GEP-NET

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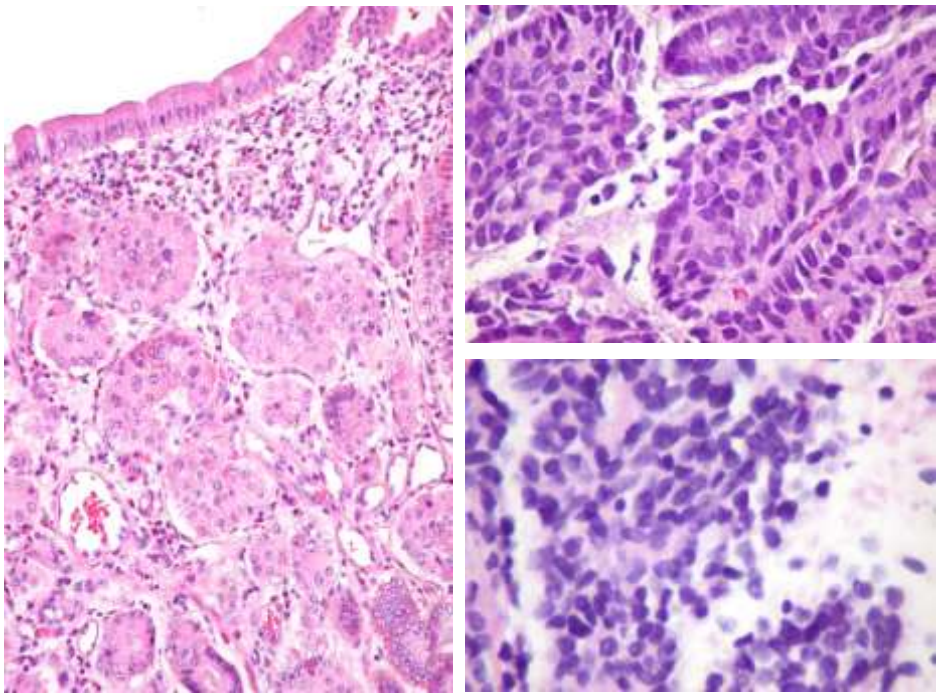
Oberndofer – 1907

Illeal Serotonin Secreting Tumor

Carcinoid (Karzinoide)



Histogenesis

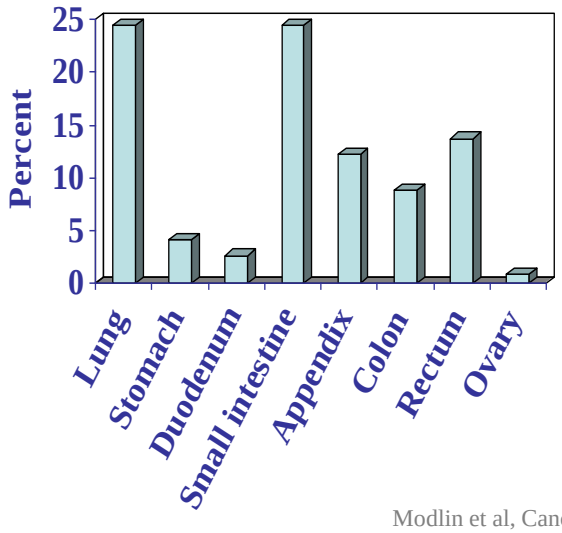
- 16 different cells

(50 different amines)

Incidence :

- 2-5% of all GI neoplasms
- ↑ last 30 years
  - Awareness
  - Improved detection/diagnosis

Distribution of 13,715 Carcinoid Tumors from 1950-1999



Modlin et al, Cancer, 97:934-959,2003

Incidence of Subtypes

Sites	%
• Colonic	10.3
• Gastric	7.4
• Pancreatic	9.5
• Appendix	10.9
• Small intestine	23.5
• Rectum	5.2

Classification

Anatomic sites:

- Forgut: stomach, proximal duodenum, billary tract, pancreas. (Celiac traid)
- Midgut: distal duodenum, SI, Appendix, RT. Colon (Superior mesentric artery)
- Hindgut: descending colon, sigmoid, rectum (Inf. mesentric artery)

Histopathologic Classification:

WHO*:

I. Well-differentiated (carcinoid): benign/uncertain behavior
II. Moderately differentiated: low grade malignancy
III. Poorly differentiated: highly aggressive
IV. Mixed, aggressive

Functional / Non-functional

Presentation:

General:

- Asymptomatic / vague symptoms
- Obstruction
- Carcinoid syndrome (18%)

Clinical

Gastric

- Multiple
- Origin: ECT
- Classification:
  - Type I: atrophic gastritis
  - Type II: Zollingen-ellison syndrome (MEN-I)
  - Type III: Idiopathic / malignant

Clinical

Colonic / Rectum

- Large
- Malignant

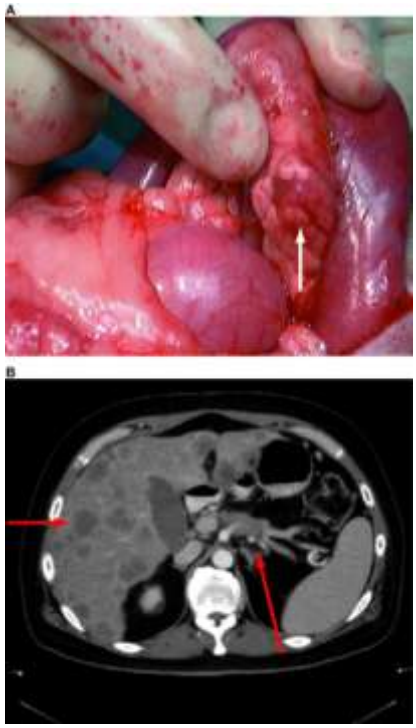
Pancreatic

- 50% with and without syndromes
- 50% present with DM

Clinical Presentation of Pancreatic NETs

Tumor	Symptoms or Signs	Incidence of Metastases	Extrapancreatic Location
Insulinoma	Hypoglycemia resulting in intermittent confusion, sweating, weakness, nausea; loss of consciousness may occur in severe cases	<15%	Rare
Glucagonoma	Rash (necrolizing migratory erythema), cachexia, diabetes, deep venous thrombosis	Majority	Rare
VIPoma, Verner-Morrison syndrome, WDHA syndrome	Profound secretory diarrhea, electrolyte disturbances	Majority	10%
Gastrinoma, ZES	Acid hypersecretion resulting in refractory PUD, abdominal pain, and diarrhea	<50%	Frequently in duodenum
Somatostatinoma	Diabetes, diarrhea, cholelithiasis	Majority	Rare
Nonfunctional	May be first diagnosed due to mass effect		

Kulke 2011



Kulke 2011

Early Diagnosis

Serum Markers for GEP-NET (%)

Markers	Sensitivity	Specificity
Chromogranin	81	100
NSE	38	73
Serotonin (mid gut)	90	88

Serum Markers:

Chromogranin A: sensitivity 81%
specificity 100%

- False positive in
  - atrophic gastritis
  - proton-pump inhibitors
  - renal failure
  - hypertension

NSE

- Poor sensitivity and specificity
- Only in PD Carcinoma
- May be useful if chromogranin A is negative

Radiologic / Imaging:

Somatostatin receptor scintigraphy (SRS):

- Good for whole body scanning
- Poor spatial resolution
- False positive:
  - Lymphoma
  - Meningioma
  - Paraganghioma / pheochromocytoma
  - Sarcoidosis
- False negative:
  - Liver mets
  - Small size insulinoma
- Recommended for midgut and forgut tumors

Tissue Diagnostic Markers:

Marker	URT	GEP-NET	Merkel	MTC
TTF1	+	-/?	-	+
CDX2	-	+	-	-
CK 5/6	-/+	0	0	-/+
CK 20	-	?	+	-
Syn	+	+	+	+

New Markers:

Pancreatic-duodenal honeobox (PDX-1):

- Transcription factor
- Pancreatic progenitor in embryonic cells
- Limited to subset of endocrine and aciner cells
- Specificity, high.

Neuroendocrine secretory protein-55 (NESP-55):

- Member of the chromogranin family
- Restricted expression in normal tissue
- Marker for adrenal chromaffin cell or islet cell phenotype!!
- Specificity?

Immunohistochemical Expression of CDX-2, PDX-1, NESP-55, and TTF-1 in Well-differentiated Neuroendocrine Tumors

Site	CDX-2	PDX-1	NESP-55	TTF-1
Stomach (N = 5)	0 (0%)	3 (60%)	0 (0%)	0 (0%)
Duodenum (N = 5)	0 (0%)	4 (80%)	0 (0%)	0 (0%)
Ileum (N = 31)	30 (97%)	0 (0%)	0 (0%)	0 (0%)
Appendix (N = 11)	11 (100%)	6 (55%)	0 (0%)	0 (0%)
Rectum (N = 12)	0 (0%)	2 (17%)	1 (8%)	0 (0%)
Pancreas (N = 39)	7 (18%)	11 (28%)	16 (41%)	0 (0%)
Lung (N = 20)	0 (0%)	0 (0%)	1 (5%)	7 (35%)

Srivastara 2009

Staging of GI Neuroendocrine Tumors

Primary tumor (T)

- TX cannot be assessed
- T1 invades lamina propria or submucosa and 1 cm or less in size (colon and appendix 2 cm or less in size)
- T2 invades muscularis propria or more than 1 cm in size (colon and appendix more than 2 cm in size)
- T3 penetrates subserosa or non-peritonalized adipose tissue (appendix more than 4 cm in size)
- T4 invades serosa or other organs

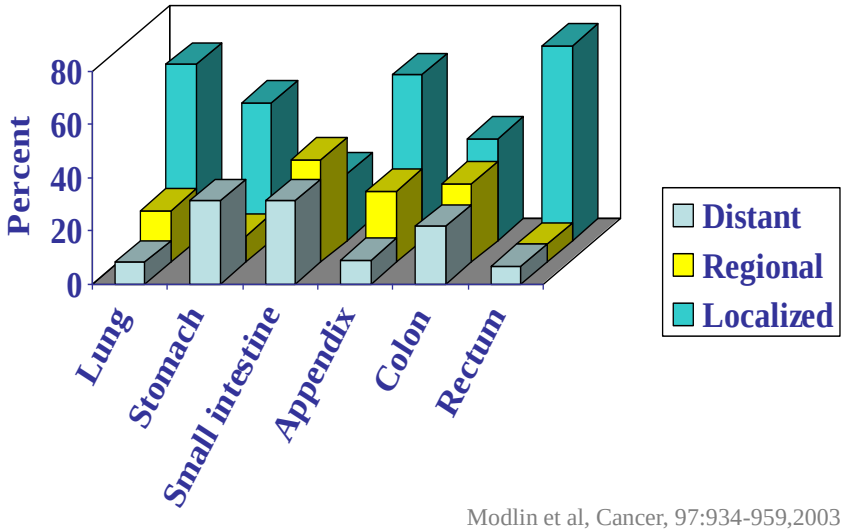
Regional lymph node (N)

- NX cannot be assessed
- N0 no metastasis
- N1 metastasis

Regional lymph node (M)

- MX cannot be assessed
- M0 no metastasis
- M1 metastasis

Distribution of Carcinoid Tumors by Stage from 1973-1991



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Management:

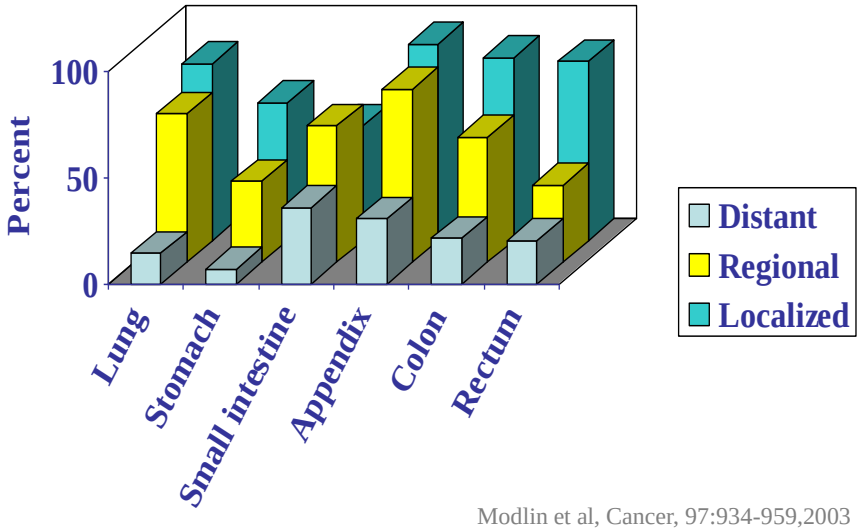
Surgery:

- Complete surgical 20%
- Debulking ↓ symptoms

Non-Surgical:

- Trans-arterial embolization
- Somatostatin analogs (hormone producing)
- Chemotherapy – 5 FU

5-year Survival Rate of Patients with Carcinoid Tumors from 1973-1991



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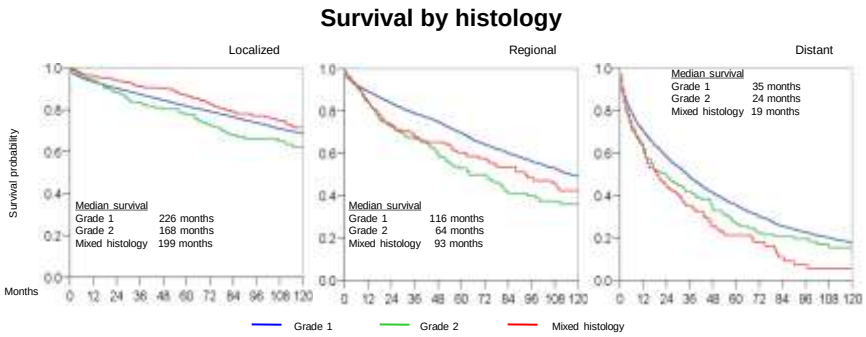
Prognostic Factors:

Factors:	P-value
*Pancreatic origin	0.0002
Poor differentiation	0.0001
Tumor size (>3cm)	0.0009
*DM	0.0008

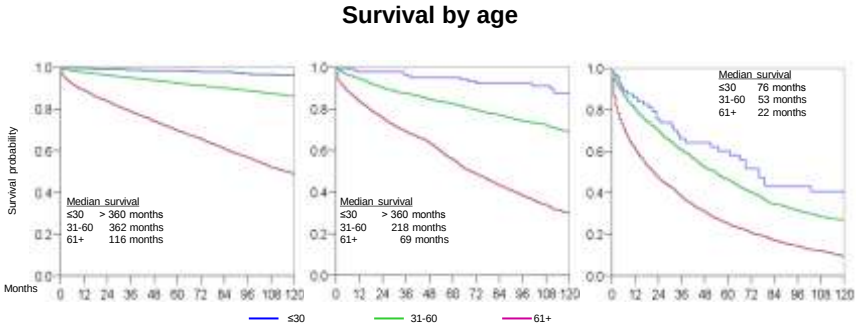
*Multivariate analysis

Survival in Patients with GEP-NET



J Clin Oncology, 18:3063-72, 2008

Survival in Patients with GEP-NET



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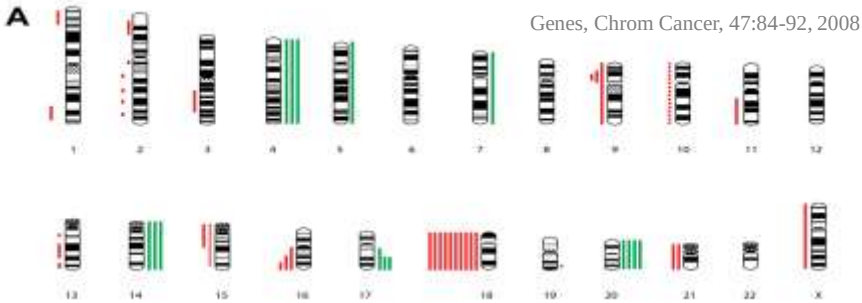
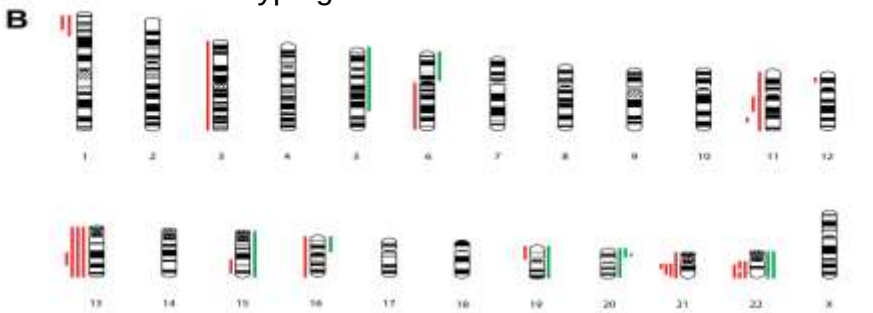
Molecular Characterization

SNP Allelotyping of Ileal Carcinoid Tumors

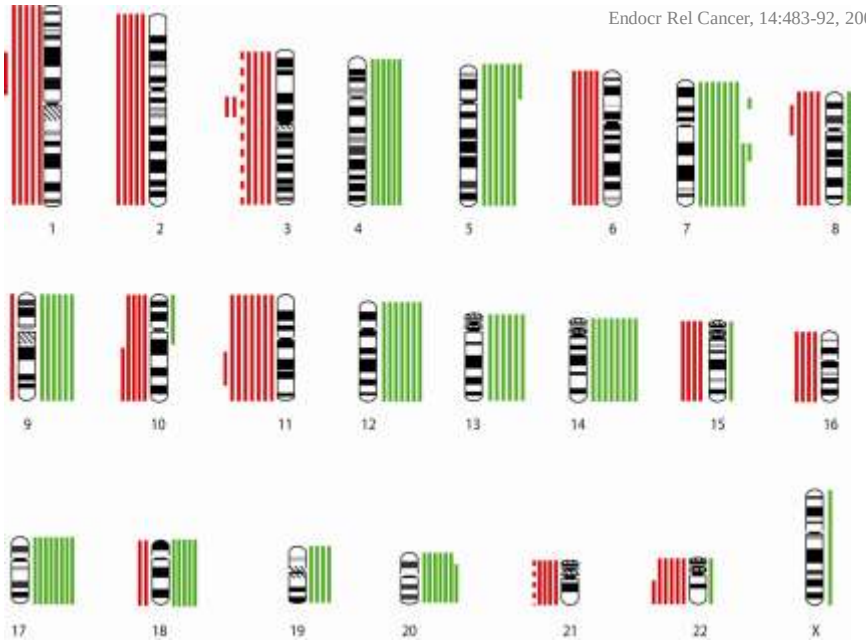


Genes, Chrom Cancer, 47:84-92, 2008

SNP Allelotyping of Non-ileal Carcinoid Tumors

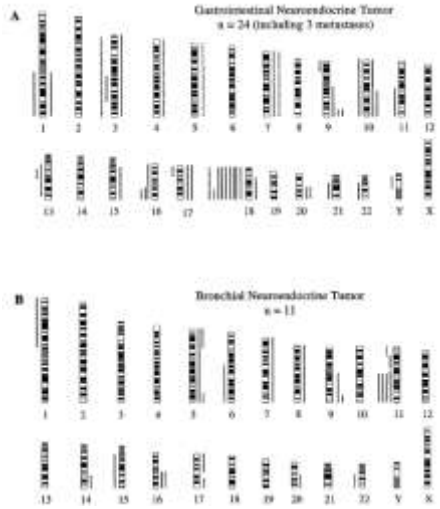


SNP Alleleotyping of Pancreatic Endocrine Tumors



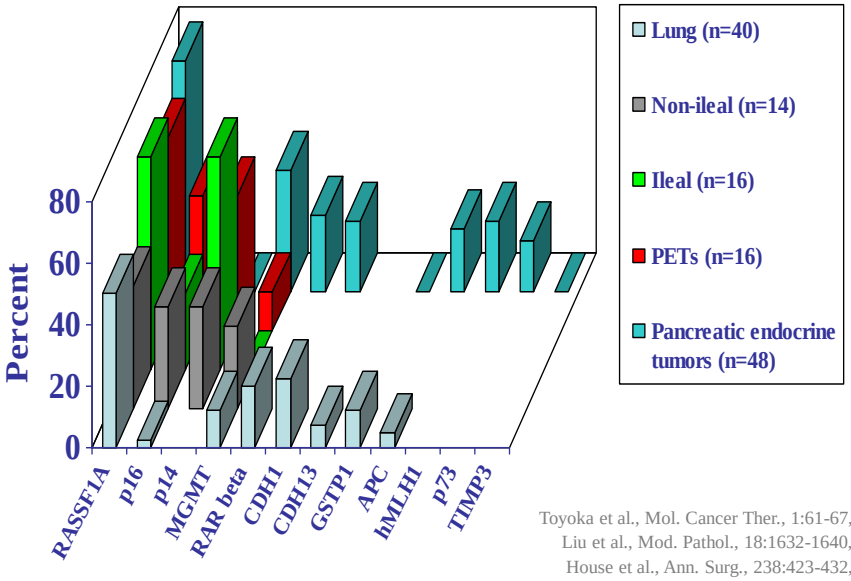
Endocr Rel Cancer, 14:483-92, 2007

CGH Analysis of 24 Gastrointestinal and 11 Lung Carcinoid Tumors



Zhao J et al., Am. J. Pathol., 157:1431-1438, 2000

Methylation in Neuroendocrine Tumors

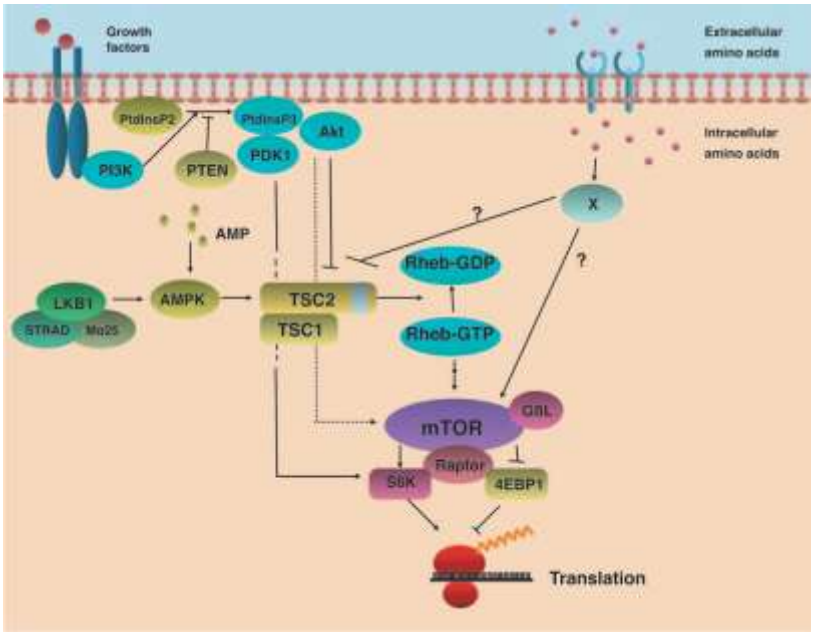


Toyoka et al., Mol. Cancer Ther., 1:61-67, 2001
Liu et al., Mod. Pathol., 18:1632-1640, 2005
House et al., Ann. Surg., 238:423-432, 2003

Genetic Syndromes	Gene	Neuroendocrine Tumors
• Multiple endocrine neoplasia 1	*MEN1*, 11q13	Foregut carcinoid tumors Pancreatic endocrine tumors
• Neurofibromatosis type 1	*NF1*, 17q11	Duodenal carcinoid tumors Pancreatic endocrine tumors (somatostatinomas)
• von Hippel Lindau	*VHL*, 3p25	Pancreatic endocrine tumors

Molecular Targets:

- Antiangiogenic factors
- mTOR inhibitors



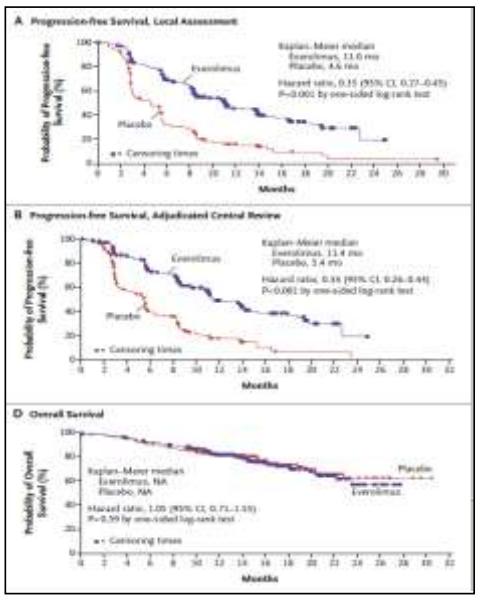
Results of Phase II Studies of Targeted Therapies in NETs

Agent	Target & mechanism	Type of trial	Response rate	Stable disease
Bevacizumab Yao, 2008	VEGF mAB	Randomized Phase II	18%	77%
Sunitinib Kulke, 2008	VEGFR1-3, PDGFR, c-Kit, RET, FLT3, Tyrosine kinase inhibitor	Phase II Gastro-enteric NET Pancreatic NET	 2% 15%	 83% 68%
Sorafenib Hobday, 2007	VEGFR2-3, PDGFR, FLT3, BRAF, c-Kit, FGFR-1 Tyrosine kinase inhibitor	Phase II Gastro-enteric NET Pancreatic NET	 7% 17%	
Temisrolimus Duran, 2006	mTOR Protein kinase inhibitor	Phase II Gastro-enteric NET Pancreatic NET	 4,8% 6,7%	
Everolimus Yao, 2008	mTOR Protein kinase inhibitor	Phase II Gastro-enteric NET Pancreatic NET	 13% 27%	 80% 60%

Everolimus for Advanced Pancreatic Neuroendocrine Tumors (RADIANT-3)

410 patients with low or intermediate-grade advanced pancreatic endocrine tumors

- Everolimus 10 mg (207 patients)
- Placebo (203 patients)



New Engl J Med 364:514-523, 2011

Conclusions:

- Rare
- Heterogeneous
- Early diagnosis, critical
- Genetic and epigenetic targets

Thank you