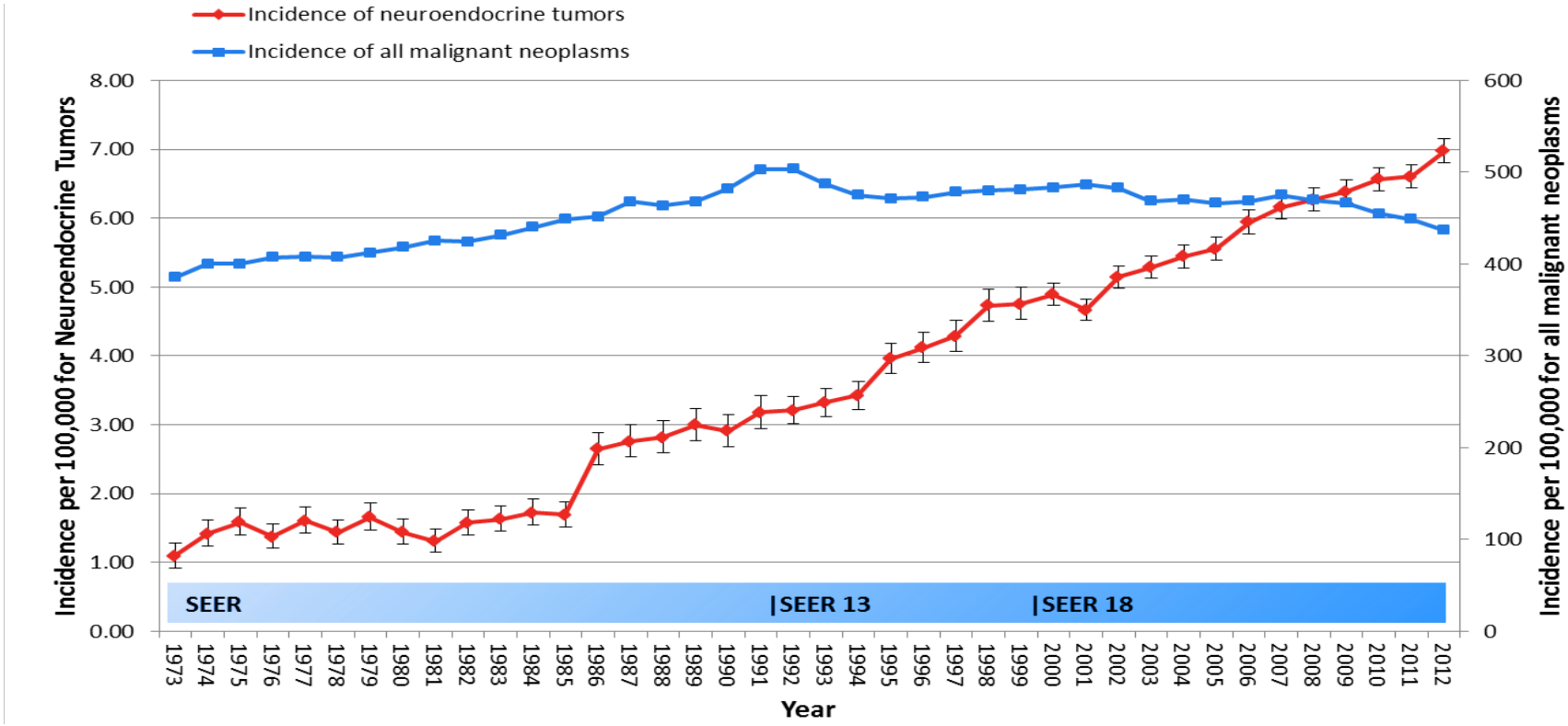
Progress in the land of small tumors: Recent advances and future directions in advanced neuroendocrine tumors

James C. Yao, MD
Professor and Chairman, Gastrointestinal Medical Oncology
University of Texas MD Anderson Cancer Center

Continued rise in incidence of neuroendocrine tumors



Dasari et al, JAMA Oncology, In Press 2017

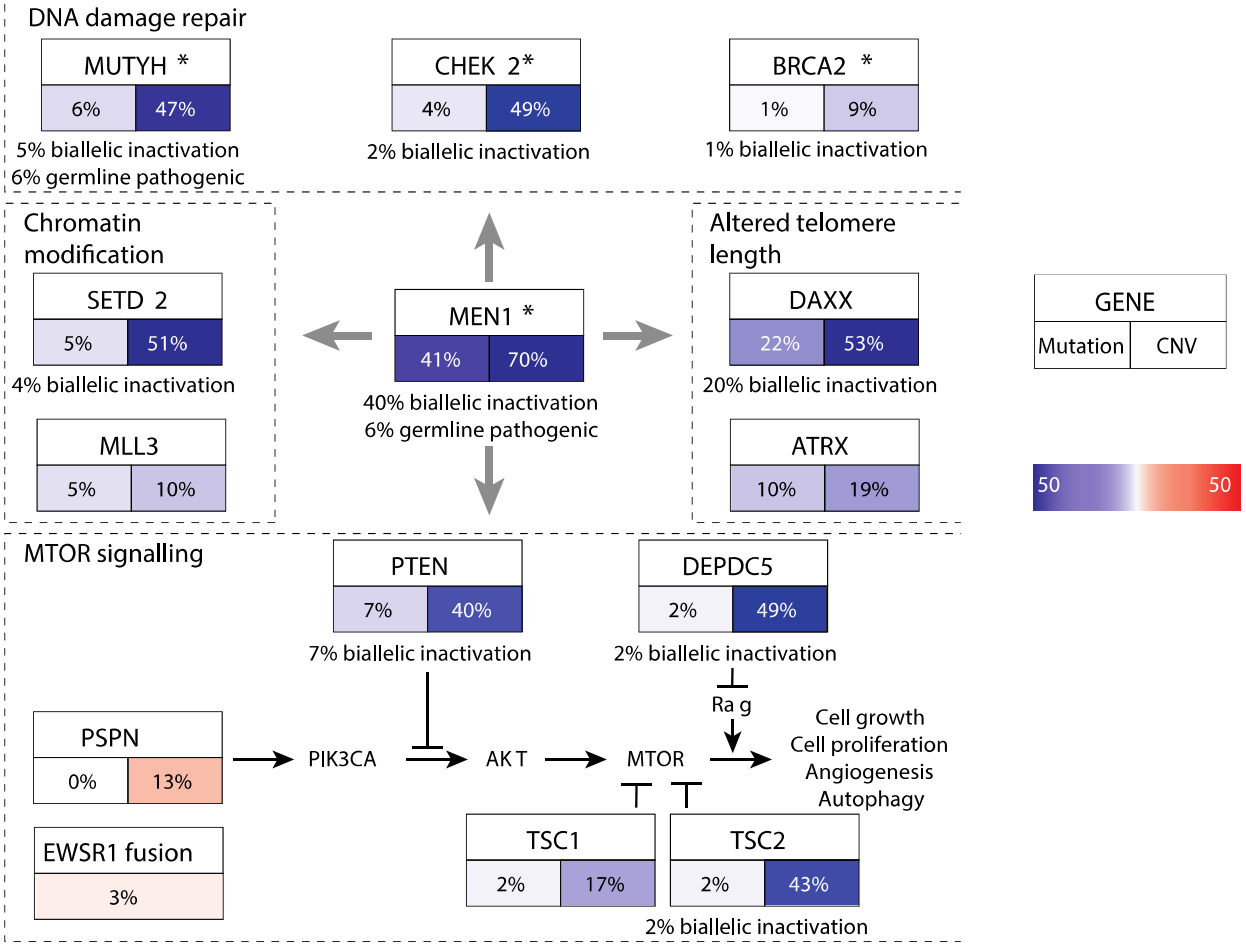
Is NET still rare?

Year	Annual incidence rate per 100,000	US prevalence count estimate
2004	5.25	103,312[1]
2012	6.98	
2014		171,321[2]

[1] 29-year limited duration prevalence. [2] 20-year limited duration prevalence

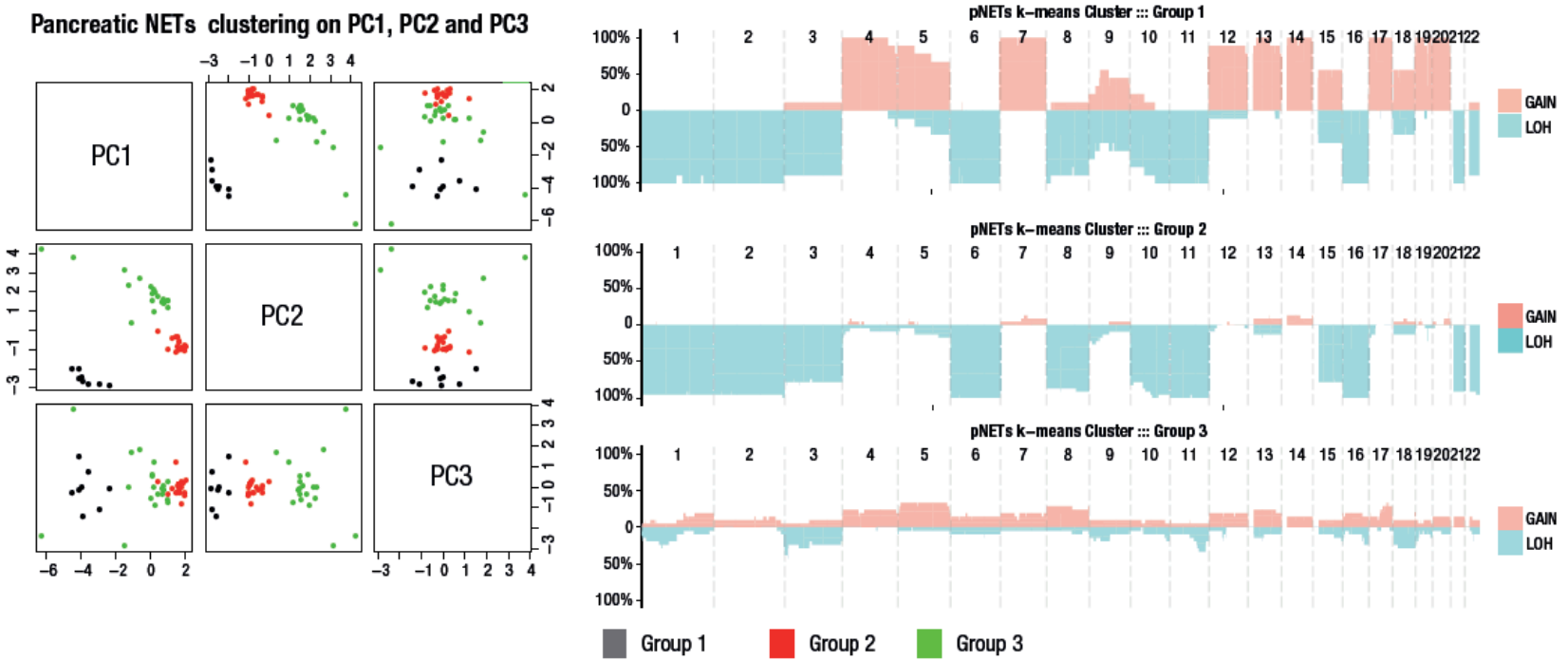
Yao et al. (2008). J Clin Oncol 26(18): 3063-3072.
Shen et al, NANETS 2016
Dasari et al, JAMA Oncology, In Press 2017

Core pathways in pancreatic NETs



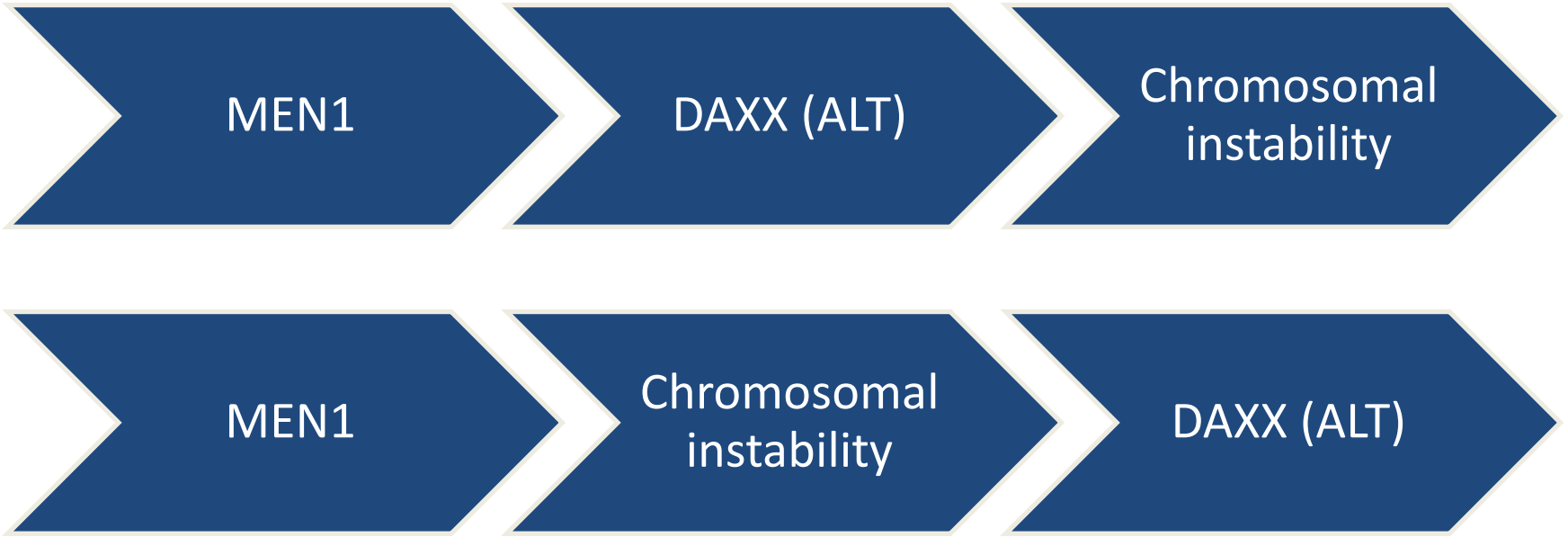
Scarpa et al, Nature 2017

Chromosomal instability in pancreatic NETs

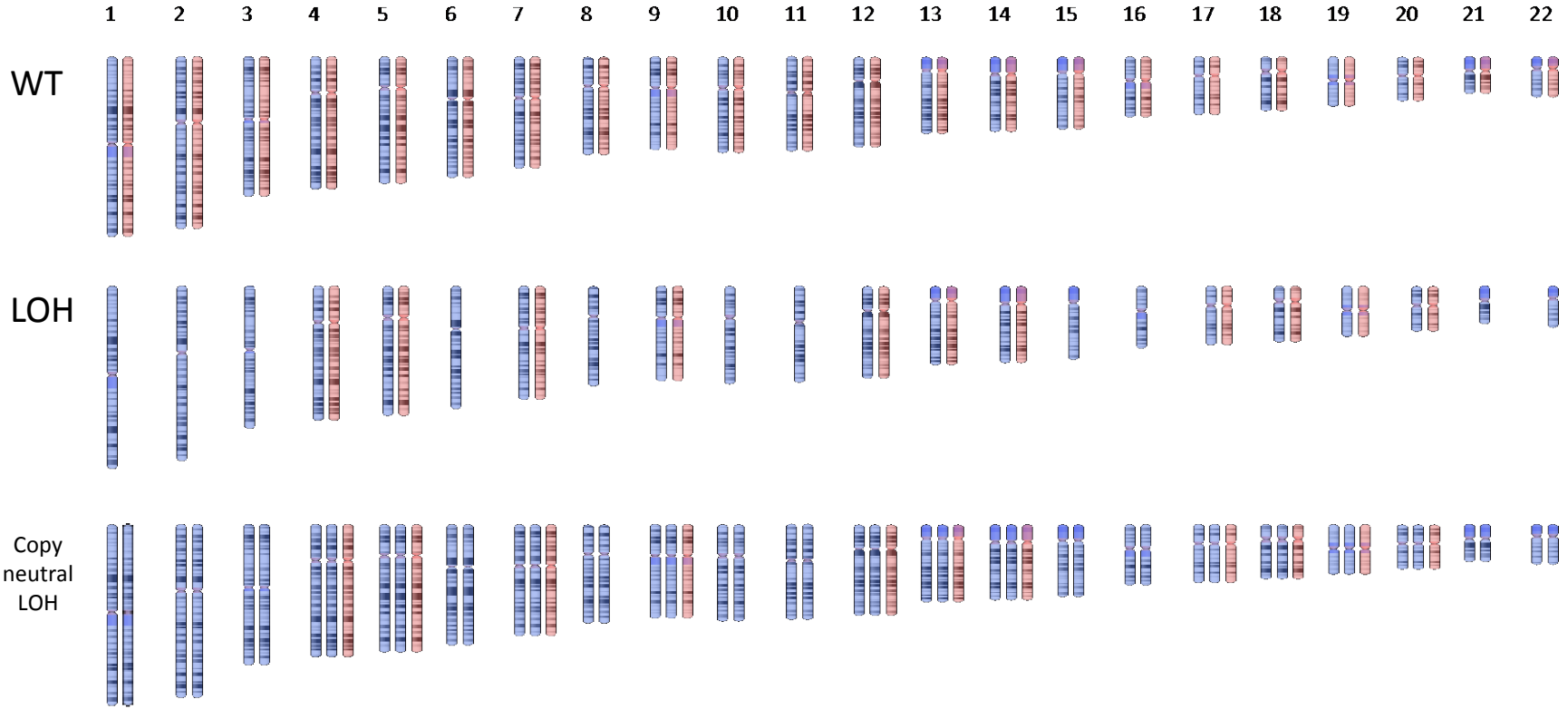


Yao et al, J Clin Oncol 34, 2016 (suppl; abstr e23284)

Genomic progression of pancreatic NET

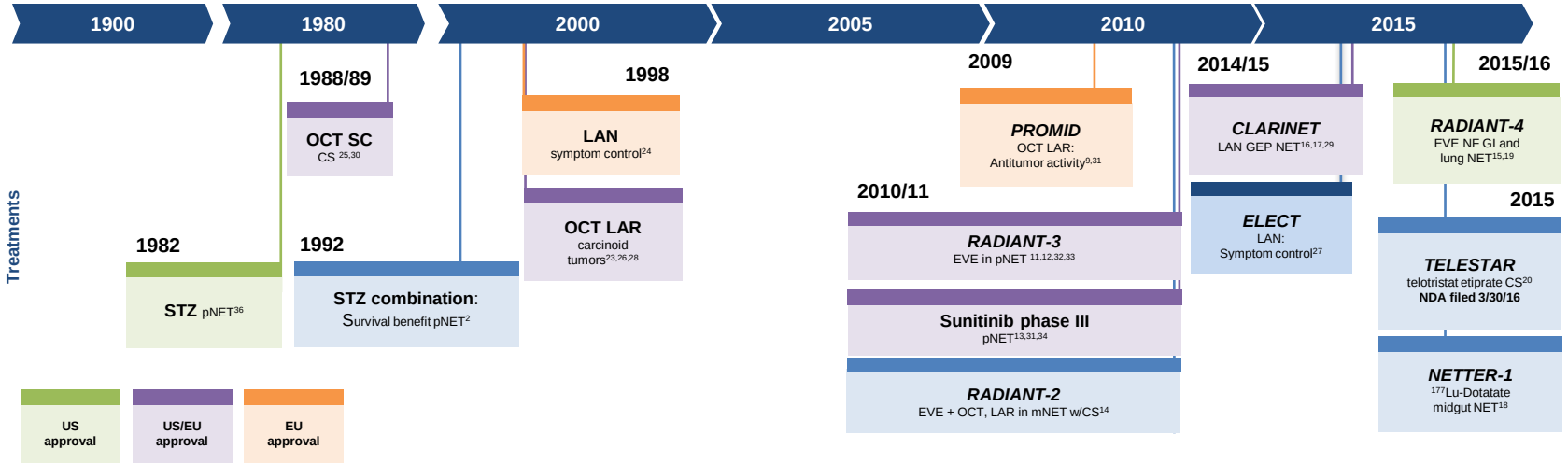


Chromosomal instability in pancreatic NETs



Approved agents for oncologic control before 2011

- pNETs: **Streptozocin**
- GI NETs: **None**

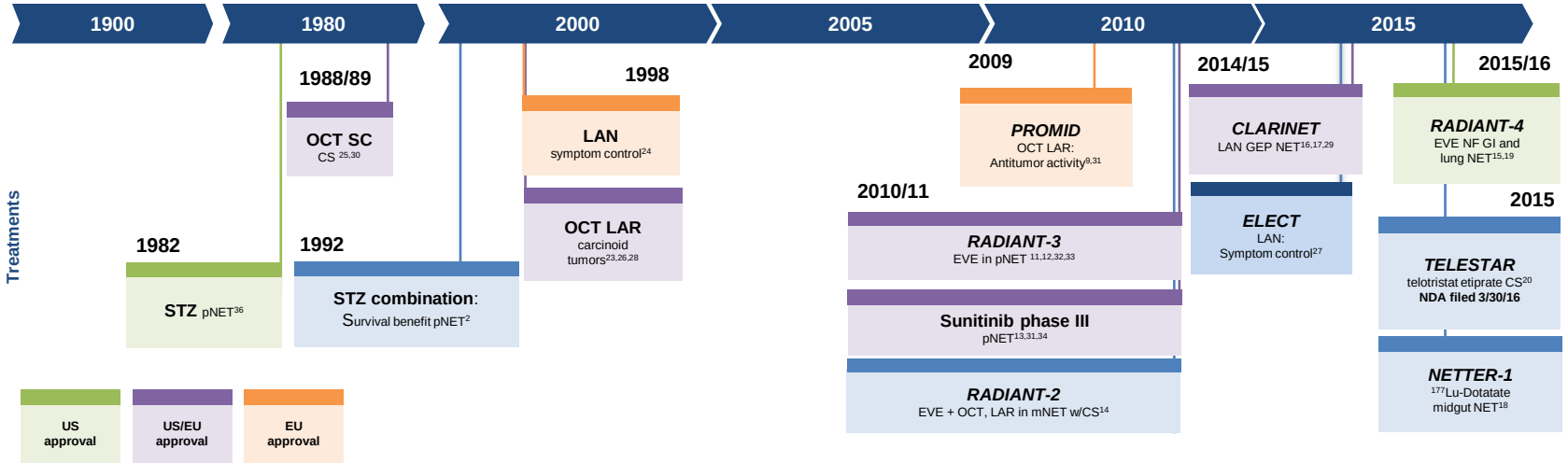


AC, atypical carcinoid; AJCC; American Joint Committee on Cancer; CS, carcinoid syndrome; ENETS, European Neuroendocrine Tumor Society; ESMO; European Society for Medical Oncology; EVE, everolimus; GEP, gastroenteropancreatic; GI NETs, gastrointestinal neuroendocrine tumors; LAN, lanreotide; LAR, long-acting repeatable; m, metastatic; NANETS, North American Neuroendocrine Tumor Society; 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

Approved agents for oncologic control
- pNETs: **Everolimus, sunitinib, lanreotide**
- GI NETs: **Lanreotide, everolimus**
- Lung Nets: **Everolimus**

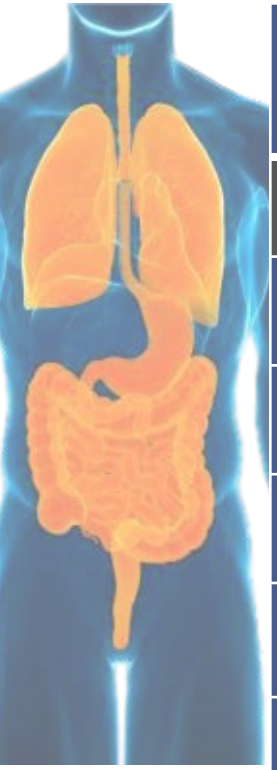
Other active agents
- pNETs: Temozolomide
- GI NETs: Octreotide, (177)Lu-DOTATATE

Approved agents for oncologic control before 2011
- pNETs: **Streptozocin**
- GI NETs: **None**



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; GI NETs, gastrointestinal neuroendocrine tumors; LAN, lanreotide; LAR, long-acting repeatable; m, metastatic; NANETS, North American Neuroendocrine Tumor Society; 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

Treatment Landscape for Advanced NETs



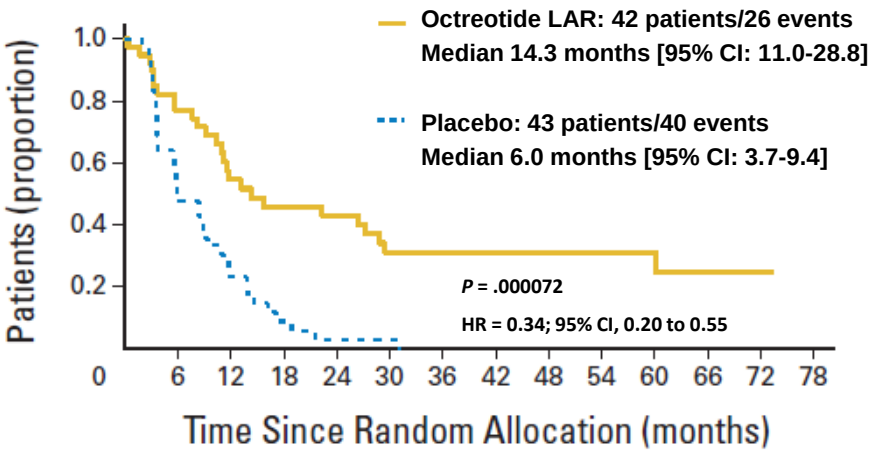
Site	Octreotide	Lanreotide	^{177}Lu-DOTATATE	Streptozocin	Sunitinib	Everolimus
Disease status	Tx naïve	Stable	Progressive over 3 yrs	Historical	Progressive over 12 mo	Progressive over 6 mo*
Lung						RADIANT 4
Stomach		CLARINET				RADIANT 4
Pancreas		CLARINET		Historical	Phase III	RADIANT 3*
Small bowel Appendix	PROMID	CLARINET	NETTER-1			RADIANT 4
Colon		CLARINET				RADIANT 4
Rectum		CLARINET				RADIANT

*RADIANT-3 requi

Rinke A, et al. *J Cli Engl J Med.* 2011.

PROMID: Octreotide LAR vs Placebo

Time to progression

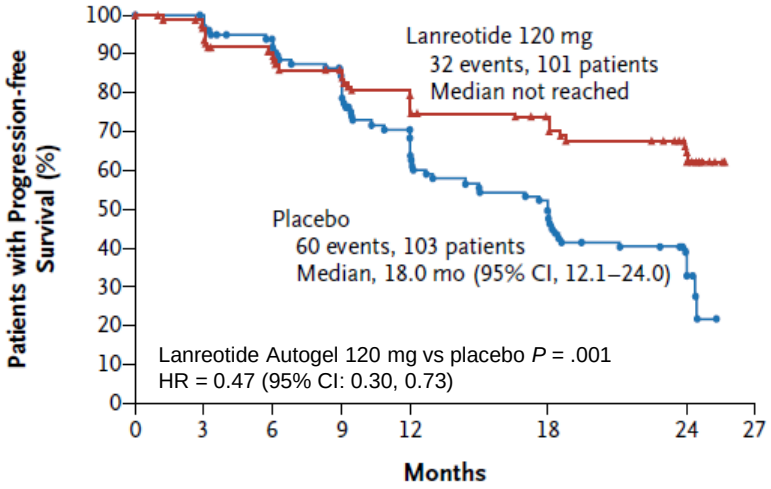


Endpoint	Octreotide LAR n = 42	Placebo n = 43
Serious adverse events (SAEs), n (%)	11 (26)	10 (23)
Most frequent SAEs, n (%)		
Gastrointestinal (GI) tract	6 (14)	8 (19)
Hematopoietic system	5 (12)	1 (2)
General health status (fatigue, fever)	8 (19)	2 (5)
AEs causing discontinuation, n (%)	5 (12)	0
Bile stones, n (%)	5 (12)	1 (2)
Treatment-related deaths	0	0

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

CLARINET: Lanreotide Autogel vs Placebo

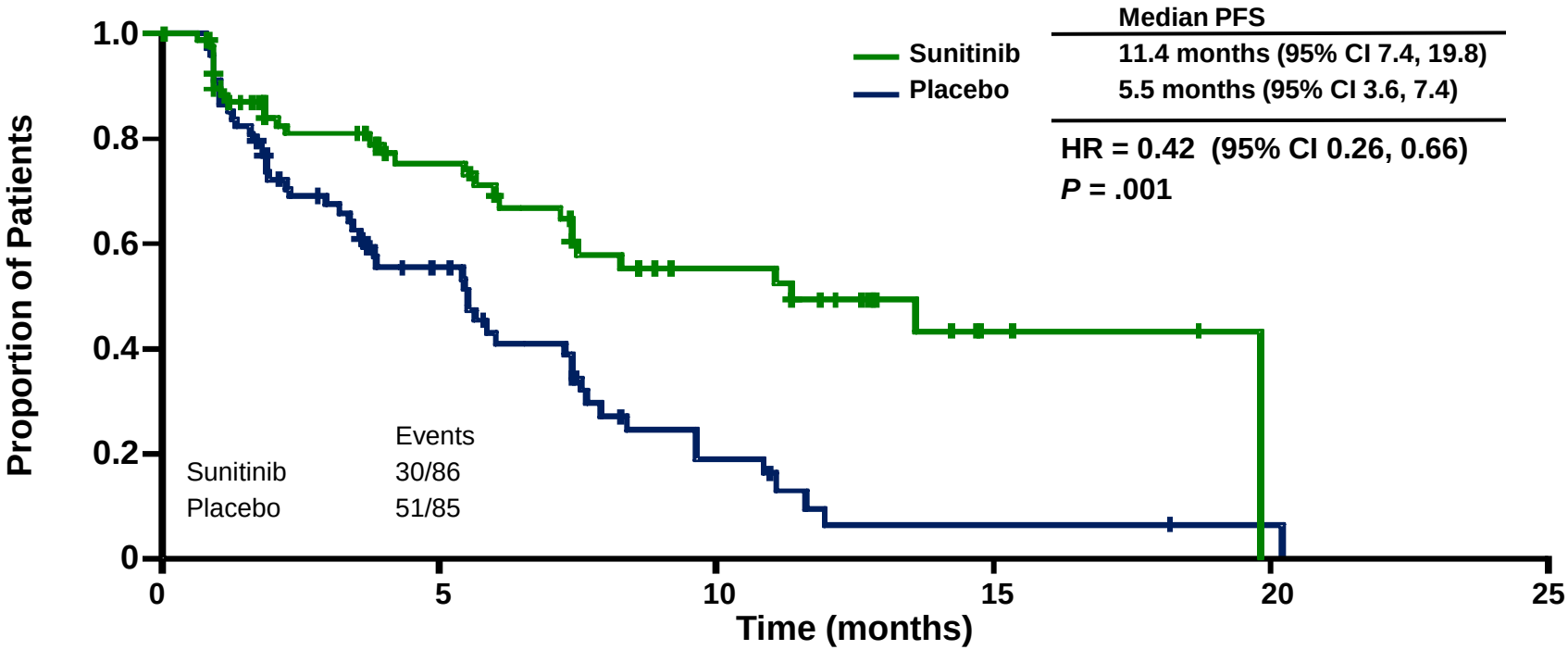
Progression-free survival (PFS)



	Lanreotide n = 101	Placebo n = 103
Any treatment-emergent AE, n (%)	89 (88)	93 (90)
Related to treatment	50 (50)	29 (28)
Severe	26 (26)	32 (31)
Moderate	44 (44)	44 (43)
Mild	17 (17)	17 (17)
Any SAE,[a] n (%)	25 (25)	32 (31)
Related to treatment	3 (3)	1 (1)
Withdrawals due to treatment-emergent AE	3 (3)	3 (3)
Related to treatment	1 (1)	0
Treatment-related AE in ≥10% of patients, n (%)		
Diarrhea	26 (26)	9 (9)
Abdominal pain	14 (14)	2 (2)
Cholelithiasis	10 (10)	3 (3)

Caplin ME, et al. *N Engl J Med.* 2014;371(3):224-233.

Sunitinib in pancreatic NET
PFS by Investigator Review

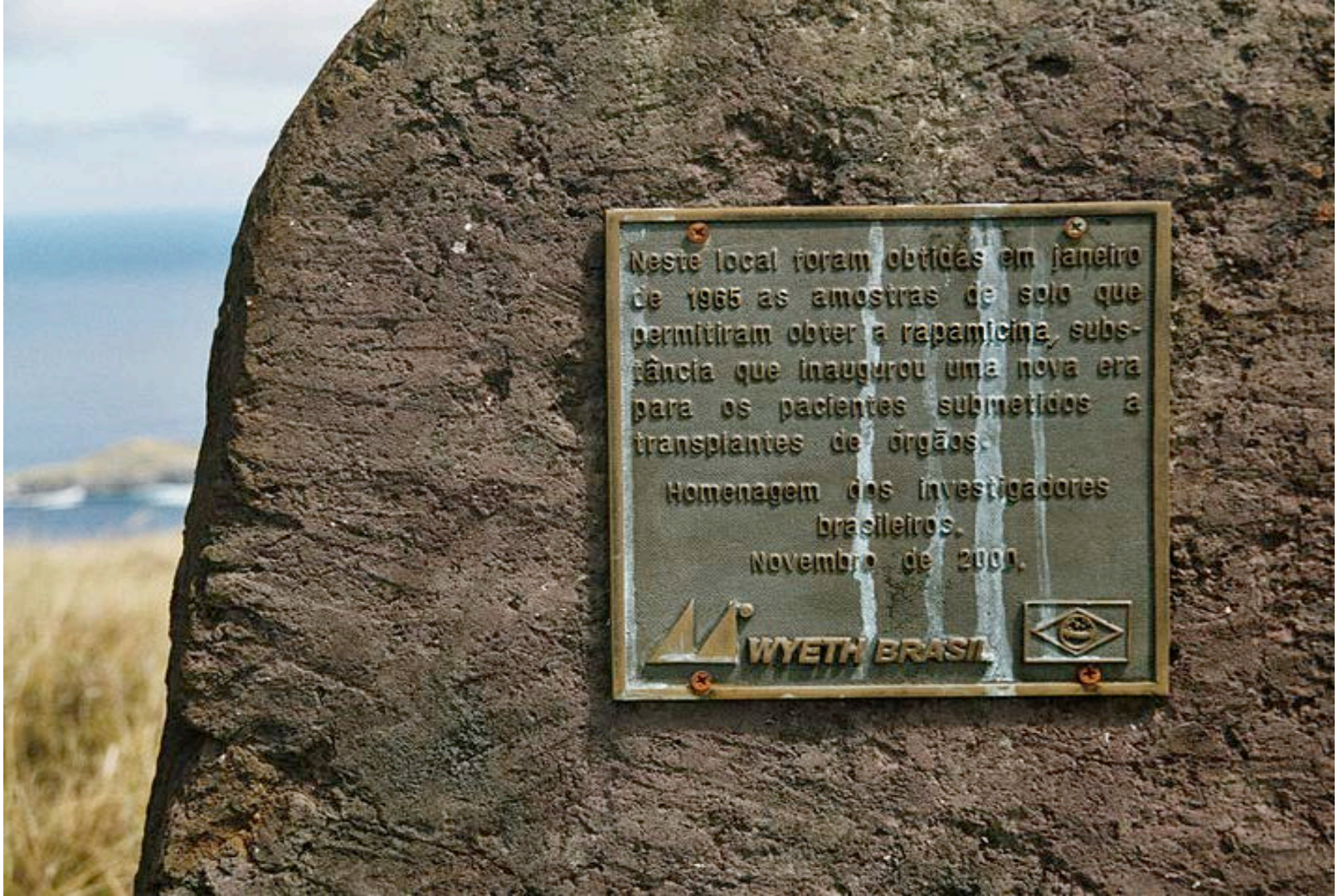


Raymond E, et al. *N Engl J Med.* 2011;364(6):501-513. Blumenthal GM, et al. Oncologist. 2012;17(8):1108-1113.

Sunitinib in pancreatic NET
Adverse events

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 (%)					
Diarrhea	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)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar-plantar erythrodysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0

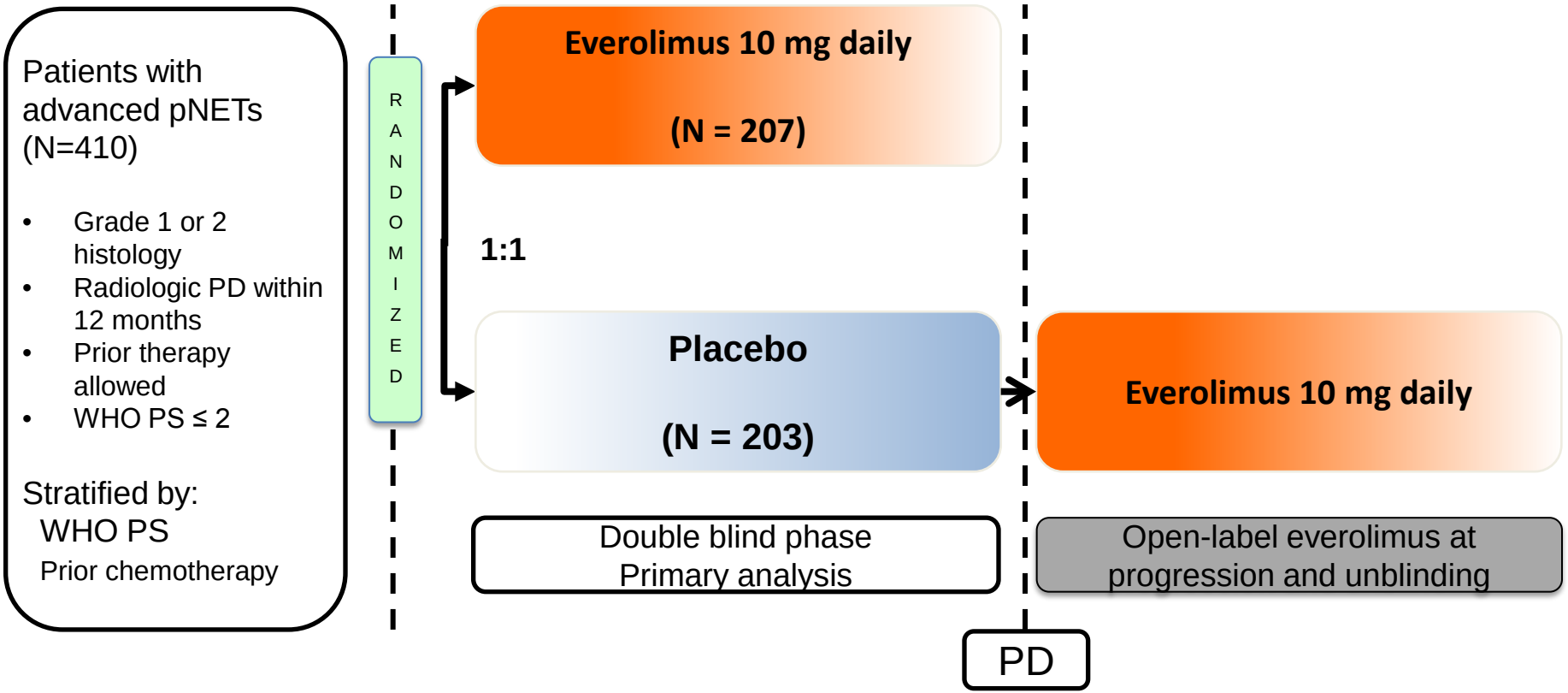
- Raymond E, et al. *N Engl J Med*. 2011;364:501-513.


Neste local foram obtidas em janeiro de 1965 as amostras de solo que permitiram obter a rapamicina, substância que inaugurou uma nova era para os pacientes submetidos a transplantes de órgãos.
Homenagem dos investigadores brasileiros.
Novembro de 2000.
WYETH BRASIL

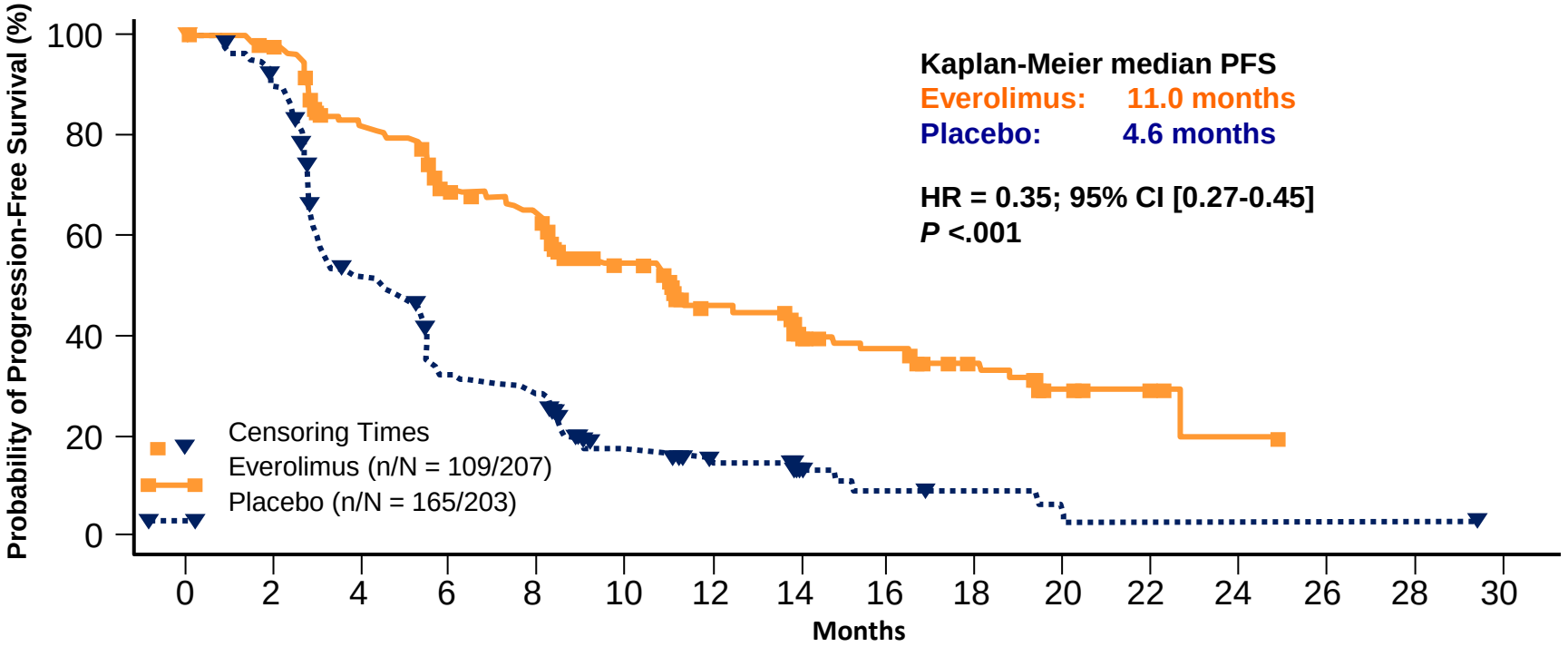
Island of Rapa Nui

Photo from NASA

RADIANT-3: Study Design

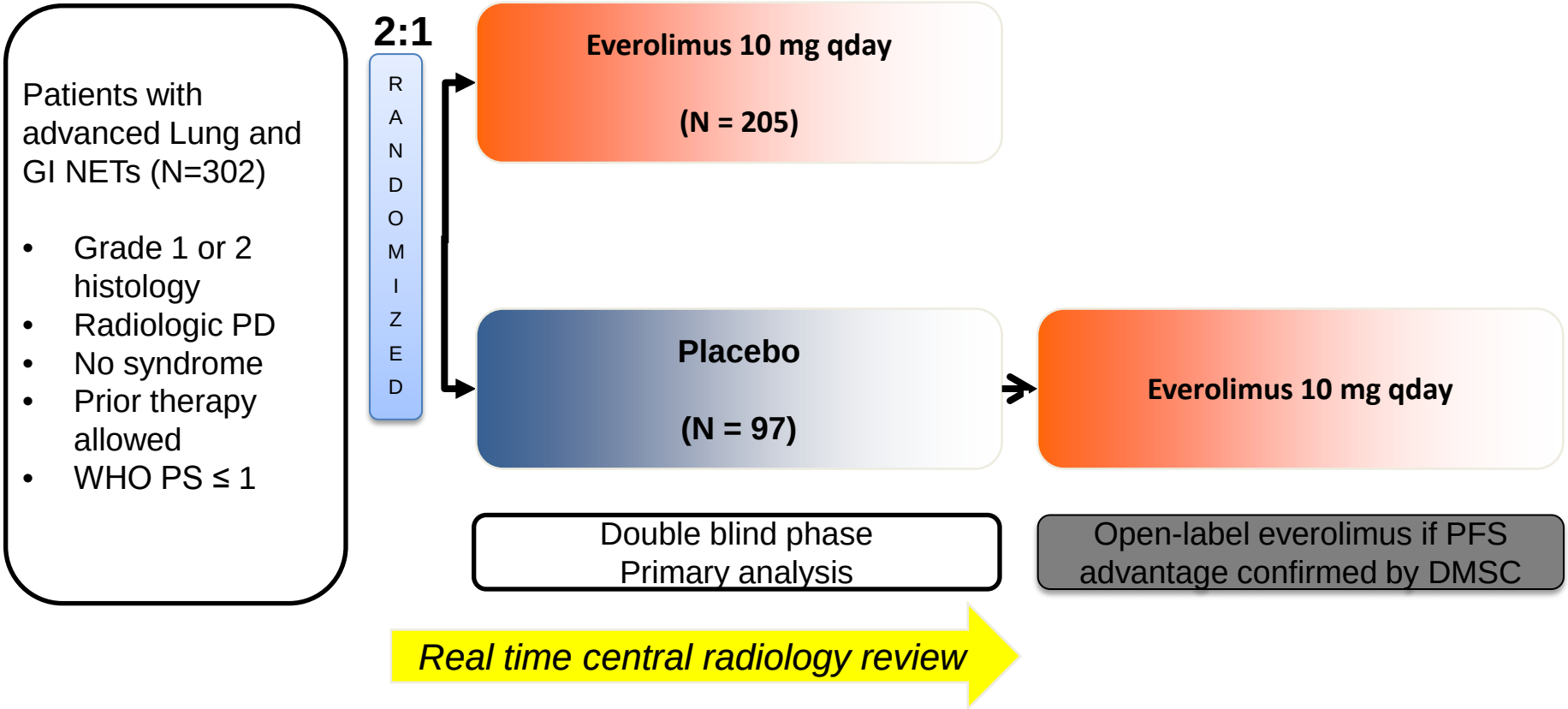


RADIANT-3: Everolimus for Advanced Pancreatic Neuroendocrine Tumors

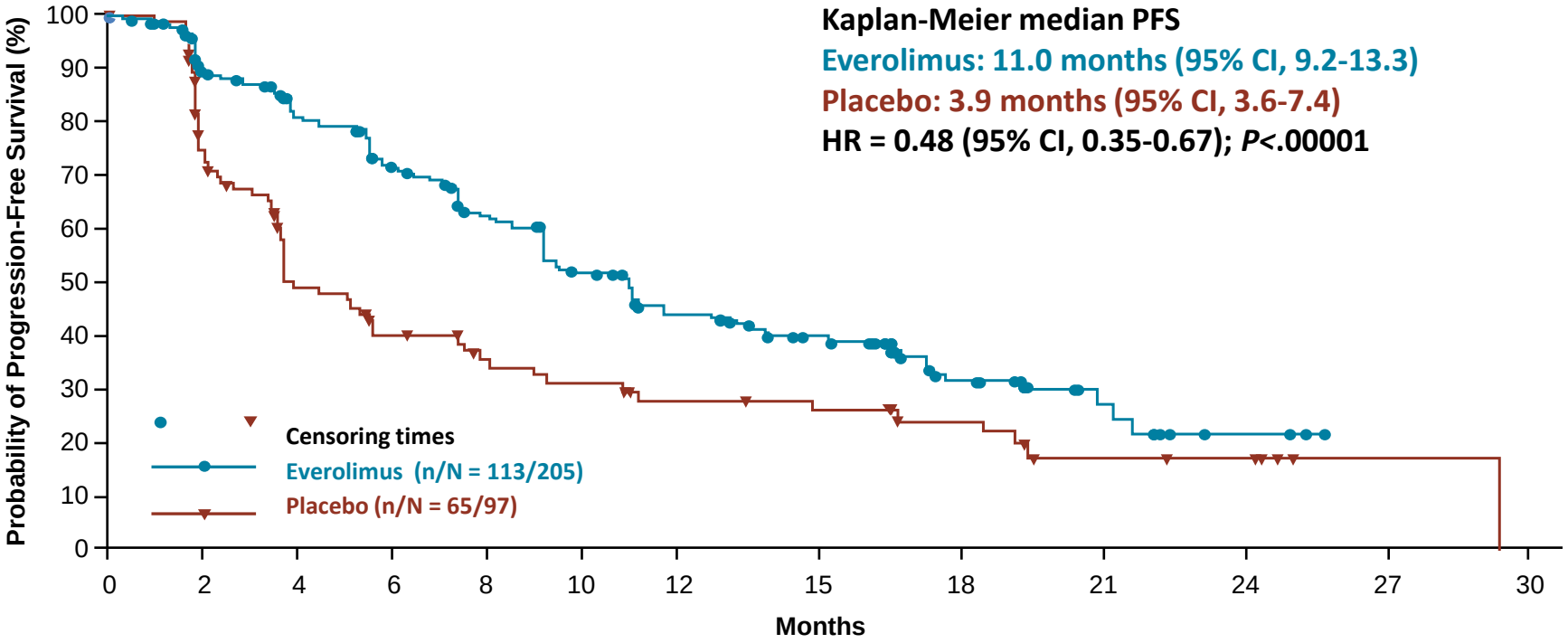


Yao JC, et al. *N Engl J Med*. 2011;364:514-523.

RADIANT-4: Study Design

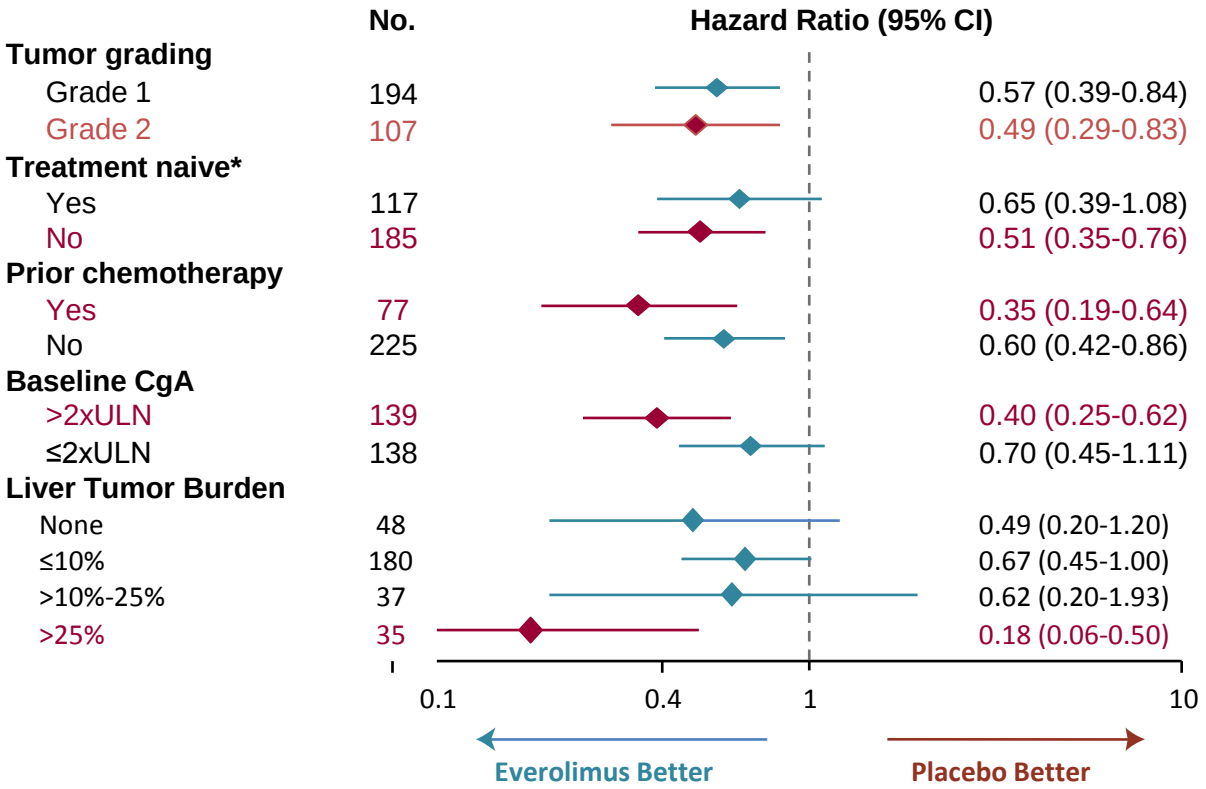


RADIANT-4: Everolimus for Advanced Neuroendocrine Tumors of the Lung or GI Tract



Yao JC, et al. *Lancet*. 2016;387(10022):968-977.

RADIANT-4: Activity in Less Favorable Subgroups



Yao JC, et al. *Lancet*. 2016;387(10022):968-977.

RADIANT-4: Safety

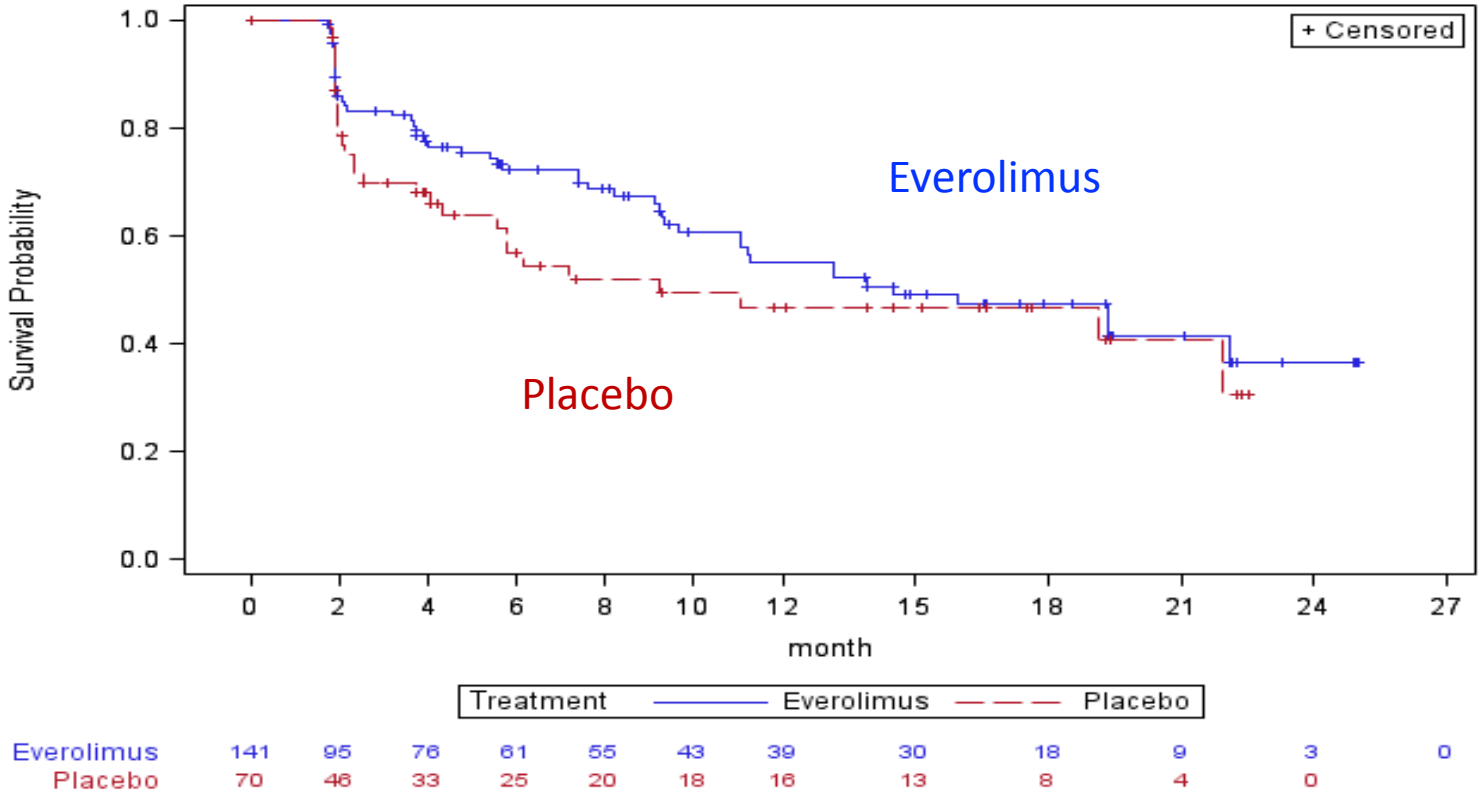
	Everolimus N = 202		Placebo N = 98	
Drug-related adverse events	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Stomatitis*	**63%**	**9%**	**19%**	**0**
Diarrhea	**31%**	**7%**	**16%**	**2%**
Fatigue	**31%**	**3%**	**24%**	**1%**
Infections†	**29%**	**7%**	**4%**	**0**
Rash	**27%**	**1%**	**8%**	**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**
Noninfectious pneumonitis‡	**16%**	**1%**	**1%**	**0**
Dysgeusia	**15%**	**1%**	**4%**	**0**

Presented are drug-related adverse events in ≥15% 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

Yao JC, et al. *Lancet*. 2016;387(10022):968-977.

RADIANT-4 QoL: Time to Definitive Deterioration

≥ 7 points on the FACT-G total score



Pavel M, et al. *J Clin Oncol.* 2016;34(suppl): Abstract e15657

Prevention of Everolimus Stomatitis Using a Dexamethasone-Based Mouthwash (SWISH Trial)

N = 92
- Females ≥18 years
- Postmenopausal locally advanced or metastatic HR+, HER2- breast cancer
- Prescribed EVE 10 mg + EXE 25 mg
- ECOG performance status ≤ 2

Baseline Oral pain assessment

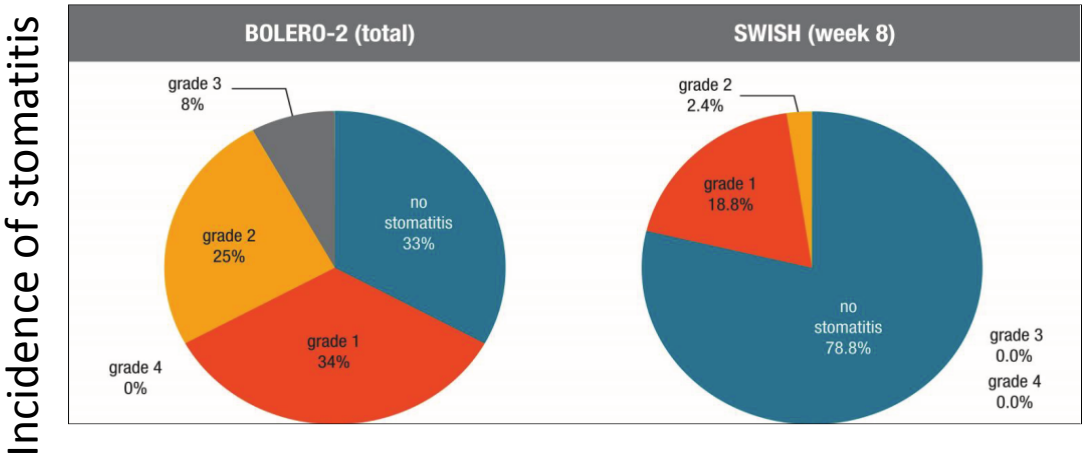
Open label, phase II, single arm
- Routine good oral care
- EVE 10 mg/day
- EXE 25 mg/day
- Alcohol-free steroid-based mouthwash[a] -10 mL (0.5 mg/5 mL dexamethasone oral solution) swish for 2 mins and spit QID

Endpoints

Primary: compare grade ≥2 stomatitis incidence at 8 weeks with BOLERO-2 results

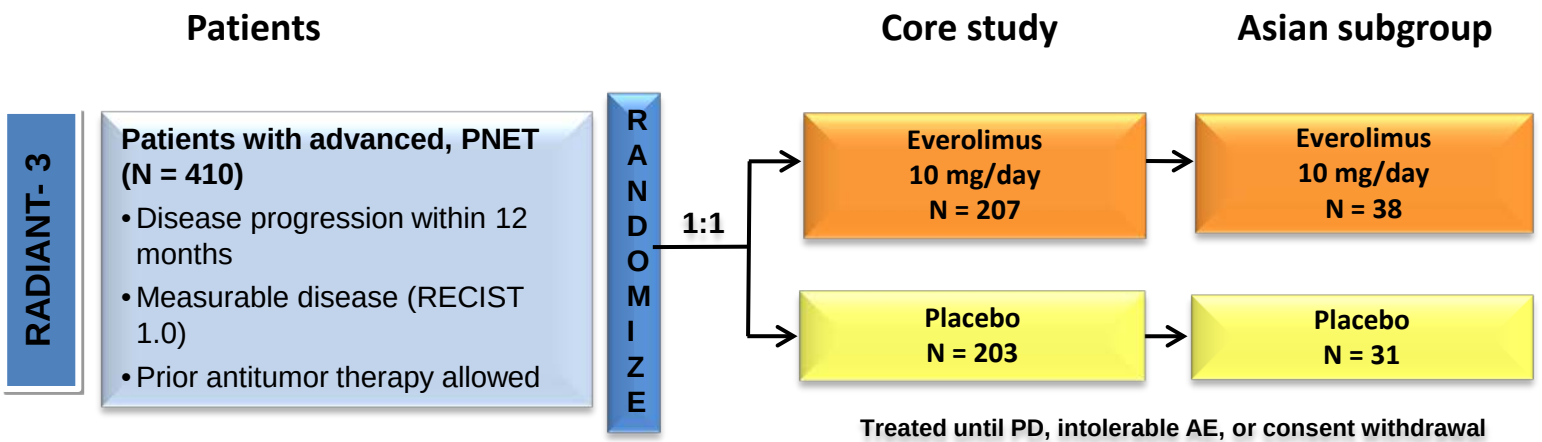
Secondary: Mouthwash use by average times/day, EVE/EXE dose intensity, all-grade stomatitis incidence and time to resolution to grade ≤1, oral pain scale, normalcy of diet

Treatment cycles (cycle 1, 2), optional cycles (cycles 3, 4)[b], and safety follow-up cycle; each cycle = 28 days



Rugo HS, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 525.

RADIANT-3 Asian subgroup



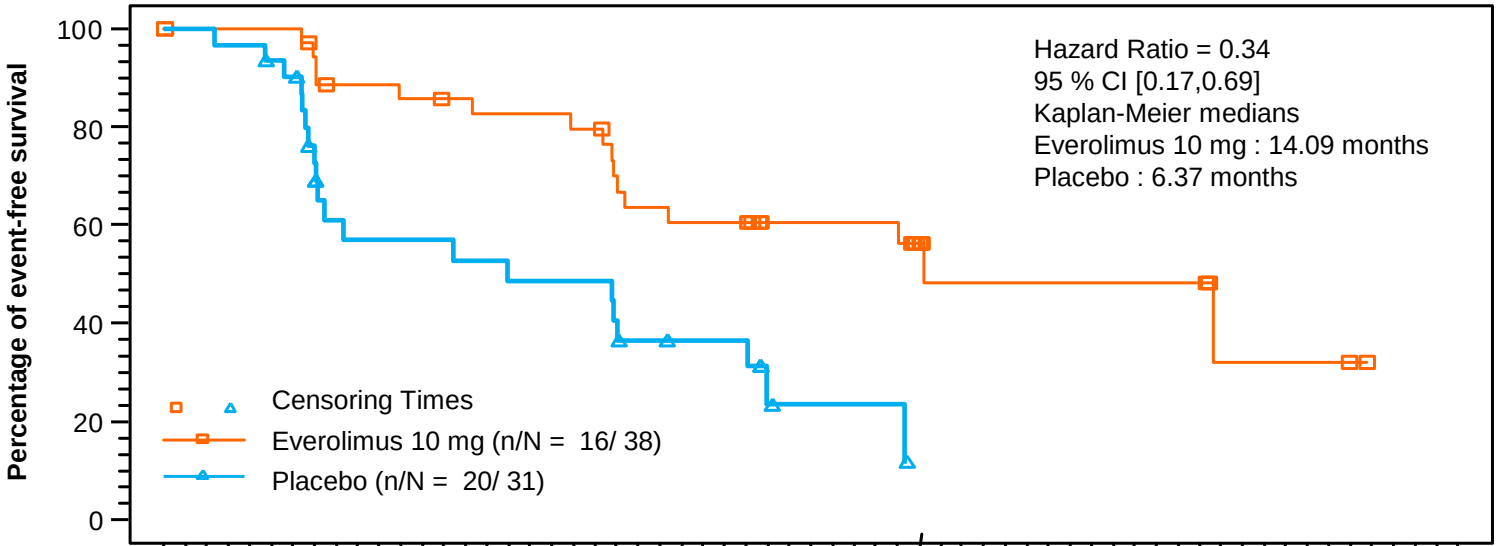
Endpoints:
- **Primary:** PFS (central)
- **Key Secondary:** OS

Stratified by:
- Prior chemotherapy
- WHO PS 0 vs 1-2

AE, adverse event; PNET, pancreatic neuroendocrine tumors; OS, overall survival; PFS, progression-free survival; PD, progressive disease; WHO PS, World Health Organization performance status

1. Yao JC et al. *N Engl J Med.* 2011;364(6):514-523.

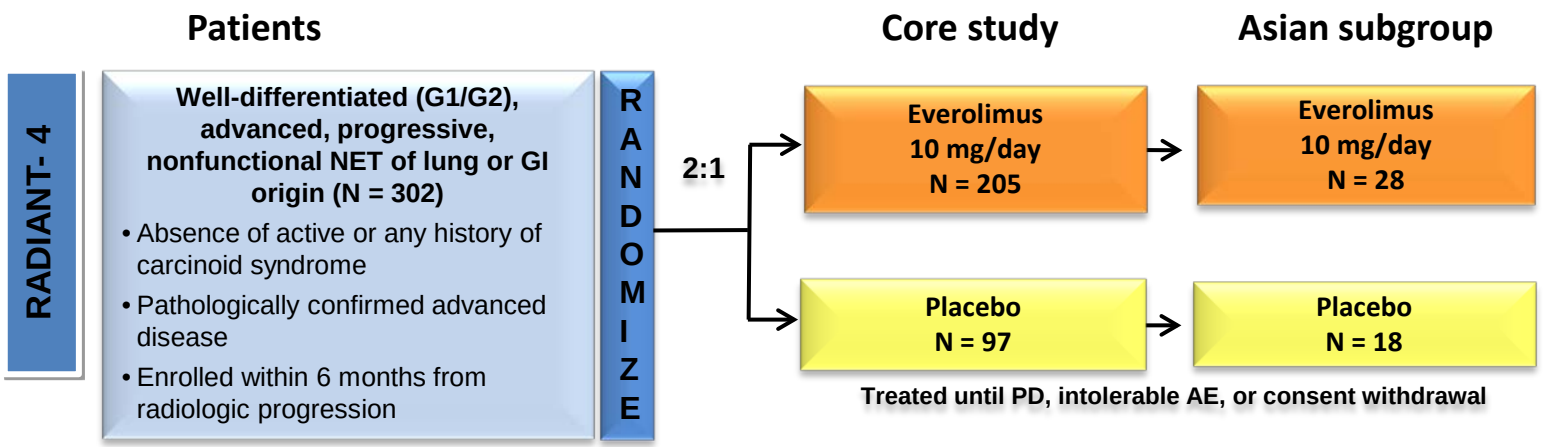
RADIANT-3 Asian subgroup: Progression-free survival



No of patients still at risk													
Everolimus	38	36	30	27	26	19	14	10	6	6	2	1	0
Placebo	31	28	14	13	12	7	2	0	0	0	0	0	0

HR: Hazard ratio, n, number of patients with response; N, number of patients randomized

RADIANT-4 East Asian Subgroup

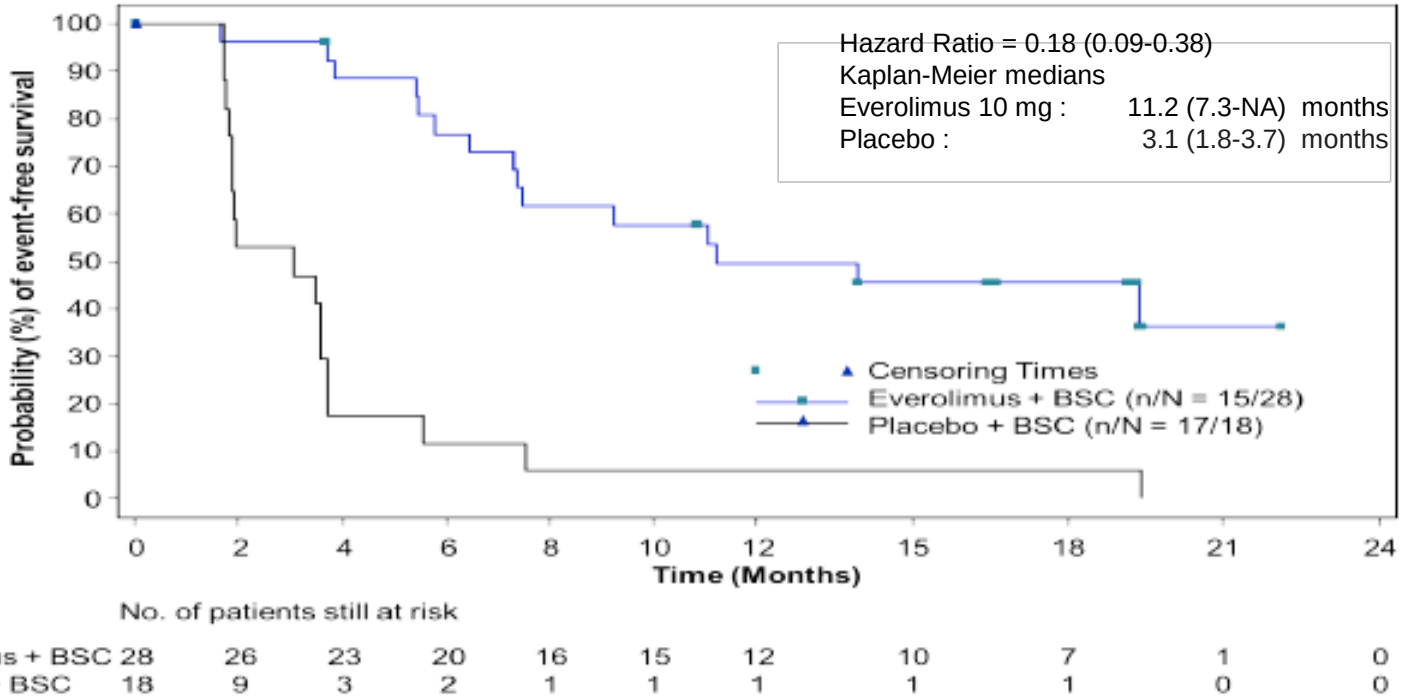


*Based on prognostic level, grouped as: **Stratum A (better prognosis)** - appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** - lung, stomach, rectum, and colon except caecum.
Crossover to open label everolimus after progression in the placebo arm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

East Asian subgroup: Patients enrolled from China, Japan, Korea, Taiwan and Thailand were included

Yao JC et al, JSMO 2016

RADIANT-4 East Asian subgroup: Progression-free survival, central radiology review



Yao JC et al, JSMO 2016

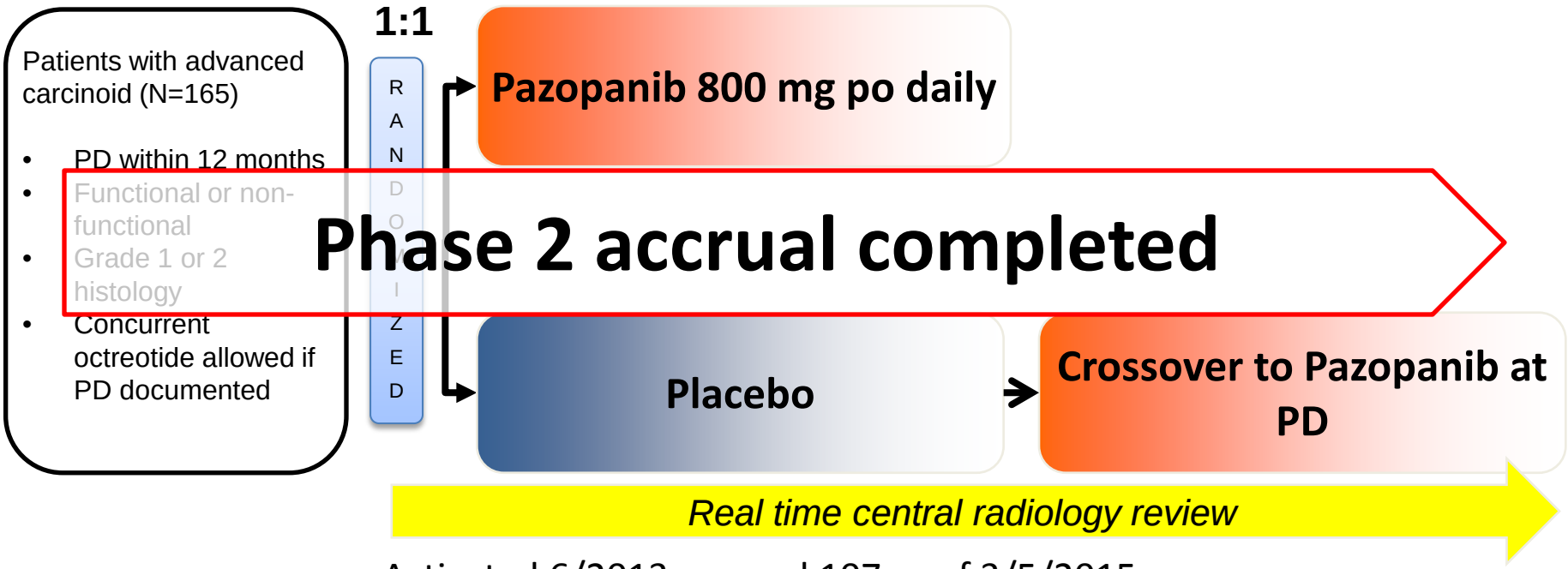
Everolimus in the East Asian subgroup: RADIANT -3 and -4 studies

	Overall population		East Asian subgroup	
	Everolimus	**Placebo**	**Everolimus**	**Placebo**
RADIANT-3 (Advanced Progressive PNET)				
Median PFS (95% CI), months	11.0 (8.4-13.9)	4.6 (3.1 -5.4)	14.09 (98.41-NA)	6.37 (2.83-10.84)
HR (95% CI)	0.35 (0.27-0.45)		0.34 (0.17-0.69)	
RADIANT-4 (Advanced Progressive Non-functional GI and Lung NET)				
Median PFS (95% CI), months	11.0 (9.23-13.31)	3.9 (3.58-7.43)	11.2 (7.3-NA)	3.1 (1.8-3.7)
HR (95% CI), p-value	0.48 (0.35-0.67)		0.18 (0.09-0.38)	

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

Yao JC et al, JSMO 2016

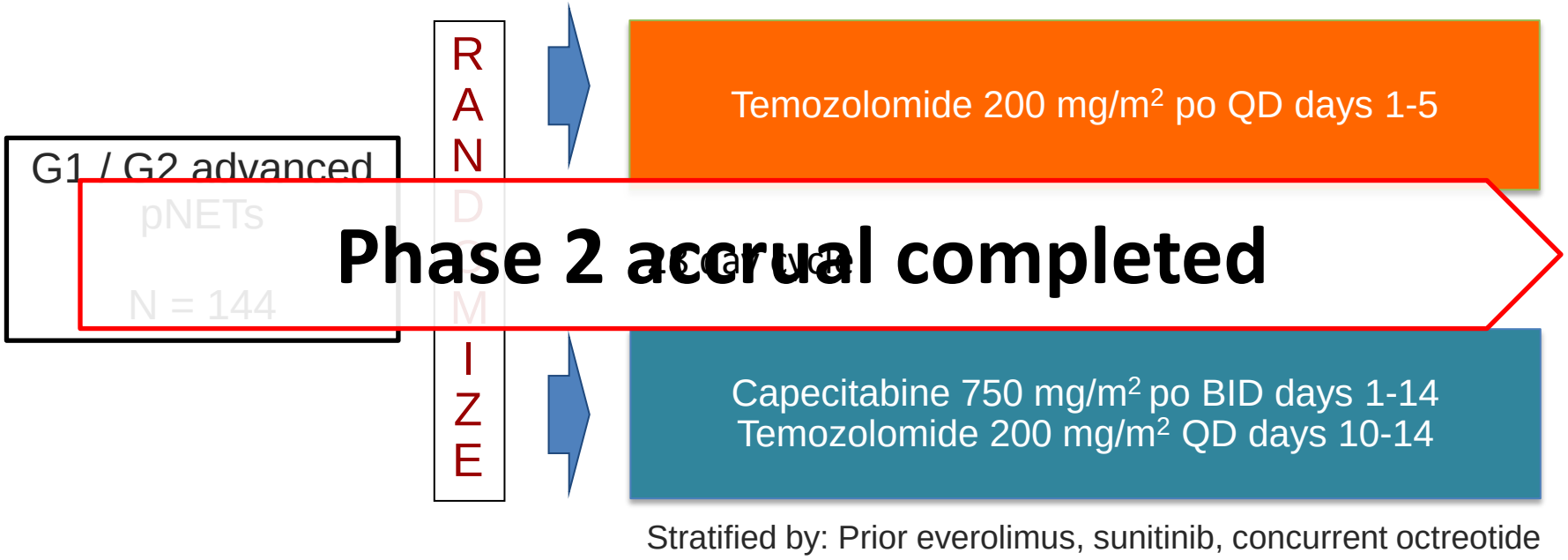
ALLIANCE 021202 (CALGB 81103): RP2 of Pazopanib vs. placebo in advanced carcinoid (Bergsland)



Activated 6/2013; accrual 107 as of 3/5/2015

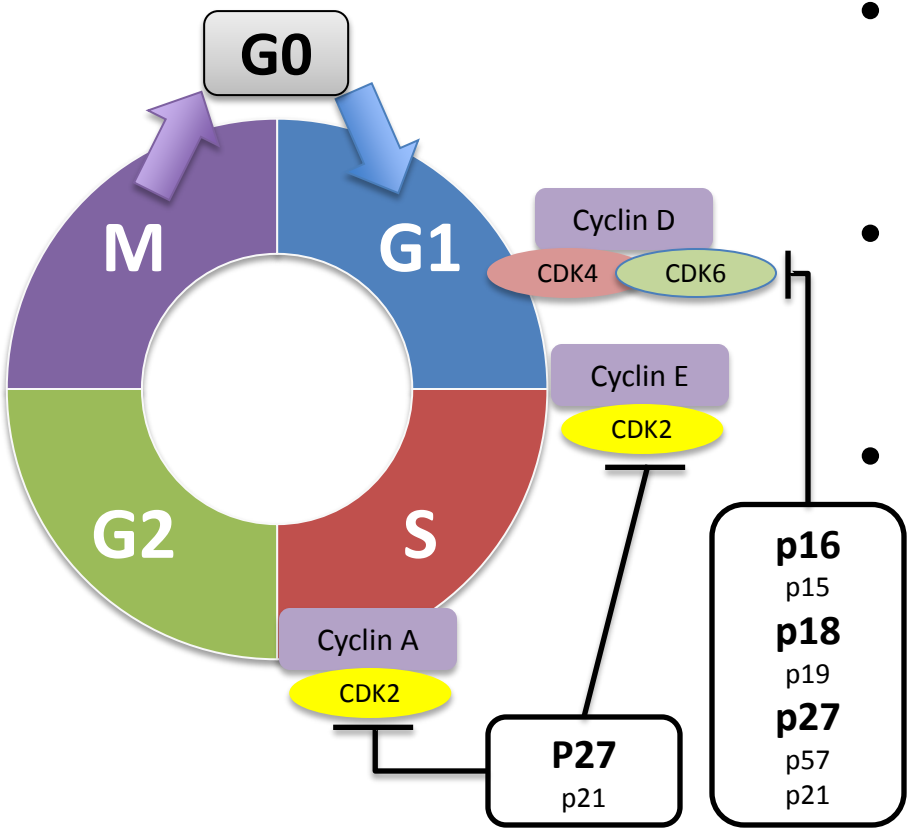
Ongoing study

E2211 Study Schema



Stratified by: Prior everolimus, sunitinib, concurrent octreotide

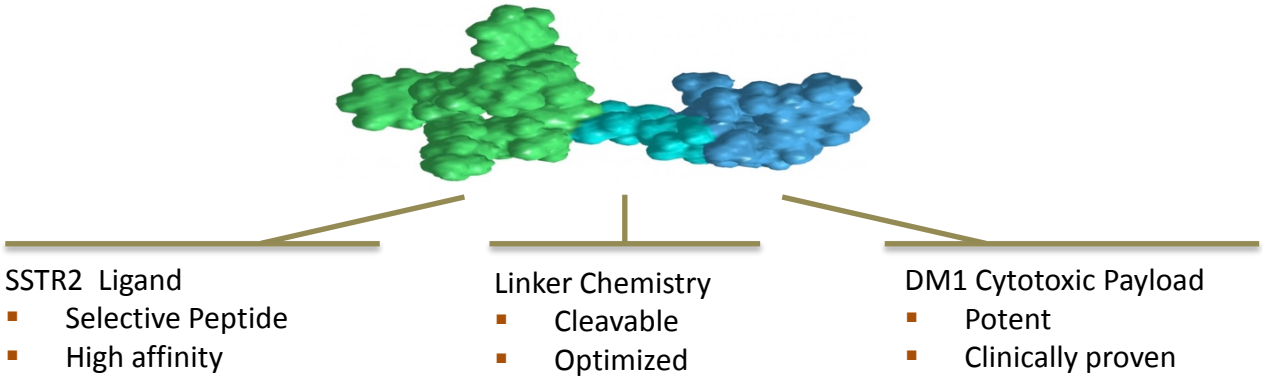
Cell cycle dysregulation in NETs



- Alterations in MEN1, p27, p18, p16 suggest cell cycle dysregulation in NET
- Phase II study of CDK 4/6 inhibitor, ribociclib MDACC completed accrual
- Combination in development

Targeting somatostatin receptor beyond PROMID, CLARINET, and NETTER-1

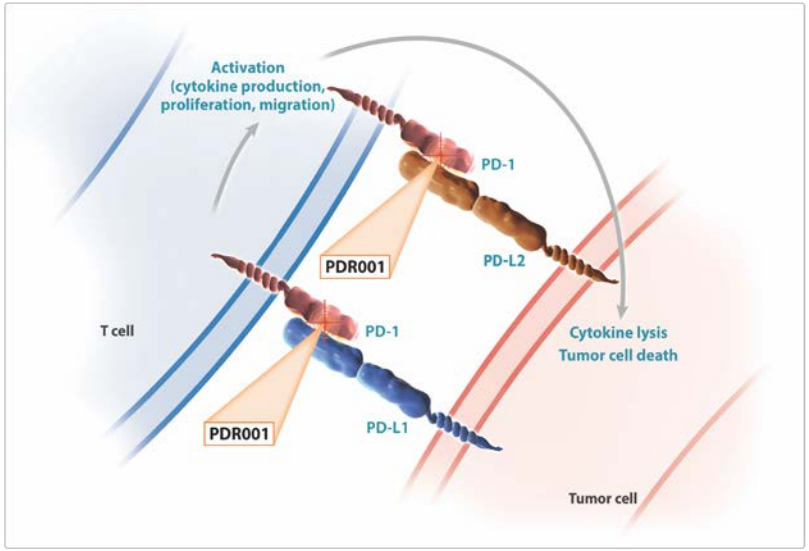
- Somatostatin Antagonists
  - 68Ga-DOTA-JR11 and 177Lu-DOTA-JR11
- PEN-221 – Phase 1/2a



Role of immunotherapy in NET

- PD1, PDL1, CTLA-4, Novel combinations
  - Anecdotal experiences and small studies in progress
  - Rigorous data on response rate and PFS in various NET subgroups lacking

Phase II study of PDR001 in patients with NET of pancreatic, GI or thoracic Origin



Progression documented within 6 months of study entry

Patients :

- Advanced, non-functional NET of pancreatic or GI origin (grade 1 or 2) or thoracic (typical or atypical) origin
- Well-Differentiated
- Prior treatment required with everolimus in lung and GI NETs. Prior sunitinib and/or everolimus required in pNET.
- ECOG status 0-2
- Measurable disease as per RECIST 1.1

→

Total (N=90)*

- GI Cohort (n=30)
- Pancreatic Cohort (n=30)
- Thoracic Cohort (n=30)

*Target enrollment from February 2017

→

PDR001 400 mg Q4W, flat dose until:

- Confirmed PD per RECIST 1.1
- Toxicity
- Patient withdrawal

No dose modifications allowed

Dose may be interrupted for up to 12 weeks

Futility Interim Analysis: ~ 30 patients with 6 months follow-up

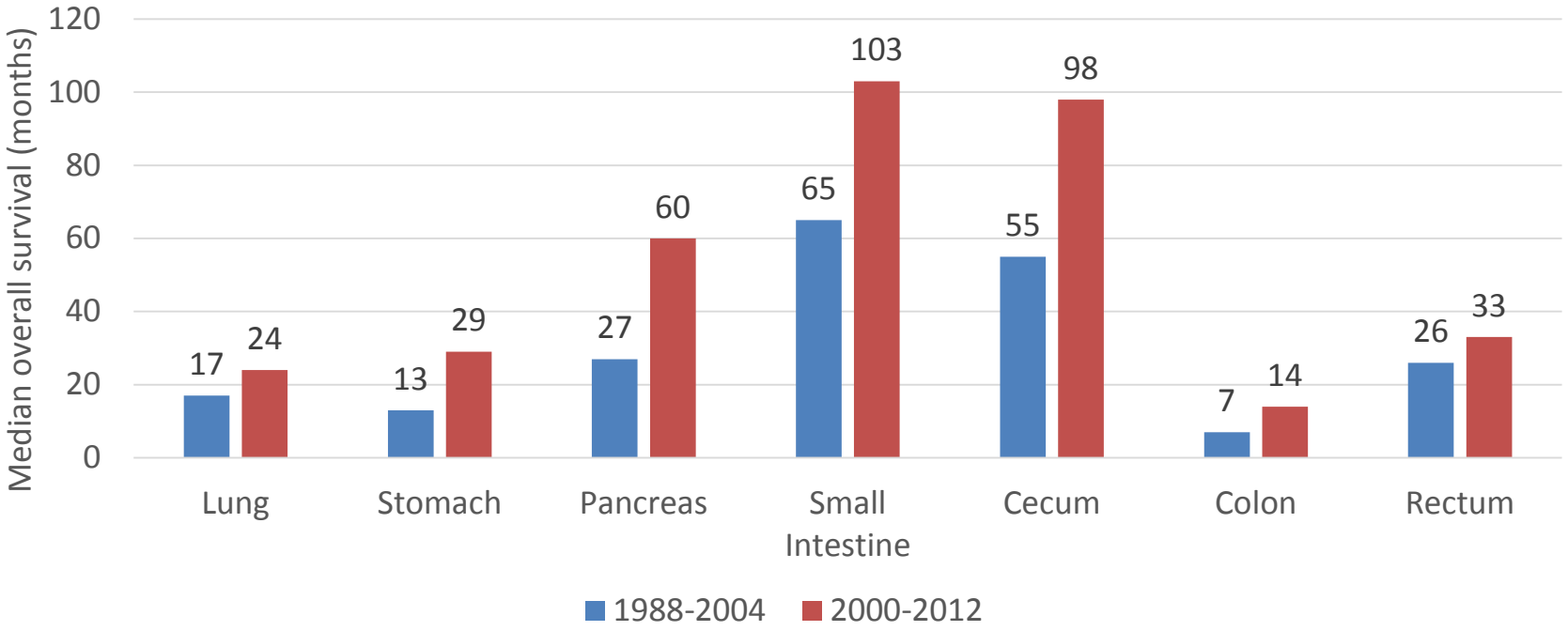
Improvement in OS for NET patients

	Total SEER 18 NET cohort (N=14757)			Distant GI NET (N=2681)			Distant pancreatic NET (N=850)		
	HR	95% CI		HR	95% CI		HR	95% CI	
2000-2004	1	Reference		1	Reference		1	Reference	
2005-2008	0.83	0.78	0.89	0.76	0.67	0.86	0.76	0.61	0.96
2009-2012	0.79	0.73	0.85	0.71	0.62	0.81	0.56	0.44	0.70

From multivariate Cox model, covariates include time periods, age, race, stage, grade and primary site. $P < 0.001$ in each comparison.

Dasari et al, JAMA Oncology, In Press 2017

Overall survival among patient with G1/2 distant metastatic NET



Yao et al. (2008). J Clin Oncol 26(18): 3063-3072.
Dasari et al, JAMA Oncology, In Press 2017