Targeted treatment of NETs

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Disclosures

- Consultancy
  - Ipsen, Lexicon, Novartis, Pfizer
- Research support
  - Novartis Oncology
- I will discuss the following investigational use in my presentation:
  - Octreotide, Lanreotide
  - Everolimus
  - Bevacizumab

Survival: stage and primary site

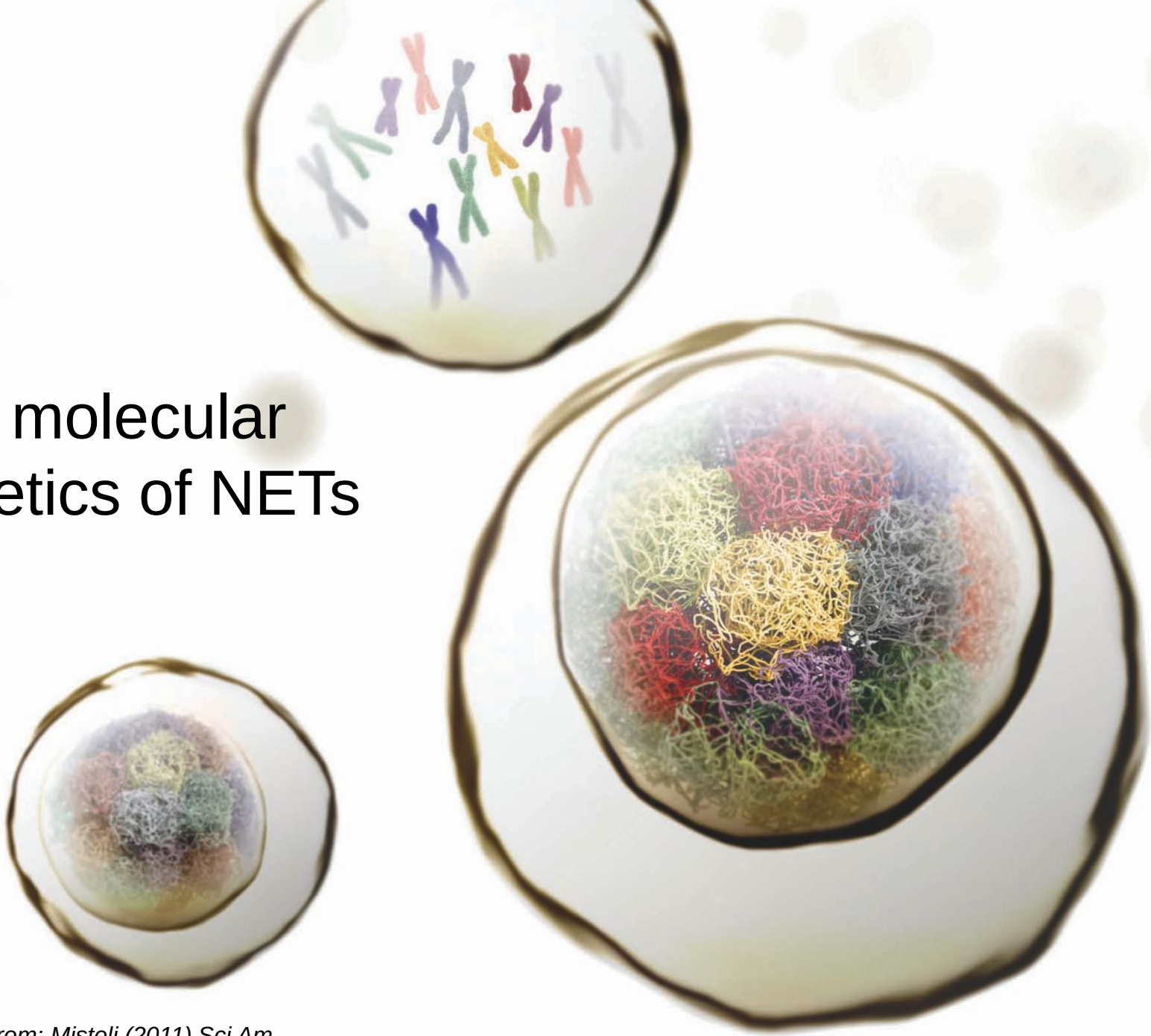
G1/G2 NETs diagnosed from 1988 to 2004

	Localized			Regional			Distant		
Primary site	Median	5-yr	10-yr	Median	5-yr	10-yr	Median	5-yr	10-yr
Thymus	92	93%	52%	68	65%	49%	40	32%	0%
Lung	NR	84%	70%	151	72%	56%	17	27%	15%
Pancreas	NR	79%	58%	111	62%	46%	27	27%	11%
Liver	47	43%	--	14	27%	--	12	26%	0%
Gastric	163	73%	56%	76	65%	43%	13	25%	9%
Duodenum	112	68%	48%	69	55%	44%	57	46%	27%
Jejunum/Ileum	115	65%	49%	107	71%	46%	65	54%	30%
Cecum	135	68%	55%	107	71%	44%	55	48%	23%
Colon	NR	85%	74%	52	46%	33%	7	14%	6%
Rectum	NR	90%	80%	90	62%	47%	26	24%	3%
Appendix	NR	88%	72%	NR	78%	67%	31	25%	11%

Median survival in months

Yao JC, et al. (2008). J Clin Oncol 26(18): 3063-3072.

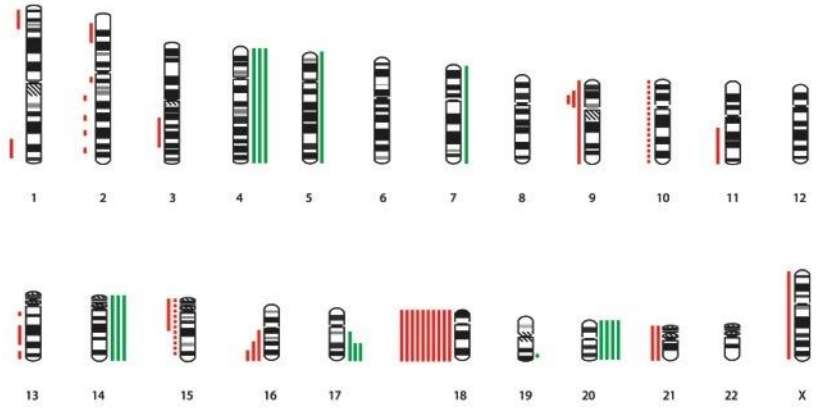
The molecular genetics of NETs



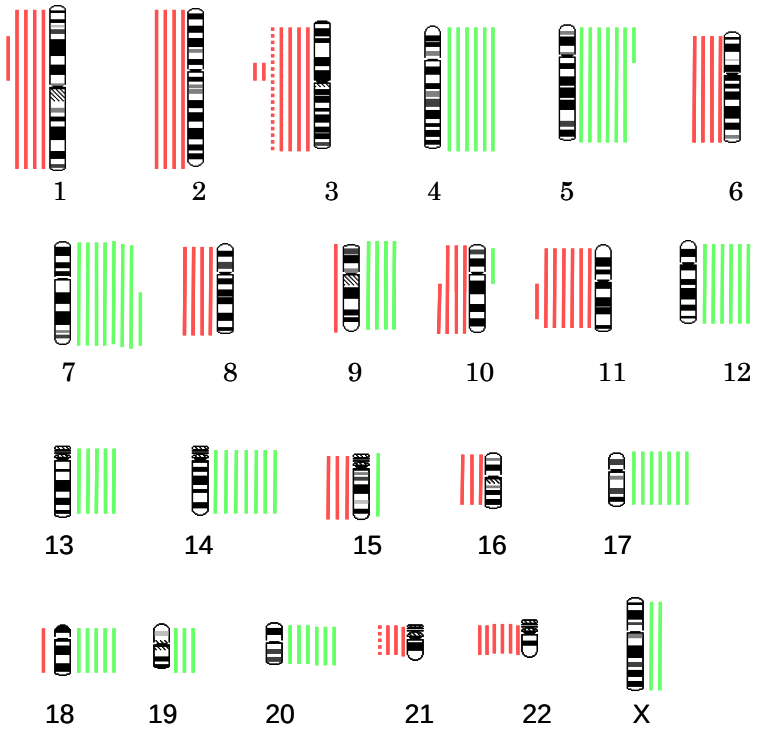
Adopted from: Misteli (2011) Sci Am

NETs: Site specific genetic changes

Ileal NETs



Pancreatic NETs

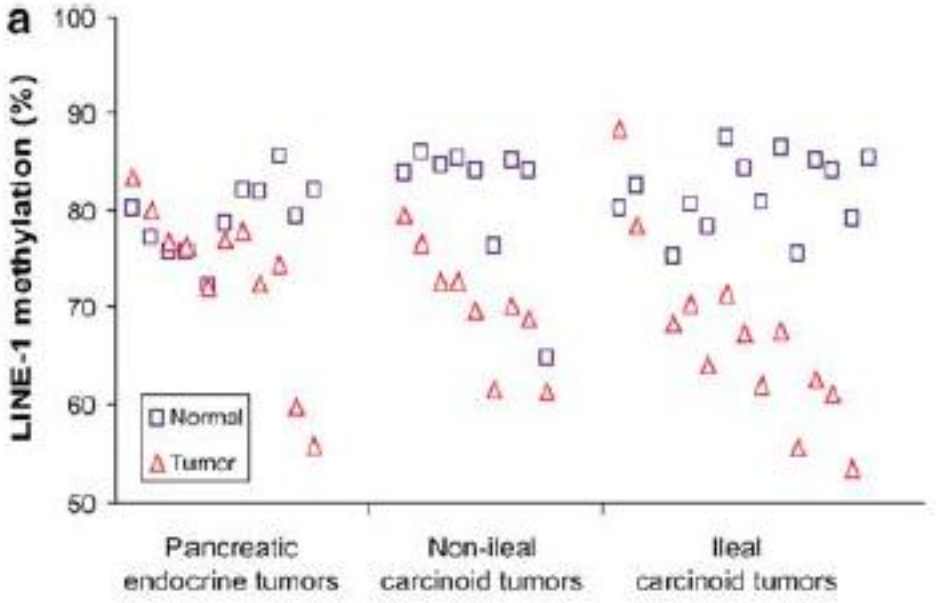


Nagano Y et al, Endocr Relat Cancer 2007
Kim H et al, Genes Chromosome Cancer 2008

Ileal NETs – Loss of Chr 18 and hypomethylation

- Frequent loss of chromosome 18
- Global hypomethylation

- Difficult to obtain normal NET cells for RNA and methylation profiling



Nagano Y et al, Endocr Relat Cancer 2007
Kim H et al, Genes Chromosome Cancer 2008
Choi IS et al, Mondern Pathology 2007

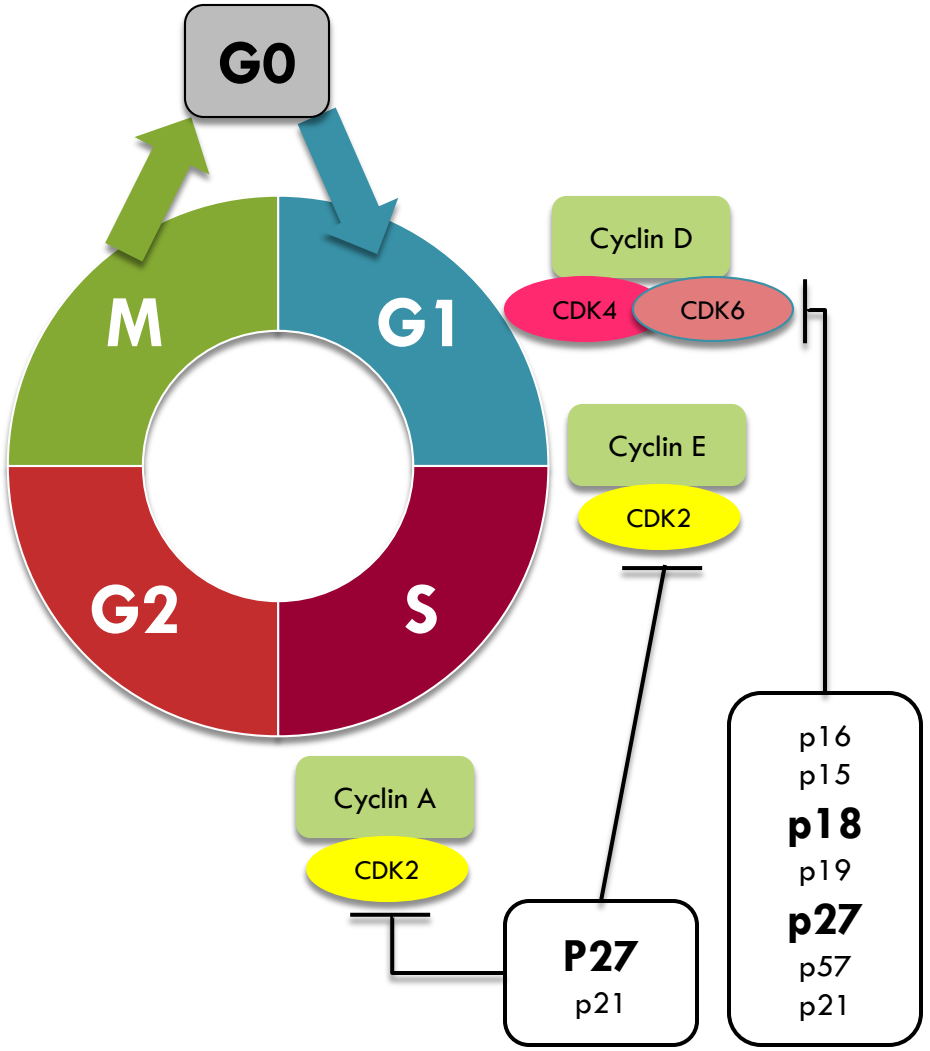
Key Pathways in Pancreatic NETs

- Involved in FOUR genetic cancer syndrome
  - MEN1, TSC2, NF1, vHL
- Whole genome sequencing identified THREE key pathways
  - MEN1
  - DAXX/ATRX - Alternative lengthening of telomeres
  - PI3K/AKT/mTOR pathway

Jiao Y et al, Science 2011
Heaphy C et al. Science 2011

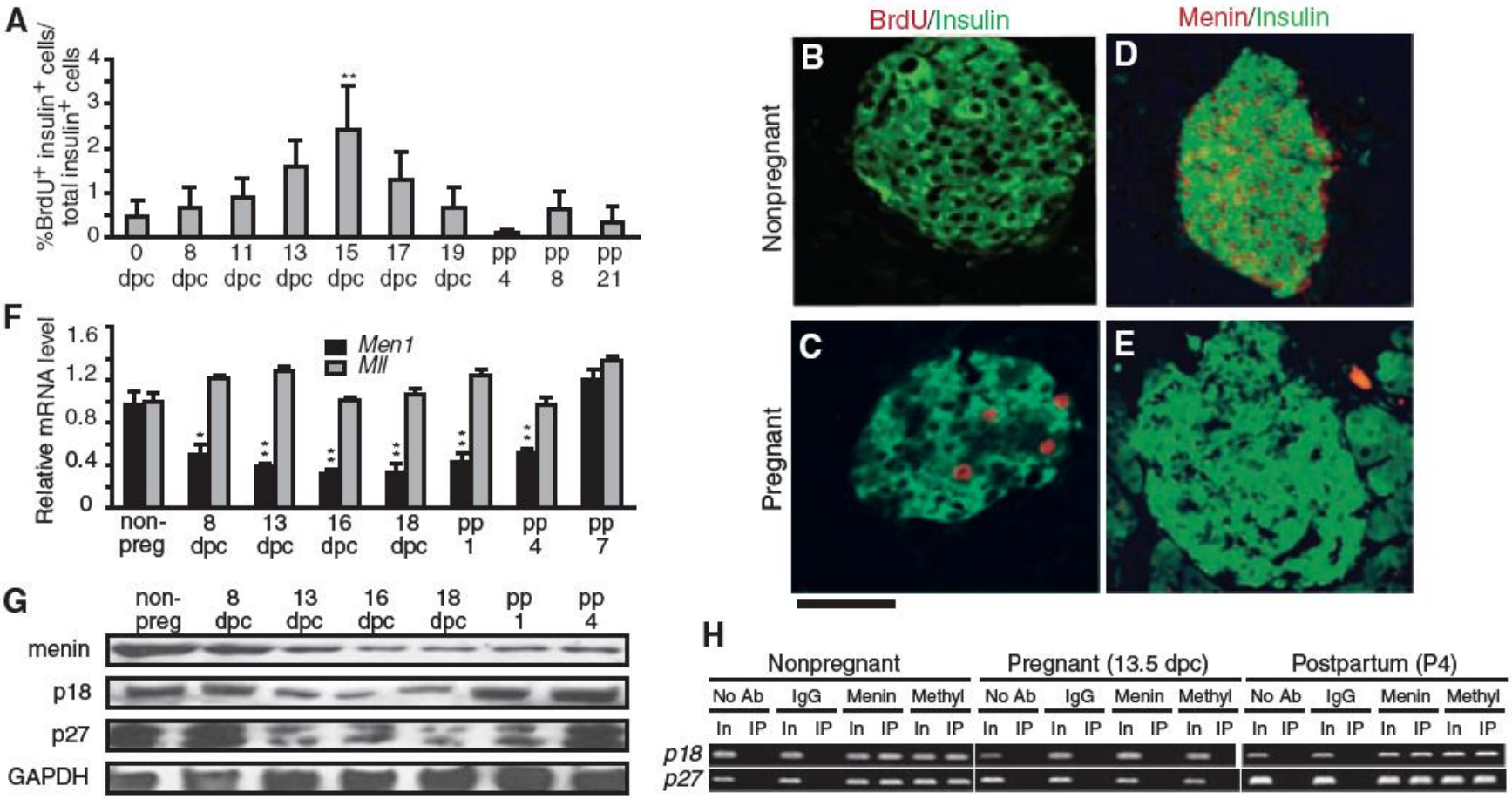
Pancreatic NETs – MEN1 and p27

- Knock out mice recapitulates phenotype[1]
- Part of histone methyltransferase complex
- Maintains expression of p27 and p18 (CDK inhibitors)[2]
- Germline p27 mutation has phenotype similar to MEN1



1. *Crabtree JS et al, PNAS 2001*
2. *Karnik SK et al, PNAS 2005*

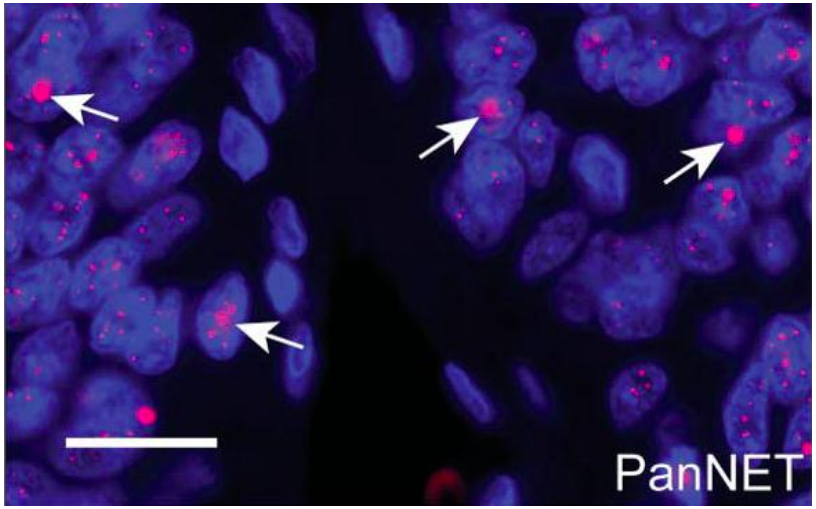
MENIN control of endocrine mass

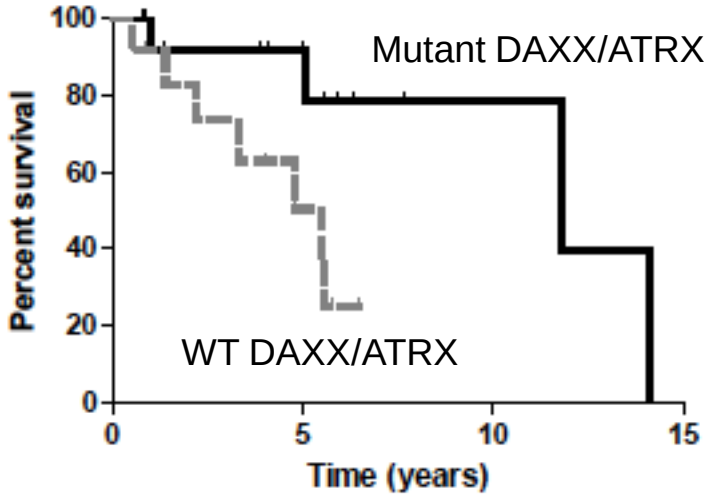


Karnik et al, Science 2007

Pancreatic NETs – DAXX/ATRX

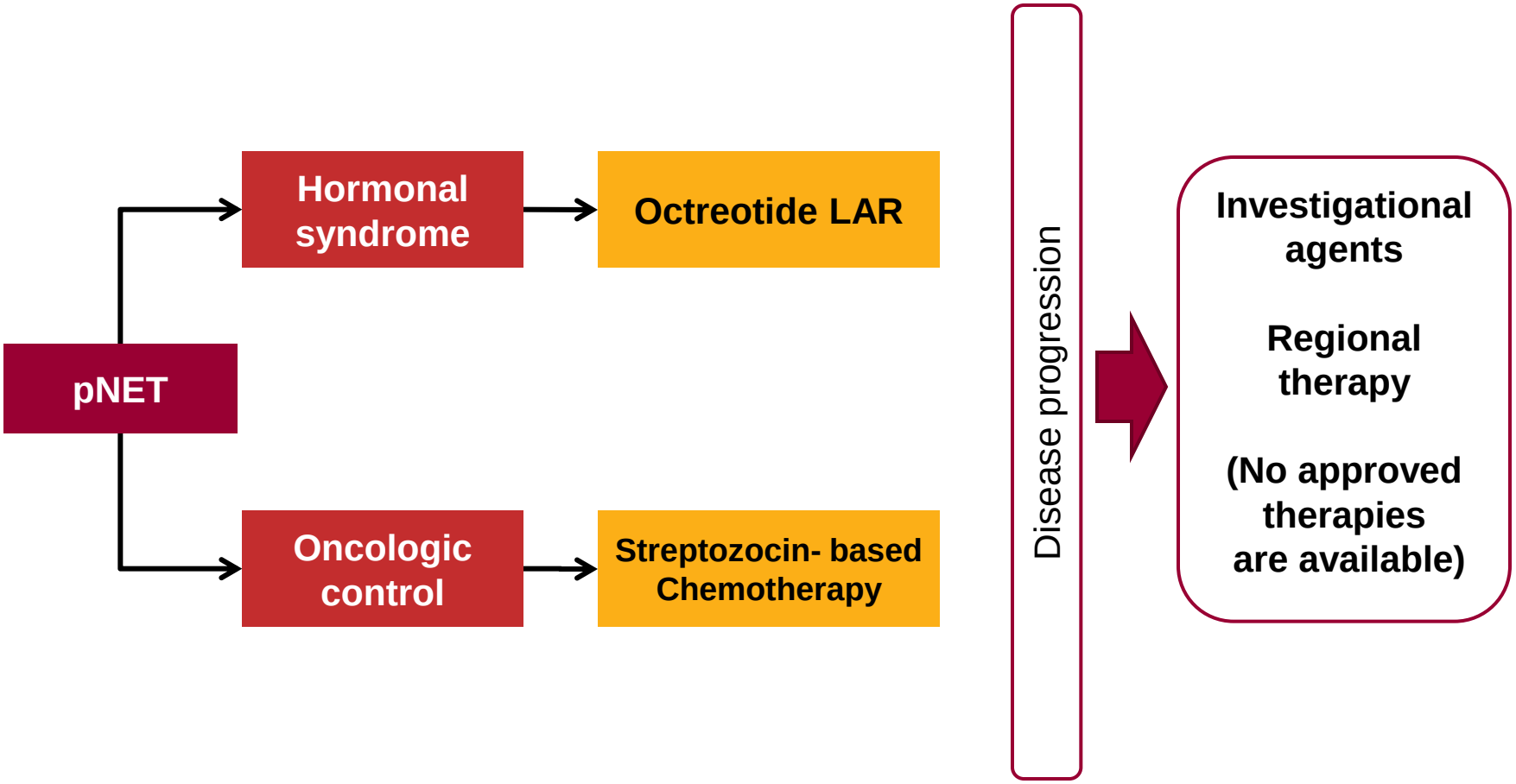
- DAXX, ATRX mutually exclusive mutations[1]
  - Good prognosis
  - Alternative lengthening of telomeres (ALT)[2]
- ALT → lower metastatic potential[3]
- ALT → long survival in GBM[4, 5]



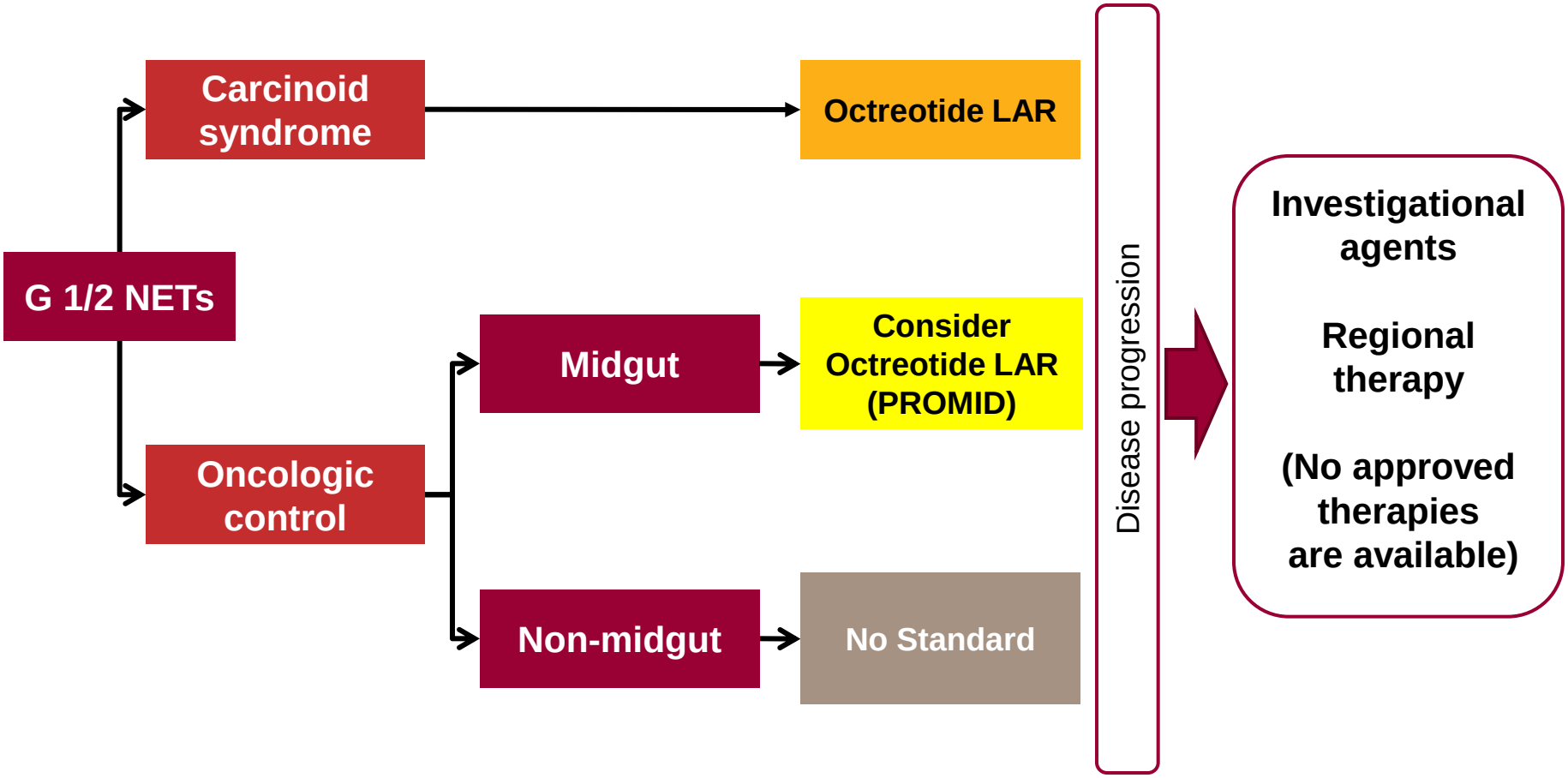


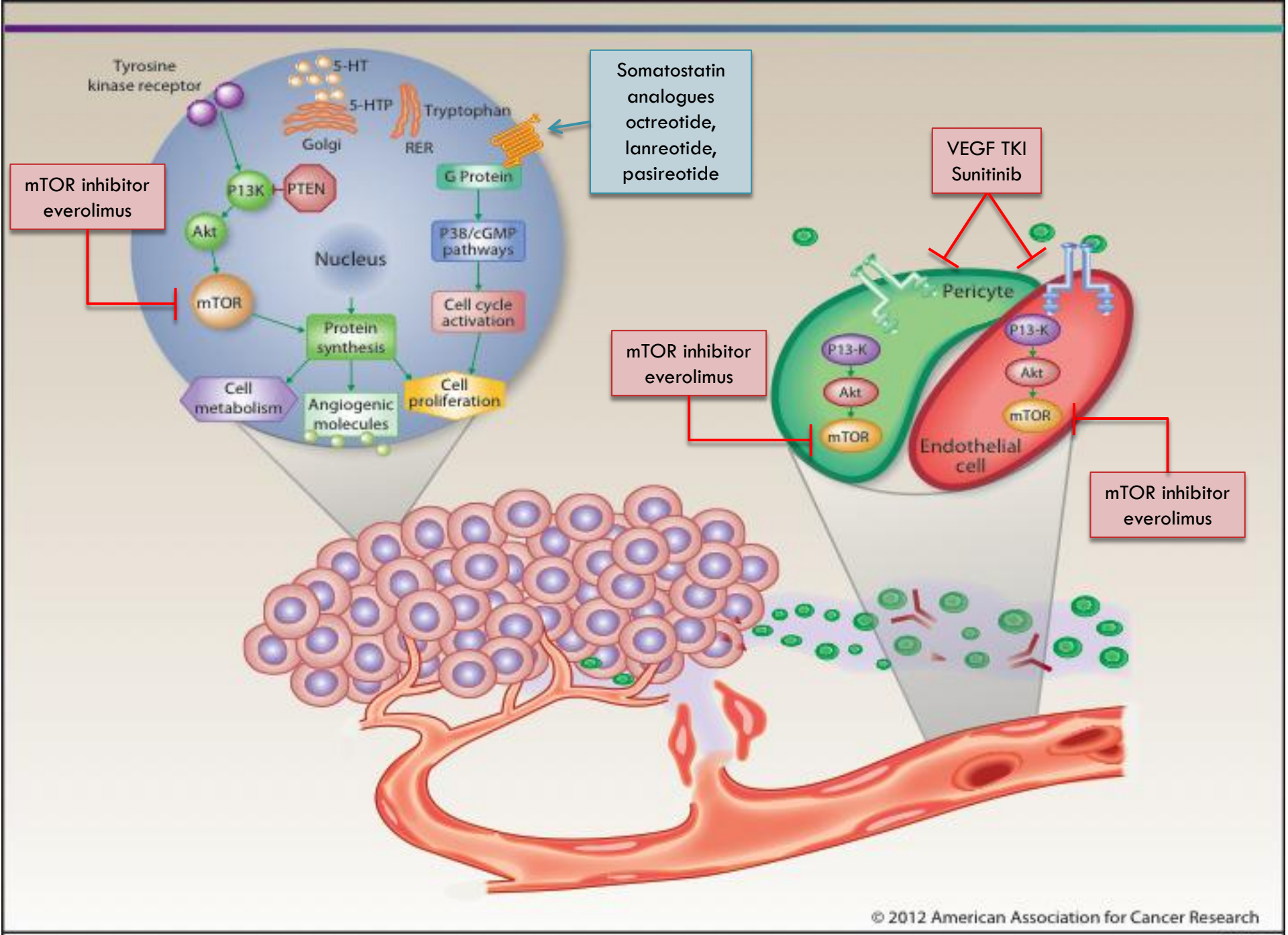
1. *Jiao Y et al. Science 2011*
2. *Heaphy C et al. Science 2011*
3. *Chang S et al. Genes Development 2003*
4. *Sampl S et al, Translational Oncology 2012*
5. *McDonal KL et al, J Neuropathol Exp Neurol. 2010*

Limited Options for Advanced pNETs (prior to May 2011)



Limited Options for Advanced Non-pancreatic NETs





Mei D, Phan A, Yao J. CCR 2012

Pancreatic NETs

Advances in the age of molecularly targeted therapy and controlled phase III clinical studies

Scientific rationale for mTOR inhibition

- mTOR activating genetic cancer syndromes associated with development of pancreatic NET
  - Tuberous Sclerosis,[1] Neurofibromatosis[1,2]
- Somatic mutations in mTOR pathway identified in pancreatic NET[3]
  - TSC2, PTEN, PIK3CA, NF1, IRS1
- Low protein expression of TSC2, PTEN associated with short PFS, OS in pancreatic NET[4]

1. *Yao JC, et al. in DeVita VT: Cancer: Principles & practice of oncology (ed 8th)., 2008, 1702-21.*
2. *Johannessen CM, et al. Proc Natl Acad Sci U S A 102:8573-8, 2005*
3. *Jiao Y, et al. Science 2011;331:1199-203.*
4. *Missiaglia E, et al. J Clin Oncol 2010;28:245-55.*

RADIANT-3: Study Design

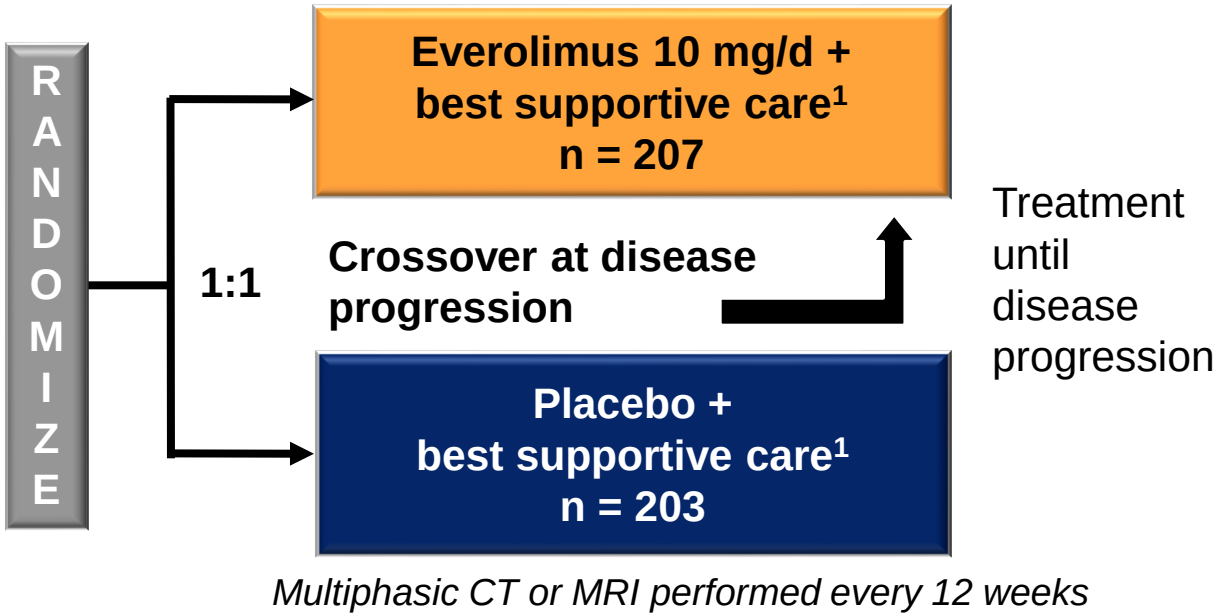
Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced pNET (N = 410)

- Advanced well or moderately differentiated
- Radiologic progression ≤12 months
- Prior antitumour therapy allowed
- WHO PS ≤2

Stratified by:

- WHO PS
- Prior chemotherapy

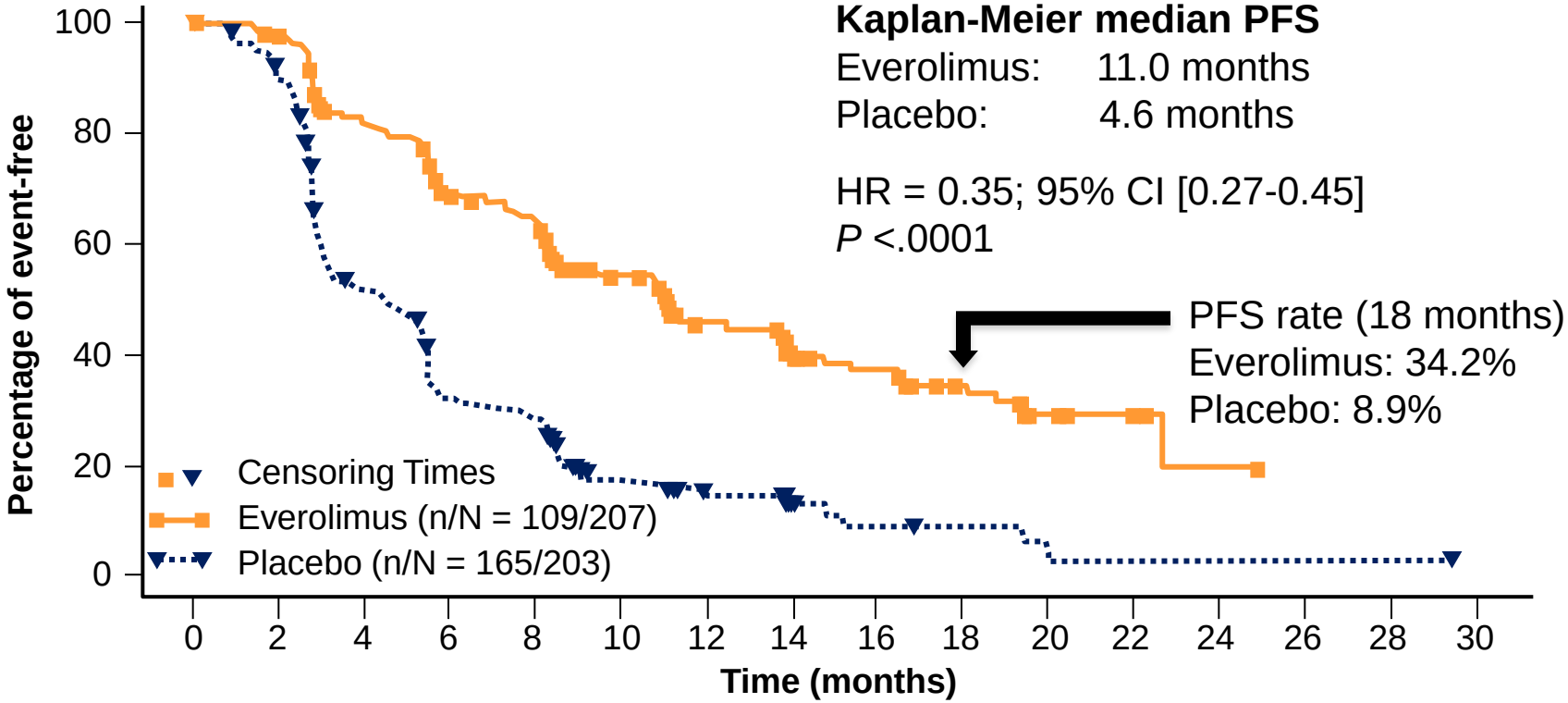


Primary Endpoint: Progression-free survival By investigator review
Secondary Endpoints: OS, ORR, biomarkers, safety, pharmacokinetics (PK)

[1]Concurrent somatostatin analogues allowed

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

RADIANT-3: PFS by Investigator Review



Number of patients still at risk

Everolimus	207	189	153	126	114	80	49	36	28	21	10	6	2	0	0	0
Placebo	203	177	98	59	52	24	16	7	4	3	2	1	1	1	1	0

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

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

Glycemic Control in Patients with Insulinoma Treated with Everolimus

To the Editor: Management of refractory hypoglycemia due to malignant insulinoma is challenging. ...

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n engl j med 360;2 nejm.org january 8, 2009

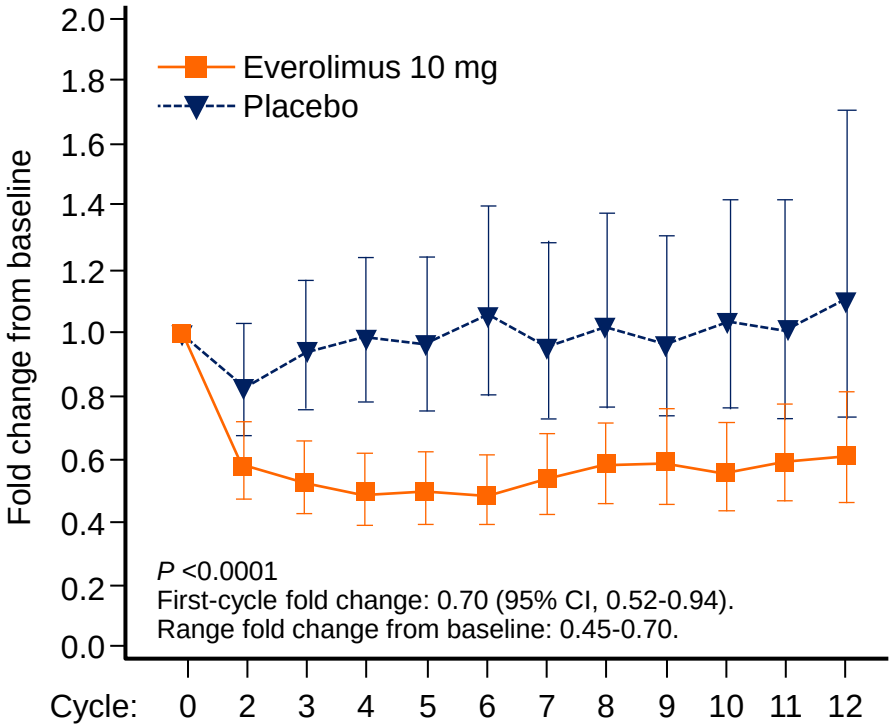
The Oncologist®
Cancer Biology

Everolimus Induces Rapid Plasma Glucose Normalization in Insulinoma Patients by Effects on Tumor As Well As Normal Tissues

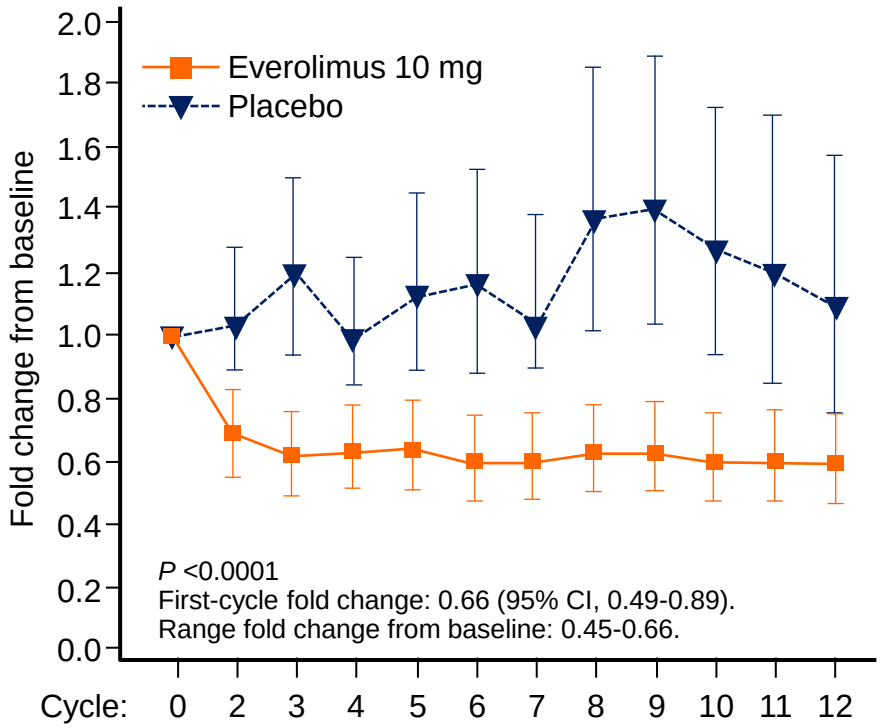
HELLE-BRIT FIEBRICH,[a] ESTER J.M. SIEMERINK,[a] ADRIENNE H. BROUWERS,[b] THERA P. LINKS,[c] WOUTER S. REMKES,[d] GEKE A.P. HOSPERS,[a] ELISABETH G. E. DE VRIES[a]

Fold Change from Baseline in Biomarkers in Response to Treatment

Gastrin*



Glucagon*



*Least-square estimates of mean fold change and 95% CI obtained using a mixed model, including terms for baseline value, treatment, time, and interaction between time and treatment. Only patients with elevated levels at baseline (>1 × ULN) were included.

†Upper limit for truncated confidence interval is out of presented range.

de Vries E, Anthony L, Sideris L, et al. ASCO 2011; Chicago, IL. Abstract 10624.

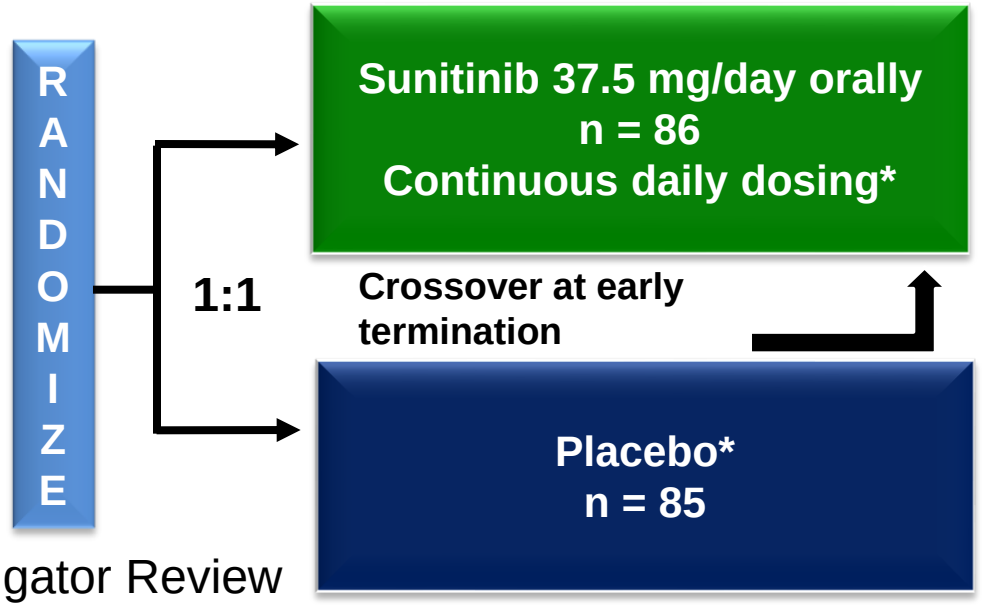
Sunitinib vs Placebo in Advanced pNET

IDMC terminated at early unplanned analysis

Key Eligibility Criteria

- Well-differentiated malignant pNET
- Disease progression ≤12 months
- Not amenable to curative treatment
- 340 patients planned
- 171 patients enrolled

No Stratification



Primary Endpoint: PFS by Investigator Review

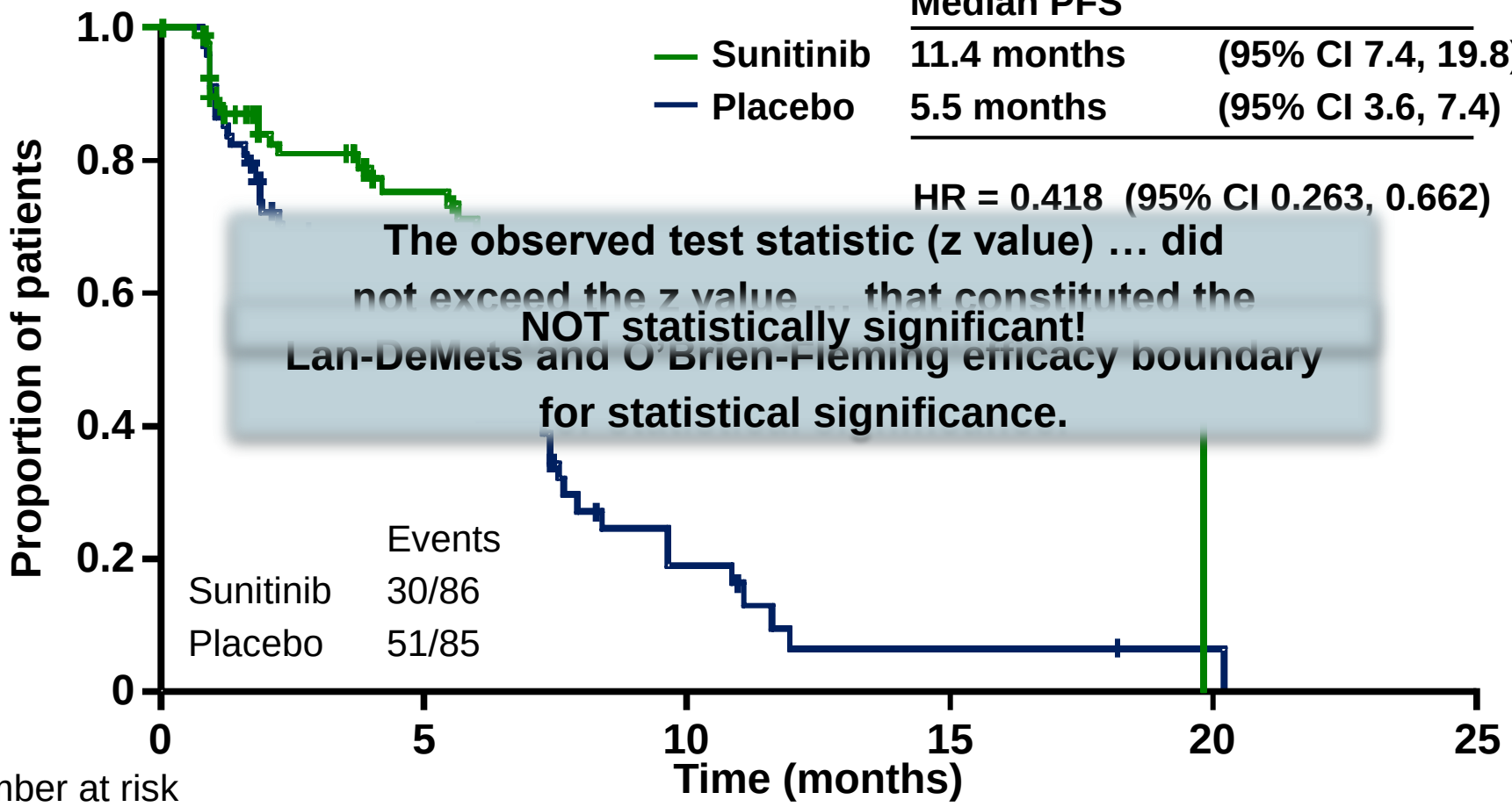
Secondary Endpoints: OS, overall response rate (ORR), time to recurrence, duration of response, safety, and patient-reported outcomes

Final analysis planned at 260 events
One interim analysis planned at 130 events

* With best supportive care
Somatostatin analogues were permitted

Raymond E, et al. N Engl J Med. 2011;364:501-513.
Blumenthal GM, et al. The oncologist. 2012;17(8):1108-13.

Sunitinib Phase III: PFS by Investigator Review



Raymond E, et al. N Engl J Med. 2011;364(6):501-513. Blumenthal GM, et al. The oncologist. 2012;17(8):1108-13.

Sunitinib Phase III In Context With Other Studies

Median PFS (months)	VEGF TKI	Placebo
Sunitinib (sunitinib phase III)[1]	**11.4 (7.4-19.8)**	
Placebo (sunitinib phase III) [1]		**5.5 (3.6 – 7.4)**
Sunitinib (phase II)[2]	7.7 (6.5 – 12.5)	
Pazopanib (phase II)[3]	14.2 (6.9 – 21.5)	
Sorafenib (phase II)[4]	11.9 (not reported)	
Placebo (everolimus phase III)[5]		4.6 (3.1 – 5.4)

1. *Raymond E, et al. N Engl J Med. 2011;364(6):501-513*
2. *Kulke MH, et al. J Clin Oncol. 2008;26(20):3403-3410.*
3. *Phan A, et al J Clin Oncol. 2010;28(15 s): Abstract 4001.*
4. *Hobday TJ, et al. J Clin Oncol. 25(18 s): Abstract 4504.*
5. *Yao JC, et al. N Engl J Med. 2011;364(6):514-523.*

Everolimus and Sunitinib in pNET

	PFS improvement	Type 1 error	Control hormone	OS benefit
Everolimus	6.4 months HR = 0.35	< 2.5%	✔	HR = 0.89 Not significant*
Sunitinib	5.9 months HR = 0.42	Not controlled	✗	HR = 0.74 Not significant*

*Data not mature. Study not designed for OS

Yao J, et al. N Engl J Med. 2011;364:514-523. de Vries E, Anthony L, Sideris L, et al. ASCO 2011; Chicago, IL. Abstract 10624. Raymond E, et al. N Engl J Med. 2011;364(6):501-513. Blumenthal GM, et al. The oncologist. 2012;17(8):1108-13.

Why don't we do OS studies in pNET?

- Incidence rate: 3/1,000,000 per year
- Distant metastasis: 64%
- Number of new cases US: 921
  - Assuming current US population of 307 million
- Number with distant metastases: 589
- Estimated sample size of OS study with ~90% power
  - 6 months Δ: 24 to 30 – 1,400 patients
  - 5 months Δ: 24 to 29 – 2,000 patients
  - 4 months Δ: 24 to 28 – 2,800 patients

Have we improved outcome?

	N	Overall survival
RADIANT-3 (phase 3)[1]		
Everolimus	207	> 36 months (not reached)
Placebo	203	36.6 months
Sunitinib phase 3[2]		
Sunitinib	86	30.5 months
Placebo	85	24.4 months
Streptozocin-based chemo[3]		
Streptozocin fluorouracil	33	16.8 months*
Streptozocin doxorubicin	36	26.4 months**

*Reported as 1.4 years. **Reported as 2.2 years.

1. Yao JC, et al. N Engl J Med. 2011 Feb 10;364(6):514-23.
2. Raymond E, et al. N Engl J Med. 2011 Feb 10;364(6):501-13.
3. Moertel CG, et al. N Engl J Med. 1992 Feb 20;326(8):519-23.

Non-pancreatic NETs

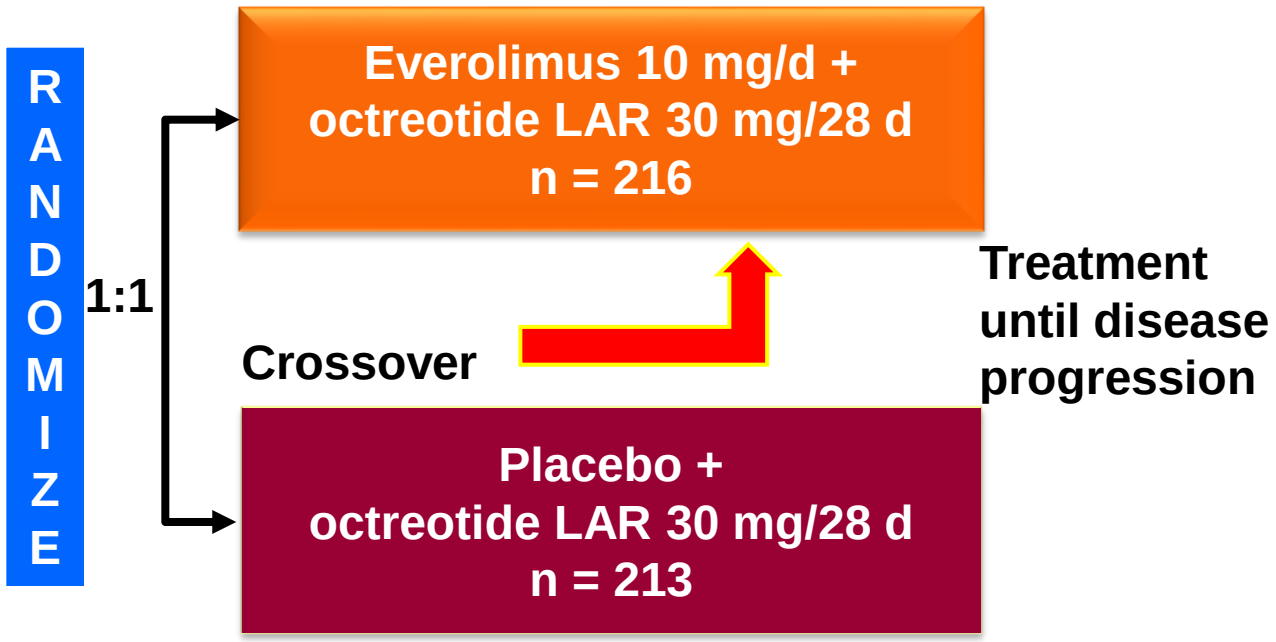
Carcinoids

RADIANT-2 Study Design

Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced NET and a history of symptoms attributed to carcinoid syndrome (N=429)

PD within 12 mo



Multiphasic CT or MRI performed every 12 wk

Primary end point:
- PFS (RECIST)

Secondary end points:
- Tumor response, OS, biomarkers, safety, PK

Enrollment January 2007–March 2008.

Pavel M, et al. Lancet 2011

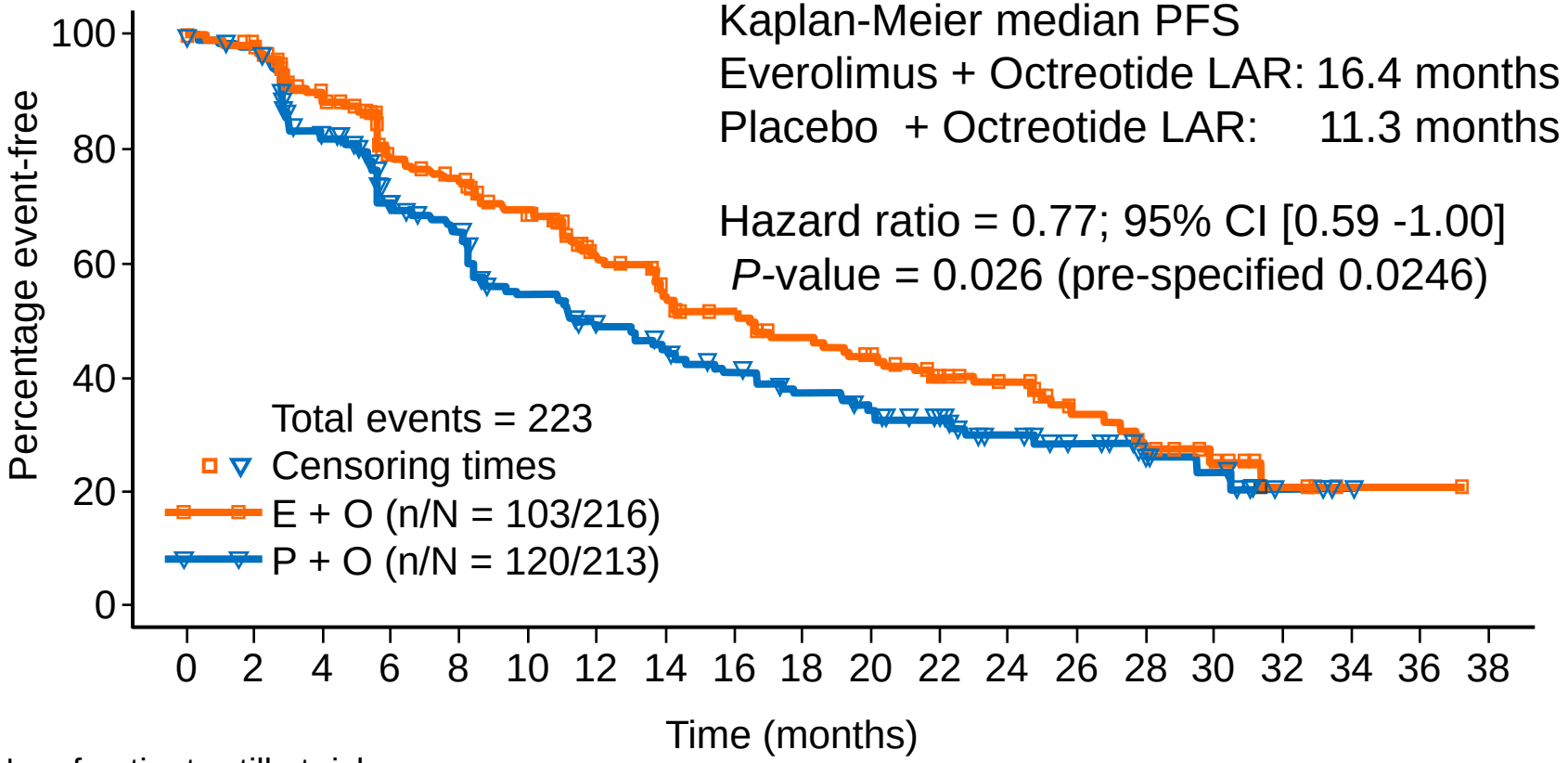
Baseline Characteristics

	Everolimus + octreotide LAR (n=216)	Placebo + octreotide LAR (n=213)
Median age, yr (range)	60 (22–83)	60 (27–81)
Male	45%	58%
Female	55%	42%
WHO PS		
0	55%	66%
1 / 2*	39% / 6%	29% / 5%
Primary site		
Small intestine	51%	53%
Lung*	15%	5%
Colon	7%	7%
Pancreas	5%	7%
Liver	3%	5%

*Statistically significant for imbalance, $P<0.05$.
1 missing PS in placebo arm.

Pavel M, et al. Lancet 2011

RADIANT-2: PFS by Central Review*



No. of patients still at risk

E + O	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
P + O	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0

* Independent adjudicated central review committee

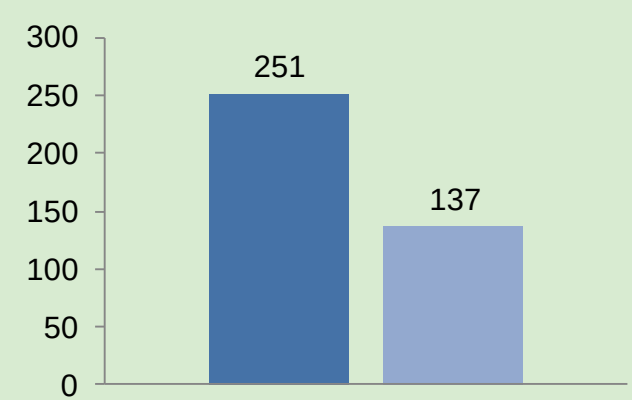
- *P*-value is obtained from the one-sided log rank test
- Hazard ratio is obtained from unadjusted Cox model

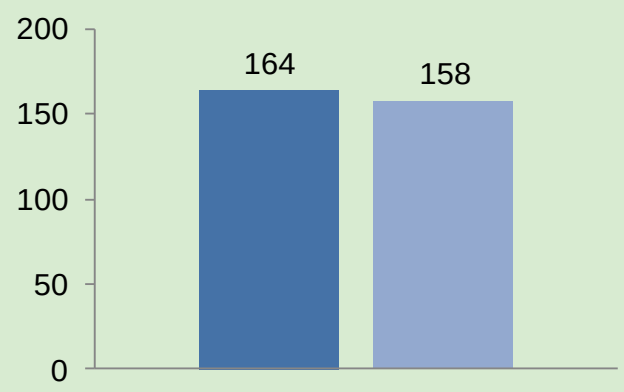
E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR

Pavel M, et al. Lancet 2011

Biomarkers at Baseline

	CgA, ng/mL		5-HIAA, µmol/day	
	E+O	**P+O**	**E+O**	**P+O**
n	212	208	187	191
Mean	1480	1002	367	386
Standard deviation	4712	3574	489	603
Median				





Yao, J. C. et al. ASCO GI 2012

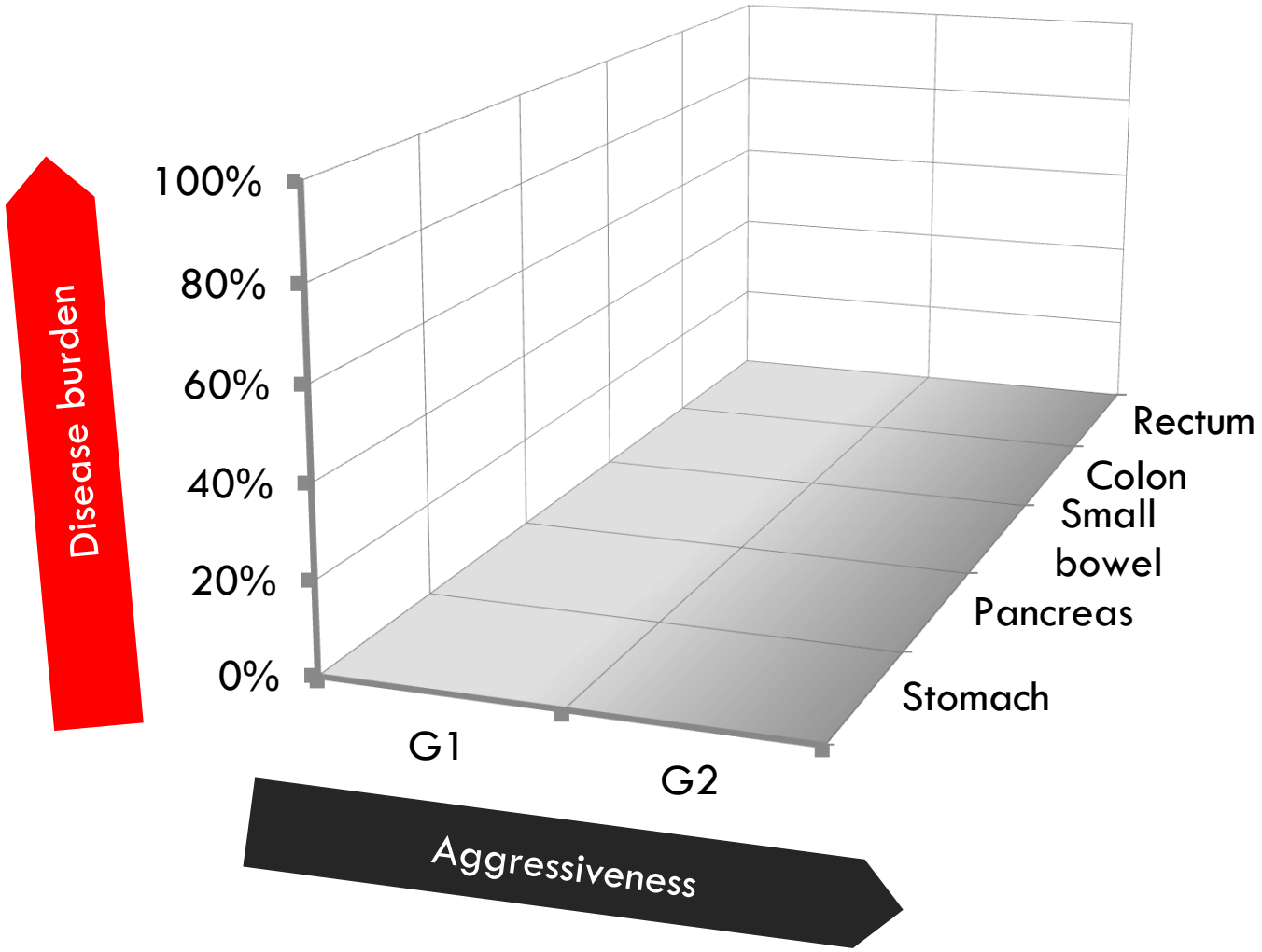
Multivariate Analysis

Variable	Groups	n	HR (95% CI), months	P*
Treatment	E+O P+O	216 213	0.62 (0.51-0.87)	0.003
WHO PS	0 ≥1	257 170	0.69 (0.52-0.90)	0.006
Baseline CgA	Elevated Nonelevated	282 138	0.47 (0.34-0.65)	<0.001
Bone involvement	Yes No	59 367	1.52 (1.06-2.18)	0.020
Lung as primary site	Yes No	44 385	1.55 (1.01-2.36)	0.044

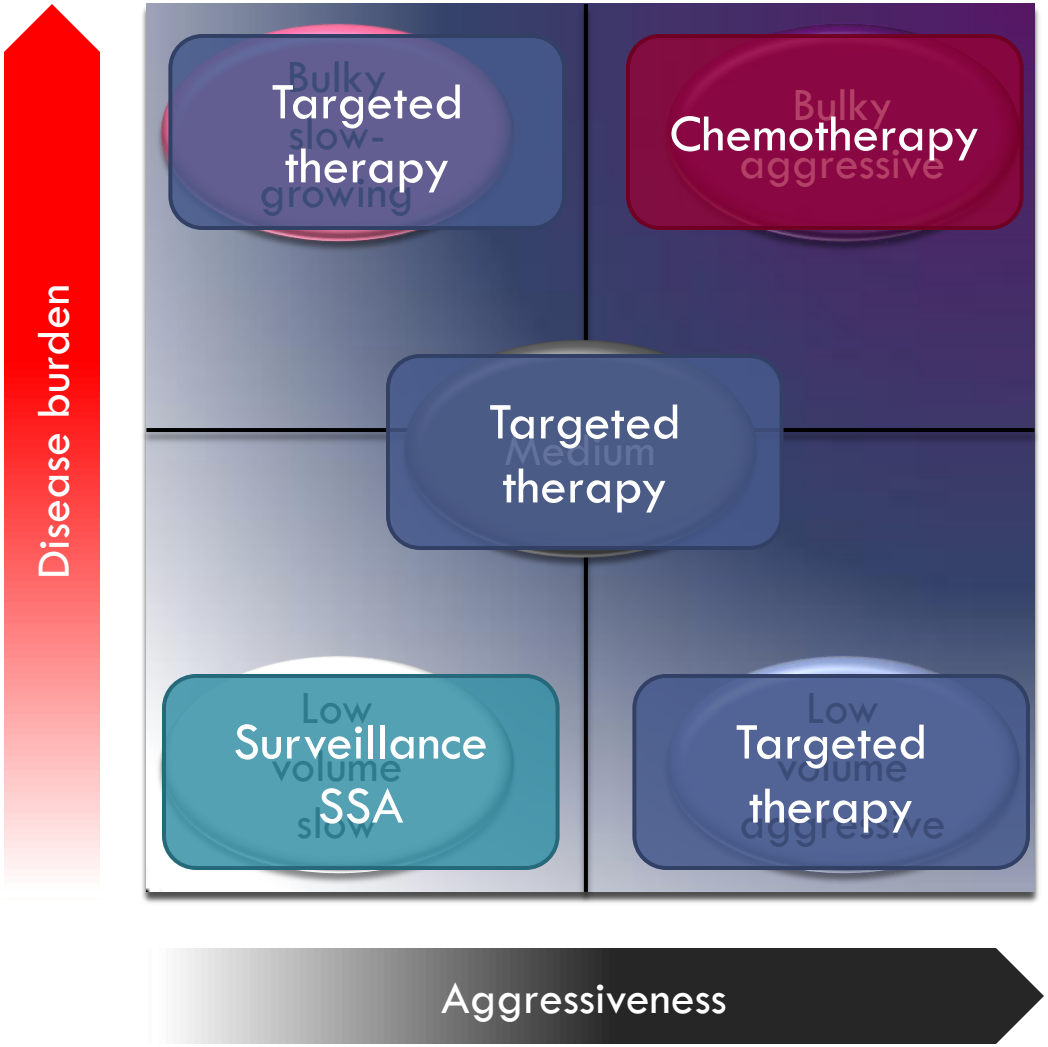
Nonelevated, ≤2× ULN; elevated, >2× ULN.
*Two-sided from Cox proportional hazards model, with variables selected using stepwise regression.

Yao, J. C. et al. ASCO GI 2012

Management of G1/2 NETs in 2012



Initial management of pNET



Targeted therapy
- Everolimus
- Sunitinib

Chemotherapy
- Streptozocin based

Pairing patients with initial therapy

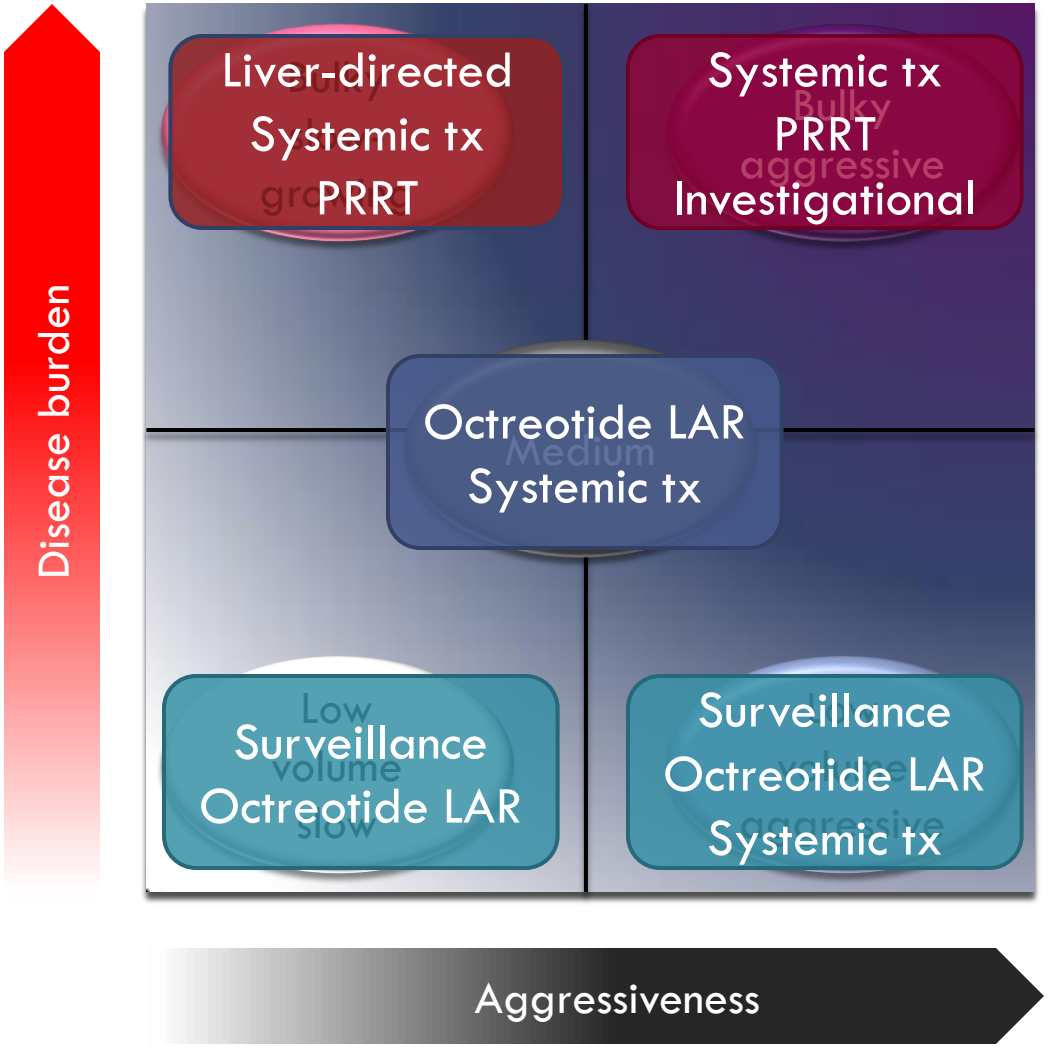
Factors favoring Everolimus

- Disease factors
  - Functional or non-functional
  - Bleeding or varices
- Co-morbidities
  - Heart disease
  - Uncontrolled HTN

Factors favoring Sunitinib

- Disease factors
- Co-morbidities
  - Severe lung disease
  - Uncontrolled DM

Initial management of non-pancreatic NETs (Carcinoids)



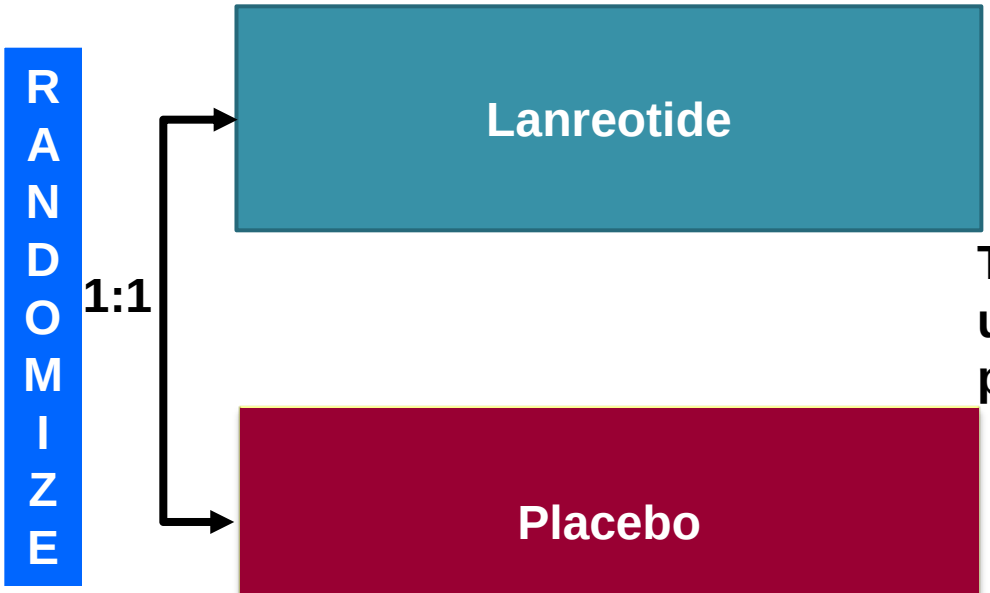
Clarinet: Lanreotide vs Placebo

Phase III, Double-Blind, Placebo-Controlled Trial – accrual completed

Non-functional advanced NET

Stratified by progression status during 3 month observation period

(N=200)



Patients treated and followed for 2-years

Primary end point:
- PFS (RECIST)

Secondary end points:
- Tumor response, OS, biomarkers, safety

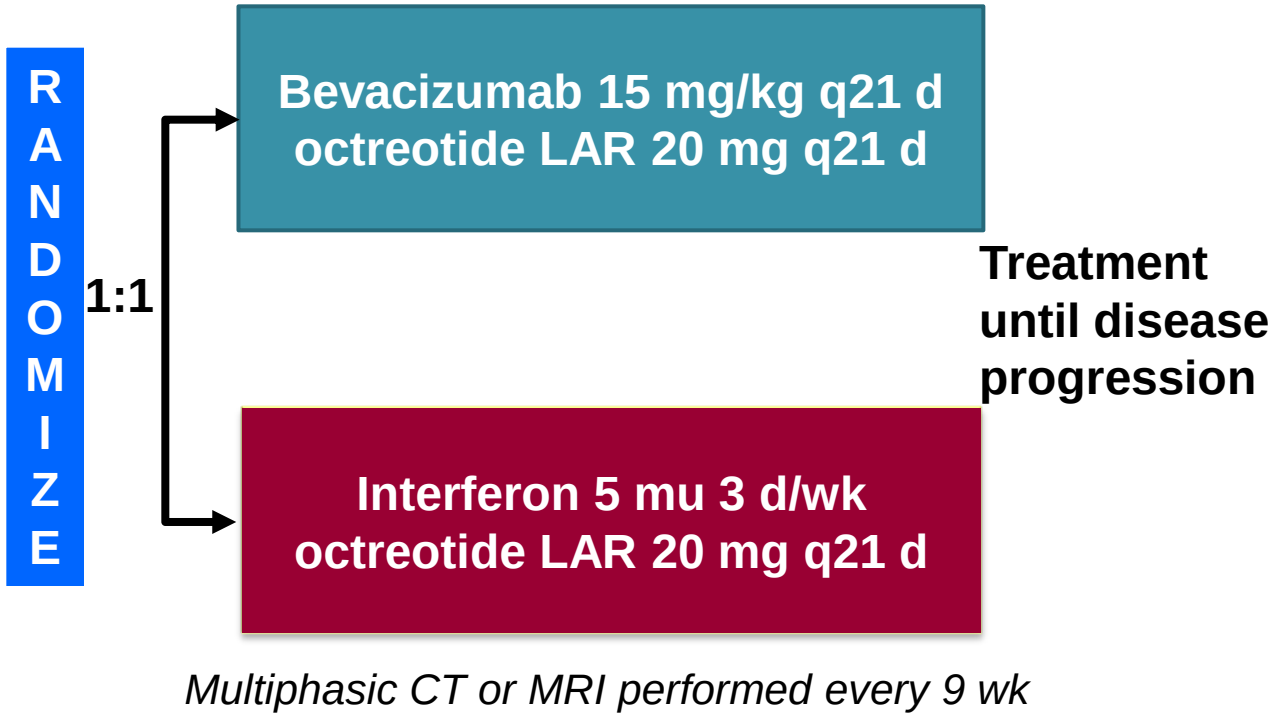
SWOG 0518: Bevacizumab vs interferon

Phase III open labeled - accrual completed

Advanced G1/2 NETs with poor prognosis

- PD
- Refractory syndrome
- G2 with 6+ lesion
- Rectal or gastric primary

(N=427)



Multiphasic CT or MRI performed every 9 wk

Primary end point:

- PFS (RECIST)

Secondary end points:

- Tumor response, OS, biomarkers, safety

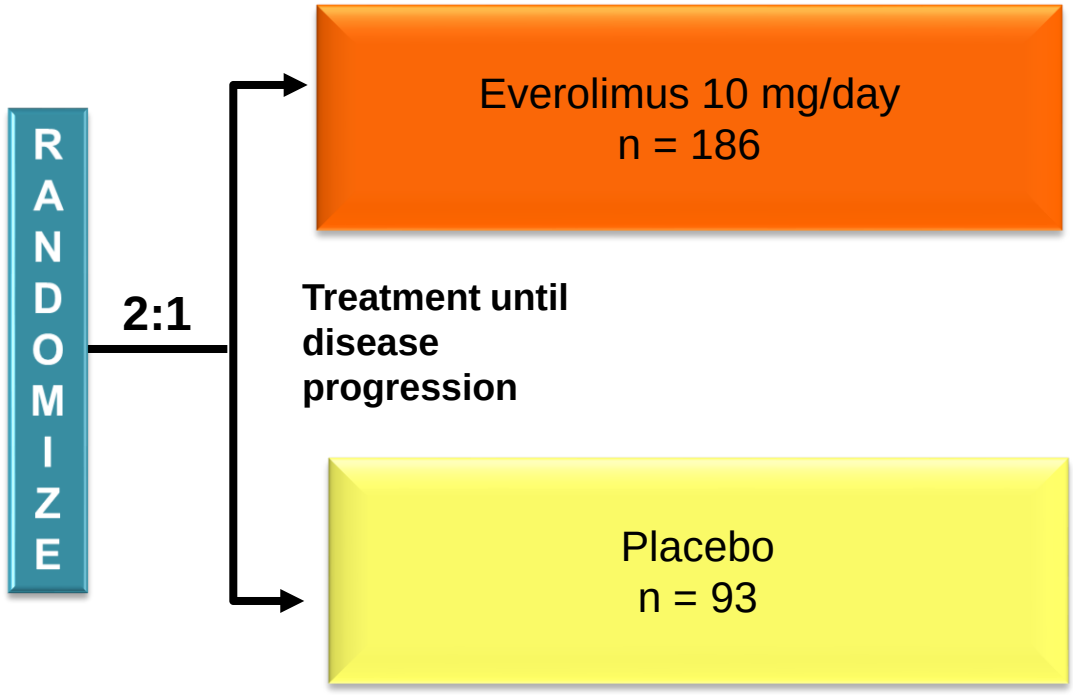
RADIANT-4

Phase III study of everolimus versus placebo in nonfunctional NET

A randomized, double-blind, multicenter, phase III study of everolimus plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced NET of gastrointestinal or lung origin

Patients with advanced NET and no history of secretory symptoms
(N = 279)

- Advanced low- or intermediate-grade NET
- Radiologic progression
- Absence of carcinoid syndrome (flushing, diarrhea, or both)
- Presence of measurable disease (RECIST v1.0)
- Previous antitumor therapy allowed
- WHO PS ≤1



Primary endpoint: PFS (real-time central radiology review)

Targeted treatment of NETs

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