



# Neuroendocrine Cancers: Biologically Targeted Treatments

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# Objectives

- To discuss the changing landscape of treatment of NETs
- To review biologically targeted treatments for NETs
- To consider individualized treatment in NETs

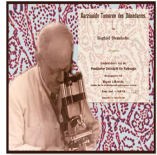


# Times are Changing



# Progress in the Land of Small Tumors

Classification/Guidelines



1907

“Karzinoide”  
coined by  
Oberndorfer<sup>1</sup>

1980

WHO classification  
Carcinoids<sup>3</sup>

2000

WHO classification  
NET and NEC<sup>6</sup>

2009

AJCC/UICC TNM  
classification  
GI/pNET<sup>10</sup>

2015/16

CANADIAN  
GUIDELINES  
PNET AND GI

2006/08

ENETS  
guidelines<sup>4</sup>;  
TNM staging<sup>5,7</sup>

2010

NANETS  
guidelines<sup>8</sup>

2012

ESMO  
guidelines<sup>22,27</sup>

2015

WHO classification  
Lung NET/carcinoids<sup>35</sup>

1900

1980

2000

2005

2010

2015

1988/89

OCT SC  
CS<sup>25,30</sup>

1998

LAN  
symptom control<sup>24</sup>

2009

PROMID  
OCT LAR: antitumor  
activity<sup>9,31</sup>

2014/15

CLARINET  
LAN GEP NET<sup>16,17,29</sup>

2015/16

RADIANT-4  
EVE NF GI and  
lung NET<sup>15,19</sup>

1982

STZ  
pNET<sup>36</sup>

1992

STZ combination:  
survival benefit pNET<sup>2</sup>

OCT LAR  
carcinoid  
tumors<sup>23,26,28</sup>

2010/11

RADIANT-3  
EVE in pNET<sup>11,12,32,33</sup>

Sunitinib phase 3 pNET<sup>13,31,34</sup>

ELECT  
LAN: symptom  
control<sup>27</sup>

2015

TELESTAR  
telotristat etiprate  
CS<sup>20</sup>  
NDA filed 3/30/16

RADIANT-2  
EVE + OCT LAR in mNET w/CS<sup>14</sup>

NETTER-1  
<sup>177</sup>Lu-Dotatate midgut  
NET<sup>18</sup>

US  
Approval

US/EU  
Approval

EU  
Approval

AC, atypical carcinoid; AJCC; American Joint Committee on Cancer; CS, carcinoid syndrome; ENETS, European Neuroendocrine Tumor Society; ESMO; European Society for Medical Oncology; EVE, everolimus; GEP, gastroenteropancreatic; LAN, lanreotide; LAR, long-acting repeatable; m, metastatic; NANETS, North American Neuroendocrine Tumor Society; NDA, New Drug Application; NEC, neuroendocrine carcinomas; NET, neuroendocrine tumors; NF, nonfunctional; OCT, octreotide; pNET, pancreatic NET; SC, subcutaneous; STZ, streptozocin; TC, typical carcinoid; UICC, Union for International Cancer Control; WHO, World Health Organization.

Slide Courtesy of Dr. James Yao

This presentation is for scientific discussion only – Please do not distribute following this meeting





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DOI 10.1245/s10434-014-4145-0

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ORIGINAL ARTICLE – ENDOCRINE TUMORS

## **Consensus Recommendations for the Diagnosis and Management of Pancreatic Neuroendocrine Tumors: Guidelines from a Canadian National Expert Group**

Simron Singh, MD, MPH<sup>1</sup>, Chris Dey, MD<sup>2</sup>, Hagen Kennecke, MD<sup>3</sup>, Walter Kocha, MD<sup>4</sup>, Jean Maroun, MD<sup>5</sup>, Peter Metrakos, MD<sup>6</sup>, Tariq Mukhtar, PhD<sup>7</sup>, Janice Pasieka, MD<sup>8</sup>, Daniel Rayson, MD<sup>9</sup>, Corwyn Rowsell, MD<sup>10</sup>, Lucas Sideris, MD<sup>11</sup>, Ralph Wong, MD<sup>12</sup>, and Calvin Law, MD<sup>1</sup>



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## Cancer Treatment Reviews

journal homepage: [www.elsevierhealth.com/journals/ctrv](http://www.elsevierhealth.com/journals/ctrv)



### Anti-Tumour Treatment

## Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus



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Timothy Asmis <sup>g</sup>, David Chan <sup>a</sup>, Shereen Ezzat <sup>h</sup>, Rachel Goodwin <sup>i</sup>, Ozgur Mete <sup>b</sup>, Janice Pasieka <sup>j</sup>,  
Juan Rivera <sup>k</sup>, Ralph Wong <sup>l</sup>, Eva Segelov <sup>m</sup>, Daniel Rayson <sup>n</sup>

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<sup>h</sup> Princess Margaret Cancer Centre, Departments of Medicine & Oncology, University of Toronto, 610 University Ave. Room 7-327, Toronto, Ontario M5G 2N2, Canada

<sup>i</sup> The Ottawa Hospital Research Institute, Department of Medical Oncology, University of Ottawa, 501 Smyth Road, Ottawa, Ontario K1H8L6, Canada

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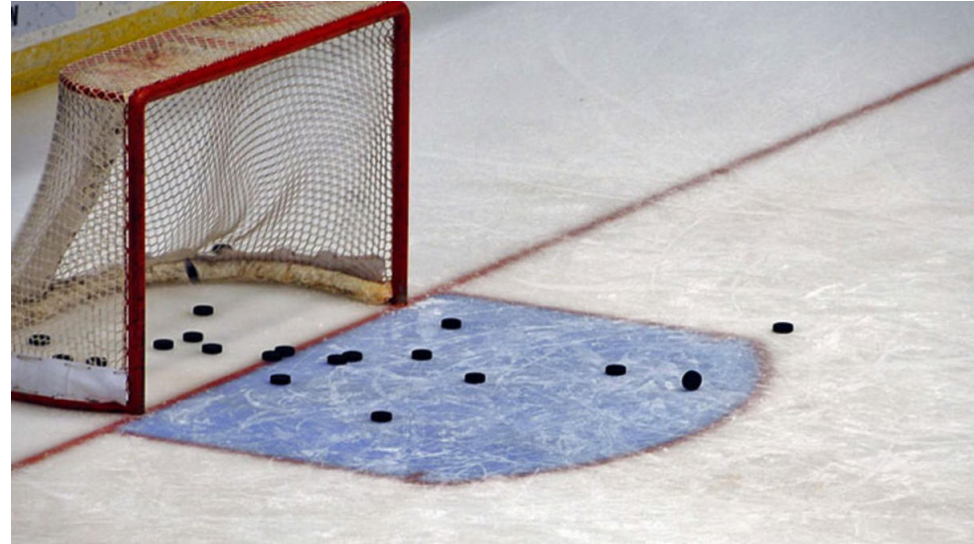
<sup>k</sup> McGill University Health Centre - Glen Campus, Bloc C - C04.5190, 1001 Decarie Blvd, Montreal, QC H4A 3J1, Canada

<sup>l</sup> CancerCare Manitoba, St Boniface General Hospital, 407 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada

<sup>m</sup> St Vincent's Clinical School, University of New South Wales, 438 Victoria St, Darlinghurst, NSW 2010, Australia

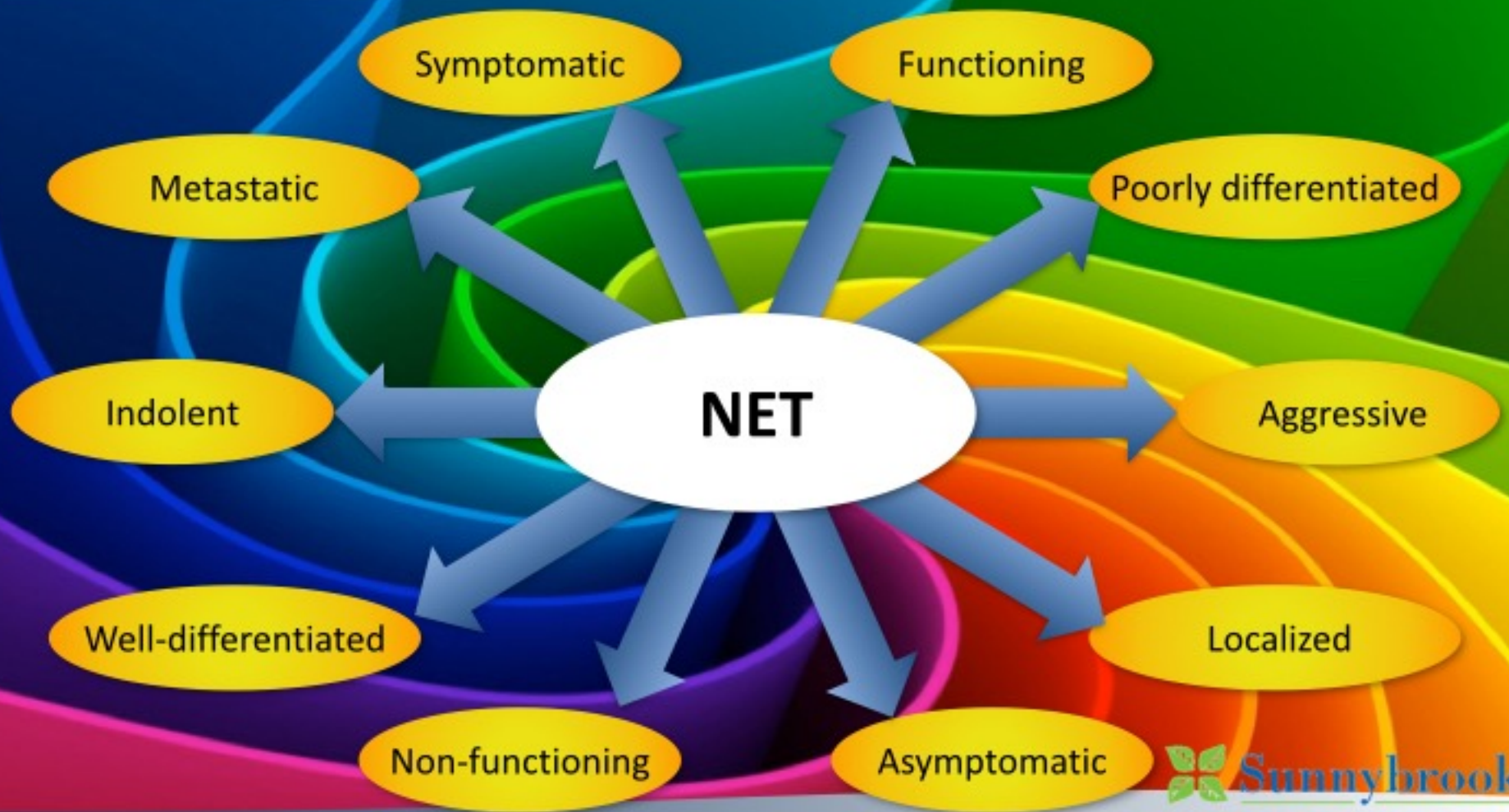
<sup>n</sup> QEII Health Sciences Centre, Division of Medical Oncology, Dalhousie University, Suite 457A Bethune Building, 1276 South Park Street, Halifax, NS B3H 2Y9, Canada

# Are all NETs equal?

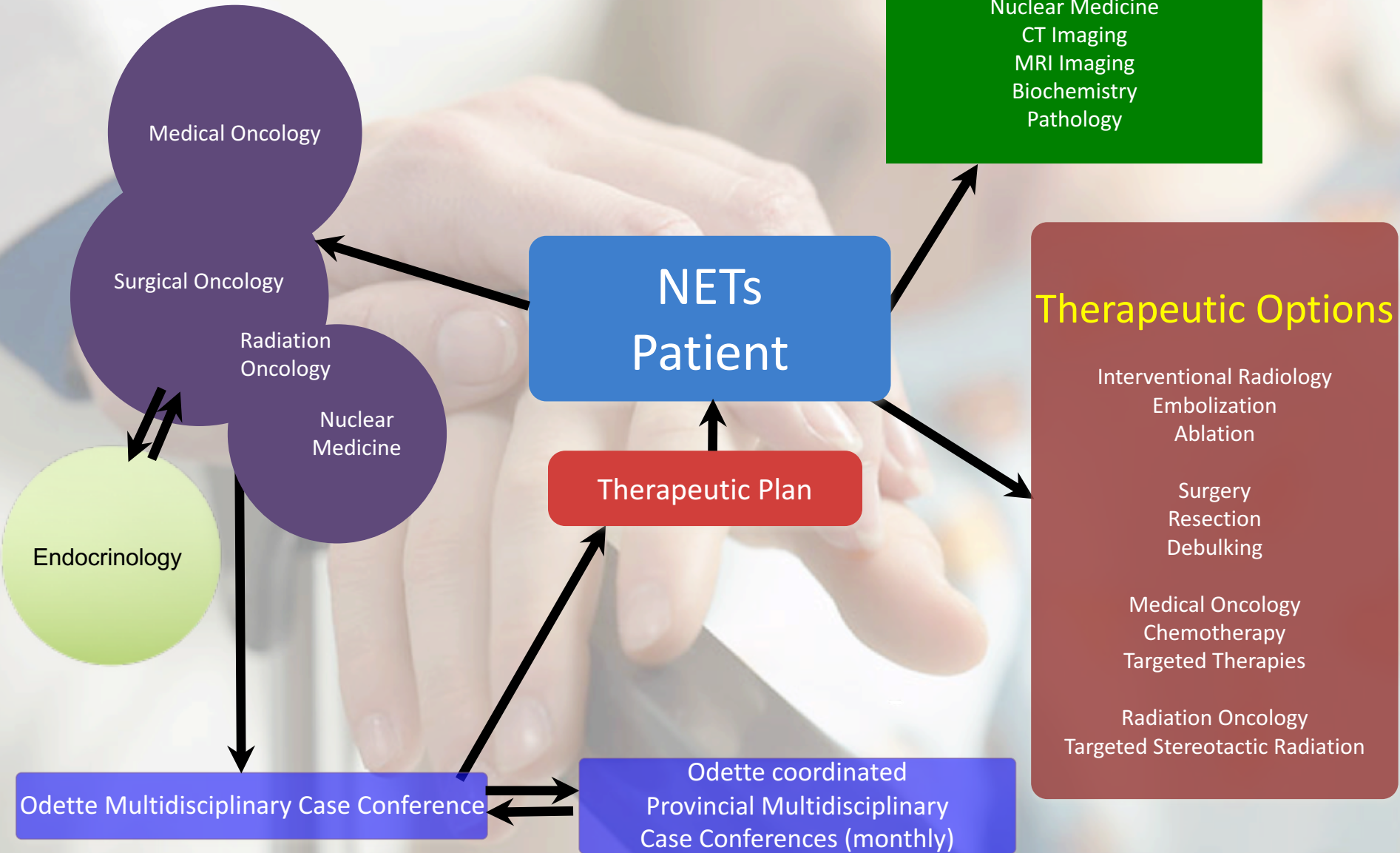




# Spectrum of NETs







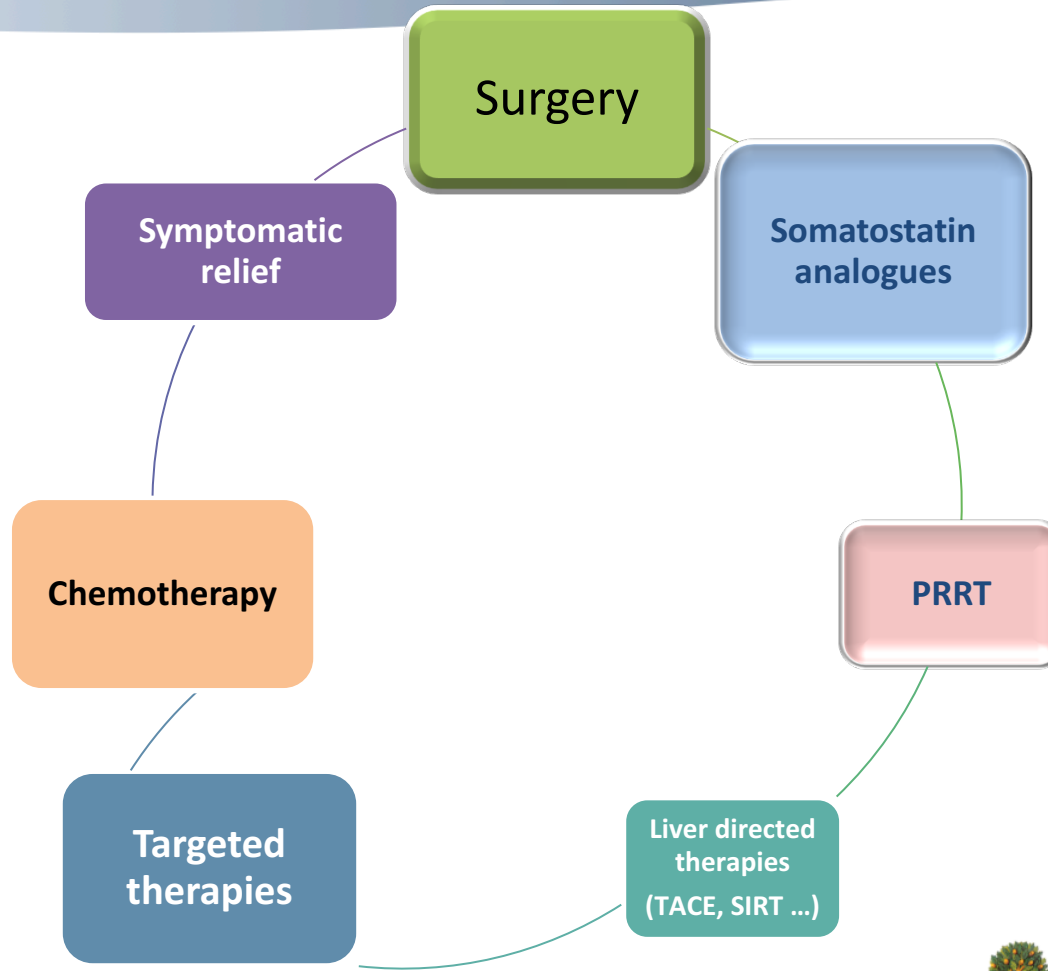


# Aims of Therapy in NET

- **Control symptoms**
  - Peptide/hormone secretion in hormonally active tumours
  - E.g., carcinoid syndrome, Zollinger-Ellison, ...
- Improve and maintain **quality of life**
- Inhibition of **tumour growth**
- Prevent **complications**
  - Carcinoid crisis, carcinoid heart disease, bleeding, ileus ...
- Prolong **survival**



# GOAL: Best-fit Therapy ...







# Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study

*James C Yao, Nicola Fazio, Simron Singh, Roberto Buzzoni, Carlo Carnaghi, Edward Wolin, Jiri Tomasek, Markus Raderer, Harald Lahner, Maurizio Voi, Lida Bubuteishvili Pacaud, Nicolas Rouyre, Carolin Sachs, Juan W Valle, Gianfranco Delle Fave, Eric Van Cutsem, Margot Tesselaar, Yasuhiro Shimada, Do-Youn Oh, Jonathan Strosberg, Matthew H Kulke, Marianne E Pavel, for the RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group\**



# RADIANT-4 Study Design

**Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)**

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression

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2:1

**Everolimus 10 mg/day**  
**N = 205**

**Placebo**  
**N = 97**

Treated until PD, intolerable AE, or consent withdrawal

## 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)

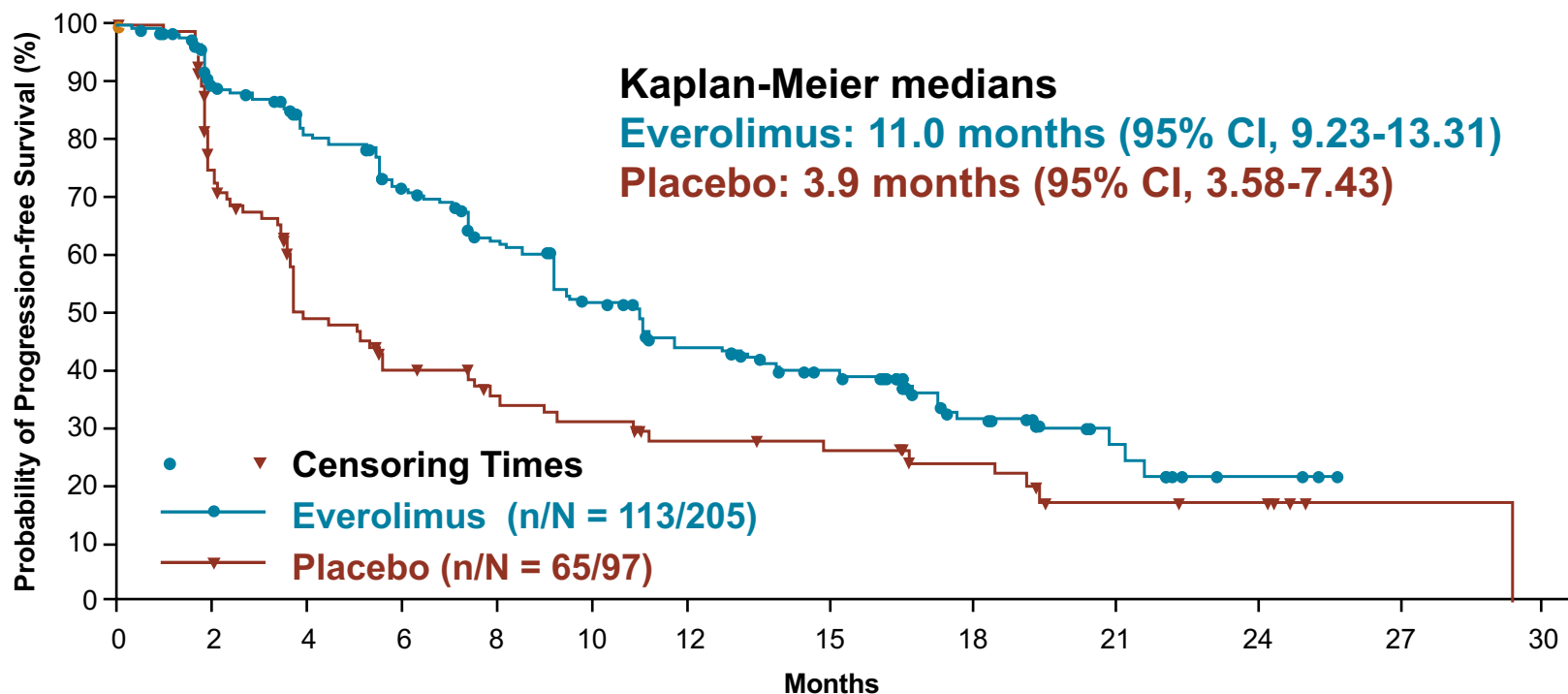
\*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** – lung, stomach, rectum, and colon except caecum.

Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

# Primary Endpoint: PFS by Central Review

**52% reduction in the relative risk of progression or death with everolimus vs placebo**

**HR = 0.48 (95% CI, 0.35-0.67);  $P < 0.00001$**



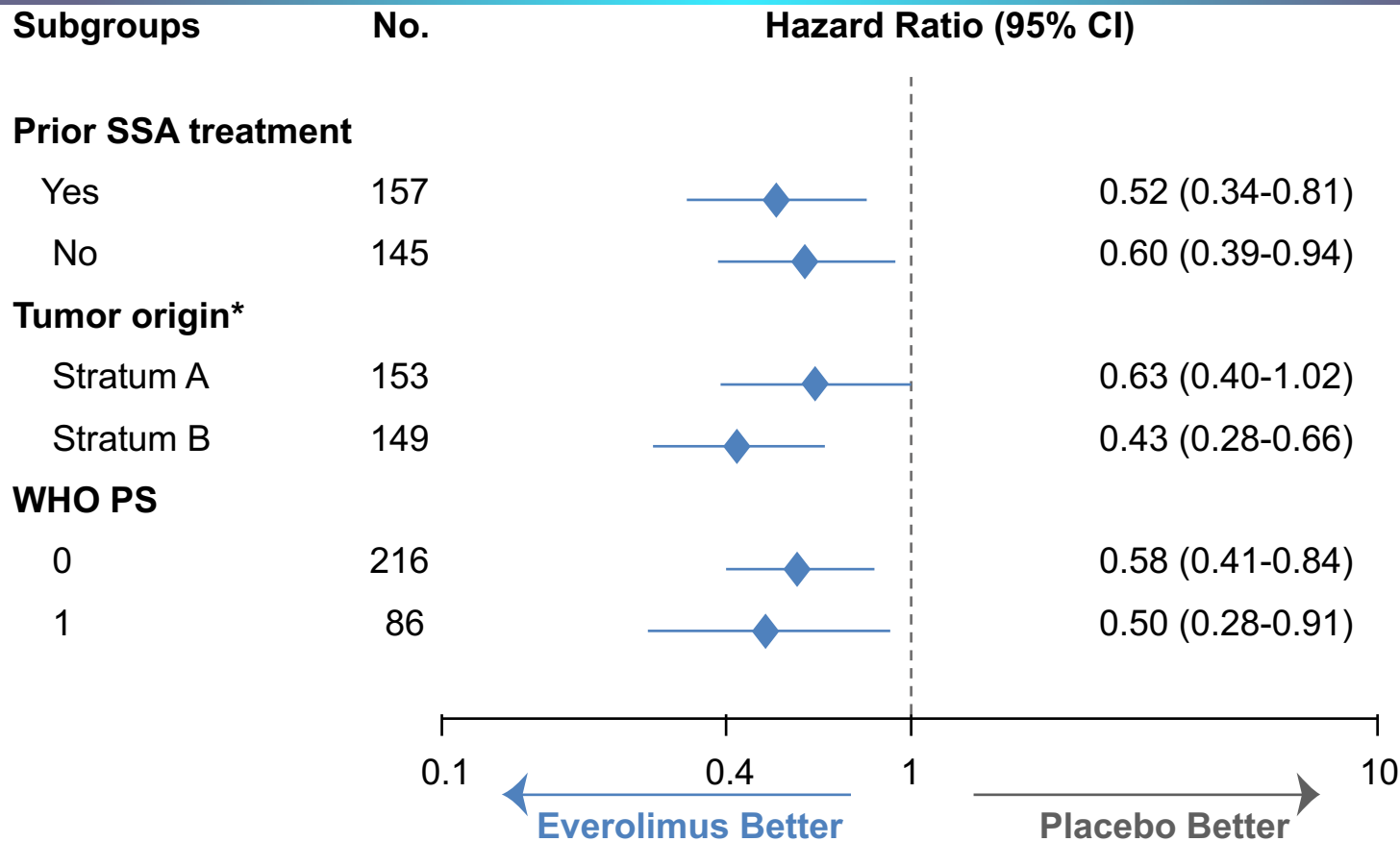
No. of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

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



# Consistent PFS HR by Stratification Factors, Central Review



\*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).

Hazard ratio obtained from unstratified Cox model.

NET, neuroendocrine tumors; SSA, somatostatin analogues; WHO PS, World Health Organization performance status.

# AEs Consistent with Known Safety Profile of Everolimus



	Everolimus N = 202		Placebo N = 98	
	All grades	Grade 3/4	All grades	Grade 3/4
<b>Drug-related adverse events</b>				
Stomatitis*	63%	9%	19%	0
Diarrhea	31%	7%	16%	2%
Fatigue	31%	3%	24%	1%
Infections†	29%	7%	4%	0
Rash	27%	1%	8%	0
Peripheral edema	26%	2%	4%	1%
Nausea	17%	1%	10%	0
Anemia	16%	4%	2%	1%
Decreased appetite	16%	1%	6%	0
Asthenia	16%	1%	5%	0
Non-infectious pneumonitis‡	16%	1%	1%	0
Dysgeusia	15%	1%	4%	0
Cough	13%	0	3%	0
Pruritus	13%	1%	4%	0
Pyrexia	11%	2%	5%	0
Dyspnea	10%	1%	4%	1%
Hyperglycemia	10%	3%	2%	0

Presented are drug-related adverse events in ≥10% of patients (safety set).

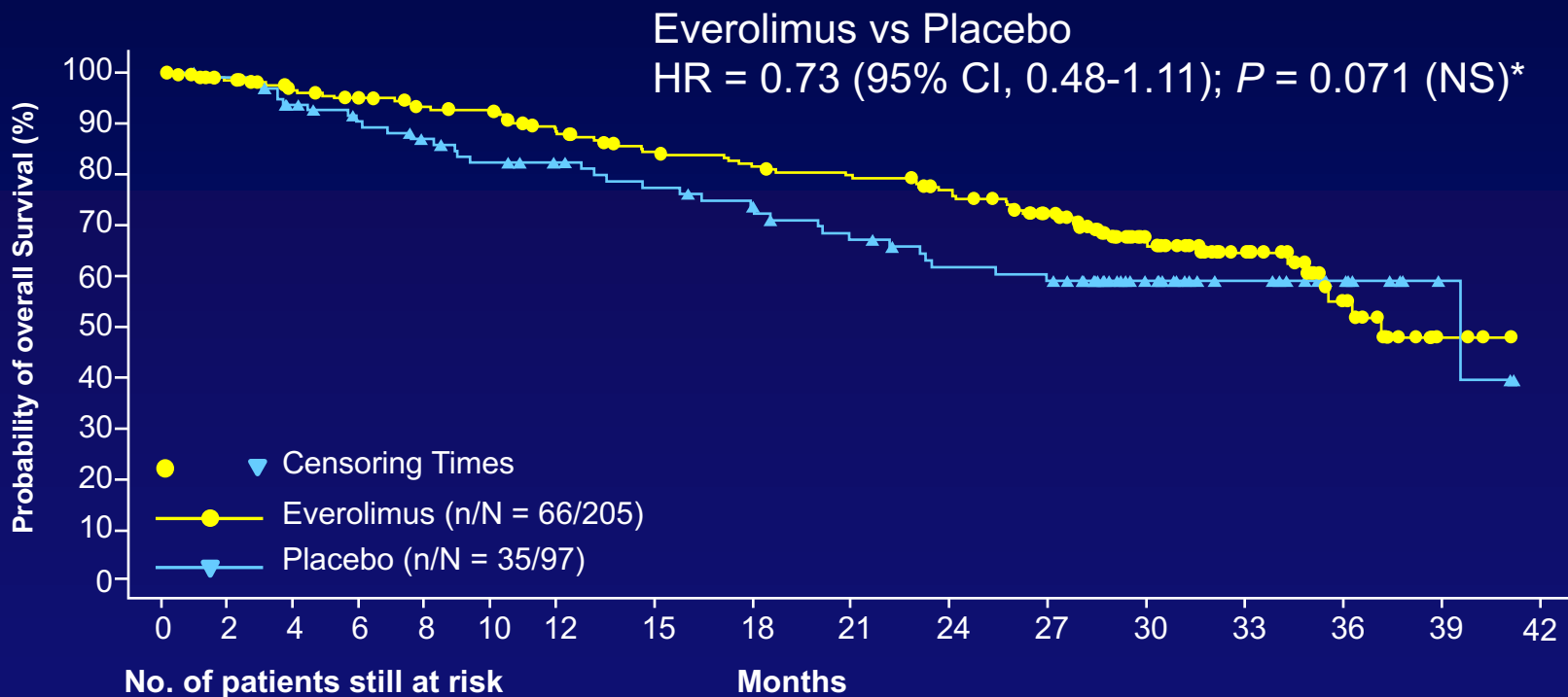
\*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.

†Includes all infections.

‡Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

# Second Interim Overall Survival Analysis

Second interim OS analysis performed with 53% of information fraction favored the everolimus arm



\*P-value boundary for significance = 0.0020.

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

Abbreviation: NS, not significant.



# Efficacy and Safety of Everolimus in Advanced, Progressive, Nonfunctional Neuroendocrine Tumors of the Gastrointestinal Tract and Unknown Primary: A Subgroup Analysis of the Phase 3 RADIANT-4 Trial

**Simron Singh**,<sup>1</sup>

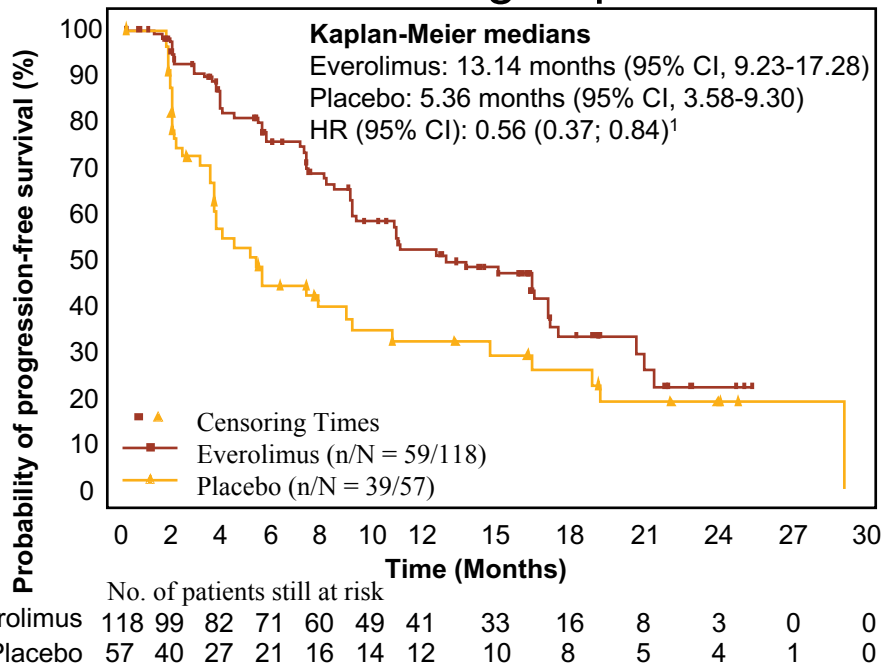
Carlo Carnaghi,<sup>2</sup> Roberto Buzzoni,<sup>3</sup> Rodney F. Pommier,<sup>4</sup> Markus Raderer,<sup>5</sup> Jiri Tomasek,<sup>6</sup> Harald Lahner,<sup>7</sup> Juan W. Valle,<sup>8</sup> Maurizio Voi,<sup>9</sup> Lida Bubuteishvili-Pacaud,<sup>10</sup> Jeremie Lincy,<sup>10</sup> Carolin Sachs,<sup>10</sup> Natsuko Okita,<sup>11</sup> Steven K. Libutti,<sup>12</sup> Do-Youn Oh,<sup>13</sup> Matthew Kulke,<sup>14</sup> Jonathan Strosberg,<sup>15</sup> James C. Yao,<sup>16</sup> Marianne E. Pavel,<sup>17</sup> Nicola Fazio,<sup>18</sup> for the RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial (RADIANT-4) Study Group

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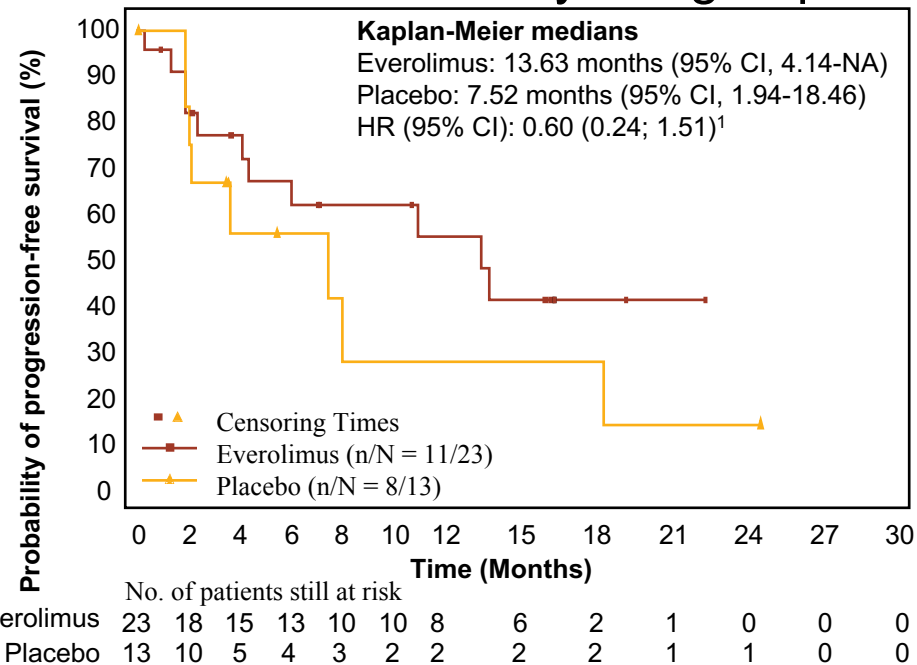
# Progression-free Survival (Central Review)

Everolimus improved median PFS in both the GI and unknown primary subgroups

## GI Subgroup



## Unknown Primary Subgroup



HR values presented are based on unstratified Cox regression analysis.

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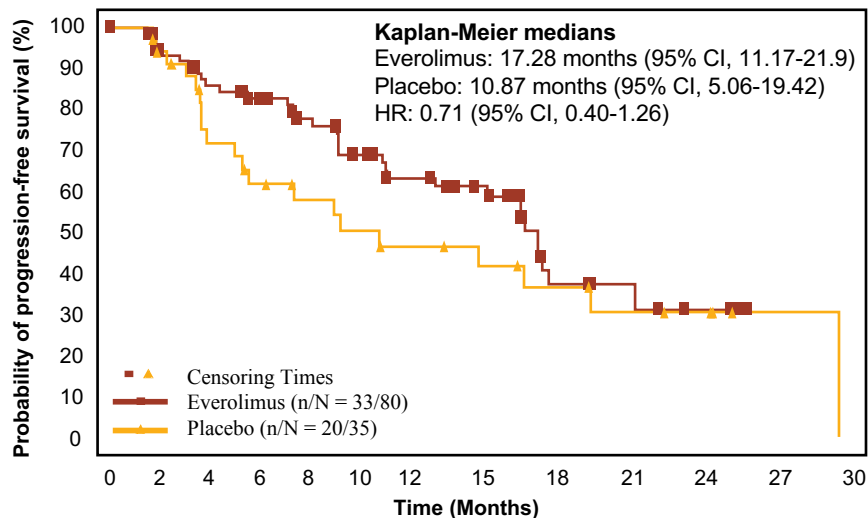
CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NET, neuroendocrine tumors; PFS, progression free survival

1. Yao *et al. Lancet* 2015;386:e-pub ahead of print.

# PFS: Midgut vs Non-midgut Subgroup

## Midgut

**29% reduction in the relative risk of progression or death and a median PFS  $\Delta$ 6.4 months with everolimus vs placebo**

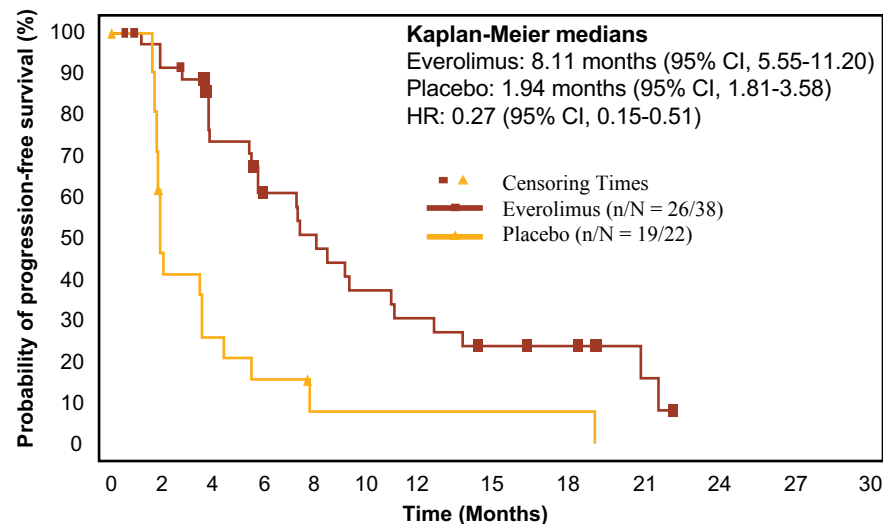


	No. of patients still at risk												
	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus	80	66	58	52	45	38	32	27	11	6	3	0	0
Placebo	35	31	22	18	15	13	11	9	7	5	4	1	0

HR values presented are based on unstratified Cox regression analysis. Duodenum (n=10) is included under midgut subgroup assuming they were located distally. Both arms received best supportive care.

## Non-midgut

**73% reduction in the relative risk of progression or death and a median PFS  $\Delta$ 6.2 months with everolimus vs placebo**



	No. of patients still at risk												
	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus	38	33	24	19	15	11	9	6	5	2	0	0	0
Placebo	22	9	5	3	1	1	1	1	1	0	0	0	0

HR values presented are based on unstratified Cox regression analysis. Both arms received best supportive care.

Midgut NET included primary tumors originating in the ileum, jejunum, caecum, duodenum, appendix, and small intestine (ileum and jejunum) while the non-midgut NET included primary tumors originating from the stomach, colon, and rectum

CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NET, neuroendocrine tumors; PFS, progression free survival



# Bronchial (Lung) NETs

- Most common type of NETs
- No standard treatment to date
- SSA are often used by extrapolating current data
- Unmet clinical need



# RADIANT-4 Study Design: Lung Subgroup

**Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)**

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression

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**Everolimus 10 mg/day**  
N = 205

**Placebo**  
N = 97

**Lung NET**  
N = 63

**Lung NET**  
N = 27

Treated until PD, intolerable AE, or consent withdrawal

## Endpoints:

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

## Core study 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.

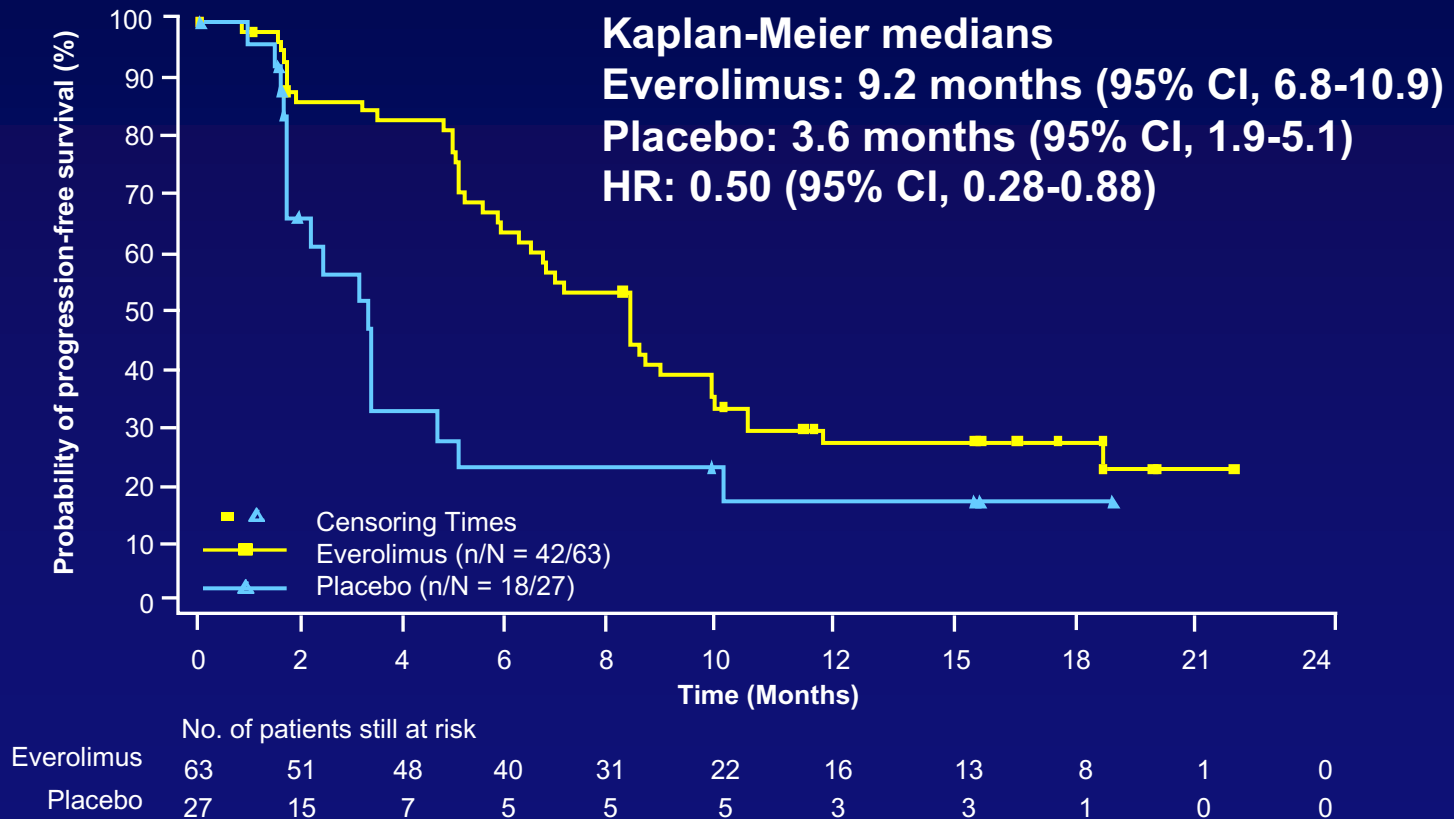
Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.



# PFS Treatment Effect in Lung NET Subgroup

## Per Central Review

50% reduction in the relative risk of progression or death with everolimus vs placebo; HR = 0.50 (95% CI, 0.28-0.88)



34 patients in prior SSA and 32 patients in SSA naive group had only liver involvement.

HR values presented are based on unstratified Cox regression analysis. Both arms received best supportive care.

Fazio N et al. 2016 European Neuroendocrine Tumor Society (ENETS), Barcelona, Spain. Abstract P1

For distribution in response to an unsolicited request for medical information subject to local NP4 approval.

# Drug-related AEs in $\geq 20\%$ of patients

Lung Subgroup	Everolimus N = 62*		Placebo N = 27	
	All grades	Grade 3/4	All grades	Grade 3/4
Stomatitis <sup>†</sup>	38 (61)	7 (11)	7 (26)	0
Rash	22 (35)	0	1 (4)	0
Fatigue	20 (32)	2 (3)	6 (22)	0
Peripheral edema	17 (27)	2 (3)	0	0
Diarrhea	16 (26)	3 (5)	2 (7)	0
Infections <sup>‡</sup>	14 (23)	5 (8)	1 (4)	0
Asthenia	14 (23)	1 (2)	0	0
Anemia	13 (21)	2 (3)	1 (4)	0
Decreased appetite	13 (21)	0	2 (7)	0

- Everolimus safety profile was similar to overall RADIANT-4 population

\*In everolimus arm, 1 patient withdrew the consent. <sup>†</sup>Includes stomatitis, aphthous stomatitis, mouth ulceration, and glossitis.

<sup>‡</sup>Includes all infections.

# RADIANT-3 Study Design

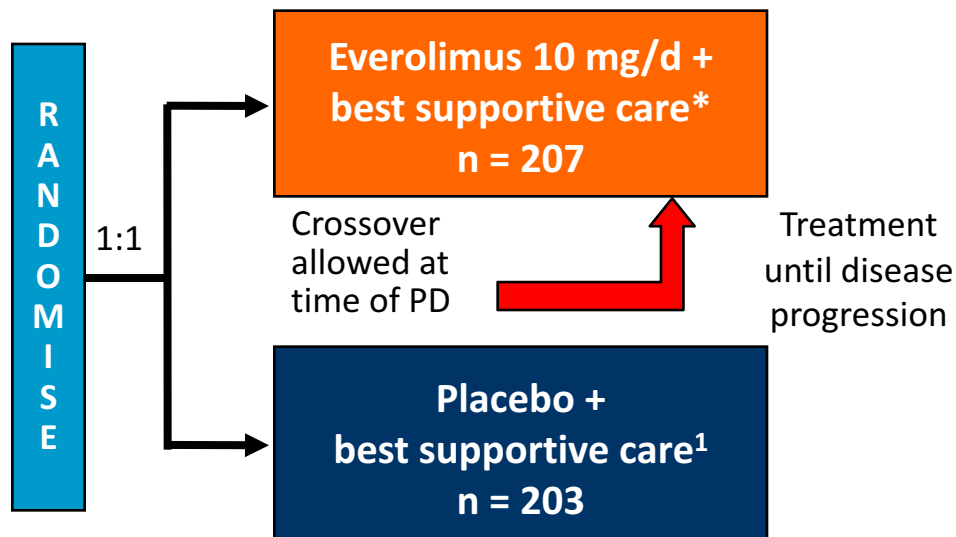
## Phase III Double-Blind, Placebo-Controlled Trial

Patients with progressive advanced pNET, N=410

- Advanced low- or intermediate-grade pNET
- Radiologic progression  $\leq 12$  months
- Prior anti-tumour therapy allowed
- WHO PS  $\leq 2$

Stratified by:

- WHO PS
- Prior chemotherapy



*Multiphasic CT or MRI performed every 12 weeks*

### Primary Endpoint:

**PFS**

**Statistical boundary  $\leq .025$**

### Secondary Endpoints:

**OS**

**ORR**

**Biomarkers**

**Safety**

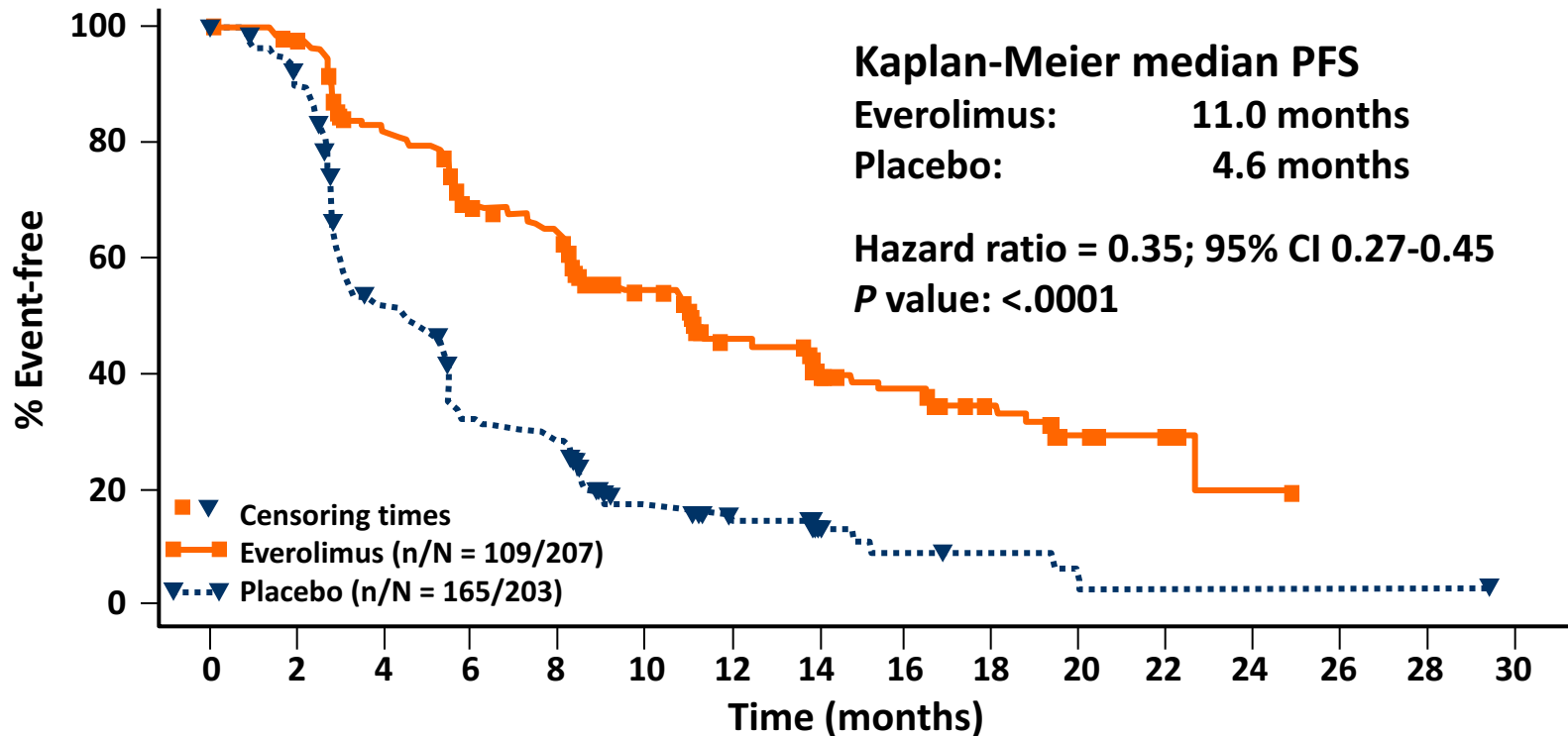
**PK**

Randomisation: August 2007-May 2009

\* Concurrent somatostatin analogues allowed



# Progression Free Survival by Investigator Review



*148 placebo patients crossed over to everolimus at the time of progression*

P value obtained from stratified 1-sided log-rank test

Hazard ratio is obtained from stratified unadjusted Cox model

Yao, JC. et al. *N Engl J Med.* 2011;364:514-523.



# RADIANT-3: Treatment-Related Adverse Events All Grades >20%

<u>Treatment duration: median (range)</u> <b>Everolimus: 8.79 mos (0.25 - 27.47)</b> <b>Placebo : 3.74 mos (0.01 – 37.79)</b>	Everolimus (n=204)	Placebo (n=203)
	All Grades	All Grades
	no. of patients (%)	
Stomatitis*	131 (64)	34 (17)
Rash	99 (49)	21 (10)
Diarrhoea	69 (34)	20 (10)
Fatigue	64 (31)	29 (14)
Infections <sup>†</sup>	46 (23)	12 (6)
Nausea	41 (20)	37 (18)
Peripheral oedema	41 (20)	7 (3)
Decreased appetite	40 (20)	14 (7)

\* Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration

<sup>†</sup> All types of infection are included





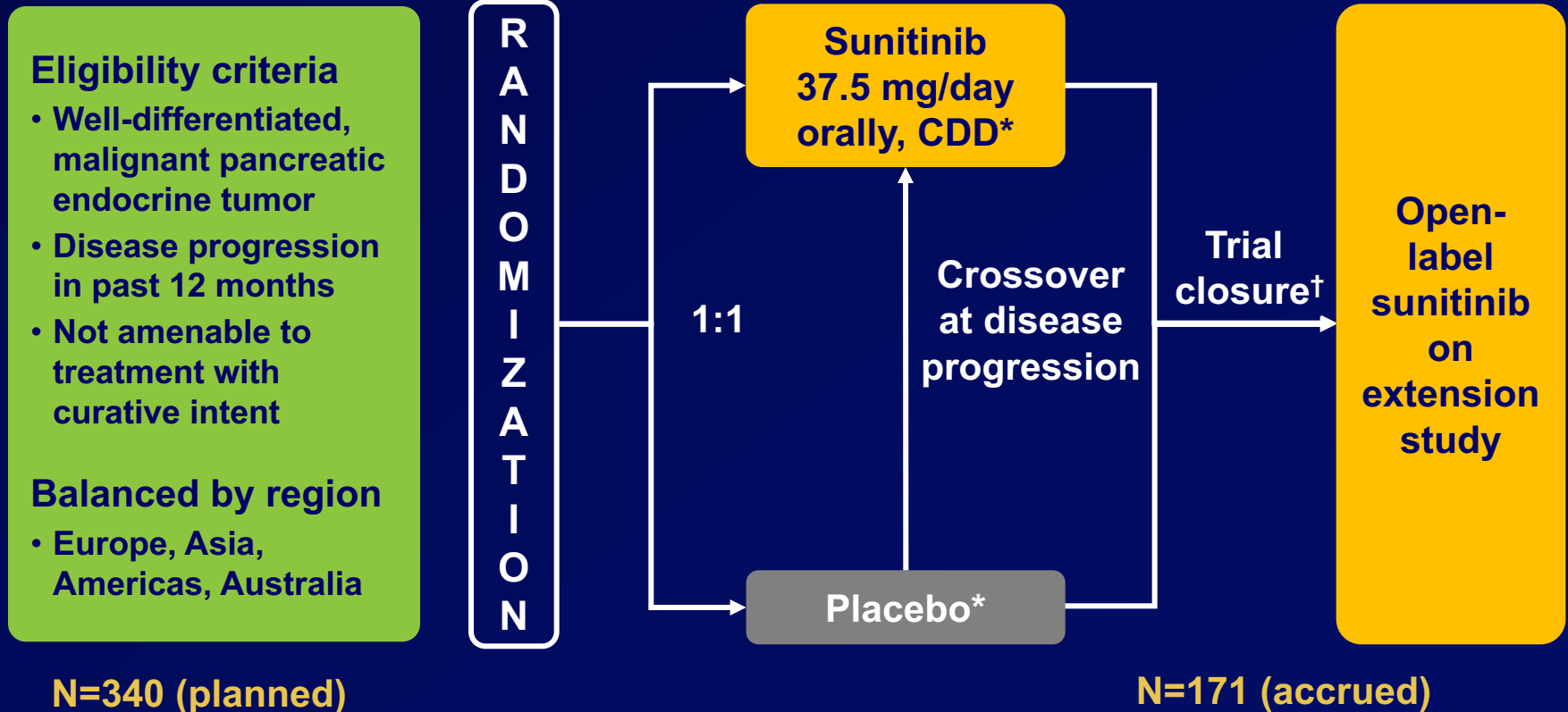
# Phase III Study: Efficacy and Safety of Sunitinib in Patients with Advanced Pancreatic NET

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



# Sunitinib Phase III Study: Randomized, Double-Blind Study Design



- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, time to tumor response, duration of response, safety, PROs

CDD = continuous daily dosing; PROs = patient-reported outcomes

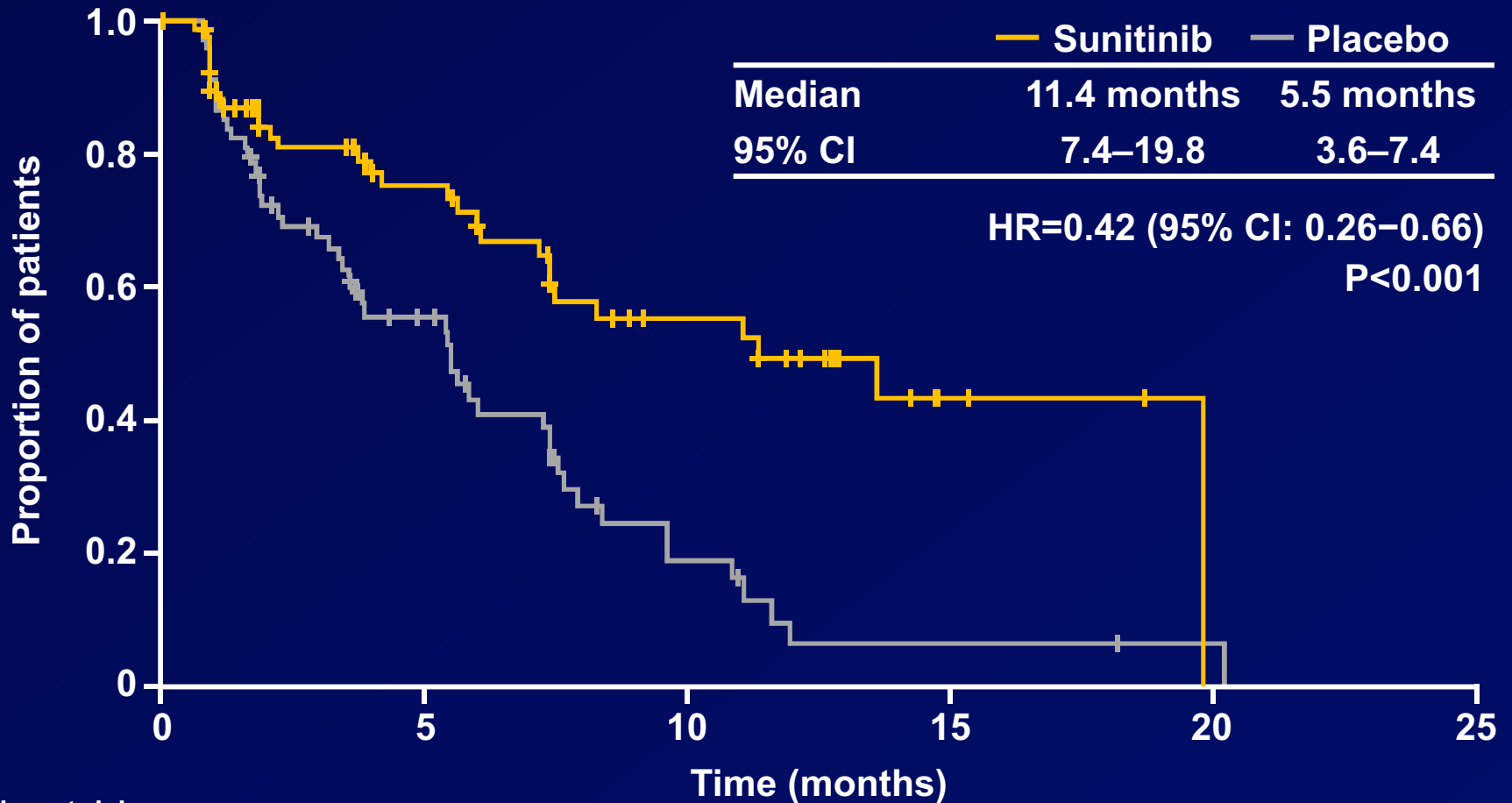
\*With best supportive care; SSAs permitted

†Early trial closure occurred due to differences in deaths, serious AEs, and PFS

Raymond E, et al  
*N Engl J Med* 2011;364:501–513



# Phase III Study: PFS (Primary Endpoint)



Number at risk

	0	5	10	15	20	25
Sunitinib	86	39	19	4	0	0
Placebo	85	28	7	2	1	0

Raymond E, et al. *N Engl J Med* 2011;364:501–513

# Safety of targeted therapies for NET in placebo-controlled phase 3 studies



## Everolimus<sup>1</sup>

- The most common AEs: **stomatitis, rash, fatigue**
- Other AEs: Infections, pneumonitis
- Grade 3/4 AEs: anemia, hyperglycemia

## Sunitinib<sup>2</sup>

- The most common AEs: **diarrhea, nausea, asthenia**
- Other AEs: Hypertension, hand-and-foot syndrome
- Grade 3/4 AEs: neutropenia, hypertension

# Treatment Landscape for Advanced NET

Site	Octreotide <sup>1</sup>	Lanreotide <sup>2</sup>	<sup>177</sup> Lu-DOTATATE <sup>3</sup>	Streptozocin	Sunitinib <sup>4</sup>	Everolimus <sup>5,6</sup>
Disease status	Treatment-naïve	Stable	Progressive over 3 years	Historical	Progressive over 12 months	Progressive over 6 months <sup>a</sup>
Lung		? SPINNET				RADIANT-4
Stomach		CLARINET				RADIANT-4
Duodenum		CLARINET				RADIANT-4
Pancreas		CLARINET		Historical	Phase 3	RADIANT-3 <sup>a</sup>
Small bowel Appendix	PROMID	CLARINET	NETTER-1			RADIANT-4
Colon		CLARINET				RADIANT-4
Rectum		CLARINET				RADIANT-4
Unknown 1°						RADIANT-4





# Where do we go to **NExTs**?



The Susan Leslie Clinic for Neuroendocrine Tumours



**Sunnybrook**  
ODETTE CANCER CENTRE  
*A Cancer Care Ontario Partner* when it matters  
MOST



# Targeted Clinical Trials

- Immunotherapy
  - Poorly Differentiated/High Grade
  - Well Differentiated/G2 and G3
  - PDL1 post Everolimus
- Combination Therapy
  - Everolimus plus Radiation to liver
- New Drugs
  - Cabozatinib





Thank You...Questions?