Pancreatic Neuroendocrine Tumors

December 15, 2015

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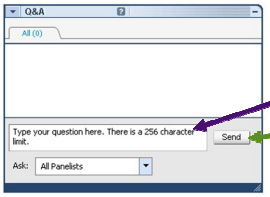

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Pancreatic Neuroendocrine Tumors

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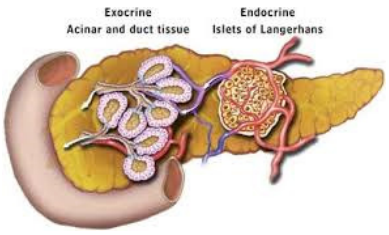
December 15, 2015

Objectives

- Review the diagnosis and epidemiology of pancreatic NET
- Review principles for management of pancreatic NET
- Discuss future directions for treatment and research

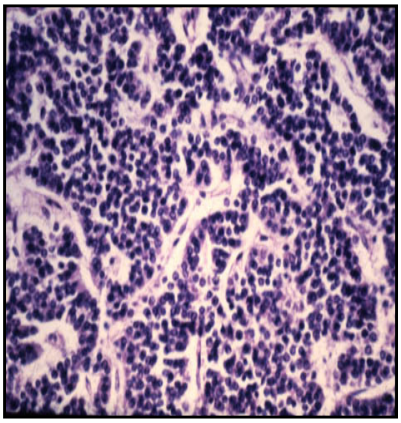
Pancreatic Cancer Subtypes



- Pancreatic NET is a different disease than pancreatic adenocarcinoma
  - Arise from different cells
  - Different prognoses
  - Different treatment options

Neuroendocrine Tumors

- Arise from cells in the diffuse neuroendocrine system throughout the body
- May pursue more indolent clinical course than other malignancies
- Ability to secrete peptides that may result in characteristic symptoms of hormone hypersecretion



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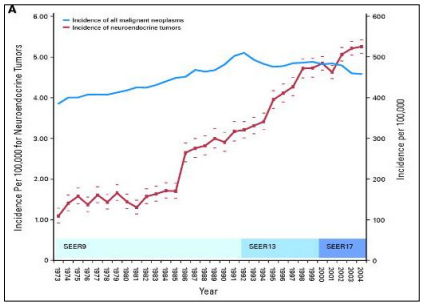
NET: Incidence Is Increasing

- Recent estimates of 5 per 100,000 population
- Increasing incidence likely due to improved awareness, classification, and diagnostic modalities



Yao JC, et al. *J Clin Oncol.* 2008;26:3063-3072.

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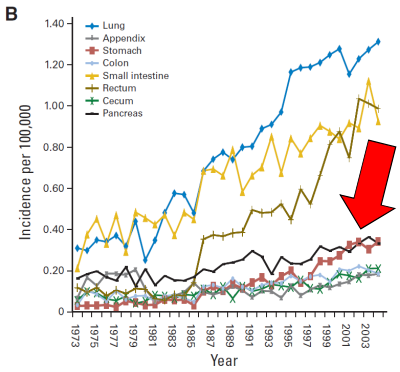
Pancreatic NET: Epidemiology



- 3-5% of all pancreatic malignancies
- Incidence 0.32/100,00 population. Higher incidence in autopsy series.
- >50% with metastatic disease at diagnosis

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Yao JC, et al. *J Clin Oncol.* 2008;26:3063-3072.

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Pancreatic NET: Genetics

- Most pancreatic NET are sporadic and not linked to a cancer genetics syndrome
- More rarely arise in the context of genetic syndrome
  - MEN1: hyperparathyroidism, pituitary adenoma, carcinoid tumors of lung, thymus
  - TSC2: subependymal giant-cell astrocytoma, angiomyolipoma
  - VHL, NF1

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Key Features of NET

- Pathologic features
  - Grade
  - Differentiation
- Primary site
  - Pancreatic NET
  - "Carcinoid": GI, lung, thymus
- Functional (hormone secreting) status

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Neuroendocrine Tumors: Histologic Classification

Differentiation	Grade	Mitotic Count	Ki-67 Index	WHO ENETS
Well differentiated	Low (G1)	< 2 per 10 HPF	≤ 2%	Neuroendocrine tumor, grade 1
	Intermediate (G2)	2-20 per 10 HPF	3-20%	Neuroendocrine tumor, grade 2
Poorly differentiated	High (G3)	> 20 per 10 HPF	>20%	Neuroendocrine carcinoma, grade 3, small cell
				Neuroendocrine carcinoma, grade 3, large cell

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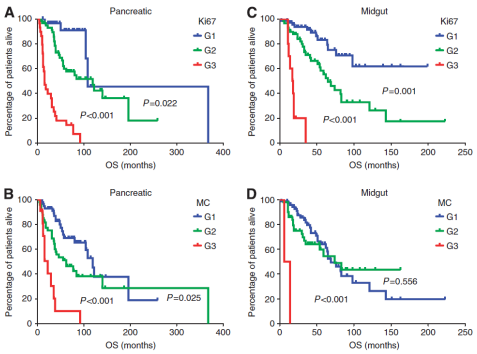
NET Grade Correlates With Prognosis



- 285 patients with metastatic pancreatic and midgut NET
- Higher-grade disease correlates with poor survival

Khan MS, et al. *Br J Cancer.* 2013;108:1838-1845.

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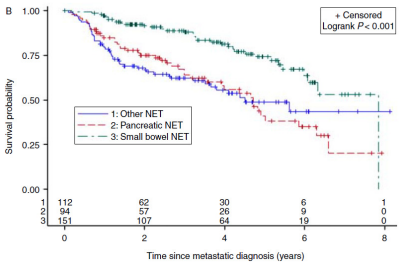
Metastatic Neuroendocrine Tumors: Survival Varies by Primary Tumor Type

Single Institution Database (N = 677)



Pancreatic NET: 3.9 yr

Small-bowel carcinoid: 7.9 yr

Ter-Minassian M, et al. *Endocr Relat Cancer.* 2013;20:187-196.

SEER Database

Median Survival (months)

Site	Localized	Regional	Distant
Appendix	>360	>360	27
Cecum	135	107	41
Colon	261	36	5
Duodenum	107	101	57
Gastric	154	71	13
Liver	50	14	12
Lung	227	154	16
Pancreas	136	77	24
Rectum	290	90	22
Small bowel	111	105	56
Thymus	110	68	40

Pancreatic NET: 2 yr

Small-bowel carcinoid: 4.6 yr

Yao JC, et al. *J Clin Oncol.* 2008;26:3063-3072.

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NET: Differences by Primary Site

- Survival varies by primary tumor site
- Pancreatic NET are more responsive to cytotoxic chemotherapy and targeted agents

Distinct treatment approaches and clinical trials for pancreatic and non-pancreatic NET

Pancreatic NET: Functional Status

- 60%–70% “non-functioning”
- 30%–40% associated with hormone hypersecretion
- Symptoms defined by hormone secreted

	Symptoms
Gastrinoma	Gastric ulcers, diarrhea
Glucagonoma	Skin rash (necrolytic migratory erythema), hyperglycemia
Insulinoma	Hypoglycemia
VIPoma	Diarrhea, hypokalemia

Neuroendocrine Tumors: Management Principles

- Resection of localized and limited metastatic disease
- Advanced disease
  - Control of hormone secretion for functional tumors
  - Control of growth of disease

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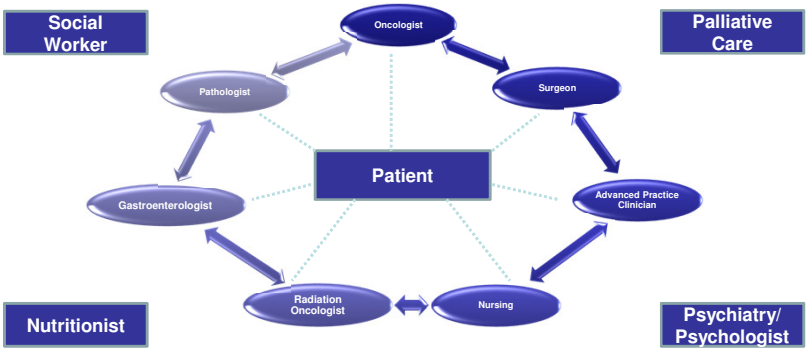
Multidisciplinary Team Approach



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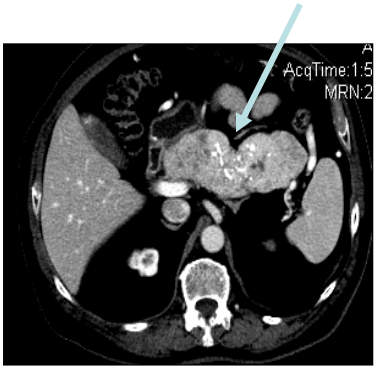
Pancreatic NET: Surgical Resection

- Enucleation, distal pancreatectomy, or Whipple depending on tumor size/location
- Multiple neoplasms common in MEN-1
- Prognosis good when complete resection performed



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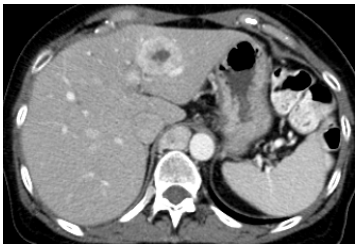
Metastatic NET:Surgical Resection

Hepatic resection considered for limited liver metastases



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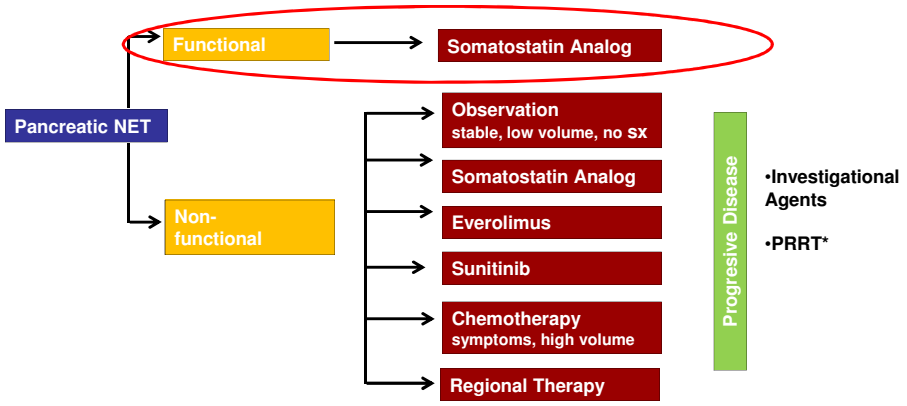
Current Pancreatic NET Treatment Landscape



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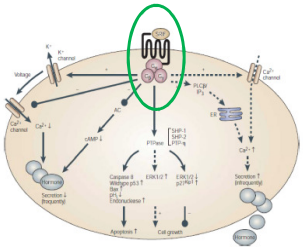
Somatostatin Analogs and NET



- Octreotide and Lanreotide
- Bind to somatostatin receptors that are highly expressed by NET (>80%)
- Can improve hormone-mediated symptoms by reducing hormone secretion

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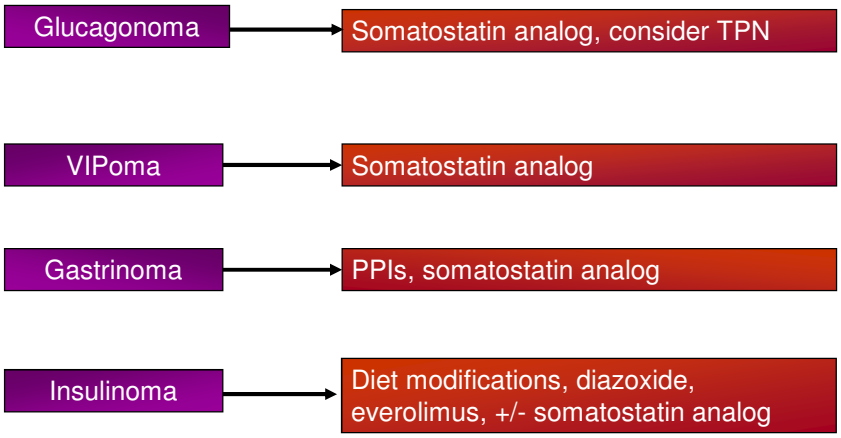
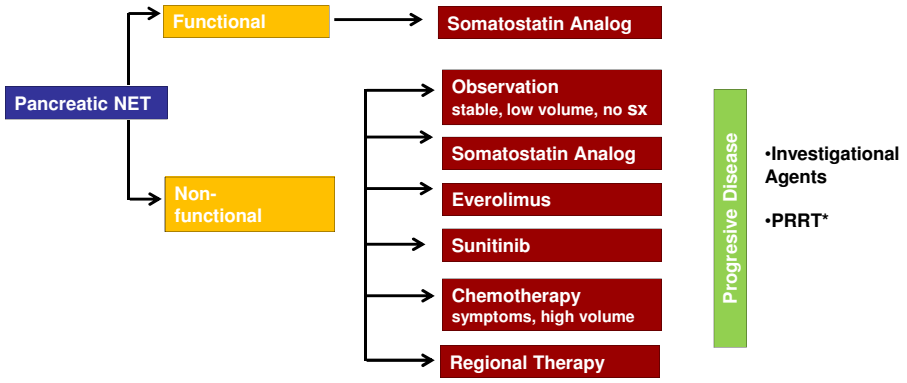
Pancreatic NET: Management of Secretory Symptoms



Options for Control of Neuroendocrine Tumor Growth

Current Pancreatic NET Treatment Landscape



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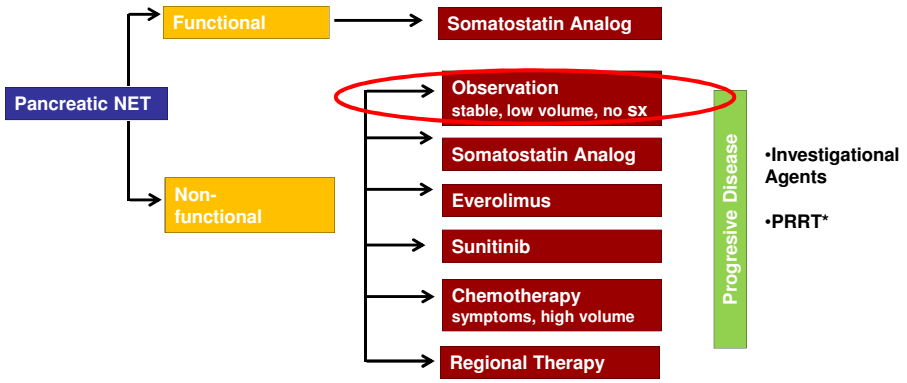
Current Pancreatic NET Treatment Landscape



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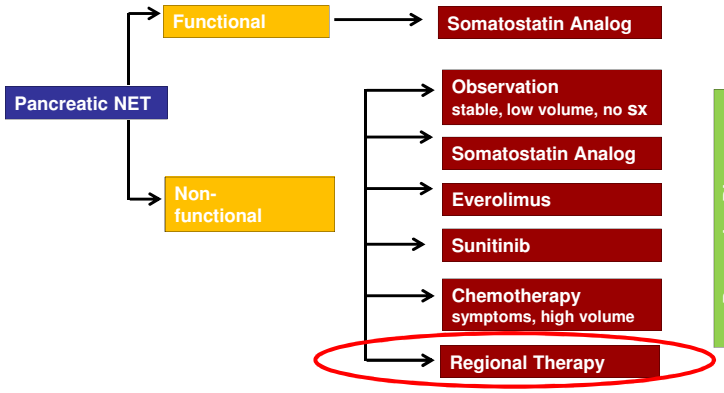
Current Pancreatic NET Treatment Landscape



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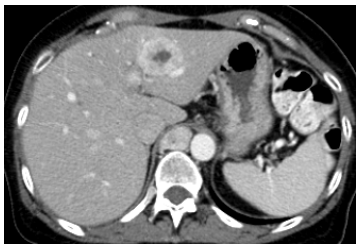
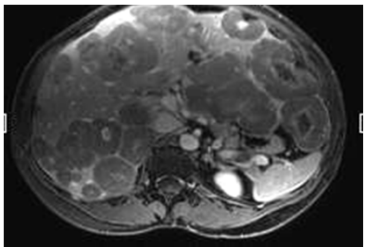
Metastatic NET: Liver-Directed Therapies

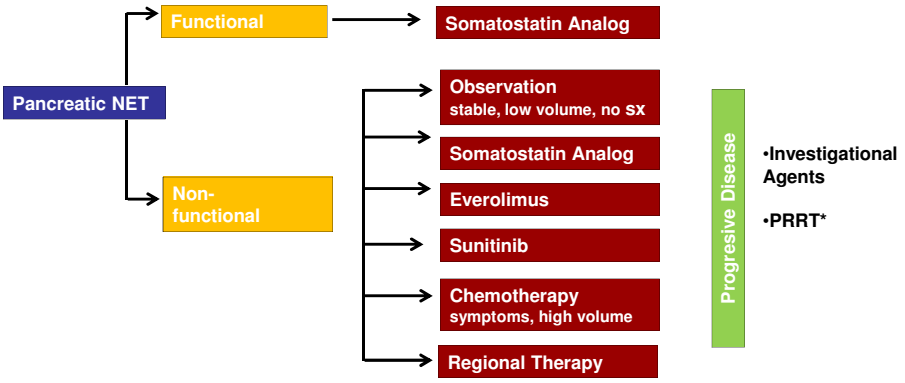
Hepatic resection considered for limited hepatic metastases…



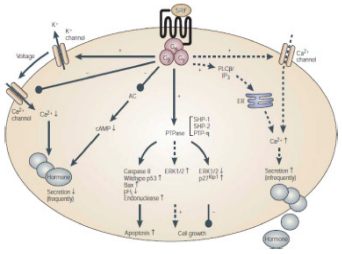
Hepatic artery embolization considered for patients with liver predominant disease that is not resectable



Current Pancreatic NET Treatment Landscape



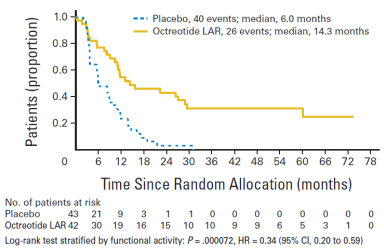
Somatostatin Analogs and NET



- Bind to somatostatin receptors that are highly expressed by NET (>80%)
- Can improve hormone-mediated symptoms by reducing hormone secretion
- **Can slow growth of disease**

Octreotide and Lanreotide for Advanced NET

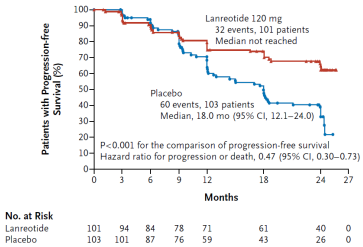
PROMID Study



N = 85 pts
Midgut only
Grade 1 (Ki67 ≤ 2%)

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

CLARINET Study



N = 204 pts
Pancreas 45%, midgut 35%,
Hindgut 7%, unknown/other 13%
Grade 1 (Ki67 < 10%)

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

Potential Somatostatin Analog-Related Side Effects

- Glucose regulation disorders
  - Hypoglycemia, hyperglycemia
- Thyroid disorders
- Cardiovascular disorders
- B_{12} deficiency
- Gallbladder disease: Cholelithiasis and gallbladder sludge

Streptozocin-Based Therapy for Pancreatic NET

- Streptozocin/doxorubicin associated with survival benefit compared to streptozocin/5-FU (2.2 vs. 1.5 years)
- Response rates 30%–40% in retrospective series
- Current use limited by side effect profile and schedule of treatment

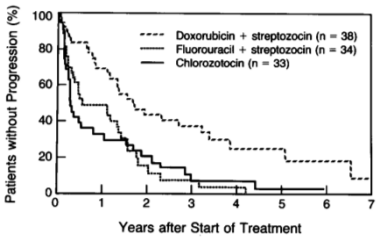


Figure 2. Length of Time to Disease Progression, According to Treatment Group.
P<0.001 for the comparison between doxorubicin plus streptozocin and fluorouracil plus streptozocin; P<0.001 for the comparison between doxorubicin plus streptozocin and chlorozotocin.

CG Moertel et al, N Engl J Med 1992; 326: 519-23

Temozolomide-Based Therapy in Pancreatic NET

Regimen	N	RR	TTP/PFS (mo)	Reference
Retrospective Series				
Tem	12	8%	NR	Ekeblad, Clin Cancer Res 2007
Tem/Capecitabine	30	70%	18	Strosberg, Cancer 2011
Tem (various regimens)	53	34%	13.6	Kulke, Clin Cancer Res 2009
Prospective Trials				
Tem/Thalidomide	11	45%	NR	Kulke, JCO 2006
Tem/Bevacizumab	15	33%	14.3	Chan, JCO 2012
Tem/Everolimus	40	40%	15.4	Chan, Cancer 2013
Tem/Capecitabine	11	36%	>20	Fine, ASCO GI 2014

RR 33%–70%; PFS 13.6–18+ mo

ECOG 2211

Low and intermediate grade advanced pNETs

n=145

RANDOMIZE

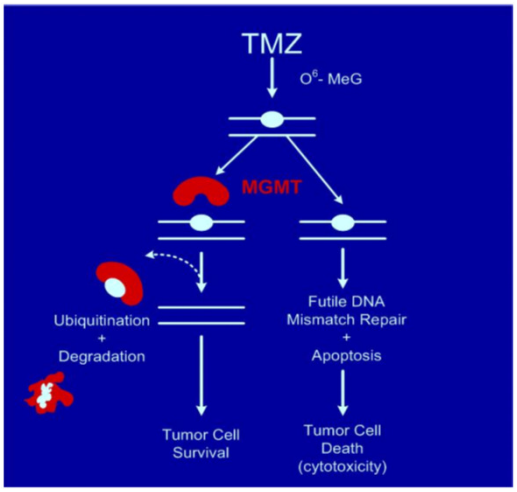
ARM A:
Temozolomide 200 mg/m^2 po QD days 1-5
28 day cycle

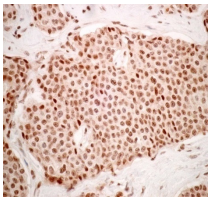
ARM B:
Capecitabine 750 mg/m^2 po BID days 1-14
Temozolomide 200 mg/m^2 QD days 10-14
28 day cycle

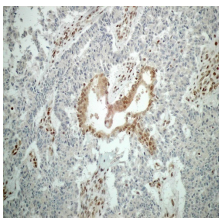
1°Endpoint: PFS
2° Endpoints: RR, OS, toxicity, MGMT correlative studies

CT scans every 3 cycles
Treatment will continue for a max of 13 cycles

O6-Methylguaninine Methyltransferase (MGMT) and Temozolomide Sensitivity



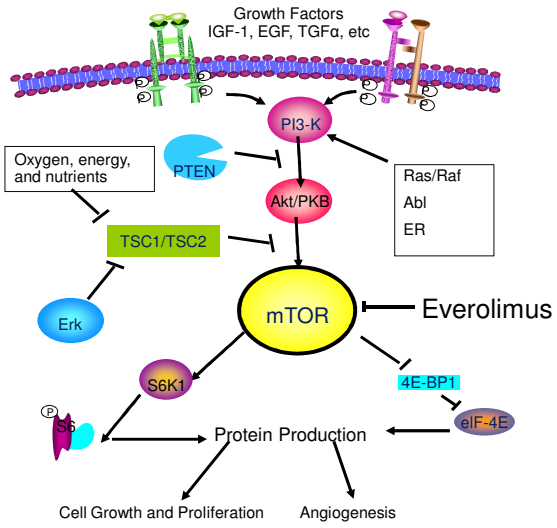

MGMT intact tumor


MGMT deficient tumor

Association of MGMT Status with Response to Temozolomide-Based Therapy

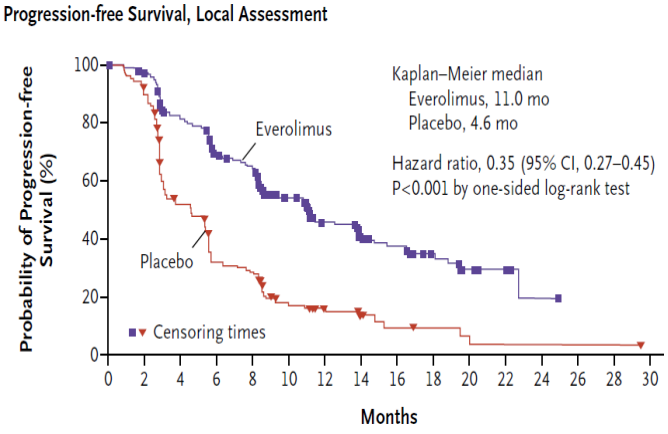
N	MGMT Status	Radiologic Response	PFS (mos)	OS (mos)	Ref.
N=21	MGMT+	0/16 (0%)	9.25	14	Kulke et al, Clin Cancer Res 2009; 15: 338-45
	MGMT-	4/5 (80%)	19	Not reached	
N=53	MGMT+		7.6	34	Walter et al, BJC 2015; 112: 523-31
	MGMT-		20	105	

mTOR Inhibitors in NET



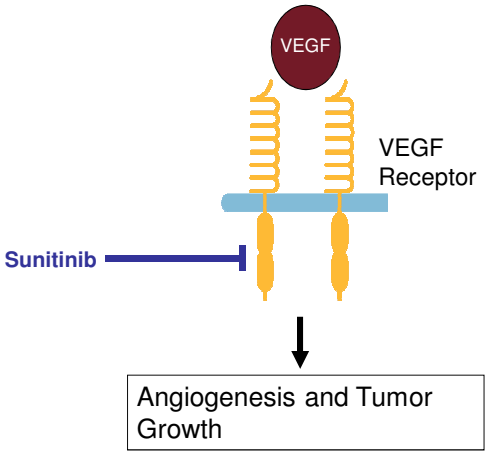
- Activation of mTOR pathway via IGF-1 is implicated in proliferation of NET
- Downregulation of TSC2 and PTEN in sporadic pancreatic NET leads to activation of mTOR pathway
- Everolimus is an mTOR inhibitor

RADIANT 3 Study: Everolimus Improves Outcome in panc NET



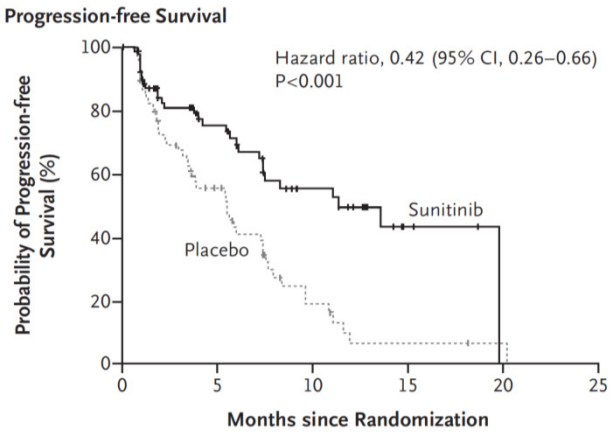
Yao, NEJM, 2011

Targeting Angiogenesis in Neuroendocrine Tumors



- NET are highly vascular
- VEGF and VEGFR overexpression has been observed in both pancreatic NET and carcinoid

Sunitinib Improves Outcome for Pancreatic NET



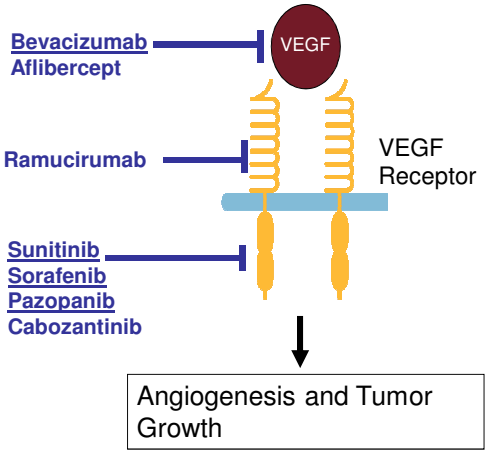
Raymond, NEJM, 2011

Targeted Therapy for Pancreatic NET

	Sunitinib[1]	Everolimus[2]
No. of patients treated	86	207
Median PFS (95% CI) vs. placebo arm	11.4 mo (7.4–19.8) vs. 5.5 mo	11.0 mo (8.4–13.9) vs. 4.6 mo
Median OS	Not reached	Not reached
Objective response rate	9%	5%
Stable disease rate	63%	73%
Specific adverse events	Hypertension (26%) Hand-foot syndrome (23%)	Pneumonitis (17%) Hyperglycemia (13%)

1. Raymond E, et al. *N Engl J Med.* 2011;364:501-513; 2. Yao JC, et al. *N Engl J Med.* 2011;364:514-523.

Targeting the VEGF Pathway in Neuroendocrine Tumors



- NET are highly vascular
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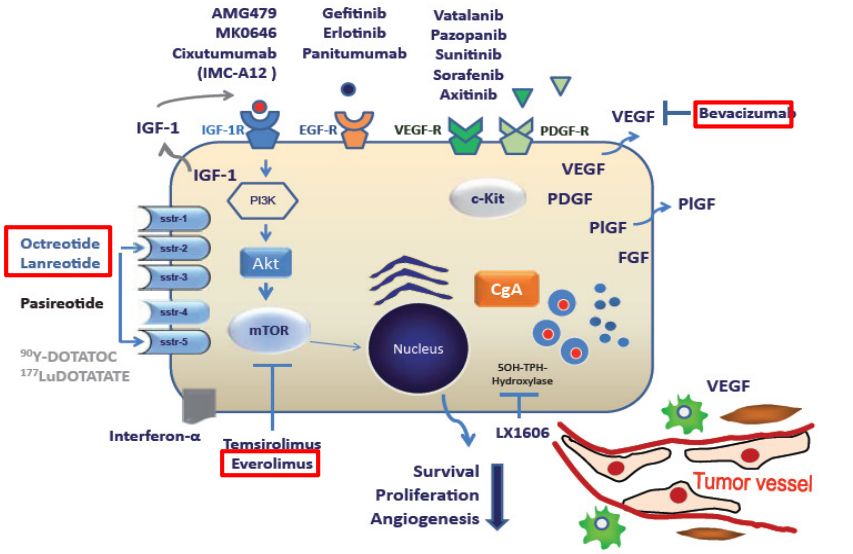
Targets for NET



Pavel, Neuroendocrinology, 2013

Randomized Phase II: CALGB 80701

Key inclusion criteria:

- **Advanced panc NET**
- **Progression within 12 mo**
- **No prior bevacizumab or mTOR inhibitor**
- **Prior treatment with SSA allowed**

Everolimus 10 mg po qd
Octreotide LAR, institutional standard

Everolimus 10 mg po qd
Bevacizumab 10 mg/kg IV q 2 weeks
Octreotide LAR, institutional standard

1°Endpoint : PFS

	Everolimus (n=75)	Everolimus + Bev (n=75)	Estimate
Median Progression-Free Survival	14.0 mos	16.7 mos	HR 0.80 (95% CI 0.55-1.17) P=0.12*
Overall Response Rate	12%	31%	P=0.005

Kulke et al, ASCO 2015

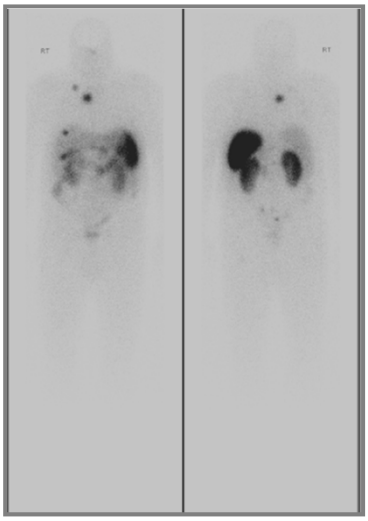
CALGB 80701: Summary of Grade 3 or 4 Adverse Events* and Dose Modifications by Treatment Arm

	Everolimus (N=74)	Everolimus + Bev (N=73)
Any grade 3 or 4 AE	49%	81%
Grade 3 or 4 hematologic AE	8%	14%
Grade 3 or 4 non-hematologic AE	43%	80%
Patients Experiencing Dose Modification	25%(E)	46% (E) 19% (B)
Patients Experiencing Dose Delay	16% (E)	33%(E) 36%(B)

* Adverse events at least possibly related to treatment

Kulke et al, ASCO 2015

Peptide Receptor Radionuclide Therapy (PRRT)



- Radiolabeled somatostatin analogs
  - Consist of SSTa + chelator + radionuclide
  - ^{111}In: Auger electrons
  - ^{90}Y: β-radiation
  - ^{177}Lu: β and γ-radiation
- Can deliver tumoricidal doses of radiation to SSTR positive tumors

PRRT for NET

Table 2. Tumor responses in GEPNET patients treated with different radiolabeled somatostatin analogs

Ligand	Tumor response						
	CR+PR %	Patient, n [ref.]	CR (%)	PR (%)	MR (%)	SD (%)	PD (%)
^{111}In-octreotide	0	26 [8]	0	0	2 (8)	15 (58)	9 (35)
^{111}In-octreotide	8	26 [9]	0	2 (8)	NA	21 (81)	3 (12)
^{90}Y-DOTATOC	29	21 [12]	0	6 (29)	NA	11 (52)	4 (19)
^{90}Y-DOTATOC	24	74 [17, 18]	2 (3)	16 (22)	NA	49 (66)	7 (9)
^{90}Y-DOTATOC	9	58 [13][a]	0	5 (9)	7 (12)	29 (50)	14 (24)
^{90}Y-DOTATOC	4	90 [14][b]	0	4 (4)	NA	63 (70)	15 (17)[c]
^{90}Y-DOTATOC	23	53 [19]	2 (4)	10 (19)	NA	34 (64)	7 (13)[d]
^{177}Lu-DOTATATE	29	310 [23]	5 (2)	86 (28)	51 (16)	107 (35)	61 (20)

ORR: 0-30%

vanVliet et al, Neuroendocrinology, 2013

PRRT for NET

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90Y-DOTATOC: More than half who were symptomatic at baseline had durable improvement in symptoms

vanVliet et al, Neuroendocrinology, 2013

PRRT for NET

- Adverse Events
  - GI: nausea, vomiting, diarrhea, abdominal pain
  - Fatigue, anorexia
- Rare serious adverse events
  - Hematologic toxicity (MDS, AML)
  - Kidney, liver failure

NETTER-1: Phase III Study of ^{177}Lu-Dotatate vs. High Dose Octreotide

Progressive, advanced SSTR+ midgut carcinoid tumors

- Radiographic progression on 20-30 mg octreotide LAR every 3-4 wks within 3 yrs
- Low-intermediate grade

RANDOMIZE

^{177} Lu-Dotatate every 8 weeks x 4 + Octreotide LAR 30 mg n= 115

Octreotide LAR 60 mg every 4 weeks n=115

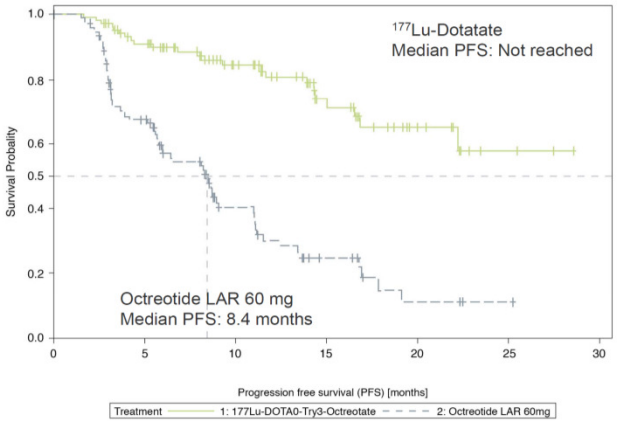
1°Endpoint : PFS

Ruszniewski et al, ESMO 2015

NETTER-1: Progression-Free Survival

N = 229 (ITT)
Number of events: 90
- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard Ratio [95% CI]
0.209 [0.129 – 0.338]
p < 0.0001



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

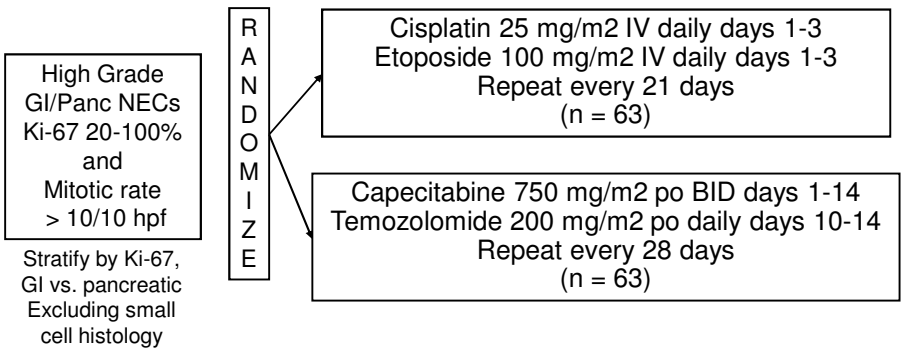
Ruszniewski et al, ESMO 2015

High Grade Neuroendocrine Carcinoma

- Typically treated with platinum-based chemotherapy
  - Ki-67 proliferation index (>55%) may predict sensitivity to platinum-based chemotherapy
  - Role of targeted agents not well defined
- Temozolomide-based chemotherapy has shown activity as second-line chemotherapy in a retrospective study

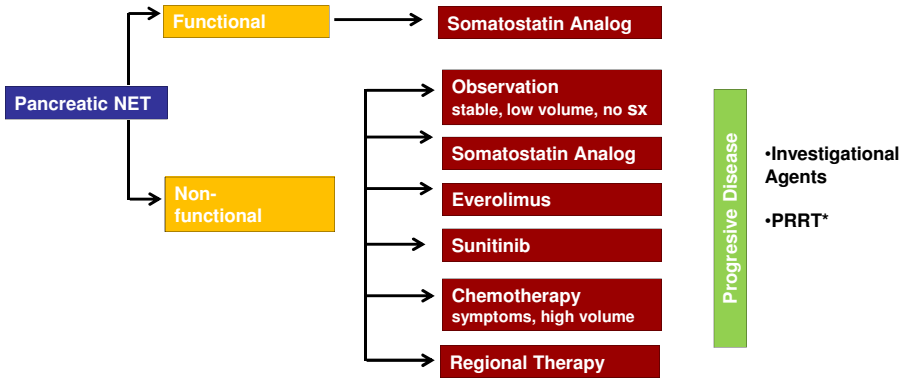
Sorbye et al, Ann Oncol, 2013
Welin et al, Cancer, 2011

EA2142: Randomized Phase II Study of Cisplatin and Etoposide vs. Temozolomide and Capecitabine for G3 Neuroendocrine Carcinomas



Primary Endpoint: PFS (improvement from 6 months to 10 months)
Secondary Endpoints: RR, OS, laboratory and imaging correlates

Current Pancreatic NET Treatment Landscape



Unanswered Questions and Future Directions

- Is there a best first line therapy?
- Is there a best sequence of therapy?
  - SEQTOR: Everolimus followed by STZ/5-FU vs. STZ/5-FU followed by everolimus
- Is there a role for combination therapy?
  - ECOG 2211: Temozolomide +/- capecitabine in pNET
  - CALGB 80701: Everolimus + octreotide +/- bev in pNET

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Unanswered Questions and Future Directions

- Can we identify predictors of response to treatment?

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DAXX/ATRX, MEN1, mTOR Pathway Genes Altered in pNET

Table 1. Comparison of commonly mutated genes in PanNETs and PDAC based on 68 PanNETs and 114 PDACs.

Genes*	PanNET	PDAC†
MEN1	44%	0%
DAXX, ATRX	43%	0%
Genes in mTOR pathway	15%	0.80%
TP53	3%	85%
KRAS	0%	100%
CDKN2A	0%	25%
TGFBR1, SMAD3, SMAD4	0%	38%

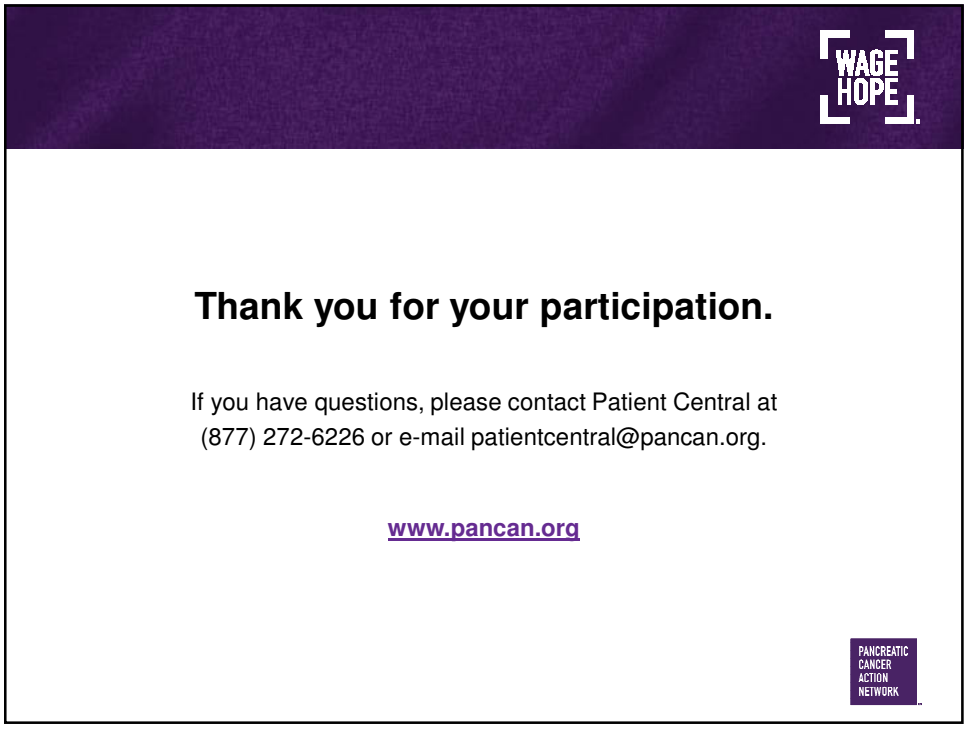
Jiao et al, Science 2011; 331: 1199-203

Treatment Options for NET

- Control of hormone hypersecretion
  - Somatostatin analogs
  - Everolimus for insulinoma
  - PPI for gastrinoma
- Control of tumor growth
  - sst analogs, everolimus, sunitinib, alkylating agents (temozolomide, streptozocin)
  - Regional therapy
  - ? PRRT
- Ongoing studies: combination therapy, novel agents

Selected clinical trials for panc NET

Study Regimen	
Temozolomide with or without capecitabine (ECOG)	NCT01824875
Capecitabine + temozolomide + bevacizumab	NCT01525082
Temozolomide + pazopanib	NCT01465659
Cabozantinib	NCT01466036
X-82 (VEGFR/PDGFR inhinitor) + everolimus	NCT01784861
Ziv-aflibercept	NCT02101918
Ibrutinib for advanced carcinoid and pNET	NCT0257530
Carfilzomib for NET [proteosome inhibitor]	NCT02318784
LEE011 for advanced foregut NET [CDK4/6 inhibitor]	NCT02420691
^{177}Lu-Octreotate vs. Sunitinib (Europe)	NCT02230176
Cisplatin and Etoposide vs.Temozolomide and Capecitabine for G3 GI/panc NEC (ECOG)	NCT02595424


WAGE
HOPE
Thank you for your participation.
If you have questions, please contact Patient Central at
(877) 272-6226 or e-mail patientcentral@pancan.org.
www.pancan.org
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