Pancreatic Neuroendocrine Tumors Webinar

Presented by
Pancreatic Cancer Action Network
www.pancan.org

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Patient and Liaison Services (PALS)
PANCREATIC CANCER ACTION NETWORK
ADVANCE RESEARCH. SUPPORT PATIENTS. CREATE HOPE.

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PANCREATIC NEUROENDOCRINE TUMORS

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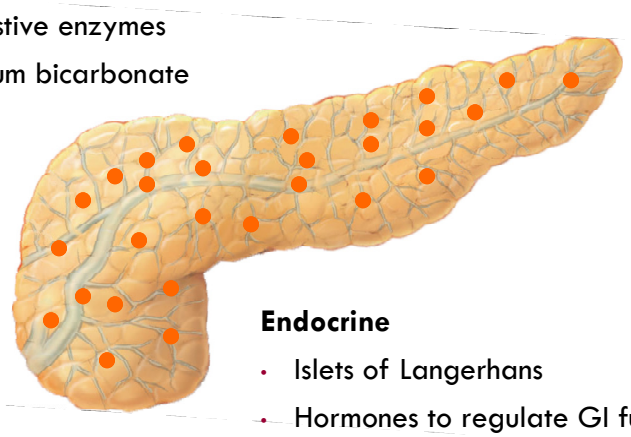
Disclosures

- Consultancy
  - Ipsen, Lexicon, Novartis, Pfizer
- Research support
  - Novartis Oncology
- I will discuss the following off label use and/or investigational use in my presentation:
  - Temozolomide, BEZ235

Exocrine

- Digestive enzymes
- Sodium bicarbonate



Endocrine

- Islets of Langerhans
- Hormones to regulate GI function
- Hormones to regulate metabolism

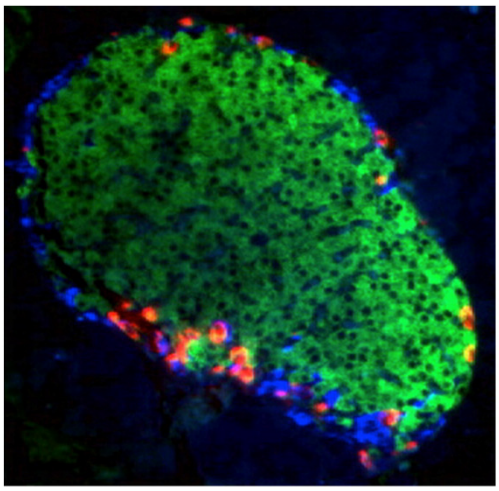
Endocrine cells in the islet of Langerhans

Insulin

Glucagon

Somatostatin

Pancreatic polypeptide



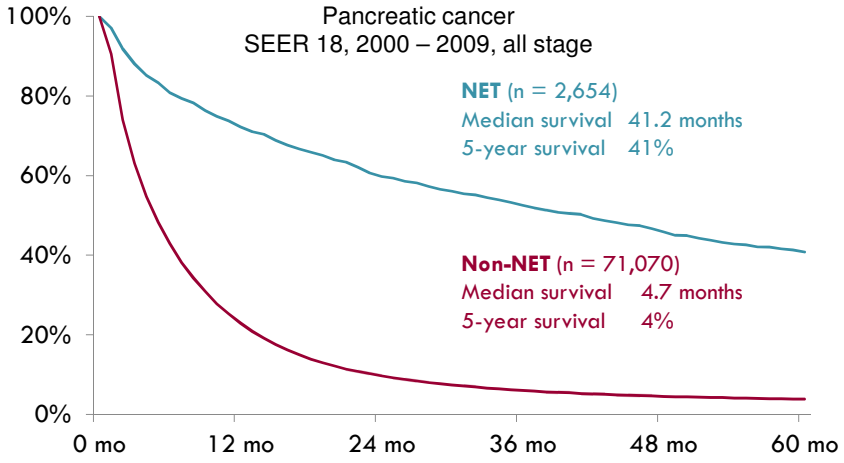
http://seungkimlab.stanford.edu/islet.html

Pancreatic NET: Benign versus malignant

- Criteria for malignant potential
  - Size, invasion, spread or metastasis
- Insulinoma < 1 cm are generally considered benign
  - Diagnosed early because of intense symptoms
- Malignant pancreatic NET
  - Mostly non-functional
  - 1- 4% of new pancreatic cancers diagnosed each year
  - 10% of all patients alive with pancreatic cancer

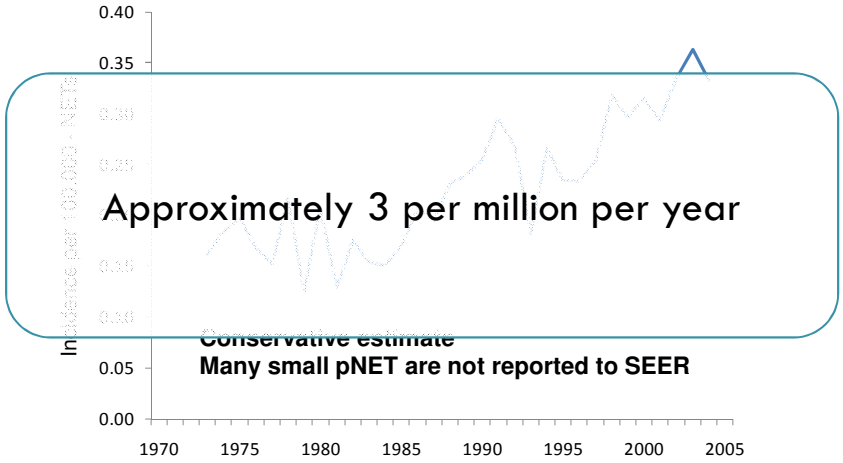
Yao JC, et al. in DeVita VT: Cancer: Principles & practice of oncology (ed 8th)., 2008, 1702-21

Malignant pancreatic NET is a different disease from pancreatic adenocarcinoma



Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER Regs Research Data, Nov 2011 Sub (1973-2009) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission

Malignant pancreatic NET each year



Adapted from: Yao JC et al, JCO 2008

Prevalence of malignant pancreatic NET

- Projected US prevalence using 2000 census data is 5,206 in 2006
  - 31-year limited duration prevalence using SEER 9
  - Among ~9% of US population – 471 cases
- Autopsy study
  - >11,000 cases from Hong Kong
  - .1%

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data, Nov 2008 Sub (1973-2006) released April 2009, based on the November 2008 submission.

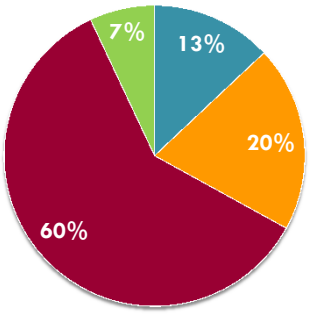
Lam KY, Lo CY. Eur J Surg Oncol 1997;23:36-42

Pancreatic NET

- Most pancreatic NET are not linked to any genetic cancer syndrome
- Small fraction pancreatic NET arise in setting of inherited cancer syndrome
  - MEN1 – hyper parathyroid, pituitary adenoma, carcinoids of lung and thymus
  - TSC2 – Subependymal giant-cell astrocytoma, angiomyolipomas
  - NF1, vHL

pNET: Survival and stage

Stage at diagnosis[1]

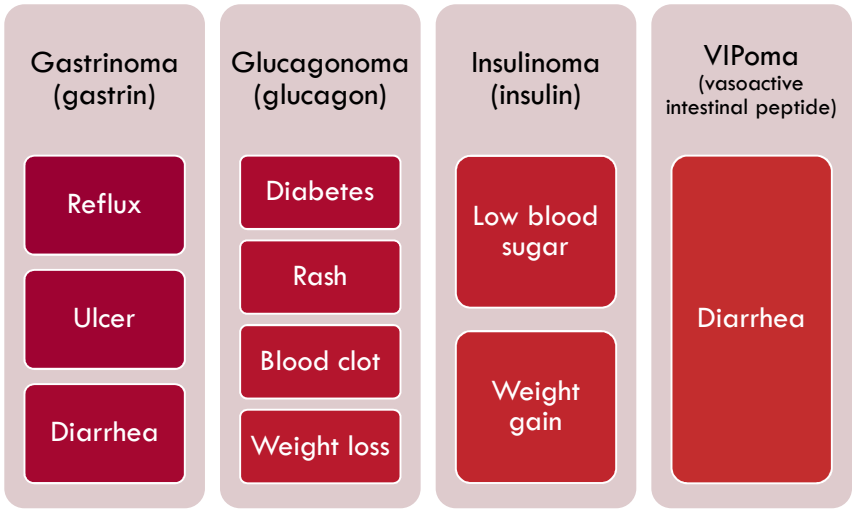


Survival by stage[2]

Localized	> 10 years
Regional	111 months
Distant	27 months
Unknown	

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data, Nov 2008 Sub (1973-2006) released April 2009, based on the November 2008 submission. 2. Yao JC et al. J Clin Oncol. 2008 Jun 20;26(18):3063-72.

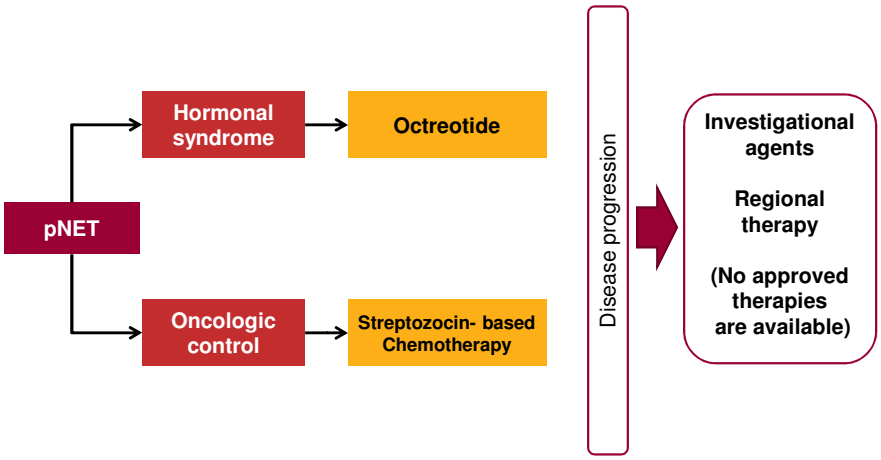
Functional pancreatic NET symptoms



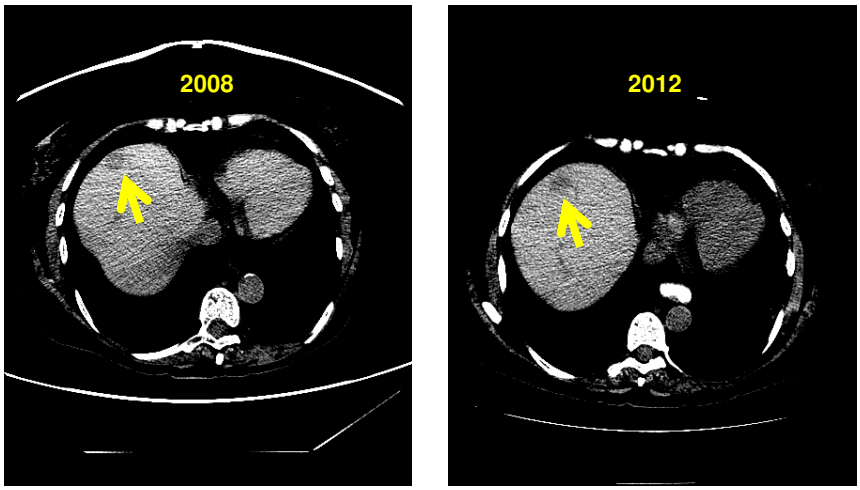
Non-functional pancreatic NET and symptoms at diagnosis

- Asymptomatic and incidentally found
- Symptoms in some patients based on location of primary tumor
  - Pancreatic head: Jaundice due to biliary obstruction
  - Pancreatic tail: Bleeding from stomach due to occlusion of splenic vein and gastric varicies

Limited options for advanced pancreatic NETs prior to May 2011

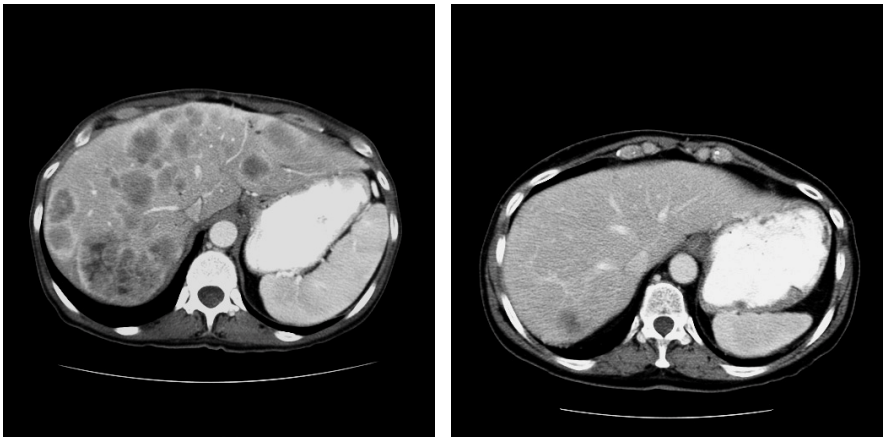


Pancreatic NET
Not everyone need treatment



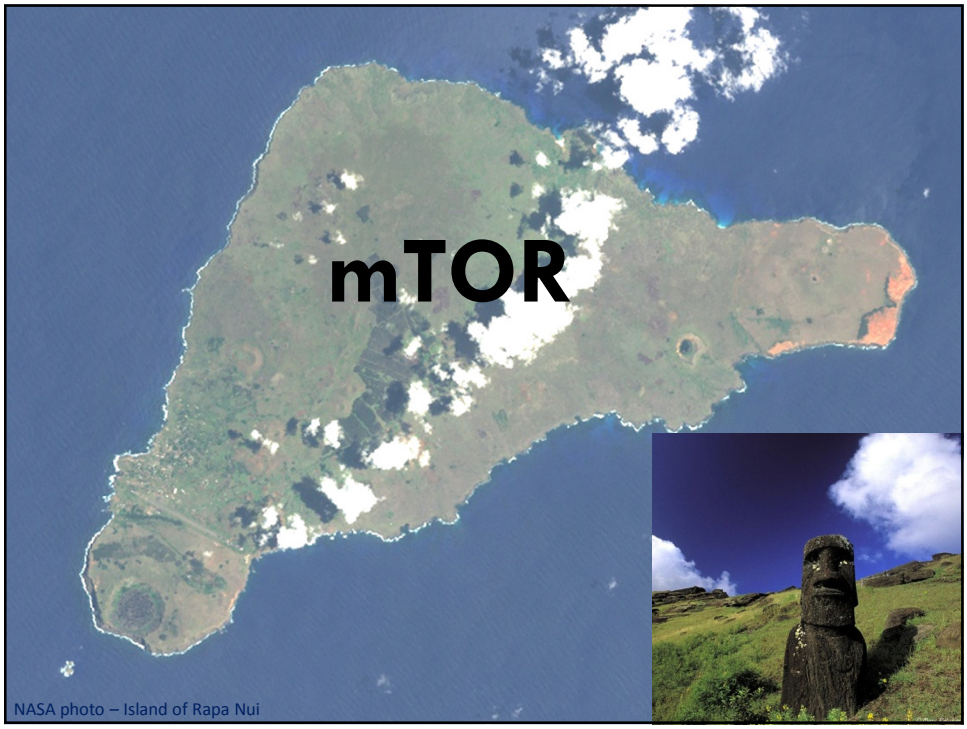
Pancreatic NET

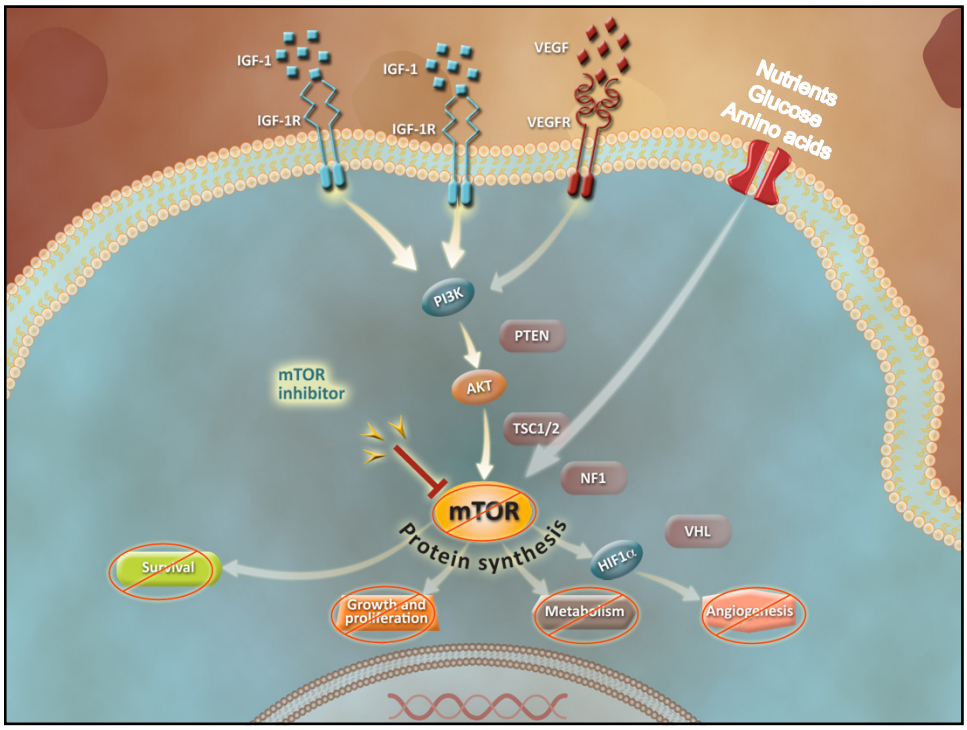
Streptozocin-based chemotherapy



Temozolomide-based chemotherapy

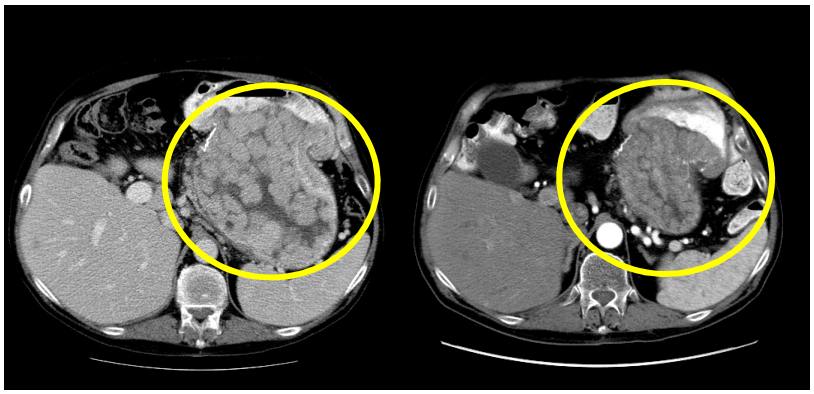
- Oral chemotherapy
  - Not FDA approved for pancreatic NET
- Reported response rates varies from 8% to 70%
- Analyses of prospective studies suggest response rate approximately 30%
- No prospective data to define if combination is better then single agent
- Risk of unusual infections with prolonged use


mTOR
NASA photo – Island of Rapa Nui


IGF-1
IGF-1
VEGF
IGF-1R
IGF-1R
VEGFR
Nutrients
Glucose
Amino acids
PI3K
PTEN
mTOR inhibitor
AKT
TSC1/2
NF1
mTOR
Protein synthesis
VHL
HIF1α
Survival
Growth and proliferation
Metabolism
Angiogenesis

M. D. Anderson Phase II study of Everolimus (initiated in 2005)

Patient with gastrinoma and gastric carcinoid

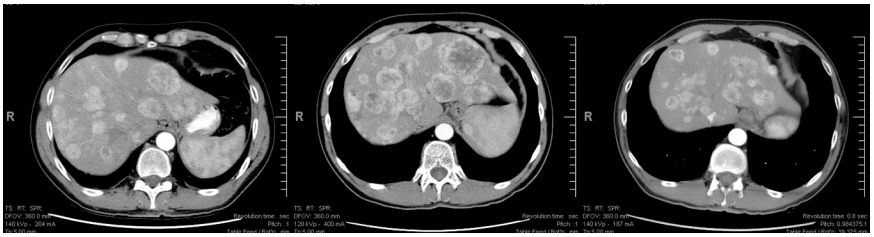


Dramatic benefit in insulinoma

	Glucose control at study entry	Glucose control during everolimus	Tumor response PFS
Patient 1 57/female MDACC	Depot octreotide, diazoxide, dexamethasone, and oral feeding q 2 hours and nocturnal continuous enteral feeding.	**Normalization of glucose;** discontinuation of diazoxide and nocturnal feedings	Partial response 16 months
Patient 2 40/female MDACC	Depot octreotide, diazoxide, and glucose tablets.	**Normalization of glucose;** discontinuation of diazoxide and glucose tablets	Partial response 29 months
Patient 3 22/female DFCI	Intermittent symptomatic hypoglycemia despite use of depot octreotide and diazoxide.	**Normalization of glucose** and discontinuation of diazoxide	Stable disease 6+ months
Patient 4 66/male UCSF	Glucose control requiring nocturnal dextrose infusion	**Normalization of glucose** and discontinuation of nocturnal dextrose infusions	Stable disease 6+ months

Kulke, Bergsland, and Yao, N Engl J Med. 360 (2): 195-7, 2009

RADIANT-1: Patient in Stratum 2 (initiated in 2006)



–2 months | baseline | +4 months

Chemotherapy → Everolimus + Octreotide

Patient remains on study 22+ months

RADIANT-3 Study Design

Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced PNET, N = 410

PD within12 mo

Stratified by:
WHO PS
prior chemotherapy

RANDOMIZE 1:1

Everolimus 10 mg/d + best supportive care* n = 207

Placebo + best supportive care* n = 203

Crossover

Treatment until disease progression

Multiphasic CT or MRI performed every 12 wk

Primary end point:
- PFS (RECIST)

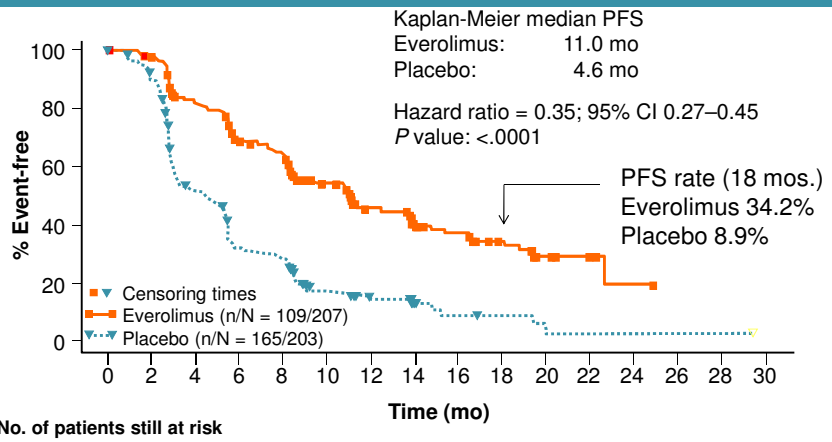
Secondary end points:
- Response, OS, biomarkers, safety, and PK

*Concurrent somatostatin analogues allowed.

Randomization August 2007–May 2009.

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

RADIANT-3
PFS by Investigator Review



No. 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 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(6):514-523.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

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ABSTRACT

BACKGROUND
Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown antitumor activity in patients with advanced pancreatic neuroendocrine tumors, in two phase 2 studies. We evaluated the agent in a prospective, randomized, phase 3 study.

METHODS
We randomly assigned 410 patients who had advanced, low-grade or intermediate-grade pancreatic neuroendocrine tumors with radiologic progression within the previous 12 months to receive everolimus, at a dose of 10 mg once daily (207 patients), or placebo (203 patients), both in conjunction with best supportive care. The primary end point was progression-free survival in an intention-to-treat analysis. In the case of patients in whom radiologic progression occurred during the study, the treatment assignments could be revealed, and patients who had been randomly assigned to placebo were offered open-label everolimus.

RESULTS
The median progression-free survival was 11.0 months with everolimus as compared with 4.6 months with placebo (hazard ratio for disease progression or death from any cause with everolimus, 0.35; 95% confidence interval [CI], 0.27 to 0.45; P<0.001), representing a 65% reduction in the estimated risk of progression or death. Estimates of the proportion of patients who were alive and progression-free at 18 months were 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (in 64% of patients in the everolimus group vs. 17% in the placebo group), rash (49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), and infections (23% vs. 6%), which were primarily upper respiratory. Grade 3 or 4 events that were more frequent with everolimus than with placebo included anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%). The median exposure to everolimus was longer than exposure to placebo by a factor of 2.3 (38 weeks vs. 16 weeks).

CONCLUSIONS
Everolimus, as compared with placebo, significantly prolonged progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors and was associated with a low rate of severe adverse events. (Funded by Novartis Oncology; RAD1ANT-3 ClinicalTrials.gov number, NCT00510068.)

From the University of Texas M.D. Anderson Cancer Center, Houston (J.C.Y.); Ohio State University Comprehensive Cancer Center, Columbus (M.H.S.); Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan (T.I.); Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France (C.L.B.); Cedars-Sinai Medical Center, Los Angeles (E.M.W.); University Hospital Gasthuisberg, Leuven, Belgium (E.V.C.); Mayo Clinic, Rochester, MN (T.J.H.); National Cancer Center Hospital, Tokyo (T.O.); Vall d'Hebron University Hospital, Barcelona (J.C.); University Medical Center, Groningen, the Netherlands (E.G.E.V.); University Hospital St. Orsola, Bologna, Italy (P.T.); Charité University Medicine, Berlin (M.E.P.); Novartis Oncology, Florham Park, NJ (S.H., T.H., J.L., D.L.); and University Hospital, Uppsala, Sweden (K.Ö.). Address reprint requests to Dr. Yao at the University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 426, Houston, TX 77030, or at jyao@mdanderson.org.

N Engl J Med 2011;364:514-23.

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

***DAXX/ATRX, MEN1,* and mTOR Pathway Genes Are Frequently Altered in Pancreatic Neuroendocrine Tumors**

Yuchen Jiao,[1*] Chanjuan Shi,[2*] Barish H. Edil,[3] Roeland F. de Wilde,[3] David S. Klimstra,[4] Anirban Maitra,[5] Richard D. Schulick,[3] Laura H. Tang,[4] Christopher L. Wolfgang,[3] Michael A. Choti,[3] Victor E. Velculescu,[1] Luis A. Diaz Jr.,[1,6] Bert Vogelstein,[1] Kenneth W. Kinzler,[1†] Ralph H. Hruban,[4†] Nicholas Papadopoulos[1†]

Pancreatic neuroendocrine tumors (PanNETs) are a rare but clinically important form of pancreatic neoplasia. To explore the genetic basis of PanNETs, we determined the exomic sequences of 10 nonfamilial PanNETs and then screened the most commonly mutated genes in 58 additional PanNETs. The most frequently mutated genes specify proteins implicated in chromatin remodeling: 44% of the tumors had somatic inactivating mutations in *MEN1*, which encodes menin, a component of a histone methyltransferase complex, and 43% had mutations in genes encoding either of the two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain–associated protein) and ATRX (α thalassemia/mental retardation syndrome X-linked). Clinically, mutations in the *MEN1* and *DAXX/ATRX* genes were associated with better prognosis. We also found mutations in genes in the mTOR (mammalian target of rapamycin) pathway in 14% of the tumors, a finding that could potentially be used to stratify patients for treatment with mTOR inhibitors.

Pancreatic neuroendocrine tumors (PanNETs) are the second-most common malignancy of the pancreas. The 10-year survival rate of patients with PanNETs is only 40% (*1–3*). PanNETs are usually sporadic but can arise in multiple endocrine neoplasia type 1 and more rarely in other syndromes, including von Hippel-Lindau (VHL) syndrome and tuberous sclerosis (*4*). "Functional" PanNETs secrete hormones that cause systemic effects, whereas "nonfunctional" PanNETs do not and therefore cannot always be readily distinguished from other neoplasms of the pancreas. Nonfunctional PanNETs grow silently, and patients often present with either an asymptomatic abdominal mass or symptoms of abdominal pain secondary to compression by a large tumor. Surgical resection is the treatment of choice, but many patients present with unresect-

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†To whom correspondence should be addressed. E-mail: npapadop1@jhmi.edu (N.P.); rhruban@jhmi.edu (R.H.H.); kinzler@jhmi.edu (K.W.K.)

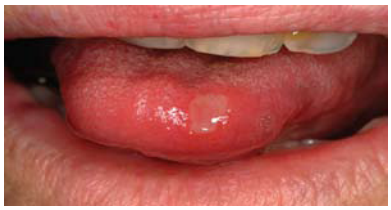
Jiao Y, et al. Science. 2011;331: 1199-1203

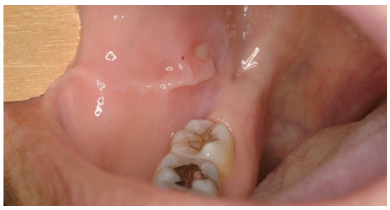
Everolimus: Treatment-Related Adverse Events

Median treatment duration Everolimus: 8.79 mos Placebo : 3.74 mos	Everolimus (n=204)		Placebo (n=203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no. of patients (%)			
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis§	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0

* Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration
† All types of infection are included
§ Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis
Yao J, et al. *N Engl J Med.* 2011;364:514-523.

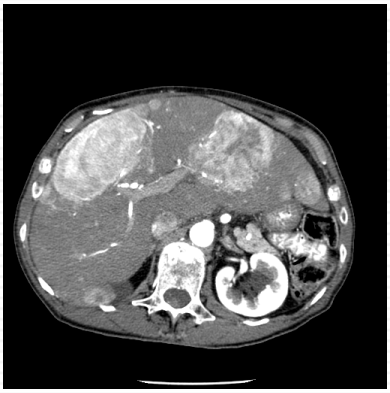
AE Management: Aphthous ulcerations





- pNET
  - Grade 1 or 2: 64% everolimus vs 17% placebo
  - Grade 3 or 4: 7% everolimus vs 0% placebo
- Advanced RCC patients: 44%
- Topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided

Angiogenesis



Sunitinib – Phase III Design

Eligibility criteria
- Well-differentiated, malignant pancreatic endocrine tumor
- Disease progression in past 12 months
- Not amenable to treatment with curative intent

RANDOMIZATION

1:1

Arm A

Sunitinib 37.5 mg/day orally, continuous daily dosing (CDD)*

Primary endpoint: PFS

Secondary endpoints:
OS, ORR, TTR, duration of response, safety, patient-reported outcomes

Arm B

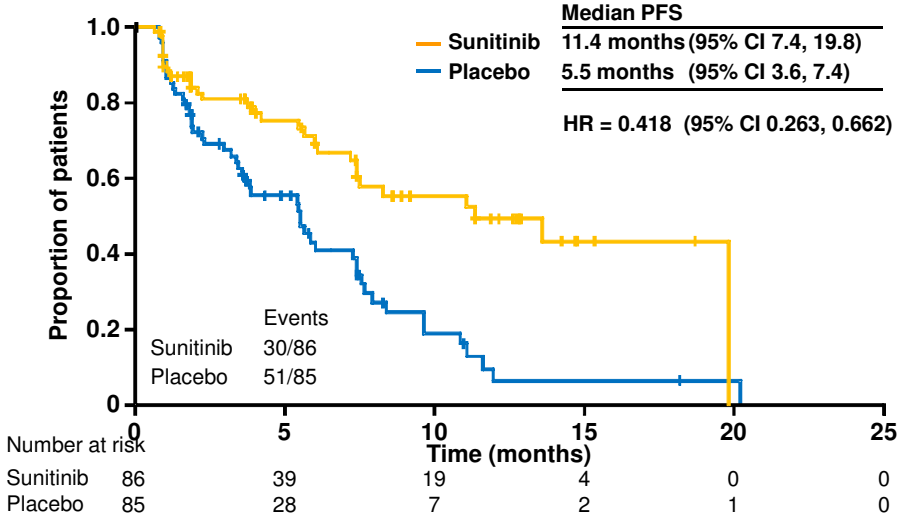
Placebo*

N = 340 (planned)
N = 171 (actual)

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

Raymond E, et al. *N Engl J Med.* 2011;364(6):501-513.

Sunitinib Phase III – Investigator PFS



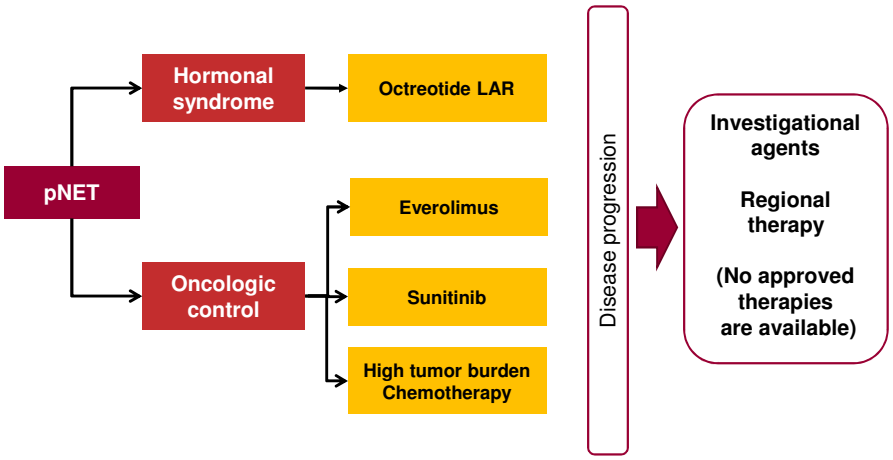
Raymond E, et al. *N Engl J Med.* 2011;364(6):501-513.

Sunitinib: Treatment-Related Adverse Events

Median treatment duration Sunitinib: 4.6 mos Placebo : 3.7 mos	Sunitinib (n=83)		Placebo (n=82)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no of patient (%)			
Diarrhea	49 (59)	4 (5)	32 (39)	2 (2)
Nausea	37 (45)	1 (1)	24 (29)	1(1)
Asthenia	28 (34)	4 (5)	22 (27)	3 (4)
Vomiting	28 (34)	0	25 (30)	2 (2)
Fatigue	27 (32)	4 (5)	22 (27)	7 (8)
Hair-color changes	24 (29)	1 (1)	1 (1)	0
Neutropenia	24 (29)	10 (12)	3 (4)	0
Abdominal pain	23 (28)	4 (5)	26 (32)	8 (10)
Hypertension	22 (26)	8 (10)	4 (5)	1 (1)
Palmar-plantar erythrodysesthesia	19 (23)	5 (6)	2 (2)	0
Anorexia	18 (22)	2 (2)	17 (21)	1 (1)
Stomatitis	18 (22)	3 (4)	2 (2)	0
Dysgeusia	17 (20)	0	4 (5)	0
Epistaxis	17 (20)	1 (1)	4 (5)	0
Headache	15 (18)	0	11 (13)	1 (1)
Insomnia	15 (18)	0	10 (12)	0
Rash	15 (18)	0	4 (5)	0
Thrombocytopenia	14 (17)	3 (4)	4 (5)	0
Mucosal inflammation	13 (16)	1 (1)	6 (7)	0
Weight loss	13 (16)	1 (1)	9 (11)	0

*Cardiac failure leading to death was reported in 2/83 (2%) patients on SUTENT and no patients on placebo.
Raymond E, et al. *N Engl J Med.* 2011;364(6):501-513.

Approved Therapy – Pancreatic NET
(after May 2011)



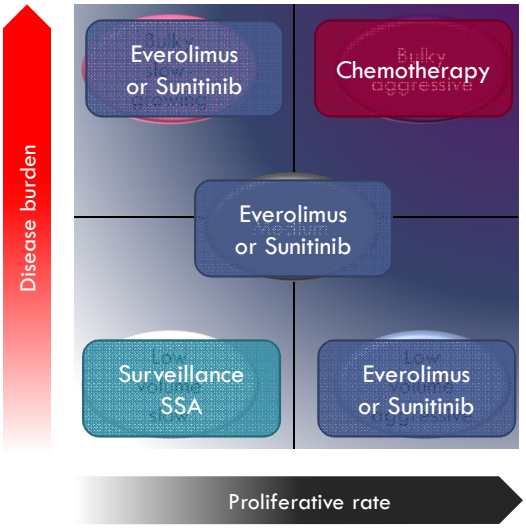
Have we improved outcome?

	N	Median overall survival
RADIANT-3 (phase 3)[1]		
Everolimus	207	>36 months
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.

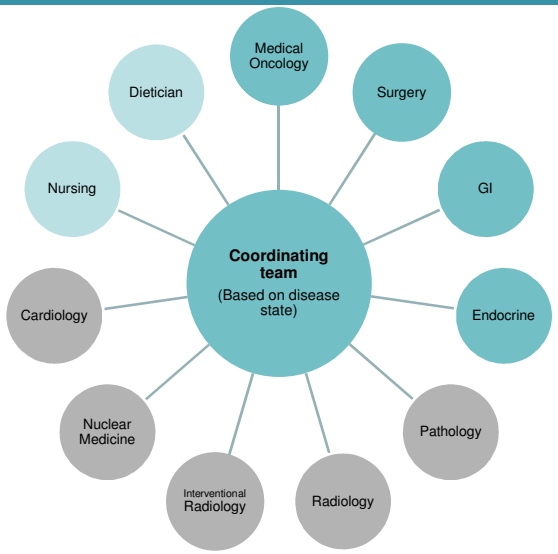
1. Yao JC, et al. N Engl J Med. 2011 Feb 10;364(6):514-23. Final survival analysis pending.
2. Raymond E, et al. N Engl J Med. 2011 Feb 10;364(6):501-13. Final survival analysis pending.
3. Moertel CG, et al. N Engl J Med. 1992 Feb 20;326(8):519-23.

Initial therapy of pNET



Multi-disciplinary approach

- Medical therapy
- Surgery
- Ablation
- Embolization
- **Clinical trials**



What is next at M. D. Anderson?

- Combination to further improve outcome
  - Everolimus + bevacizumab (completed)
  - Everolimus + IGF1 inhibitor (completed)
  - Everolimus + Pasireotide (to start soon)
  - Everolimus + radioembolization
- More complete blockade of PI3K/mTOR pathway
  - BEZ 235 inhibits TORC1, TORC2, and PI3K

PANCREATIC NEUROENDOCRINE TUMORS

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Gastrointestinal Medical Oncology

Thank you for your participation

Pancreatic Cancer Action Network
www.pancan.org

If you have any questions about our Patient and Liaison Services (PALS) program, please contact (877) 272-6226 or e-mail pals@pancan.org.

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