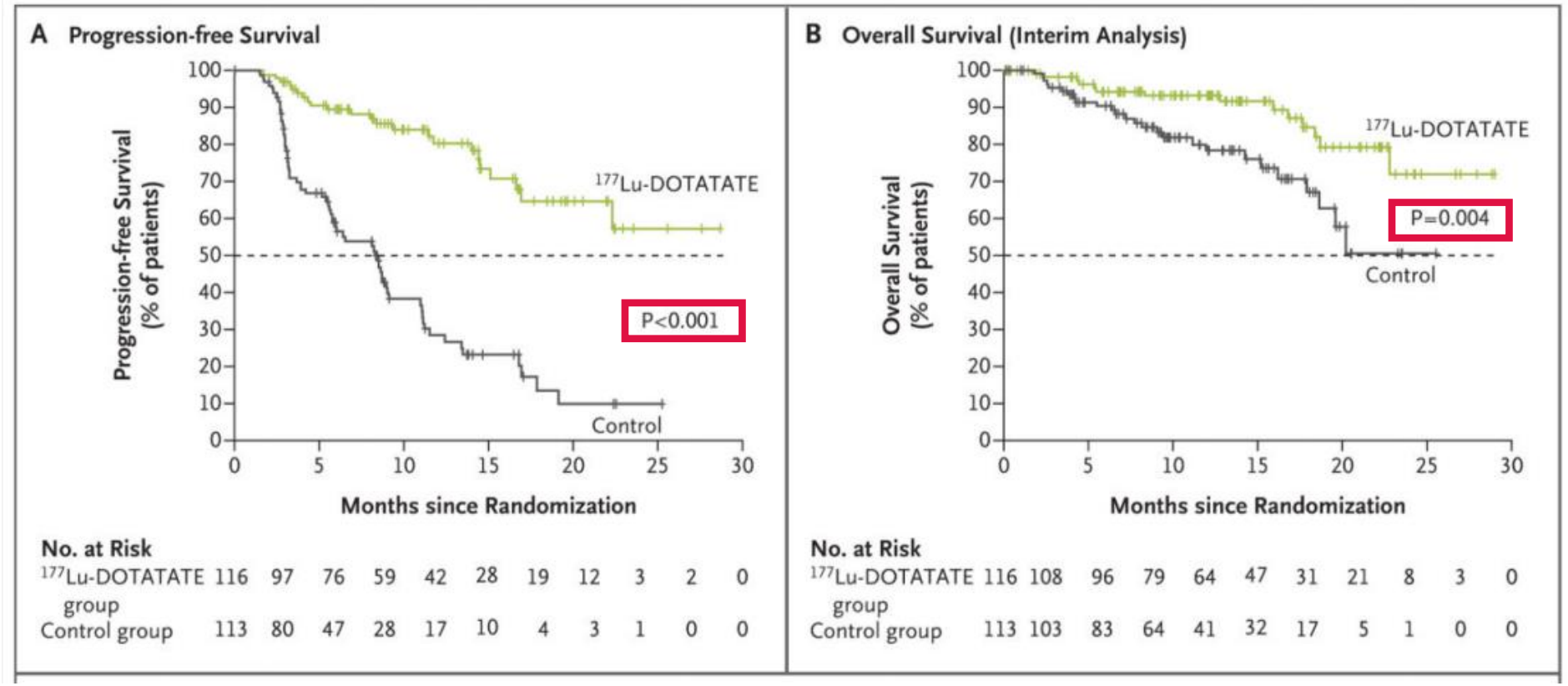


Kwekkeboom DJ A, et al. J Clin Oncol 2008

Peptide receptor radionuclide therapy

177 Lutetium

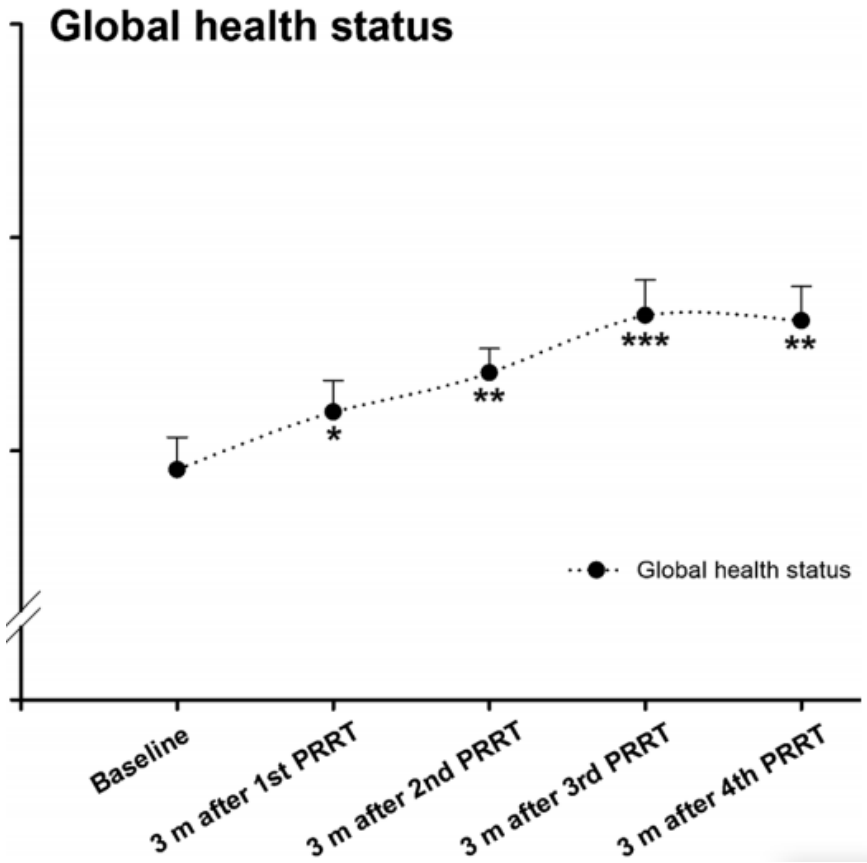
NETTER-1 STUDY

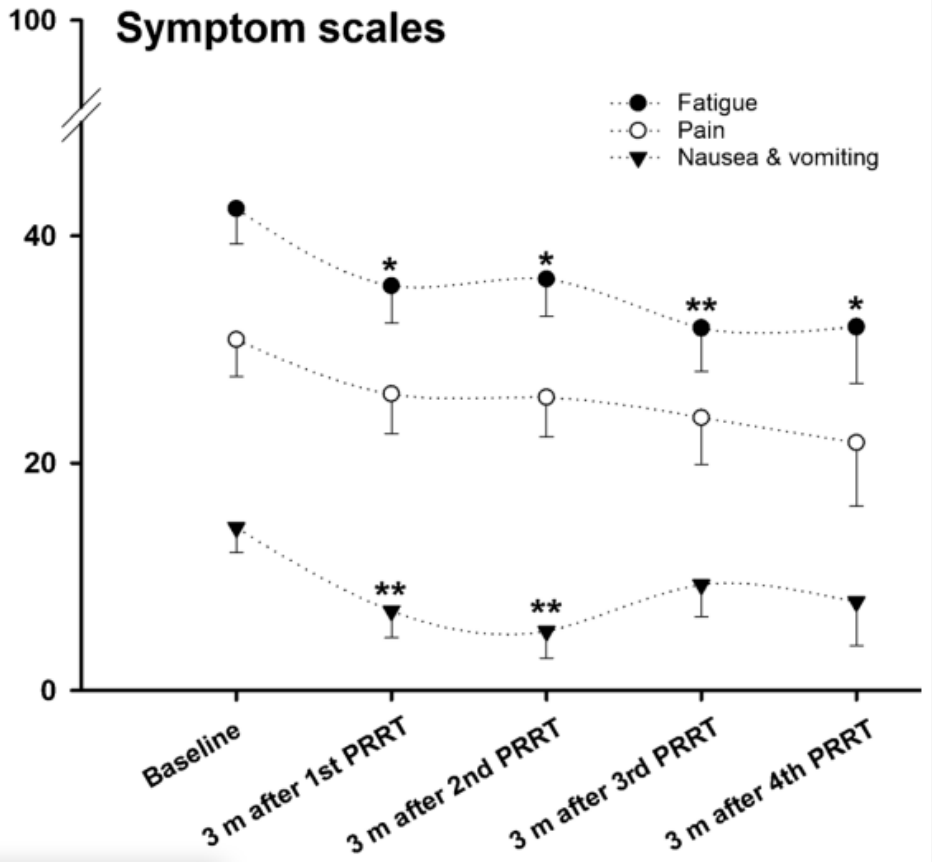


Strosberg J, et al. N Engl J Med. 2017;376:125-35.

PRRT and Quality of Life

177 Lutetium





Marinova M, et al. Eur J Nucl Med Mol Imaging 2017

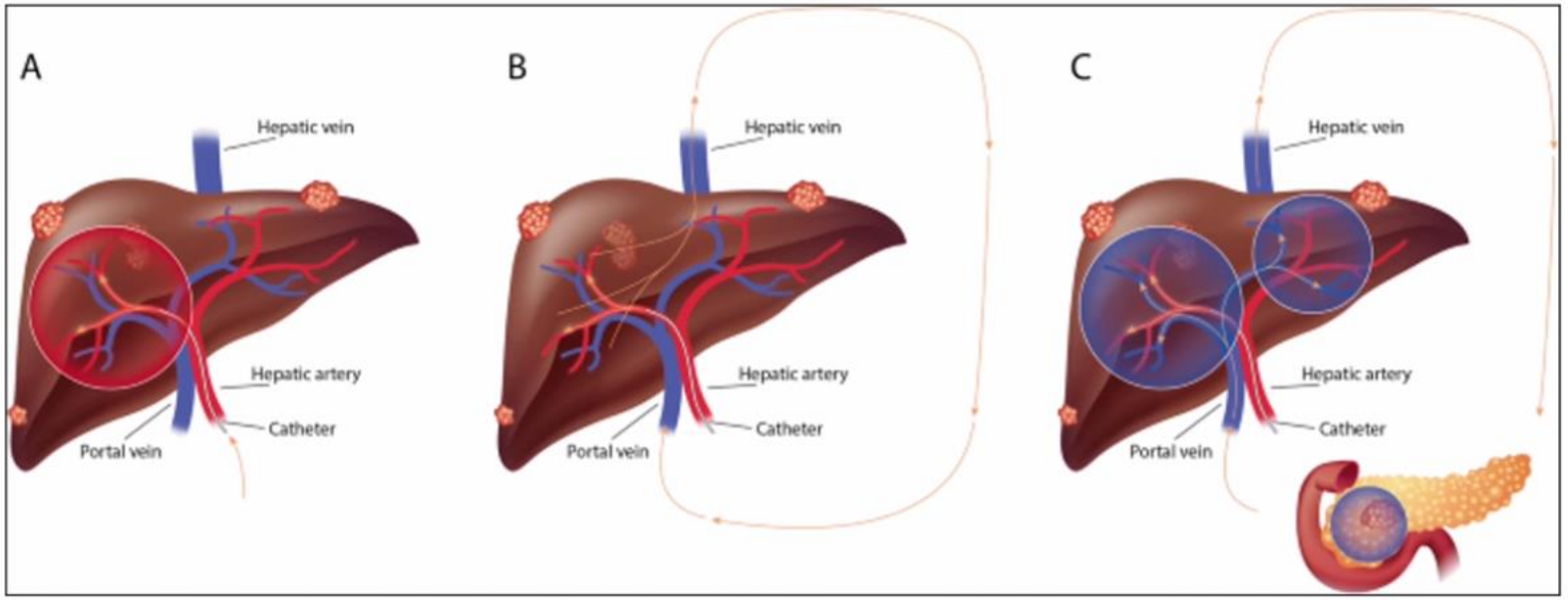
Thanks!

www.drorlandotorres.com.br

Zoom Meeting

Orlando Torres | LO Dimitry Garry | Wooil Kwon | Susumu Hijioka | Vikram Chaudhari | Mahesh Goel

View



Treatment principle.

A IA administration of ^{177}Lu-DOTATATE selectively in the right or left hepatic artery (right in th

B Systemic circulation of ^{177}Lu-DOTATATE after IA administration.

C Treatment of whole liver (second-pass) and other organs

MCR NUSA DUA LIVE

Unmute | Start Video | 14 Participants | 8 Chat | Share Screen | Record | Breakout Rooms | Reactions | Leave

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Targeted Therapy

Trial	Description	Patients	Drug	End Point
TALENT	Phase II single arm European multicenter trial in 2 parallel cohorts. Advanced, progressive PanNET and GI-NETs.	Pancreatic 55 GI – 56	Lenvatinib 24mg/day till progression or intolerance	ORR 44% PANET 16% GINET PFS – 15.7months
SANET-ep	Randomized phase III Chinese multicenter trial – Surufatinib in extrapancreatic NETs	129 Surufatinib, 69 placebo	Surufatinib 300mg/day vs placebo. Crossover design.	Median PFS- 9.2 vs 3.8 months
SANET-p	Randomized phase III Chinese multicenter trial Unresectable/metastatic well differentiated pancreatic NETs with progression on up to 2 lines of therapy. Surufatinib in PanNETs	113 Surufatinib, 59 placebo	Surufatinib 300mg/day vs placebo. Crossover design	Median PFS- 10.9 vs 3.7 months
AXINET	Axitinib in extrapancreatic NETs -Advanced G1/G2 extrapancreatic NETs.	126 axitinib, 130 placebo 40% GI, 17% lung, 32% other	Octreotide LAR + Axitinib vs Octreotide LAR + Placebo	Primary ORR 17 Median months

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Recording

SYMPOSIUM PANCREAS-2

8 SEPTEMBER 2021 - NUSA DUA ROOM

TOPIC :

"Systemic Treatment Of Metastatic And Unresectable PNETs"

Prof. Orlando JM Torres, MD, PhD
FEDERAL UNIVERSITY OF MARANHÃO, BRAZIL

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BALI A-PHPBA 2021 VIRTUAL CONGRESS

No surgery

- Technical contraindication (cavernoma...)
- Patient contraindication (poor general status)
- Extrahepatic metastatic disease
- pNEC G3

Observation possible

- Sporadic asymptomatic NF pNET G1 < 2 cm
- MEN-1 asymptomatic NF pNET G1 < 2 cm
- NEM-1 gastrinoma < 2 cm

Surgery required

Basically all other!!!

METASTATIC AND UNRESECTABLE

Souche R, et al. J. Clin. Med. 2020

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Susumu Hijioka
Mahesh Goel
Vikram Chaudhari
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Wooil Kwon
Vikram Anil Chaudhari, MD
SPEAKER
Vikram Chaudhari
Prof. Orlando Jorge M Torres, MD, PhD
SPEAKER
Orlando Torres
国立がん研究センター
National Cancer Center Ja
Susumu Hijioka, MD
CHAIRPERSON
Mahesh Goel, MD, PhD
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